The Little Black Book of Gastroenterology

LITTLE BLACK BOOK SERIES

Series Editor: Daniel K. Onion

THIRD EDITION

JONES & BARTLETT LEARNING

David W. Hay

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Series Editor: Daniel K. Onion

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Dedication

The First Edition was dedicated:
To my parents, William Hay (1927–1998) and Elizabeth Bethune Hay, who gave me every opportunity and taught me the value of kindness.

To my children, Gillian and Colin, who make me proud and bring me joy.

The Second Edition was dedicated:
To Nancy I. Belanger with love and gratitude.

The Third Edition is dedicated:
To Michael J. Griffin and Michael J. Saletta, my steadfast partners in the practice of gastroenterology.

Contents

Notice ix
Preface xi
Medical Abbreviations xiii
Journal Abbreviations xvii

Chapter 1 Approaching Common Clinical Problems 1

1.1 Abdominal Pain 1
1.2 Dysphagia and Odynophagia 6
1.3 Nausea and Vomiting 7
1.4 Belching 9
1.5 Bloating 10
1.6 Flatulence 10
1.7 Constipation 11
1.8 Acute Diarrhea 14
1.9 Chronic Diarrhea 17
1.10 Malabsorption and Maldigestion 19
1.11 Gastrointestinal Bleeding 21
1.12 Evaluating Suspected Liver Disease 26

Chapter 2 Esophagus 33

2.1 Gastroesophageal Reflux Disease 33
2.2 Barrett's Esophagus 41
2.3 Benign Esophageal Strictures and Rings 44
2.4 Eosinophilic Esophagitis and the Ringed Esophagus 46
2.5 Congenital Esophageal Stenosis and the Ringed Esophagus 47
2.6 Foreign Bodies 47
2.7 Esophageal Cancer 49
2.8 Caustic Ingestion 51
2.9 Achalasia 53
2.10 Noncardiac Chest Pain 54
2.11 Diffuse Esophageal Spasm and Related Spastic Disorders 56
2.12 Mallory-Weiss Tears 56
2.13 Boerhaave's Syndrome 57
2.14 Zenker's (Hypopharyngeal) Diverticulum 57
2.15 Epiphrenic Diverticulum 58
2.16 Rumination Syndrome 58
2.17 Candida Esophagitis 59
2.18 Herpes Simplex Esophagitis 60
2.19 Cytomegalovirus Esophagitis 60
2.20 Esophageal Manifestations of HIV Infection 61
2.21 Esophageal Leiomyoma 62
2.22 Esophageal Papilloma 62
2.23 Esophageal Intramural Pseudodiverticulosis 62
2.24 Esophageal Inlet Patch 62

Chapter 3 Stomach and Duodenum 63

3.1 Gastritis 63
3.2 *Helicobacter Pylori* 63
3.3 Peptic Ulcer 68
3.4 NSAID Gastropathy 71
3.5 Stress Ulcer 73
3.6 Treatment of Bleeding Peptic Ulcer 75
3.7 Nonulcer Dyspepsia 76
3.8 Gastroparesis 77

3.9 Hiatal Hernia 79
3.10 Gastric Volvulus 80
3.11 Gastric Cancer 81
3.12 MALT and Other Gastric Lymphomas 83
3.13 Gastric Polyps 84
3.14 Subepithelial Gastric Lesions 85
3.15 Zollinger-Ellison Syndrome 86
3.16 Bezoars 88
3.17 Gastric Antral Vascular Ectasias 88
3.18 Dieulafoy's Ulcer 89
3.19 Ménétrier's Disease 90

Chapter 4 Inflammatory, Functional, and Other Intestinal Disorders 91

4.1 Irritable Bowel Syndrome 91
4.2 Physical and Sexual Abuse and GI 96
4.3 Food Allergy 97
4.4 Colonic Diverticulosis and Diverticulitis 98
4.5 Lactose Intolerance 102
4.6 Appendicitis 103
4.7 Crohn's Disease 105
4.8 Ulcerative Colitis 113
4.9 Collagenous Colitis 118
4.10 Lymphocytic Colitis 119
4.11 Diversion Colitis 119
4.12 Celiac Disease 119
4.13 Short Bowel Syndrome 121
4.14 Bowel Obstruction 123
4.15 Colonic Volvulus 124
4.16 Acute Colonic Pseudo-obstruction 125
4.17 Chronic Intestinal Pseudo-obstruction 126
4.18 Intussusception 127
4.19 Radiation Proctitis and Enteritis 127
4.20 Pneumatosis Intestinalis 128
4.21 Typhlitis 128
4.22 Eosinophilic Gastroenteritis 129
4.23 Meckel's Diverticulum 129
4.24 Endometriosis 129
4.25 Epiploic Appendagitis 129
4.26 Narcotic Bowel Syndrome 130

Chapter 5 Neoplastic Intestinal Disorders 131

5.1 Colorectal Cancer 131
5.2 Adenomatous Colonic Polyps 141
5.3 Hereditary Nonpolyposis Colon Cancer Syndrome 144
5.4 Familial Adenomatous Polyposis and Related Syndromes 146
5.5 Peutz-Jeghers Syndrome 149
5.6 Juvenile Polyps and Juvenile Polyposis 150
5.7 Miscellaneous Polyposis Syndromes 151
5.8 Carcinoid Tumors of the Gut 152

Chapter 6 Infectious Intestinal Disorders 155

6.1 *Clostridium difficile* Colitis and Antibiotic-Associated Diarrhea 155
6.2 *Campylobacter* 158
6.3 *Salmonella* 159
6.4 *Shigella* 160
6.5 *E. coli* O157:H7 161
6.6 Cholera and Other *Vibrio* Diseases 162
6.7 *Yersinia enterocolitica* 163
6.8 Enterotoxigenic, Enteropathogenic, Shiga-Toxigenic, and Enteroinvasive *E. coli* 163
6.9 *Plesiomonas* 163

6.10 *Aeromonas* 163
6.11 Giardiasis 163
6.12 Amebiasis 164
6.13 Cryptosporidiosis 166
6.14 *Cyclospora* 166
6.15 *Isospora belli* and Microsporidia 167
6.16 *Blastocystis hominis* 167
6.17 *Dientamoeba fragilis* 168
6.18 Viral Gastroenteritis 168
6.19 Diarrhea in HIV 168
6.20 Intestinal Helminths 169
6.21 Bacterial Overgrowth 169
6.22 Food Poisoning 170
6.23 Whipple's Disease 171

Chapter 7 Anorectal Disorders 173

7.1 Hemorrhoids 173
7.2 Anal Fissure 174
7.3 Anorectal Fistula and Abscess 175
7.4 Fecal Incontinence 176
7.5 Pruritus Ani 177
7.6 Fecal Impaction 177
7.7 Solitary Rectal Ulcer Syndrome 178
7.8 Proctalgia Fugax 179
7.9 Cancer of the Anal Canal 179
7.10 Hirschsprung's Disease 179

Chapter 8 Vascular Disorders of the Gut 181

8.1 Acute Mesenteric Ischemia 181
8.2 Chronic Mesenteric Ischemia 182
8.3 Ischemic Colitis 183
8.4 Angioectasias of the GI Tract 184
8.5 Abdominal Aortic Aneurysm 185

Chapter 9 Pancreas 187

9.1 Acute Pancreatitis 187
9.2 Chronic Pancreatitis 192
9.3 Pancreatic Cancer 195
9.4 Cystic Neoplasms of Pancreas 197
9.5 Islet Cell Tumors 198

Chapter 10 The Biliary Tree 201

10.1 Cholecystitis and Biliary Colic 201
10.2 Bacterial Cholangitis 206
10.3 Cholangiocarcinoma 207
10.4 Gallbladder Cancer 208
10.5 Ampullary Cancer 209
10.6 Gallbladder Polyps 210
10.7 Sphincter of Oddi Dysfunction (Biliary Dyskinesia) 210
10.8 Choledochal Cysts and Choledochocele 212
10.9 HIV-Related Biliary Disease 212
10.10 Painful Rib Syndrome 213

Chapter 11 Infections of the Liver 215

11.1 Hepatitis A 215
11.2 Hepatitis B 217
11.3 Hepatitis C 221
11.4 Other Causes of Viral Hepatitis 225
11.5 Hepatic Schistosomiasis 226
11.6 Pyogenic Liver Abscess 227

Chapter 12 Metabolic and Inflammatory Liver Disease 229

12.1 Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis 229
12.2 Primary Biliary Cirrhosis 231
12.3 Primary Sclerosing Cholangitis 233
12.4 Autoimmune Hepatitis 236

12.5 Hemochromatosis 238
12.6 Wilson's Disease 241
12.7 Alpha-1 Antitrypsin Deficiency 243
12.8 Acute Intermittent Porphyria 244

Chapter 13 Neoplastic Liver Disease 247
13.1 Hepatocellular Carcinoma 247
13.2 Hepatic Masses 250

Chapter 14 Drug- and Toxin-Induced Liver Disease 251
14.1 Alcoholic Liver Disease 251
14.2 Drug-Induced Liver Injury 253
14.3 Acetaminophen Overdose 253

Chapter 15 Complications of End-Stage Liver Disease 255
15.1 Portal Hypertension and Variceal Hemorrhage 255
15.2 Ascites 259
15.3 Spontaneous Bacterial Peritonitis 261
15.4 Hepatic Encephalopathy 263
15.5 Hepatorenal Syndrome 265
15.6 Hepatopulmonary Syndrome 266
15.7 Portopulmonary Hypertension 266

Chapter 16 Vascular Liver Disease 267
16.1 Budd-Chiari Syndrome 267
16.2 Venoocclusive Disease 268
16.3 Ischemic Hepatitis (Shock Liver) 268
16.4 Portal Vein Thrombosis 269

Chapter 17 Liver Disease in Pregnancy 271
17.1 HELLP Syndrome 271
17.2 Acute Fatty Liver of Pregnancy 272

Chapter 18 Procedures 275
18.1 Upper Endoscopy (EGD) 275
18.2 Colonoscopy 275
18.3 Sigmoidoscopy 276
18.4 Endoscopic Retrograde Cholangiopancreatography 276
18.5 Percutaneous Endoscopic Gastrostomy 276
18.6 Liver Biopsy 277
18.7 Liver Transplantation 277
18.8 Enteral Nutrition 278
18.9 Parenteral Nutrition 279

Chapter 19 Pearls in Gastroenterology 281

Index 283

Notice

The author, editor, and publisher have made every effort to provide accurate information. However, they are not responsible for errors or omissions, or for any outcomes related to the use of the contents of this book and take no responsibility for the use of the products described. Drugs and medical devices are discussed that may have limited availability controlled by the Food and Drug Administration (FDA) for use only in research study or clinical trial. The drug information presented has been derived from reference sources, recently published data, and pharmaceutical tests. Research, clinical practice, and government regulations often change the accepted standard in this field. When consideration is being given to use of any drug in the clinical setting, the healthcare provider or reader is responsible for determining FDA status of the drug, reading the package insert, and prescribing information for the most up-to-date recommendations on dose, precautions, and contraindications and determining the appropriate usage for the product. This is especially important in the case of drugs that are new or seldom used.

Preface

This short text is intended to be a practical resource for clinicians treating adults and adolescents. I have written the text from my viewpoint as a clinical gastroenterologist with a love of teaching. I expect that this text will also be of value to medical students and residents on gastroenterology or medicine rotations. It should not be difficult to read the entire volume over the course of a typical clerkship. Gastroenterology fellows will find it helpful as a quick reference and as a valuable resource for reviewing prior to board certification examinations. Mid-level providers, gastrointestinal nurses, and assistants will find concise discussions relevant to their daily work. There are more than 2000 references cited so that the reader can quickly find the most relevant clinical evidence on a topic.

The first section deals with the approach to common clinical problems such as abdominal pain, gastrointestinal bleeding, and jaundice. In these sections, a practical diagnostic approach is suggested. The individual diseases are discussed in the remainder of the text. There are many cross-references to take the reader from a complaint (eg, abdominal pain) to a specific diagnosis (eg, biliary colic).

For each chapter, I have listed one or two review articles. These were usually the papers that I found most helpful in understanding the topic. *The Little Black Book of Gastroenterology* uses the concise format outlined below:

Review Articles: Lists valuable review articles
Cause: Agent, if known
Epidemiology
Pathophysiology
Symptoms
Signs
Course of Disease
Complications
Differential Diagnosis: The differential diagnosis of diseases with similar presentations
Laboratory Tests: The available tests and their interpretation
X-ray: Imaging studies
Endoscopy: Endoscopic findings
Treatment

The last chapter is a brief list of "pearls" of clinical gastroenterology. Each pearl is cross-referenced to the appropriate chapter so that the reader can understand the evidence on which the pearl is based.

I would like to thank and acknowledge the work of those who helped me complete this project. The task would have been impossible without the expertise and tireless good cheer of librarian Cora Damon. I would like to thank Nancy Belanger for her extensive assistance in the preparation of the manuscript and tables. The text was vastly improved by the revisions suggested by Diane Brandt, Michael Saletta, Stephen Frost, and Michael Griffin. I am grateful to Dan Onion for offering me the opportunity to write the text and for his many practical suggestions.

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Medical Abbreviations

<	less than
<<	much less than
>	more than
>>	much more than
5-ASA	5-aminosalicylate
5' NT	5' nucleotidase
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptophan
6-MP	6-mercaptopurine
6-TG	6-thioguanine
AAAs	abdominal aortic aneurysms
ab	antibody
ac	before meals
ACBE	air contrast barium enema
ACE	angiotensin-converting enzyme
ACG	American College of Gastroenterology
ACS	American Cancer Society
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
AFB	acid-fast bacillus
AFP	alpha fetoprotein
ag	antigen
AGA	American Gastroenterological Association
AHCPR	U.S. Agency for Healthcare Policy and Research
AIH	autoimmune hepatitis
AIP	acute intermittent porphyria
aka	also known as
ALA	5-aminolevulinate
ALD	alcoholic liver disease
alk phos	alkaline phosphatase
ALT	SGPT; alanine aminotransferase
AMA	antimitochondrial antibodies
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic autoantibodies
anti-HBc	antibody to hepatitis B core antigen
AP	acute pancreatitis
APC	adenomatous polyposis coli
ARDS	adult respiratory distress syndrome
ASA	acetylsalicylic acid (aspirin)
ASCA	antibodies to saccharomyces cerevisiae
ASGE	American Society for Gastrointestinal Endoscopy
ASGPR	asialoglycoprotein antibodies
ASMA	anti-smooth muscle antibody
AST	SGOT; aspartate aminotransferase
ATPase	adenosine triphosphatase
AZA	azathioprine
BAO	basal acid output
BE	barium enema
BICAP	bipolar electrocautery
bid	2 times a day
BM	bowel movement
BUN	blood urea nitrogen
bx	biopsy
C&S	culture and sensitivity
C. diff	*Clostridium difficile*
Ca	cancer or calcium, depending on context
CA 19-9	carbohydrate antigen 19-9
CAD	coronary artery disease
cAMP	cyclic AMP
CBC	complete blood count
CBDS	common bile duct stones

cc	cubic centimeter
CCK	cholecystokinin
CD4	
CEA	carcinoembryonic antigen
cfu	colony-forming units
CHF	congestive heart failure
Cl	chloride
CMP	comprehensive metabolic profile[1]
cmplc	complications
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CP	chronic pancreatitis
CPK	creatinine phosphokinase
Cr	creatinine
CRC	colorectal cancer
CREST	calcinosis, Raynaud's, esophageal reflux, sclerodactyly, telangiectasias
CRP	C-reactive protein
crs	course
CT	computerized tomography
Cu	copper
CXR	chest x-ray
d	day(s)
DALMs	dysplasia-associated lesions or masses
DES	diffuse esophageal spasm
DIC	disseminated intravascular coagulation
diff dx	differential diagnosis
DJD	degenerative joint disease
DNA	deoxyribonucleic acid
DS	double strength
DU	duodenal ulcer
DVT	deep venous thrombosis
dx	diagnosis or diagnostic
EBV	Epstein-Barr virus
EE	eosinophilic esophagitis
eg	for example
EGC	early gastric cancer
EGD	esophagogastroduodenoscopy
EKG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EmA	antiendomysial
EMG	electromyography
ENT	ear, nose, and throat
epidem	epidemiology
ERCP	endoscopic retrograde cholangiopancreatography
EST	endoscopic sclerotherapy
ESWL	extracorporeal shock wave lithotripsy
EUS	endoscopic ultrasound
EVL	endoscopic variceal ligation
F	female or Fahrenheit
FAP	familial adenomatous polyposis
FB	foreign body
FDA	(U.S.) Food and Drug Administration
Fe	iron
FHF	fulminant hepatic failure
FIT	fecal immunochemical test
flex sig	flexible sigmoidoscopy
FNA	fine-needle aspiration
FOBT	fecal occult blood test
GAVE	gastric antral vascular ectasia
GE	gastroesophageal
GERD	gastroesophageal reflux disease
GGTP	gamma-glutamyl transpeptidase
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
gm	gram
GU	gastric ulcer
HAART	highly active antiretroviral therapy
H&E	hematoxylin and eosin
H&P	history and physical
H2RA	histamine-2 receptor antagonist
HBIG	hepatitis B immune globulin

[1]A comprehensive metabolic profile (CMP), consists of glucose, electrolytes, albumin, total protein, Ca^{++}, BUN, Cr, bilirubin, alk phos, and transaminases.

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
hct	hematocrit
HCV	hepatitis C virus
HE	hepatic encephalopathy
hep	hepatitis
Hg	mercury
Hgb	hemoglobin
HGBV-C	hep GB virus-C
HGV	hepatitis G virus
HH	hereditary hemochromatosis
HIDA	hepatobiliary iminodiacetic acid
HIV	human immunodeficiency virus
HLA	human leukocyte antigens
HMG-CoA	hydroxymethyl-glutaryl-coenzyme A
HNPCC	hereditary nonpolyposis colon cancer
Hp	*Helicobacter pylori*
HPV	human papillomavirus
hr	hour(s)
HRS	hepatorenal syndrome
hs	at bedtime
HSV	herpes simplex virus
HTN	hypertension
HUS	hemolytic uremic syndrome
hx	history
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICU	intensive care unit
ie	that is
IEU	idiopathic esophageal ulcer
Ig	immunoglobulin
im	intramuscular
IMA	inferior mesenteric artery
INR	international normalized ratio
ITP	idiopathic thrombocytopenic purpura
IU	international units
iv	intravenous
IVC	inferior vena cava
K	potassium
kg	kilogram
KOH prep	potassium hydroxide preparation
KUB	abdominal X-ray (kidneys, ureters, bladder)
L	liter
LCHAD	long chain 3-hydroxyacyl-CoA
LDH	lactate dehydrogenase
LES	lower esophageal sphincter
LFTs	liver function tests (bilirubin, AST/ALT, alk phos, albumin)
LLQ	left lower quadrant
LUQ	left upper quadrant
lytes	electrolytes
M	male
MALT	mucosa-associated lymphoid tissue
mcg	microgram
MCV	mean corpuscular volume
MELD	model for end-stage liver disease
MEN	multiple endocrine neoplasia
mEq	milliequivalent
mets	metastases
Mg	magnesium
mg	milligram
MI	myocardial infarction
min	minute
mOsm	milliosmole
MR	
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MSI	microsatellite instability
Na	sodium
NAFLD	nonalcoholic fatty liver disease
NaOH	sodium hydroxide
NAPQI	N-acetyl-p-benzoquinoneimine
NASH	nonalcoholic steatohepatitis
NDDIC	National Digestive Diseases Information Clearinghouse
NG	nasogastric
NGT	nasogastric tube

NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NNT	number needed to treat
no.	number
NOMI	nonocclusive mesenteric ischemia
npo	nothing by mouth
NS	normal saline
NSAID	nonsteroidal anti-inflammatory drug
NUD	nonulcer dyspepsia
O&P	ova and parasites
O_2	oxygen
OCG	oral cholecystogram
osm	osmoles
OTC	over the counter
pANCA	perinuclear antineutrophil cytoplasmic antibodies
pathophys	pathophysiology
PBC	primary biliary cirrhosis
PBG	porphobilinogen
PCR	polymerase chain reaction
PE	physical examination
PEG	percutaneous endoscopic gastrostomy
PET	positron emission tomography
PHG	portal hypertensive gastropathy
PI	protease inhibitor
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear leukocytes
PN	parenteral nutrition
po	by mouth
PO_4	phosphate
PPD	
PPI	proton pump inhibitor
PPoma	pancreatic polypeptide
pr	by rectum
prn	as needed
PSC	primary sclerosing cholangitis
PT	prothrombin time
pt(s)	patient(s)
PTHC	percutaneous transhepatic cholangiography
PTT	partial thromboplastin time
PUD	peptic ulcer disease
q	every
qd	daily
qid	4 times a day
qod	every other day
QT	
rbc	red blood cell
RCT	randomized controlled trial
RIBA	radioimmunoblot assay
RLQ	right lower quadrant
RNA	ribonucleic acid
ROS	review of systems
RR	relative risk
RUQ	right upper quadrant
rx	treatment
SBFT	small bowel follow-through
SBP	spontaneous bacterial peritonitis
sc	subcutaneous
SEMS	self-expanding metal stent(s)
si	sign(s)
SLE	systemic lupus erythematosis
SMA	superior mesenteric artery
SO	sphincter of Oddi
SSRIs	selective serotonin reuptake inhibitors
supp(s)	suppository/suppositories
sx	symptom(s)
tab	tablet
TB	tuberculosis
tbsp	tablespoon
TACE	Transarterial chemoembolization
TG	triglycerides
TIBC	total iron-binding capacity
tid	3 times a day
TIPS	transjugular intrahepatic portosystemic shunt

tiw	3 times a week
Tm/S	trimethoprim/sulfamethoxazole
TNF	tumor necrosis factor
TNM	tumor, nodes, metastases
TPN	total parenteral nutrition
TSH	thyroid-stimulating hormone
tsp	teaspoon
U	units
UA	urinalysis
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
UGI	upper gastrointestinal
US	ultrasound
U.S.	United States
UTI	urinary tract infection
VIP	vasoactive intestinal peptide
VOD	venoocclusive disease
vs	versus
wbc	white blood cells or white blood count
WD	Wilson's disease
yr	year(s)
ZE	Zollinger-Ellison syndrome
Zn	zinc

Journal Abbreviations

Most of the journal abbreviations are in the format used by the National Library of Medicine. Several frequently used journals have been more concisely abbreviated. These include:

Am Fam Phys	American Family Physician
Am J Med	American Journal of Medicine
Am J Surg	American Journal of Surgery
Arch IM	Archives of Internal Medicine
BMJ	British Medical Journal
Clin Perspect Gastro	Clinical Perspectives in Gastroenterology
Cmaj	Canadian Medical Association Journal
Curr Gastroenterol Rep	Current Gastroenterology Reports
Curr Opin Gastro	Current Opinion in Gastroenterology
Dig Dis Sci	Digestive Diseases and Sciences
Dis Mo	Disease-a-Month
GE	Gastroenterology
Hepatogastro	Hepatogastroenterology
Jama	Journal of the American Medical Association
Nejm	New England Journal of Medicine

Chapter 1

Approaching Common Clinical Problems

1.1 Abdominal Pain

Sx: The hx is the cornerstone of the efficient dx of abdominal pain. There are many different ways to obtain a hx and everyone develops an individual style. It is best to begin by letting the pt describe the pain without any leading questions. Say to the pt, "Tell me the whole story about your pain beginning with the first time in your life you had a pain anything like this." Many pts will give a neat, chronological story and others will wander. It is worthwhile to give the pt some time to present the story in his or her own way, but it often becomes necessary to direct the pt to establish the following points:

- *Timing:* When did the pain first begin? How often does it occur? When an episode occurs, how long does it last? Is the pt entirely well between episodes, or is the pain always present to some degree? Is the pain present 24 hours a day, 7 days a week? A pain present for years is unlikely to be malignant. Upper abdominal pain that occurs in discrete attacks is more likely to be biliary. Pain that is constant is often functional (eg, IBS in the setting of sexual abuse) or is readily diagnosed with imaging studies, hx, and physical exam (eg, malignancy, musculoskeletal pain, intra-abdominal inflammation or infection).
- *Character:* Ask the pt to describe the pain. If the pt finds the pain indescribable, offer a multiple choice list, such as, "Is the pain sharp, dull, aching, burning, or stabbing?" Asking the pt to characterize the pain is helpful in evaluating pts who have multiple pain complaints, since each of the pains can be referred to separately.
- *Radiation:* Ask the pt if the pain radiates anywhere. Upper abdominal pain radiating to the back suggests biliary colic, PUD, or an esophageal source. Acute perforation of a viscus can cause shoulder pain. Pain radiating to the groin or testicle suggests a urinary tract source. Pain radiating to the leg or thigh suggests a nonabdominal cause. Pain radiating to the neck or arm suggests a cardiac cause.
- *Relieving or exacerbating factors:* Ask the pt, "Is there anything that makes the pain predictably worse, such as eating, BMs, stressful situations, or any kind of position or activity?" Identify factors that predictably bring relief, such as OTC remedies. These points help to establish if the pain is of GI origin and if it is more likely related to the bowel or to the UGI tract.

- *Associated sx:* A complete ROS is necessary. Depending on the nature of the sx, it is important to establish whether there has been weight loss, fever, anorexia, nausea, melena, or hematochezia.
- *Medications:* Many abdominal sx are related to medications, including OTC and herbal preparations. The duration of use should be determined.
- *Past medical and family hx:* These histories help to establish risk factors for specific disorders and the safety and appropriateness of invasive tests.

Si: A complete physical exam is done, including assessment of vitals, skin, lymph nodes, the neck, heart, lungs, and joints; where indicated, a neurologic evaluation is done. The abdomen is usually the most informative part of the exam in creating a diff dx.

- *General abdominal exam:* Bowel sounds are evaluated. Very active bowel sounds suggest the possibility of infection or early obstruction. Bowel sounds may be absent with intra-abdominal catastrophe or ileus. The abdomen is assessed for tenderness to percussion. Percussion tenderness suggests peritoneal irritation. Palpation is done to look for masses or tenderness. If a pt seems to react with surprising drama, the exam can be continued while the pt is distracted with questions. If the abdomen is tender, the pt is asked to lift the head and shoulders a few inches off the table to see if the tenderness on palpation changes. Pain that worsens with this maneuver is often from the abdominal wall. Pain that is unchanged or that improves with tensing the abdominal muscles is often from an intra-abdominal source. The costal margins should be carefully examined with firm palpation to look for evidence of the painful rib syndrome (p 213). The aorta should be palpated for tenderness or enlargement.
- *Inflammation and peritonitis:* Percussion tenderness, rebound tenderness, or pain with shaking of the pelvis suggests peritoneal irritation. In diffuse peritonitis, the abdomen may become rigid. A positive **psoas sign** (pain on extension of the thigh with the pt lying laterally on the opposite hip) may occur with retroperitoneal inflammation. A positive **obturator sign** (pain on internal rotation of the flexed thigh) may indicate an inflammatory process in the pelvis. A **Murphy's sign** (the abrupt cessation of inspiration when examiner is palpating the RUQ because of worsening of the pain) strongly suggests cholecystitis.
- *Liver and spleen:* Hepatomegaly can be assessed by percussion and palpation. Percussion of the upper border should be firm and that of the lower border lighter. The normal liver span is 12-15 cm in the midclavicular line. The normal liver is usually palpable with deep inspiration. It is often easier to palpate the liver edge by using both hands with palms lying on the rib cage and the fingers hooked over the edge of the costal margin. A similar technique is helpful for the spleen. The spleen is usually not palpable, and percussion in the LUQ may reveal its lower margin.
- *Stigmata of liver disease:* See p 26.
- *Rectal and pelvic exams* are often needed depending on the differential being considered.

Approach to Dyspepsia: Chronic or recurrent pain centered in the upper abdomen is usually referred to as dyspepsia. Many pts with dyspepsia have GERD, which can be suspected based on clues such as retrosternal burning pain, gross regurgitation, or dysphagia to solids. Some GERD pts will have sx exclusively in the epigastrium, and this group may be difficult to identify without additional tests such as EGD, a therapeutic trial of a PPI, or pH probe (p 33).

About 10-25% of pts with dyspeptic sx have peptic ulcer disease (p 68) (GE 1998;114:579). About 60% of pts with dyspepsia never have an organic cause found and are said to have nonulcer dyspepsia (p 76). The remainder of the differential is listed in Table 1.1. The painful rib syndrome (p 213) should be easily identified on physical exam but is often overlooked.

It is often helpful to obtain a CBC, CMP, amylase, and lipase. The AGA has published guidelines for evaluating dyspepsia (GE 2005;129:1753). Pts on NSAIDs with dyspepsia should have the drug stopped/changed or a PPI added. In pts >55 yr of age who have new-onset dyspepsia, EGD is appropriate to rule out gastric cancer. Pts with alarm sx of weight loss, recurrent vomiting, dysphagia, bleeding, family hx of gastric cancer, or anemia should also undergo EGD. Pts <55 yr of age with no alarm features should be tested for *Helicobacter pylori* (Hp) (p 63), ideally with stool antigen or breath testing. If positive, they are treated and EGD is considered only if sx fail to improve after an additional 4 weeks of PPI rx. If a young pt is Hp negative, an empiric 4- to 8-week course of a PPI is appropriate. EGD is considered only if the pt fails to improve or if sx rapidly recur after stopping rx. There is little point to obtaining a UGI barium study since it is not sensitive enough to be a reliable negative test and a UGI series showing GU or a possible cancer requires EGD.

If no cause of sx is identified at EGD, clinical judgment is used to determine how vigorously to pursue the rest of the diff dx. CT scan and US of the abdomen, gastric

Table 1.1 Causes of Dyspepsia

Condition	Discussed on Page
Gastroesophageal reflux disease	33
Peptic ulcer disease	68
Nonulcer dyspepsia	76
Pancreatitis	187
Biliary colic	201
Gastroparesis	77
Pancreatic cancer	195
Lactose intolerance	102
Air swallowing	9
Giardia	163
Gastric cancer	81
Other intra-abdominal neoplasms	—
Crohn's disease	105
Irritable bowel syndrome	91
Sphincter of Oddi dysfunction	210
Celiac disease	119
Chronic mesenteric ischemia	182
Porphyria	244
Lead poisoning	—
Painful rib syndrome	213
Other parasites	169
Angina	—
Somatization disorder	—

emptying scan, 24-hr pH probe, SBFT, testing for *Giardia* and other parasites, or dietary trials may be selectively indicated.

Approach to Attacks of Upper Abdominal Pain: If pain comes in discrete attacks, in between which the pt feels well, then biliary colic (p 201) should be strongly considered. CBC, CMP, amylase, and lipase are generally indicated, and an RUQ US should be obtained. If the US is negative, the differential may need to be broadened to include the causes of dyspepsia (Table 1.1). If further evaluation shows no convincing cause of pain, the possibility of a false-negative US needs to be considered. About 80% of pts with a good story for biliary colic, a negative US, and no other evident cause of dyspepsia will get relief with cholecystectomy. Some physicians use gallbladder emptying tests to select pts for cholecystectomy (Am J Surg 1997;63:769). A radionuclide scan (p 203) with an ejection fraction of <35% (in response to CCK stimulation) is considered abnormal. However, there is no high-quality evidence (ie, an RCT) showing that radionuclide scanning improves outcome for this challenging group of pts (Am J Gastro 2003;98:2605).

Approach to Acute Abdominal Pain: If hx suggests that the pain is entirely new (not an exacerbation of a chronic problem) and that the pain is of very recent onset (typically hours), the differential considerations are different (Table 1.2). Appendicitis typically presents with midabdominal pain that later moves to the RLQ but can be variable. Biliary colic, cholecystitis, pancreatitis, and cholangitis usually present with acute upper abdominal pain. Bowel obstruction usually presents as severe, crampy pain and distension usually in a pt with a prior hx of abdominal surgery. In acute mesenteric ischemia, the pain is severe and out of proportion to the initial physical exam findings. In ischemic colitis, there is usually intense, crampy lower abdominal pain with bloody diarrhea. In dissecting abdominal aortic aneurysm, there may be a pulsatile mass and hypotension, but these findings are not universal. In diverticulitis, the pain is usually (but not always) in the LLQ and associated with fever. The pain of renal colic is often in the flank and may radiate to the groin in a pt with a benign belly. Other considerations include perforated ulcer disease, ectopic pregnancy, ruptured ovarian cyst, ovarian abscess or torsion, drug seeking, epiploic appendagitis, and acute presentations of Crohn's disease.

A CBC, CMP, amylase, lipase, pregnancy test, and UA are generally indicated. A flat and upright view of the abdomen may demonstrate obstruction. In some cases an upright film centered on the diaphragm is done to look for free air. Depending on the severity of the sx, studies such as a CT scan may be warranted.

These considerations are reviewed separately for each disease entity.

Approach to Chronic Lower Abdominal Pain: Pain centered in the lower abdomen often has a colonic source. Crampy pain, diarrhea, relief of pain with passage of BMs, change in BMs, and rectal bleeding are features that suggest a colonic source of sx. Chronic pain from the colon is most often due to irritable bowel syndrome (p 91) or constipation (p 11). Rectal bleeding, weight loss, or a change in bowel habits (BM frequency, caliber) may suggest CRC (p 131). Diverticulitis usually presents with acute pain, but in some pts onset of sx can be more gradual (p 98). If diarrhea is prominent, infectious colitis is a possibility, though most pts with infectious colitis present with acute sx. Chronic bloody diarrhea and weight loss suggest ulcerative colitis (p 113) or Crohn's colitis (p 105).

If pain seems unrelated to BMs, gynecologic and urinary tract causes should be considered. Musculoskeletal causes of pain are usually evident by hx and exam.

Table 1.2 Causes of Acute Abdominal Pain

Category	Condition	Discussed on Page
Gastrointestinal		
	Appendicitis	103
	Perforated ulcer disease	68
	Bowel obstruction	123
	Acute mesenteric ischemia	181
	Ischemic colitis	183
	Infectious gastroenteritis	155
	Diverticulitis	98
	Perforated bowel	—
	Acute presentations of Crohn's disease	105
	Epiploic appendagitis	129
Pancreatic and Biliary		
	Biliary colic	201
	Cholecystitis	201
	Cholangitis	206
	Pancreatitis	187
Urologic		
	Renal colic	—
	Pyelonephritis	—
	UTI	—
Gynecologic		
	Ectopic pregnancy	—
	Pelvic inflammatory disease	—
	Ruptured ovarian cyst	—
	Ovarian abscess	—
	Ovarian torsion	—
Retroperitoneal		
	Retroperitoneal hemorrhage	—
	Dissecting aortic aneurysm	185
	Psoas abscess	—
Thoracic		
	Myocardial infarction	—
	Lower lobe pneumonia	—
Other		
	Drug seeking	—
	Narcotic withdrawal	—
	Diabetic ketoacidosis	—

If the hx suggests a high probability of cancer or inflammatory bowel disease, colonoscopy is warranted. The approaches to suspected irritable bowel syndrome (p 91) and constipation (p 11) are discussed in separate sections.

Approach to Chronic Diffuse Pain: Pts with chronic diffuse pain that occurs 24 hours a day, 7 days a week are challenging. They fall broadly into 2 groups. The first group includes pts

with illnesses such as intra-abdominal malignancy or inflammation who undergo imaging studies or have findings on exam that are diagnostic. The second, more difficult group includes pts with chronic abdominal pain, typically with multiple pain complaints, many prior physician visits, and many diagnostic tests that have been unrevealing. A careful H&P is done to categorize the complaints. It is essential to obtain records of *all* prior evaluations prior to any new studies. Many of these pts will turn out to have functional or psychiatric diagnoses. It is vital not to overlook the connection between this pattern of complaints, medical evaluations, and hx of physical or sexual abuse (p 96). It is important for the pt to see that the physician has considered each complaint carefully. Do not appear dismissive or trivialize the pt's difficulties.

1.2 Dysphagia and Odynophagia

GE 1999;117:229

Sx/Si: **Dysphagia** is the sensation that a swallowed food bolus sticks in the chest. Ask the pt, "If I gave you a bite of steak, bread, or apple to eat and told you that you had to wolf it down, would it stick in your chest?" Pts may perceive the sticking at the sternal notch even though the bolus is at the GE junction. Sometimes the sticking is relieved by swallowing liquid or by lifting the arms over the head or with other body position changes. Amazingly, some pts do not identify the bolus as stuck, but instead will complain of pain and excessive salivation. Pts often do not report these episodes unless specifically asked. Some pts have dysphagia to liquids as well as solids. They may experience nasal regurgitation. Many of these pts have motor disorders of the esophagus. Another group has problems with the initial nonesophageal phases of swallowing, called **oropharyngeal dysphagia**. Sx are usually above the sternal notch, sometimes with aspiration, coughing, or drooling. The physical exam is usually not helpful in the evaluation of swallowing except for revealing neurologic disease in some pts with oropharyngeal dysphagia.

Odynophagia, or painful swallowing, is less common than dysphagia. Acute odynophagia suggests the possibility of infections (candida, herpes, CMV) or pill esophagitis. There may be evidence of oral thrush or herpes infection of the oropharynx in some pts.

Diff Dx: **The causes of dysphagia** are listed in Table 1.3. Strictures due to GERD and benign esophageal rings (Schatzki's rings) are the most frequent causes. In dysphagia due to GERD without a stricture, the sx are usually brief and not associated with prolonged food impaction. Esophageal cancer is often associated with weight loss. Extrinsic compression of the esophagus is usually due to malignancy. A Zenker's diverticulum can be associated with a mass in the neck or coughing food debris hours after it was eaten. In congenital esophageal stenosis, the pt may describe a lifetime of being a slow eater.

Dysphagia to liquids raises the possibility of achalasia, diffuse esophageal spasm, and related spastic disorders. The evaluation of oropharyngeal dysphagia usually results in a dx of a neuromuscular or other disorder not related to the GI tract and is not further discussed in this text (see GE 1999;116:455 for a comprehensive review).

Pill esophagitis is a frequent cause of **odynophagia**. Doxycycline, alendronate, quinidine, ASA, other NSAIDs, and potassium tabs are the most frequent offenders (J Clin Gastroenterol 1999;28:298). Esophagitis due to candida, herpes, or CMV often presents with

Table 1.3 Causes of Dysphagia and Odynophagia

Dysphagia	Discussed on Page	Odynophagia	Discussed on Page
Esophageal strictures and rings	44	Pill esophagitis	—
GERD without stricture	33	Herpetic esophagitis	60
Esophageal cancer	49	Candida esophagitis	59
Extrinsic compression	—	CMV esophagitis	60
Benign esophageal tumors	62	Idiopathic esophageal ulcer	61
Zenker's diverticulum	57		
Other esophageal diverticula	58		
Eosinophilic esophagitis	46		
Congenital esophageal stenosis	47		
Achalasia	53		
Diffuse esophageal spasm	56		
Other spastic disorders	56		
Oropharyngeal causes	—		

painful swallowing. Idiopathic esophageal ulcer is seen in HIV infection. The other listed causes of dysphagia should also be considered in pts with painful swallowing.

Approach to Dx and Rx: Most pts with intermittent solid food dysphagia are best served with EGD for dx and possible rx with esophageal dilatation. Pts with severe sx and those with a story suggestive of a Zenker's diverticulum (p 57), other proximal lesions, or achalasia (p 53) should have a barium swallow. Some pts with severe sx have long and complex strictures, and a barium swallow helps the endoscopist decide how to proceed with dilatation. A Zenker's diverticulum presents a perforation risk during endoscopy because it can be difficult to pass the scope beyond the diverticulum. If EGD is normal, biopsies of mid- and lower esophagus should be obtained to rule out eosinophilic esophagitis (p 46). If EGD is normal and the pt has solid food dysphagia, empiric dilatation can be considered in the hope of relieving sx by dilating rings missed at EGD (Clin Gastroenterol Hepatol 2005;3:299). If EGD is not readily available, a barium swallow with a 13-mm barium tablet is a good test to detect stricture and rule out a mass. However, barium swallow is not therapeutic and is insensitive for esophagitis. Pts with sx suggesting a motor disorder may be candidates for esophageal manometry testing after a structural abnormality has been excluded.

Pts who are awaiting evaluation need to be cautioned to cut food in small pieces and to chew carefully to avoid food impaction. If sx of GERD are present, it is reasonable to begin a PPI while awaiting diagnostic testing.

1.3 Nausea and Vomiting

GE 2001;120:263

Diff Dx: Nausea is a nonspecific sx with an enormous diff dx. Acute nausea and vomiting without substantial abdominal pain are most often related to infectious gastroenteritis, food poisoning, drugs, systemic infection, metabolic abnormalities, migraine, increased intracranial

pressure, labyrinthitis, or any cause of acute pain. Many other acute illnesses can cause vomiting with pain (eg, obstruction), but usually there are obvious clues. In most cases, the cause of acute nausea and vomiting can be readily determined.

Chronic nausea can be a more difficult problem. Vomiting increases the probability that a structural cause will be found. Some of the many causes of nausea and vomiting are listed in Table 1.4. Morning sickness of pregnancy must not be overlooked. Numerous drugs cause nausea, including cancer chemotherapy, analgesics, hormonal preparations, antibiotics,

Table 1.4 Causes of Nausea and Vomiting

Category	Disorder	Discussed on Page
Gastrointestinal		
	Infectious gastroenteritis	155
	Food poisoning	170
	Gastric outlet obstruction	—
	Gastroparesis	77
	Gastroesophageal reflux disease	33
	Nonulcer dyspepsia	76
	Bowel obstruction	123
	Intra-abdominal inflammation	—
	Intra-abdominal malignancy	—
	Eosinophilic gastroenteritis	129
	Gastric volvulus	80
	Pseudo-obstruction	125, 126
Medications		
	Cancer chemotherapy	—
	NSAIDs	—
	Antibiotics	—
	Digoxin	—
	Many others	—
Central Nervous System		
	Eating disorders	—
	Rumination syndrome	58
	Migraine	—
	Increased intracranial pressure	—
	Psychiatric disorders	—
Endocrine and Metabolic		
	Fluid and electrolyte disorders	—
	Acute intermittent porphyria	244
	Hyperthyroidism	—
	Addison's disease	—
	Renal failure	—
Postoperative		
	Postoperative	—
Other		
	Systemic infection	—
	Morning sickness	—

antivirals, and cardiovascular drugs. Structural diseases of the stomach, such as gastric outlet obstruction due to malignancy or ulcer disease, are usually associated with pain or weight loss. Gastroparesis is often considered as a cause of chronic nausea, but the pathogenesis is unclear, and gastroparesis should not be accepted as the cause without excluding other etiologies. GERD is associated with nausea, and pts may interpret gross regurgitation as vomiting. Labyrinthine disorders are usually associated with clues on exam or hx, such as vertigo or nystagmus. A syndrome of cyclical vomiting that may be a migraine equivalent occurs in children and adults (Dig Dis Sci 1999;44:23S). While many other diseases can present with nausea and vomiting (eg, bowel obstruction, pancreatitis, cholecystitis, hepatitis, adrenal insufficiency, renal failure, electrolyte disorders, narcotic withdrawal), they rarely do without offering some other substantial clinical or laboratory clue to dx.

Approach to Dx and Rx: The most efficient approach is usually evident after a careful hx, physical exam, and selective use of laboratory tests (CBC, CMP, pregnancy test, amylase, lipase). In most cases, the cause can be identified and treated. If a dx is not evident after initial evaluation, short-term empiric rx with an antiemetic or prokinetic such as metoclopramide may be appropriate for some pts.

Very few trials have compared **antiemetic** regimens, and several classes of agents are available (Am Fam Phys 2004;69:1169). Anticholinergics (scopolamine) and antihistamines (meclizine, diphenhydramine, hydroxyzine) are popular for motion sickness and labyrinthine disorders. Phenothiazines (eg, prochlorperazine 5-10 mg po tid-qid or 25-mg supps pr bid or 2.5-10.0 mg iv q 3-4 hr to a maximum of 40 mg daily) are effective in many causes of nausea and vomiting. Other phenothiazines include promethazine, triethylperazine, chlorpromazine, and perphenazine. IV promethazine should not be routinely used for nausea because of the risk of serious tissue injury. Serotonin antagonists (eg, ondansetron and others) are effective, more expensive, and widely used in chemotherapy pts. The choice of prokinetics is limited, and metoclopramide (5-10 mg po qid) is most frequently used.

For many pts, empiric rx is not appropriate and further evaluation is needed. The selective use of EGD, gastric emptying scan, abdominal CT scan, plain films of the abdomen, MRI of the brain, SBFT, and psychiatric evaluation may be appropriate. The nature, duration, and severity of complaints guide the extent of the evaluation.

1.4 Belching

Postgrad Med 1997;101:263

Diff Dx: Belching (eructation) is the involuntary expulsion of air from the esophagus and stomach. Regurgitation of swallowed air from the stomach is a normal physiological event. Some pts swallow air into the esophagus/hypopharynx and immediately expel it in a belch. Several organic disorders can be associated with belching, including GERD (p 33), gastroparesis (p 77), gastric outlet obstruction due to malignancy (p 87) or PUD (p 68), and achalasia (p 53). Aerophagia (air swallowing) is an unconscious habit or is related to anxiety, chewing gum, tobacco, postnasal drip, COPD, asthma, or ill-fitting dentures. Aerophagia can also be a response to pain in the stomach or esophagus.

Approach to Dx and Rx: If the hx or physical suggests an organic etiology, further testing is needed. A trial of a PPI may be considered for the question of GERD (p 33). If an organic etiology seems unlikely, air swallowing is discussed with the pt. It is most effective if the physician masters air swallowing and is able to match the pt belch for belch during the interview.

Those with suspected aerophagia should be counseled to minimize swallowed air by avoiding chewing gum, hard candy, smoking, and carbonated beverages. Pts should be educated that their sx are not caused by production of gas by the stomach. A pencil held clenched between the teeth is said to decrease air swallowing but the value of this technique has been questioned (Am J Gastroenterol 1998;93:2276).

1.5 Bloating

Clin Perspect Gastro 2000;July:209; Postgrad Med 1997;101:263

Diff Dx: Bloating can be a sx associated with many organic diseases including GERD, gastroparesis, PUD, pancreatic disease, malabsorption, intestinal infection, constipation, diverticular disease, drug side effects, and intra-abdominal malignancy. While this is a daunting list, it is rare that bloating would be the sole sx in these disorders. Bloating as a single sx (or associated with generalized discomfort) is usually not related to the excess production of gas (Gut 1991;32:662), but is probably a manifestation of IBS (p 91). Dietary management to minimize gas production may benefit these pts because they have abnormal sensitivity to volumes of gas that pts without IBS do not find distressing.

Approach to Dx and Rx: The H&P is used to determine if there are clues that may take the clinician in a direction other than irritable bowel syndrome. Dietary hx as detailed for the flatulent pt (p 10) is appropriate. In the absence of other clues, the approach is that outlined for IBS (p 91). Measures to decrease flatus (described in the next section) can be tried.

1.6 Flatulence

Clin Perspect Gastro 2000;July:209; Postgrad Med 1997;101:263

Diff Dx: Normal subjects produce up to 2500 mL of flatus a day and pass it up to 20 times daily. Rectal gas is a combination of swallowed air (rich in nitrogen) and gas produced from colonic bacterial metabolism that produces hydrogen, methane, and malodorous sulfur gases (Gut 1998;43:100). Some pts will complain of frequent passage of flatus because of poor sphincter tone. A small number of pts will have excess gas from serious malabsorptive diseases (p 19) such as celiac disease, small bowel bacterial overgrowth, and pancreatic insufficiency. The remainder have an anatomically normal gut and have excessive flatus either from air swallowing or from gas produced by bacterial fermentation of carbohydrates.

Excessive colonic production of gas may be of a variety of dietary sources. **Lactose** intolerance is a frequent cause (p 102). **Fructose** (found in high concentration in figs, dates, prunes, pears, apples, grapes, some vegetables, and in soft drinks sweetened with high

fructose corn syrup) can cause flatulence because it is less efficiently absorbed than other sugars (Am J Gastro 2004;99:2046). **Sorbitol** (found in sugarless gum, many hard candies, and food sweetened for diabetics, as well as in apples, pears, prunes, and peaches) is minimally absorbed and causes distressing sx due to bacterial fermentation (Gut 1988;29:44). Legumes (such as beans, broccoli, cabbage, and cauliflower) have complex carbohydrates that cannot be fully digested because humans lack α-galactosidase. Starches and dietary fiber also provide substrates for intestinal gas production.

Approach to Dx and Rx: The H&P is used to look for clues to serious underlying disease and to assess rectal tone. Dietary hx is obtained for lactose, fructose, sorbitol, legumes, and fiber. The pt is watched for evidence of air swallowing. If there are clues to serious disease, further evaluation is indicated (see Malabsorption, p 19). Those with poor sphincter tone are educated as to the nature of the problem, and incontinence is treated (p 176). Flatus passed more than 20 times daily is abnormal. Colonic fermentation should be suspected if the flatus is especially malodorous, nocturnal, or meal related. The pt can be evaluated for lactose intolerance (p 102) and can be given diets low in offending carbohydrates. Those with odorless flatus, belching, and bloating may be suspected of air swallowing, but dietary trials are still worthwhile. Collection of rectal gas to distinguish air swallowing (flatus high in nitrogen) from colonic fermentation (high in methane and hydrogen) has been reported but is impractical for widespread use (Am J Gastroenterol 1998;93:2276).

Oral activated charcoal is of no benefit (Am J Gastroenterol 1999;94:208), but a charcoal-lined pillow (Toot Trapper) is effective at reducing noxious odor (Gut 1998;43:100). Beano, a commercially available α-galactosidase preparation, is effective in reducing flatulence associated with legumes.

1.7 Constipation

Am J Gastro 2005;100 Suppl 1:S1; GE 2000;119:1766; Cleve Clin J Med 1999;66:41

Sx: Constipation is a term used by pts to describe a wide variety of complaints related to defecation. To the physician, constipation is usually defined as a BM frequency of less than 3 per week. More complex definitions have been proposed but are not of practical significance except for scientific study (Gut 1999;45[suppl 2]:II43). Pts may use the term constipation to mean excessive straining, painful defecation, hard stools, abdominal pain, or the failure to have a daily BM. The quality and time course of each complaint should be noted. The use of mechanical means (vaginal or perineal pressure, a finger in the rectum, enemas) to evacuate stool suggests pelvic floor dysfunction. Dietary hx is crucial since in many cases dietary fiber is inadequate. Ask the pt to describe a typical breakfast, lunch, and dinner. Determine servings of cereal, whole-grain bread, rice, pasta, vegetables, and fruit as a rough method of determining dietary fiber. Many pts will eat only 1 or 2 servings daily of high-fiber foods, and the most likely cause of their sx becomes evident quickly.

Si: Rectal exam is done to look for evidence of masses, fissures, strictures, painful spasm of the sphincter, or impaction. The pt is asked to strain in simulated defecation while the examiner watches for prolapse or paradoxical contraction of the anal sphincter. Paradoxical

contraction of the sphincter when simulating defecation suggests pelvic floor dysfunction. Rectocele is detected by vaginal examination. Neurologic exam may be appropriate.

Diff Dx: (Am J Gastroenterol 1999;94:567) The common causes of constipation are listed in Table 1.5. There are 2 **primary** mechanisms for constipation. In **slow transit constipation**, feces is moved slowly from cecum to rectum because of decreased contractions. Alternatively, uncoordinated contractions of the left colon may act as a functional barrier. In **pelvic floor dysfunction**, feces is stored in the rectum for an excessive period because of lack of coordinated mechanisms for rectal emptying. There are numerous secondary causes of constipation. Inadequate dietary fiber, inadequate fluid, and ignoring the urge for a BM are frequent causes. Constipation can be secondary to structural lesions, drugs, IBS, neurologic diseases, or metabolic causes.

Approach to Dx: The H&P is used to evaluate the probability of a secondary cause of constipation. In general, obstructing colon cancer should be considered in new-onset

Table 1.5 Causes of Constipation

Cause	Example
Slow transit constipation	—
Pelvic floor dysfunction	—
Dietary	Inadequate fiber, inadequate fluids
Behavioral	Ignoring urge for BM
	Psychiatric illness
Structural	Colon cancer
	Colonic stricture
	Volvulus
	Anal fissure with spasm
	Rectal prolapse
	Rectocele
Systemic	Hypercalcemia
	Hypothyroidism
	Hypokalemia
	Diabetes
	Addison's disease
	Scleroderma
Neurologic	Parkinson's disease
	Multiple sclerosis
	Spinal cord injury
	Autonomic neuropathy
	Hirschsprung's disease
Drugs	Multiple causes including:
	Iron
	Narcotics
	Cholestyramine
	Calcium channel blockers
	Anticholinergics
Functional	IBS

constipation in a pt over 50 yr and in selected younger pts. Alarm sx such as weight loss, hematochezia, and sudden constipation in older pts prompt colonoscopy. Colonoscopy has the advantage in older pts of allowing highly effective CRC screening (by detection and removal of polyps incidental to the pts' sx), but flex sig and BE are adequate if the only purpose is to rule out obstruction. BE alone is not adequate because of poor visualization of the rectum and limited views of overlapping loops of sigmoid colon. A TSH, electrolytes, and serum Ca^{++} should be considered.

If no secondary cause of constipation is found, empiric rx with a 25-gm fiber diet, six 8-oz glasses of water daily, moderate exercise, and planned time for BMs (15 min bid) is appropriate. If pts do not respond to these measures, a **colonic transit study** may be helpful. Pts are given a gelatin capsule containing 24 radio-opaque rings (commercially available in the U.S. as Sitzmarks [Konsyl Pharmaceuticals, New Jersey]), and 5 days later a KUB is done (Gut 1969;10:842). If there are 5 or fewer markers remaining, transit is normal. There are numerous variations of this test in which markers are ingested on multiple days to allow colonic transit times to be calculated for right and left colon. This may yield additional diagnostic information (GE 1987;92:40). If transit time is normal, "constipation" may be IBS (p 91), or the problem may be of psychogenic origin. Slow transit constipation is diagnosed when more than 5 markers are scattered through the colon. Pelvic floor dysfunction is suspected when markers bunch up in the rectosigmoid. Other clues to pelvic floor dysfunction include excessive straining, paradoxical tightening of the sphincter with attempts to simulate defecation on physical exam, and manual attempts using pressure or a finger to evacuate stool. Some pts have features of both disorders.

Some specialized centers perform **anorectal manometry**, **balloon expulsion tests**, and **barium defecography** to evaluate pelvic floor dysfunction, rectocele, and Hirschsprung's disease. These techniques are not widely available, and their role in selecting rx is not well established (GE 1999;116:735; Am J Gastro 2005;100:1605).

Rx: A variety of agents are available to treat constipation. However, the evidence supporting their use is limited in most cases by low-quality studies of short duration (Am J Gastro 2005; 100 Suppl 1:S1).

- *General measures:* Pts are instructed to slowly increase fiber to a goal of 25 gm daily. They may feel bloated or gassy at the outset, but generally this improves. A list of common high-fiber foods is provided, and pts are encouraged to read food labels. A diary of fiber intake and BMs can be helpful in reaching the target. In pts who cannot reach target with diet, fiber supplements can be given. Popular choices include psyllium (eg, Metamucil 1 tsp po up to tid provides 3 gm fiber/dose), methylcellulose (eg, Citrucel 1 tbsp po up to tid, which provides 2 gm of fiber/dose), and polycarbophil (eg, FiberCon 500-mg tabs, up to 6 gm daily). Pts should be instructed to drink at least six 8-oz glasses of water. Daily, moderate exercise and planned time for BMs (15 min bid) should be encouraged.
- *Osmotic laxatives:* Osmotic laxatives are the first choice of laxative in pts who fail to improve with general measures. These agents cause fluid to be retained in the gut lumen. Polyethylene glycol (also called glycoLax) 17 gm po qd is a tasteless, well-tolerated, and effective choice for the rx of chronic constipation (Aliment Pharmacol Ther 2007;25:703). Milk of Magnesia 1-2 tbsp po qd-bid is inexpensive, but the taste is a problem and renal failure is a contraindication. Sorbitol (usually 1-2 tbsp po bid) and lactulose (1-3 tbsp po up to tid) are effective but cause flatulence and cramps, and are very sweet tasting. Sorbitol is cheaper than lactulose.

- *Lubiprostone:* This agent is a selective chloride channel activator that promotes intestinal fluid secretion. A dose of 24 mcg po bid improves BM frequency and decreases bloating and pain (J Clin Gastro 2007;41:345). Side effects include nausea, headache, and diarrhea. There are, as of yet, no comparative studies of lubiprostone against the less expensive osmotic laxatives.
- *Stimulant laxatives:* These agents promote motility and colonic secretion. There is weakly suggestive evidence that these agents may damage the enteric nervous system (Dis Colon Rectum 1973;16:455). For that reason, these agents are often the last choice for chronic use. Common choices are senna (eg, Senokot 2 tabs qd to 4 tabs bid) and bisacodyl (eg, Dulcolax 5 mg po qd). Misoprostol 300 mcg po qid is another alternative in refractory pts (Dig Dis Sci 1994;39:929).
- *Tegaserod:* This serotonin receptor agonist is effective for chronic constipation (Am J Gastro 2005;100:362) but was withdrawn from the U.S. market because of cardiovascular ischemic events.
- *Methylnaltrexone:* Narcotic-induced constipation can be a difficult problem in pts with advanced illness such as malignancy. Methylnaltrexone, a mu-opoid receptor agonist given sc qod, is effective in these ill pts (Nejm 2008;358:2332).
- *Biofeedback:* This modality can be used to train pts to relax their pelvic floor during defecation. Programs are not readily available and are labor intensive. However, they are safe and often effective (Dig Dis Sci 1993;38:1953). Biofeedback should be used prior to surgery in pelvic floor dysfunction.
- *Surgery:* Carefully selected pts with chronic, disabling sx of slow transit constipation that is refractory to medical rx and who have no evidence of pseudo-obstruction (p 257) can be treated with ileorectal anastomosis with good results (Ann Surg 1991;214:403). Pts with evidence of pelvic floor dysfunction usually get relief with surgery, though straining is still common postoperatively (Gut 1988;29:969).

1.8 Acute Diarrhea

Dis Mo 1999;45:268; Am J Gastroenterol 1997;92:1962

Sx/Si: This discussion focuses on the approach to acute diarrhea in adults from developed nations. Acute diarrhea refers to the abrupt onset of passage of frequent, poorly formed stools. It is an illness that generally lasts <2 weeks but may last up to a month. Only pts with more severe illness require medical evaluation. Clues to severe illness include profuse watery stool with dehydration, dysentery (the passage of many small volume stools with blood and often pus), temp >101°F, illness >48 hr, more than 6 stools/day, severe pain, and illness in an immunocompromised or elderly host.

The epidemiologic and medical hx guides the evaluation. It is important to determine: (1) the duration and severity of sx, (2) a hx of recent antibiotic use, (3) the travel hx, (4) current medicines, especially OTC preparations and new medicines, (5) whether a male pt has sex with men, (6) whether the illness is part of an outbreak, (7) the pt's water source, (8) recent ingestion of suspicious food or undercooked meat, and (9) if the pt is immunocompromised.

On exam, the pt's volume status should be assessed (postural vital signs, mucous membranes). Abdominal findings should be noted and impaction ruled out by rectal exam, at which time FOBT can be done.

Diff Dx: Acute diarrhea is most often infectious. Infections and other common causes of acute diarrhea are listed in Table 1.6. Food poisoning is usually of short duration and is often associated with vomiting. Ischemic colitis is often associated with pain and bloody diarrhea. Many drugs cause diarrhea. In recipients of anal intercourse with sx of proctitis (small frequent stools, sense of painful rectal spasm, and incomplete emptying), gonorrhea, herpes, *Chlamydia*, and syphilis are considerations. Diarrhea in HIV-infected pts is discussed on p 168.

Approach to Dx: Pts with mild illness do not need additional evaluation. In those with high fever, blood in the stool, illness as part of an outbreak, or other suggestions of an invasive pathogen, it is reasonable to culture the stool and treat presumptively with a quinolone for a bacterial pathogen. Some prefer to skip the culture in these circumstances, but a positive culture may guide rx if the pt fails to do well or relapses. Most laboratories now culture routinely for *E. coli* O157:H7 in submitted stool samples, but it is important to check your lab. This pathogen should be sought in bloody diarrhea (especially if fever is absent or low grade), after eating undercooked hamburger, in outbreaks, or when there is evidence of HUS (p 161). Some authors use stool wbc or stool lactoferrin to select pts for stool culture or empiric rx, but the poor performance characteristics of these tests (Ped Infect Dis J 1996;15:486)

Table 1.6 Causes of Acute Diarrhea

Disorder	Agent	Discussed on Page
Food poisonings	Many	170
Viral infections	Many	168
Bacterial infections	*Salmonella*	159
	Campylobacter	158
	Shigella	160
	E. coli O157:H7	161
	Yersinia	163
	Aeromonas	163
	Plesiomonas	163
	Other *E. coli*	163
Protozoan infections	*Amebiasis*	164
	Giardia	163
	Cyclospora	166
	Cryptosporidium	166
	Isospora	167
Sexually transmitted disease		—
Drugs		—
Partial bowel obstruction		123
Fecal impaction		177
Ischemic colitis		183
Bacterial overgrowth		169

makes this common practice questionable. If the epidemiology suggests *Giardia* or the illness has lasted more than 1-2 weeks, testing the stool for *Giardia* antigen is appropriate. Testing the stool for *C. diff* is needed if there is recent antibiotic use or the pt is hospitalized, and empiric rx pending the result should be considered if the pt is ill. In the pt who has diarrhea for more than 1-2 weeks, testing the stool for *Cryptosporidia, Cyclospora*, and *Isospora* may be worthwhile. Stool for O&P is very low yield in acute diarrhea. Testing may be appropriate in travelers returned from endemic areas.

Approach to Rx:

- *Fluid and diet:* Sport drinks, diluted fruit juice, broths, and soups augmented with saltine crackers are usually adequate to meet salt and fluid needs. In substantially volume-depleted pts, oral rehydration solutions can be used, but iv fluids are commonly used for rapid, effective relief. As the illness subsides, noodles, rice, potatoes, boiled vegetables, bananas, and yogurt can be tried. Caffeine is avoided, and milk products are commonly withheld, though acute lactase deficiency is not common.
- *Empiric rx for invasive infection:* It is reasonable to consider empiric rx of pts with features suggesting invasive diarrhea (temp >101°F, dysentery, FOBT positive, positive for wbc, or lactoferrin if done) because rx shortens the duration of illness by about a day (Clin Infect Dis 1996;22:1019; Arch IM 1990;150:541). Ciprofloxacin 500 mg po bid or norfloxacin 400 mg po bid for 3-5 days are common choices. If *E. coli* O157:H7 is suspected, antibiotics are not used (see p 161).
- *Antimotility rx:* Loperamide 4 mg followed by 2 mg after each loose stool to a maximum of 16 mg per 24 hr is given in most cases for symptomatic relief. It had been a concern that pts with invasive pathogens may worsen with antimotility agents (Jama 1973;226:1525), but this is uncommon. Loperamide should be avoided in pts with dysentery or *E. coli* O157:H7 for fear of inducing HUS (p 161) (J Pediatr 1990;116:589).
- *Traveler's diarrhea* (Nejm 1993;328:1821; Clin Infect Dis 2006;43:1499): Travelers to high-risk areas should take dietary precautions and only eat steaming hot food, carbonated beverages (skip the ice), dry foods (bread), acidic foods (citrus), and high-sugar foods (jellies and syrups). Since most episodes are due to bacterial pathogens (most commonly enterotoxigenic *E. coli* [p 163]), the traveler should bring a quinolone (unless going to an area with high quinolone resistance) and loperamide. Treatment is begun promptly if diarrhea occurs. Three days of bid rx (eg, cipro 500 mg po bid) is generally sufficient. Chemoprophylaxis is not routinely recommended for healthy travelers unless a short-duration diarrheal illness would be intolerable. Many pts going on a hard-earned international vacation would prefer to avoid diarrhea and request prophylaxis. Medically ill pts and those taking a PPI (which reduces stomach acid content and predisposes to infection) should receive prophylaxis. A single dose of a quinolone daily (eg, ciprofloxacin 500 mg po daily) is >80% effective unless the pt is traveling to an area with a high incidence of quinolone-resistant bacteria (especially *Campylobacter*). In that case, azithromycin may also be advisable. Rifaximin, a poorly absorbed antibiotic active against a wide range of enteric pathogens, is an alternative for prophylaxis (200 mg po daily or bid) or for treatment (200 mg po tid). However, rifaximin should not be used if there is dysentery or infection known to be due to an invasive organism. Bismuth subsalicylate 2 tabs po qid is 65% effective and inconvenient (Jama 1987;257:1347).

1.9 Chronic Diarrhea

GE 1999;116:1464; Nejm 1995;332:725

Sx/Si: Chronic diarrhea is usually defined as diarrhea lasting >4 weeks and characterized by 4 or more loose stools daily. Stool weight is typically in excess of 250 gm/day. The diff dx is long and can be narrowed substantially by the hx and exam. The hx is used to broadly categorize the sx. The clinician should assess if the sx suggest an illness that is (1) functional, (2) structural (eg, IBD), (3) colonic, (4) malabsorptive/small bowel, (5) infectious, (6) related to important psychiatric or psychosocial factors, or (7) present in an immunocompromised or HIV-infected host.

Stool frequency and character are determined. Periods of constipation alternating with diarrhea suggest a functional illness such as IBS or a low-fiber diet. Blood in the stool, weight loss, and nocturnal diarrhea argue against a functional cause. Extraintestinal manifestations of IBD (joint sx, perianal disease, skin, or eye sx [p 106]) can be helpful clues. Frequent small-volume stools, crampy lower abdominal pain, and a sense of incomplete evacuation suggest a distal colonic process. Diarrhea with crampy midabdominal pain, large-volume stools, bloating, and borborygmi (bowel sounds audible at a distance) suggest a small bowel or malabsorptive cause. Stools that are oily, greasy, and difficult to flush may contain fat, suggesting malabsorption. Abrupt onset of sx with large-volume diarrhea and fever may suggest an infectious cause. Inquiries must be made about stress, depression, and sexual abuse (p 96).

Dietary hx is crucial. Determine the consumption of lactose (milk, frozen yogurt, ice cream, other dairy products), sorbitol (breath mints, sugarless gum, apples, pears, prunes, peaches, diabetic foods), fructose (figs, dates, prunes, pears, apples, grapes, and soft drinks sweetened with high fructose corn syrup), and dietary fiber.

The physical exam identifies localized tenderness, masses, and evidence of systemic disease. The rectal exam is crucial in the evaluation of sphincter tone and impaction. A complaint of "chronic diarrhea" is often undiagnosed incontinence.

Diff Dx: The causes of chronic diarrhea are listed in Table 1.7. Dietary causes include excessive caffeine, lactose (p 102), sorbitol (p 11), and fructose (p 10). Causes of malabsorption are discussed on p 19. Fecal incontinence (p 176) or fecal impaction (p 177) are missed without a proper rectal exam. Bile salt malabsorption may occur as a result of defects in the ileal bile salt transporter (J Clin Invest 1997;99:1807) or due to ileal resection. Bile salts that are malabsorbed cause diarrhea in pts with an intact colon by stimulating colonic fluid secretion.

Approach to Dx: Based on the sx and si, the disease is characterized and the approach varies:

- *Sx and si suggest functional causes:* If the sx sound diet related or are those of longstanding IBS, consider a CBC, CMP, and FOBT. Dietary trials (exclude milk products, caffeine, sorbitol; consider fiber if diarrhea alternates with constipation) and a follow-up office visit are often adequate. If sx persist, additional evaluation and rx as detailed in the IBS section are appropriate (p 91). Laxative screening may be needed.
- *Sx and si suggest IBD:* If the sx suggest IBD, colonoscopy and SBFT or CT enterography are usually needed to make a dx and assess the extent and severity of illness. The approach is outlined in the sections on Crohn's disease (p 105) and ulcerative colitis (p 113).

Table 1.7 Causes of Chronic Diarrhea

Common Causes	Discussed on Page
Irritable bowel syndrome	91
Fecal incontinence	176
Fecal impaction	177
Chronic infection	See Table 1.6
Inflammatory bowel disease	105, 113
Drugs	—
Diet	—
Malabsorption	19
Colon cancer	131
Collagenous colitis	118
Lymphocytic (microscopic) colitis	119
Surreptitious laxative use	—
Diabetic neuropathy	—
Postgastrectomy diarrhea	71
Radiation enteritis	127
Bile salt malabsorption	17
Hyperthyroidism	—
Hormone-secreting tumors	198, 86
HIV infection	168
Scleroderma	—
Amyloid	—
Carcinoid	152
Mastocytosis	—

- *Sx and si suggest colonic causes:* Colonic sx are those of crampy lower abdominal pain, an uncomfortable sensation of rectal spasm (tenesmus), and frequent small-volume stools. Infection vs IBD vs IBS are the main considerations. Consider CBC, CMP, TSH, stool C&S, and stool for *C. diff*. If these are negative, a colonoscopy with bx (for IBD or microscopic colitis [p 118]) may be needed. If the sx are those of proctitis (small-volume stools with urgency and blood but without systemic illness), a flex sig may be adequate.
- *Sx and si suggest malabsorption or disease of the upper gut:* See p 19 regarding the evaluation of malabsorption.
- *Sx and si suggest an infectious cause:* Extensive stool testing may be worthwhile if the onset was very abrupt with a large volume of stool, fever, and systemic sx. Consider stool tests for C&S, *C. diff*, *Giardia* antigen, *Cryptosporidium*, *Cyclospora*, and determination of stool O&P on 3 samples. The yield of the O&P studies is very low. If amebiasis is a consideration, the antigen test may be superior (p 158). The technique for detection of *Cryptosporidium* and *C. diff* will depend on the local lab. Antigen tests or special stains may be used. An empiric trial of metronidazole for *Giardia* is often reasonable. If a dx is not made, colonoscopy or SBFT or CT enterography may be needed to rule out abrupt-onset IBD.
- *Immunocompromised host:* Consider HIV testing and testing for unusual causes of infection (p 168).

- *Additional studies are warranted if sx persist after focused evaluation.* If the sx sound functional but are refractory, consider a stool laxative screen and reexplore the abuse hx. A TSH should be obtained. It may be necessary to do a low-yield colonoscopy and SBFT or CT enterography to rule out IBD. A trial of cholestyramine (4 gm po tid) for possible bile salt malabsorption should be tried. Loperamide, antidepressants, and antispasmodics may need to be considered. If the sx warrant further evaluation, the considerations for testing include:
  - *72-hr stool collection:* This study is done on a 100-gm fat diet (p 20), at which time a laxative screen and total weight and fat are recorded. If stool weight and fat are normal, then the yield for organic disease with more extensive testing is very low. If diarrhea is large volume, then evaluation for hormone-secreting tumors and reevaluation of possible malabsorption or small bowel disease (with SBFT or bx) may be warranted.
  - *Test stool for electrolytes and osmoles:* This is done to calculate the stool osmolar gap, which equals $(290 - 2 \times ([Na^+] + [K^+])$ in mOsm/kg. The value of 290 mOsm/kg in this equation is the normal expected osmolality of stool. If diarrhea is due to an osmotically active particle (such as Mg^{++} antacids, lactulose, sorbitol), the gap is usually >125 mOsm/kg. In a pure, secretory diarrhea, nearly all the osmotic particles are related to Na^+ and K^+, and the gap is <50 mOsm/kg. If the measured osmolality is <290 mOsm/kg, water may have been added to the stool.
  - *Laxative screen:* Commercially available tests are available to screen stool liquid for bisacodyl and urine for anthraquinones. Phenolphthalein (now off the U.S. market) is detected by a pink color when NaOH is added to the stool supernatant. Room searches (after asking the pt) are a consideration in hospitalized pts.
  - *Evaluate for small bowel bacterial overgrowth:* See p 169.
  - *Tests for hormone-secreting tumors:* See sections on islet cell tumors (p 198), gastrinoma (p 86), and carcinoid (p 152). A urine for pheochromocytoma testing (metanephrines and VMA) is a consideration.
  - *Small bowel bx:* This may uncover unusual diseases such as Whipple's or celiac disease missed by other means (see Malabsorption and Maldigestion, next section).
  - *Evaluation for mesenteric ischemia:* See p 182.
  - *Consider HIV* even in the absence of risk factors or clues.

General Rx: While completing an evaluation, minimizing caffeine, milk products, and using loperamide (2-4 mg up to qid) is reasonable to give some sx relief.

1.10 Malabsorption and Maldigestion

Compr Ther 1997;23:672

Pathophys: Malabsorption is often a term used very loosely by clinicians to include maldigestion and malabsorption. Normal **digestion** involves the hydrolysis of proteins, fats, and carbohydrates by pancreatic enzymes in the gut lumen. Digestion creates amino acids, fatty acids, monoglycerides, and monosaccharides. Fatty acids and monoglycerides are held in solution in the aqueous environment by bile salts secreted from the liver into bile. The products of digestion are moved into the epithelial cells by active transport in the process called

absorption. Fatty acids and monoglycerides are reassembled into triglycerides and transported via the **lymphatics** to the systemic circulation. Interference with the process at any of these 3 levels can result in clinical evidence of malabsorption/maldigestion.

Sx/Si: Pts with malabsorption typically present with weight loss and diarrhea. The stool is of high fat content so it might look greasy or oily, or be difficult to flush. There may be bloating, excessive flatus, and borborygmi. In very advanced cases, there may be a syndrome associated with specific nutrient deficiencies such as anemia associated with folate or B_{12} deficiency, bleeding with vitamin K deficiency, or metabolic bone disease from vitamin D deficiency. However, it is now uncommon for pts to present with these advanced findings.

Diff Dx: The causes of **maldigestion** include: (1) pancreatic insufficiency due to chronic pancreatitis (p 192) or pancreatic cancer (p 195), (2) poor mixing due to gastric or weight reduction surgery (causing unregulated release of stomach contents, bypassing the duodenum or parts of jejunum), or (3) ZE syndrome (p 86), in which low duodenal pH inactivates enzymes. **Malabsorption** is most often due to celiac disease (p 119) because of loss of absorptive surface. In bacterial overgrowth (p 169), malabsorption is the result of mucosal damage and bile salt deconjugation by bacteria. Some infections, notably *Giardia* (p 163), can cause a malabsorptive picture by mucosal inflammation. In short bowel syndrome (p 121), malabsorption comes from inadequate surface area. Crohn's disease can cause malabsorption, but there are usually ample clues to its presence. Rare but important causes include Whipple's disease (p 171), eosinophilic gastroenteritis (p 129), radiation enteritis (p 127), and small bowel lymphoma. Abetalipoproteinemia (Jama 1993;270:865) and lymphangiectasia (Am J Gastroenterol 1993;88:887) cause malabsorption by preventing fat from being transported from the enterocyte via the lymphatics to the systemic circulation.

Approach to Dx: If a pt has sx or si suggestive of malabsorption but with no clues to a more specific etiology (such as celiac disease), a CBC and CMP are appropriate. If anemia is present, levels of folate, B_{12}, and iron should be determined. A 72-hr fecal fat study should be done. The sample is collected after 3 days of a 100-gm fat diet that is continued throughout the collection. More than 7 gm/day is abnormal, but mild increases of up to 14 gm are very common in any cause of diarrhea. In steatorrhea (fat malabsorption), there is typically >14 gm of fat/24 hr in the stool (GE 1999;116:1464). If steatorrhea is not present, then the dx might not be malabsorption. If the pt is reluctant to do a 72-hr collection, a qualitative fecal fat on a single sample can be a helpful positive but is not a reliable negative.

If the fecal fat is elevated, the etiology must be determined. A trial of pancreatic enzymes (p 195) is a practical way to evaluate for pancreatic insufficiency. If enzyme replacement results in improvement, then the cause of pancreatic insufficiency is determined with imaging tests and hx. If enzyme replacement is not helpful, then a small bowel bx and/or tests for bacterial overgrowth (p 169) are appropriate. Small bowel bx will detect the rare conditions listed in the differential. Some experts would use serologic tests for celiac disease (p 119) prior to considering bx. If a small bowel bx is normal, then an SBFT or CT enterography to look for other structural abnormalities can be helpful. Tests for pancreatic insufficiency that are more sensitive than a trial of pancreatic enzymes may need to be considered (p 192).

1.11 Gastrointestinal Bleeding

Med Clin N Am 2000;84:1183; Am J Gastroenterol 1998;93:1202

Sx/Si: The H&P is used to assess the acuity and severity of bleeding and to determine if bleeding is from an upper or lower source. It is important to determine if the pt has risk factors for bleeding such as NSAID use, anticoagulant use, or liver disease. Blood loss can present as (1) hematemesis (bloody vomitus, either red and fresh or coffee grounds), (2) melena (stool that looks black and shiny like tar and is sticky, malodorous, and difficult to flush), (3) hematochezia (maroon stool or bright red bleeding with or without stool), or (4) sx related to the effects of blood loss such as syncope, MI, dyspnea, or weakness. Upper tract bleeding is easily diagnosed if there is hematemesis. Melena also suggests upper bleeding but can be seen in slow, lower bleeds. Melena can be confused with the dull black stool of iron, bismuth subsalicylate, beets, and greens. Hematochezia can be from a lower bleed or from a brisk upper bleed.

Vital signs are taken. If pulse and blood pressure are normal, it may be useful to obtain postural vital signs. The pt is asked to sit up and dangle the legs for a few minutes, and pulse and blood pressure are repeated. In rough terms, a rise in pulse of >10 points generally indicates that the pt is at least 1 liter volume depleted. The greater the pulse rise, the more specific (and less sensitive) the test; some authors use a pulse rise of 30 points to signify volume depletion (Jama 1999;281:1022). A postural drop in systolic blood pressure >20 mm Hg (which should generally go along with a pulse rise) may indicate volume depletion of a couple of liters. However, postural vital signs are neither sensitive nor specific and need to be 1 piece of data in context. Up to 10% of euvolemic pts have postural hypotension, especially if they have chronic HTN. It is unnecessary to check posturals in the bleeding pt with resting tachycardia or hypotension because they are clearly volume depleted. Postural vitals can be misleading in pts on beta-blockers, those with intrinsic heart disease, and those with autonomic dysfunction (Jama 1999;281:1022). Other important findings on exam include stigmata of chronic liver disease (p 26), abdominal findings, the appearance of the stool, and evidence of systemic illness.

Diff Dx: The causes of GI bleeding are listed in Table 1.8. UGI bleeding is bleeding that arises proximal to the ligament of Treitz. Aortoduodenal fistula is a very rare cause of bleeding and is not discussed elsewhere in the text (Am J Surg 1980;46:121). The small bowel is an uncommon cause of acute bleeding. Most acute large-volume lower bleeding is from colonic diverticula.

Approach to Acute Bleeding: Laboratory assessment includes CBC, platelet count, CMP, and PT/PTT to look for coagulopathy. An EKG is reasonable in pts over 50 yr or for those with cardiac risk factors. In the acute setting, a type and crossmatch should be done for 2-6 units depending on the fitness of the pt, the initial Hgb, and the estimated magnitude of the bleed. The blood bank should be instructed to crossmatch a unit each time one is transfused in the critically ill pt. This ensures that blood stays available if the bleeding is massive. The Hgb may markedly underestimate blood loss in an acute bleed. At equilibrium, every 1 gm below normal represents about 1 unit (500 mL of whole blood) of blood lost (Ann IM 1994;121:278). An elevation of the ratio of BUN/Cr >36:1 is a strong clue that the bleeding is from the upper tract if the pt is not on diuretics and does not have renal failure (Am J Gastroenterol 1997;92:1777). An isolated elevation in the PT should suggest the possibility of

Table 1.8 Causes of Gastrointestinal Bleeding

	Cause	Discussed on Page
Upper GI Bleeding		
	Peptic ulcer disease	68, 75
	Erosive gastritis	80
	Esophageal/gastric varices	255
	Esophagitis	33
	Mallory-Weiss tears	56
	Gastric cancer	81
	Portal hypertensive gastropathy	256
	Gastric antral vascular ectasias	88
	Angioectasias	184
	Dieulafoy's ulcer	89
	Gastric lymphoma	83
	Other gastric malignancies	—
	Benign gastric tumors	—
	Aortoduodenal fistula	21
Small Bowel Bleeding		
	Angioectasias	184
	Tumors	—
	Ulcers	—
	Meckel's diverticulum	129
	Other diverticula	—
	Crohn's disease	105
	Intussusception	127
	Parasites	158
Colonic GI Bleeding		
	Colonic diverticula	98
	Angioectasias	184
	Ischemic colitis	183
	Inflammatory bowel disease	105
	Colon cancer	131
	Colonic ulcers due to NSAIDs	—
	Stercoral ulcers	178
	Infectious colitis	155
	Radiation colitis	127
	Hemorrhoids	173
	Anal fissure	174
	Postpolypectomy bleeding	—
	Solitary rectal ulcer	178
	Colonic varices	255
	Vasculitis	—
	Endometriosis	129

liver disease and varices. This finding may prompt the use of octreotide (p 255) in the massively bleeding pt who is awaiting EGD. Some clinicians use NGT aspirate to identify upper bleeds. However, an aspirate can be negative from an actively bleeding DU or from other lesions not actively bleeding at the time of the passage of the tube. The clinical and lab data are used to determine if the bleeding is more likely to be upper or lower and if it is acute or chronic.

- *Acute upper bleeding:* If bleeding is thought to be upper tract in origin, the pt is stabilized and undergoes EGD. Not only is EGD generally diagnostic, but it is also therapeutic for bleeding ulcer disease (p 75) and varices (p 255). The endoscopic findings can also be used to predict the likelihood of ongoing bleeding and can be used in determining the safety of prompt discharge in acute upper bleeding. If the pt with suspected upper bleeding has a normal endoscopy, then colonic or small bowel sources need to be considered. The most likely causes of upper bleeding missed at initial EGD are Dieulafoy's ulcer (p 89) and angioectasias (p 184). There is no role for barium studies in acute bleeding.
- *Acute lower bleeding:* In large-volume hematochezia, the evaluation depends on the severity of the bleed and whether colonoscopy is possible. In pts with large-volume hematochezia and hemodynamic instability, bleeding from the upper tract needs to be considered. In this very select group, it is reasonable to do EGD after volume resuscitation. Some clinicians forgo EGD if an NG aspirate shows copious amounts of bile. If ongoing active bleeding prevents colonoscopy or the magnitude of the bleeding makes it imperative to find the source before the pt can complete a colonoscopy prep, then imaging for a source of bleeding is appropriate. The options are tagged rbc scan or CT angiography. **Multidetector CT angiography** has a sensitivity to detect blood loss at a rate of >0.3 mL/min. It provides precise anatomic localization of the bleeding site in positive studies and can give additional information such as the detection of masses or inflammatory disease. It is widely available after hours in most institutions, and its use is increasing (Radiographics 2007;27:1055). To perform a **tagged rbc scan** the pt's red cells are labeled with technetium-99 and reinjected. If bleeding occurs at rates >0.1 mL/min, extravasation into the bowel lumen can be identified (Am J Roentgenol 1987;148:869). The scan is highly accurate if positive within 2 hr and an upper tract source has been excluded by EGD (Am J Gastroenterol 1994;89:345). The scan is more likely to be misleading if long scanning times are required (J Nucl Med 1992;33:202). If the site is localized by a high-quality scan and bleeding does not stop, angiographic therapy or surgical resection is performed. Blind colectomy should be avoided because of the high morbidity (Dis Colon Rectum 1982;25:441). Angiography can be diagnostic and therapeutic but is associated with a high incidence of complications, requires more vigorous bleeding than an rbc scan requires for visualization (≥0.5 mL/min), and surgery is still frequently required (GE 2000;118:978). The use of angiography varies widely among institutions, and its value depends greatly on local expertise. If bleeding stops or slows enough for an adequate colonoscopy prep, the pt should undergo colonoscopy to look for a treatable cause of the bleeding and possibly for endoscopic rx (p 101). If colonoscopy is negative, evaluation of the small bowel may be needed.

Approach to Obscure Bleeding: (GE 2007;133:1694) When the source of continued bleeding (either recurrent visible bleeding or occult bleeding) is not evident from an initial EGD/colonoscopy, it is reasonable to consider repeating these exams. The yield of repeat endoscopy may be as high as 35% (Brit J Surg 1983;70:489). The quality of the initial exam and the experience of the endoscopist should be considered in the decision. Capsule endoscopy is usually the next test for obscure bleeding. In this exam, the pt swallows a pill-sized camera that sends images of the small intestine wirelessly to a recorder. If a lesion is identified that should be treated endoscopically, then endoscopy is performed. This procedure is done with either push enteroscopy (using a long endoscope) or with double-balloon enteroscopy (using a specialized endoscope with balloons that are used to advance it deeply into the small intestine). If the lesion cannot be reached endoscopically, then surgery with intraoperative endoscopy may be needed. Surgery is performed if capsule endoscopy identifies a bleeding tumor. The limitations of capsule endoscopy include the inability to precisely locate the lesion or to provide therapy of bleeding lesions. The chief risk is failure of the capsule to pass through narrow areas of intestine, thereby requiring surgical removal. However, if the capsule does become stuck, it is often at the bleeding site, making it easier for the surgeon to find the lesion. Not all angioectasias of the small intestine need to be treated; observation with iron therapy and avoiding anticoagulants is often adequate. CT angiography, CT enterography (using large-volume, low-density oral contrast to distend the small intestine), SBFT, Meckel's scan (p 129), and tagged rbc scan might be considered if the cause of bleeding remains obscure.

Approach to Visible Small-Volume Rectal Bleeding: (Jama 1997;277:44) This is a common complaint in primary care practice. About 3% of the population report having blood in the toilet, and 12-15% report blood on tissue within the prior 6 months. The optimal strategy for evaluation has not been established. The major uncertainty is whether to examine all or part of the colon. In an older age primary care population, blood mixed with stool and short duration of bleeding are associated with serious disease. In older pts, the clinical hx does not identify a subgroup well served by a limited exam such as sigmoidoscopy. A practical approach is to offer colonoscopy to any pt over age 50 yr who has not had CRC screening. For younger pts with a long-standing complaint, a sigmoidoscopy can be a less expensive alternative to a low-yield colonoscopy (Am J Gastroenterol 2000;95:1184). Flex sig will detect proctitis, distal polyps (such as in FAP, p 146), and the unusual distal cancer. Anoscopy is performed to look for fissure or hemorrhoids. If sigmoidoscopy is chosen, the pt should be informed of the limitations of the test. The need for further study if bleeding persists must be emphasized, since a small proportion of young pts have a neoplastic cause of bleeding out of reach of the sigmoidoscope. The advantages of choosing colonoscopy as the initial test in a young pt are that it usually provides an immediately reassuring negative test and that young pts generally tolerate sedated colonoscopy much better than unsedated sigmoidoscopy.

Approach to FOBT-Positive Stool: (Nejm 1999;341:38) Pts with a positive FOBT obtained in screening should have colonoscopy because it is more accurate than BE and flex sig. The yield in the screening setting is about 3% for CRC and 30% for adenomatous polyps (Nejm 1993;328:1365). Pts with normal colonoscopies and localizing upper tract sx, weight loss, or anemia may benefit from EGD. The yield of EGD is 25-40% in asymptomatic pts. EGD may result in changes in management such as the discontinuation of NSAIDs or the addition of acid-blocking rx (Nejm 1998;339:153). However, EGD adds substantially to the costs of

screening for colon cancer with FOBT. The AGA position statement recommends EGD for pts with positive FOBT and negative colonoscopy (GE 2000;118:197). The position statement concedes that the clinical and economic impact requires further study. The cost of EGD would add substantially to the cost of colon cancer screening with FOBT if all pts with normal colonoscopies have EGD. It seems reasonable to educate the asymptomatic pt who has no need for NSAIDs regarding the purpose of EGD. Many will opt not to proceed with a test that generally does not change the quality of their lives. Neither NSAIDs nor warfarin can be accepted as a cause of positive FOBT because the yield of full investigation is similar to that seen in pts not on those agents (Am J Med 1996;100:598).

Approach to Iron Deficiency Anemia: In women in their reproductive years, iron deficiency is usually related to menses and pregnancy losses. In males and postmenopausal women, GI tract blood loss is the most common cause. The cause of iron deficiency is found in the upper tract in 40%, in the small bowel in 3%, and in the colon in 22%; it is not found in 34% of pts (Nejm 1999;341:38). The initial endoscopic evaluation can be directed to the site of sx (Nejm 1993;329:1691), but the other end should be examined if the initial exam is normal. Celiac disease can present as iron deficiency in the absence of other sx. The use of random bx of the duodenum at EGD to detect celiac disease is controversial. The yield was 3% in one large series (Gut 1993;34:1102). The practice was not advocated in an AGA position paper because of the low yield (GE 2000;118:197). Nevertheless, the practice seems reasonable in populations with a high prevalence of celiac disease, such as northern Europeans. There is an association between iron deficiency and Hp infection. The argument has been made that it is reasonable to test for Hp in iron-deficient pts and to treat those who are infected (Am J Gastro 2005;100:453).

The optimal evaluation of iron deficiency in **premenopausal women** has not been determined. A retrospective study from a referral center suggested that 12% of such pts had important GI lesions, including gastric cancer (3%) (Am J Med 1998;105:281). Referral bias limits the value of these observations. Because iron deficiency is most commonly related to menses, these women usually can be managed with iron and regulation of menses. However, endoscopic evaluation should be considered in women over age 40 yr, in those with abdominal sx, substantial anemia (Hgb <10 gm/dL), or FOBT-positive stool, or in whom the anemia seems out of proportion to the perceived menstrual losses (Lancet 1998;352:1953).

Approach to Rx: The specific cause of bleeding is identified and treated. Some general guidelines include:

- *Initial resuscitation in acute bleeding:* Volume resuscitation is performed by rapid infusion of NS through large-bore (18 gauge or greater) peripheral ivs. Fluids can be wide open until pulse and blood pressure are acceptable. Postural vital signs after each liter may be helpful. At least 2 reliable ivs should be maintained until the acute illness is resolved.
- *Transfusion:* The appropriate threshold for transfusion of rbcs has not been established in clinical studies. The goal is to transfuse only as much blood as is needed to minimize the risk of end organ damage (eg, MI). Transfusion is almost never indicated if Hgb >10.0 gm/dL and is almost always indicated if Hgb is <6 gm/dL (Arch Pathol Lab Med 1998;122:130). It is common clinical practice to keep the Hgb of a young healthy pt with acute bleeding >7.0 gm/dL and to aim for a Hgb >9.0 gm/dL in pts with known coronary disease and those thought to be at risk for ischemia. Chronic blood loss is often well tolerated, and transfusion is needed at lower levels of Hgb than with acute blood loss. Sx, age,

and the expected course of bleeding also affect the decision. The threshold to transfuse will be lower in a pt who has bleeding that is likely to continue.

- Fresh frozen plasma should also be given to pts with active bleeding and an INR >1.5 (Jama 1994;271:777). Fresh frozen plasma is also indicated after replacement of more than 1 blood volume (about 10 units in a 70-kg adult) if continued bleeding and a coagulopathy are present (Jama 1994;271:777). The usual starting dose is 2 units (unless coagulopathy is severe), and the effect is measured by repeating the INR within an hour of transfusion. Additional units are given if the INR does not fall below 1.5. The half-life of factor VII is only 5-6 hr (longer for most other factors), and repeat dosing may be needed. The INR is followed serially if the pt is actively bleeding. In some cases (warfarin use, malabsorption, poor diet, recent antibiotics), an elevated INR is due to vitamin K deficiency. Vitamin K 10 mg sc qd × 3 should be given, though a full response will usually take 1-3 days. Platelet transfusion is appropriate in major acute bleeding if platelet count is <50,000/mm^3. A dose of 6 units will raise platelet counts by 50,000/mm^3 (Jama 1994;271:777).
- *Hospital length of stay:* In UGI hemorrhage, there is an excellent clinical tool for determining the appropriate length of stay (Am J Med 1996;100:313). A risk score based on endoscopic findings, timing of bleeding, hemodynamics, and comorbidities is generated. The risk score can be used to predict the safety of discharge from the hospital. There is no similar guideline for lower GI bleeding.

1.12 Evaluating Suspected Liver Disease

Sx: (Sherlock S, Dooley J. Diseases of the liver and biliary system. 10th ed. Boston: Blackwell Science, 1997:5-6) Several aspects of the hx and exam should be emphasized in the pt with suspected liver disease. Abdominal pain and fever may be a clue to biliary obstruction from stones or mass. Risk factors for viral hepatitis should be identified (blood transfusion, sexual practices, iv drug abuse, travel). Pruritus may suggest a chronic cholestatic disease. Nonspecific sx of liver disease include fatigue, arthralgias, decreased libido, impotence, and ovulatory failure. Alcohol consumption should be carefully evaluated, and a complete list of current and past prescription medicines, OTC remedies, and herbal remedies should be obtained. Herbal hepatotoxicity is of growing importance (Jama 1995;273:502). Occupational hx and the family hx of liver disease should be obtained.

Si: On exam, the liver span is determined by **percussion** and is usually 12-15 cm. The liver margin is **palpated** by standing facing the supine pt's feet and hooking the fingers over the RUQ. A liver palpable with deep inspiration is a normal finding. Rarely, a friction **rub** may be heard or felt due to tumor, recent bx, or inflammation. The liver may be **pulsatile** from tricuspid insufficiency. The **venous hum** of portal HTN (heard between umbilicus and xiphoid) and the arterial murmur of hepatocellular carcinoma are rare. Jaundice may first be evident as scleral icterus. **Vascular spiders** are red lesions that are seen on the upper trunk, neck, face, and hands. They have a central arteriole and smaller radiating branches that look like a spider's legs and can be made to blanch with central pressure. They usually indicate cirrhosis but can be seen in pregnancy, viral hepatitis, or rarely in normal pts. **Palmar erythema** may be noted. **Dilated veins** over the abdominal wall may indicate portal HTN. Testes may be atrophic in cirrhosis. Gynecomastia is rare.

Massive **ascites** due to portal HTN is easily detected, but the exam can be misleading. The flanks bulge due to fluid and there is stony dullness to percussion. The line on the flank where there is a change from dullness to tympany should be determined. By rolling the pt obliquely and repeating percussion, the line of dullness shifts as the fluid moves to a dependent position. This finding of **shifting dullness** confirms ascites, but false positives (with bowel contents and movement of the mesentery) and false negatives occur. A **fluid wave** is identified in the supine pt by tapping briskly on one side of the abdomen while a receiving hand waits on the other end for the fluid wave. There is a perceptible delay between tapping and receiving the wave. Fat can cause a similar finding, so an assistant must press down on the abdominal wall to prevent confusion.

Asterixis (a flapping tremor caused by momentary loss of muscle tone) is associated with hepatic encephalopathy. It is best brought out by having the pt hold the wrist dorsiflexed with arms outstretched. **Fetor hepaticus** is a sour fecal smell in the breath due to exhaled mercaptans that should have been cleared by the liver.

Diff Dx: Pts come to an evaluation for suspected liver disease in several ways. The largest group have asymptomatic elevations of LFTs. Others will present with jaundice, evidence of cirrhosis on physical exam, an abnormal imaging test, or fulminant hepatic failure. The liver diseases that need to be considered are listed in Table 1.9.

Table 1.9 Causes of Liver Disease

Disease	Discussed on Page
Alcoholic liver disease	250
Drug hepatotoxicity	252
Hepatitis A	215
Hepatitis B	217
Hepatitis C	221
Other viral agents	225
Fatty liver	229
Nonalcoholic steatohepatitis	229
Autoimmune hepatitis	236
Hemochromatosis	238
Wilson's disease	241
Primary biliary cirrhosis	231
Primary sclerosing cholangitis	233
Alpha-1 antitrypsin deficiency	243
Ischemic hepatitis	268
Budd-Chiari syndrome	267
Hepatocellular carcinoma	247
Other hepatic neoplasms	250
Disorders of pregnancy	271
Occupational hepatotoxins	—
Herbal and other ingested hepatotoxins	—
Biliary obstruction	29
Hepatic masses	250

Approach to Asymptomatic, Persistently Abnormal Transaminases: (Nejm 2000;342:1266)

If there is no obvious cause (such as alcohol or recent hepatotoxic drugs), studies should be obtained (Table 1.10). These routinely include tests for hep B (HBsAg and anti-HBc), hep C (serum antibody), hemochromatosis (Fe/TIBC), Wilson's disease (ceruloplasmin if pt <40 yr old), and autoimmune hepatitis (ANA, f-actin antibody, IgG level). The liver should be imaged with US to look for structural abnormalities (eg, tumor, echogenicity suggesting hepatocellular disease, the irregular contour of cirrhosis) and bile duct dilatation due to obstruction. A PT and albumin evaluate synthetic function and can be a clue to serious chronic disease. Thrombocytopenia may suggest cirrhosis. If the first round of testing does not yield a dx, additional testing can be considered on clinical grounds as outlined in the table. Rarely, hep C is missed by antibody testing. A hep C viral RNA determination by PCR is reasonable, especially if risk factors are present. Other lower-yield considerations are an alpha-1 antitrypsin level, ACE level and CXR for sarcoid, and an AMA for PBC even if alk phos is normal. Consideration should be given to nonhepatic causes of abnormal transaminases, such as celiac disease (see p 119 for dx testing [Lancet 1998;352:26]), adrenal insufficiency (GE 1995;109:1324), anorexia nervosa (Arch IM 2005;165:561), and primary diseases

Table 1.10 Evaluation of Persistently Elevated Transaminases

Disease	Test
Routinely obtain the following:	
Hep B	Hep B surface antigen
	Hep B IgM core ab
Hep C	Hep C ab
Autoimmune hepatitis	Antinuclear ab
	F-actin ab
	IgG level
Hemochromatosis	Fe/TIBC
Wilson's disease	Ceruloplasmin (if pt <40 yr)
Mass/obstruction/cirrhosis	US or CT scan
Evaluate ? of cirrhosis	PT, platelets
	Albumin
Consider the following:	
Alpha-1 antitrypsin deficiency	Alpha-1 antitrypsin level
Primary biliary cirrhosis	Antimitochondrial ab
Primary sclerosing cholangitis	MRCP/ERCP
Prolonged hep A	Hep A IgM ab
Missed dx of hep C	Hep C by PCR
Older-onset Wilson's	Ceruloplasmin
Celiac disease	Tissue transglutaminase
Muscle disease	CPK, aldolase
Sarcoid	ACE level, chest x-ray
Adrenal insufficiency	Cortisol level
Anorexia nervosa	Not a laboratory dx
Disorders of pregnancy	HCG level

of muscle (check CPK and aldolase). Muscle disease is more likely to be the cause if AST >>ALT. If no cause is found with this testing, the most likely dx is nonalcoholic fatty liver disease (p 229). Abnormal tests lead to further evaluation as outlined in the chapters discussing the disorders in question.

If abnormalities persist >6 months, the traditional approach has been liver bx. However, in the current era of extensive and accurate serum testing, bx does not appear to affect management. In a study of 1124 adults referred for abnormal LFTs, 81 had negative serum testing (all the studies listed previously) and underwent bx. There were 8 normal bx, and all the remaining bx showed evidence of fatty liver or of NASH (with varying degrees of fibrosis) (Am J Gastroenterol 1999;94:3010). In light of this study, it is difficult to justify the morbidity of bx unless effective therapies for NASH make the distinction between NASH and milder forms of fatty liver disease more important.

Approach to Abnormal Alkaline Phosphatase: (Mayo Clin Proc 1996;71:1089) Alk phos is secreted by bile duct epithelial cells. Synthesis increases when bile ducts are obstructed. However, increases can come from bone disease (Paget's, malignancy, fractures), in pregnancy from the placenta (causing levels twice normal), in growing children, and in adolescents (up to 3 times normal). Alk phos also increases with age, and the yield of chasing a value <20% above the upper limit of normal is very low.

The first step in evaluation is to confirm that it is of liver origin by obtaining a GGTP or a 5' nucleotidase (5' NT). If GGTP or 5' NT is normal, then the alk phos elevation is not of hepatic origin. A bone scan may be helpful to evaluate elevated alk phos of bony origin. If alk phos and GGTP or 5' NT are elevated, then diagnostic possibilities include (1) bile duct obstruction (from stones, strictures, or neoplasia), (2) infiltrative liver disease (sarcoid, lymphoma, tuberculosis, fungal infections), (3) intrahepatic obstruction from tumor, and (4) cholestatic liver disease (drugs, PBC, PSC, occasionally hep A). Hyperthyroidism, renal cell cancer, and CHF can also increase alk phos. US and AMA should be obtained. If there is obstruction, then ERCP is generally indicated to identify and remove stones or to diagnose and stent obstructing tumors. If alk phos levels are <50% above normal and the initial studies are normal, then observation is appropriate (Nejm 2000;342:1266). If alk phos is >50% elevated and initial studies are normal, then MRCP (or selectively ERCP) is done to look for PSC or other evidence of obstruction. If MRCP is normal, then a liver bx to look for evidence of PBC with a negative AMA is usually indicated.

Approach to Jaundice: Jaundice can arise from mechanical obstruction, intrinsic liver disease, or overproduction of bilirubin from hemolysis. **Hemolysis** is suspected when (1) the bilirubin is >6.0 mg/dL, (2) the indirect (unconjugated) fraction is >50% of the total (usually 80%), (3) the remainder of the LFTs are normal, (4) splenomegaly is present (a variable finding), and (5) there is anemia with a reticulocytosis. **Mechanical obstruction** presents acutely in the form of common duct stones. These pts usually have sudden pain, sometimes radiating to the back, and may have fever if there is associated cholangitis (infected bile). In the first few days of illness, the transaminases may be as high as 300-1000, sometimes raising the question of viral hepatitis. As obstruction persists, the alk phos climbs and the transaminases fall. Obstruction from malignancy often presents as painless jaundice. Jaundice from **intrinsic liver disease** can present in a **hepatocellular** pattern (transaminases >5-10 times normal, alk phos <3 times normal) or a **cholestatic** pattern (transaminases >5 times normal, alk phos >3-5 times normal). Hepatocellular patterns are seen with viral hepatitis, some drug hepatitis

(especially acetaminophen), autoimmune hepatitis, ischemic hepatitis, Wilson's disease, mononucleosis, and environmental toxins. Cholestatic patterns are seen with alcoholic hepatitis (in which transaminases are usually <300 mg/dL and AST > ALT), PBC, PSC, some drug hepatitis, and, on occasion, hep A.

The initial evaluation of jaundice includes a CBC, CMP, PT, and US. If there is no evidence of hemolysis and the hx and US do not suggest obstruction or a mass, then the studies detailed for abnormal transaminases (plus hep A IgM antibody) are obtained. If the pattern is cholestatic, an AMA is also obtained. If obstruction is seen, it is generally evaluated with ERCP. If the presentation is acute and ascites is seen on the US, Budd-Chiari should be considered. Ascites should be evaluated (p 259). If the story suggests obstruction and the US shows normal ducts, it is important to consider that bile duct dilatation may be minimal early in the course of obstruction from stones. If there is underlying cirrhosis, the bile ducts may not dilate at all despite obstruction.

Evaluation of Cirrhosis: The evaluation of an adult pt with stigmata of cirrhosis or with an imaging test suggesting cirrhosis is similar to that of asymptomatic elevated transaminases (p 28). Testing for hep A is not necessary since that illness is never chronic. Alcohol, hep B, and hep C are the most common causes. Studies should be obtained for hep B (HBsAg, and anti-HBc), hep C (serum antibody and PCR study if the ab is negative and the cause is not found), hemochromatosis (Fe/TIBC, ferritin), Wilson's disease (ceruloplasmin), autoimmune hepatitis (ANA, f-actin ab, IgG level), and alpha-1 antitrypsin deficiency. Hep E has been recently shown to cause cirrhosis in immunocompromised individuals, but this need not be pursued without an exposure risk (p 225). An AMA should be obtained if there is substantial elevation of alk phos or other features of PBC (p 231). The liver should be imaged to rule out mass or obstruction. Long-standing obstruction can cause cirrhosis. MRCP or ERCP may be appropriate to evaluate the question of PSC (p 233) if the alk phos is very high or the pt has IBD. Evaluation for hepatic vein thrombosis (Budd-Chiari syndrome) is very selectively indicated (p 267). Endoscopy is indicated in established cirrhosis to look for varices that may benefit from medical rx to prevent bleeding (p 255). Liver bx confirms the presence of cirrhosis and may give clues to the etiology. However, in most cases the etiology is evident from the hx and lab studies, and liver bx is not needed. In about 5-10% of cases, the etiology is not determined (so-called "cryptogenic cirrhosis").

Approach to Isolated Elevated Bilirubin: The most common cause of an isolated elevated bilirubin is **Gilbert's syndrome**. Hyperbilirubinemia in Gilbert's syndrome is caused by an inherited deficiency in enzymes for bilirubin glucuronidation. The dx is made by the presence of an unconjugated hyperbilirubinemia (>60% indirect/unconjugated fraction), no evidence of hemolysis, and otherwise normal LFTs. It affects >2% of the population and is found incidentally on biochemical testing. Life expectancy is normal, and there is no clinical illness (Scand J Gastroenterol 1989;24:617). Rare causes of isolated hyperbilirubinemia include Crigler-Najjar syndrome, Dubin-Johnson, and Rotor syndrome (Sherlock S, Dooley J. Diseases of the liver and biliary system. 10th ed. Boston: Blackwell Science, 1997:210-213).

Approach to Fulminant Hepatic Failure (FHF): (Lancet 1997;349:1081) This condition is defined by the abrupt onset of massive hepatic necrosis. It usually occurs in pts without underlying liver disease, but it can be seen in Wilson's disease, hep D infection in hep B carriers, and

Table 1.11 Child-Pugh Classification of Severity of Liver Disease

	Points Scored		
Clinical Feature	**1 Point**	**2 Points**	**3 Points**
Encephalopathy	None	Grades 1 and 2	Grades 3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1-2	2-3	>3
Albumin (gm/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (sec prolonged)	1-3	4-6	>6

Grade A: 5-6 points
Grade B: 7-9 points
Grade C: 10-15 points

autoimmune hepatitis. The most common causes are acetaminophen overdose, viral hepatitis, acute fatty liver of pregnancy, Reye's syndrome, *Amanita phalloides* mushroom poisoning, hyperthermia, vascular occlusion, and rarely other drugs or other viruses (Am J Gastroenterol 1993;88:1000). The course is complicated by cerebral edema in 80%. Cerebral edema is the most common cause of death in these pts. Other complications include renal failure, bacterial infection, hypoglycemia, hemorrhage, and circulatory collapse. Management is complex, and pts should be treated in referral centers with a liver transplant program. The outlook is grim, with 60-80% mortality.

Approach to Elevated Prothrombin Time (PT): The question of liver disease is often raised by the finding of an elevated PT. The differential is largely between vitamin K deficiency and hepatic disease. The pt should be given vitamin K 10 mg sc qd × 3 and the PT repeated. If the PT normalizes with vitamin K within a few days (typically improvement is seen in 24 hr), the cause was vitamin K deficiency. Otherwise intrinsic liver disease is likely.

Approach to Cholangitis: Pts with cholangitis present with the combination of fever, upper abdominal pain, and jaundice. In elderly, demented, or immunosuppressed pts, pain and fever may not be obvious. The most common cause of cholangitis is bacterial infection secondary to bile duct obstruction from stones (p 206). Ascariasis is a common cause of cholangitis in Asia (p 169). When cholangitis is suspected, US is obtained to rule out hepatic abscess and to look for evidence of obstruction. ERCP is usually needed for dx and rx.

Approach to Hepatic Mass: See p 250.

Child-Pugh Classification: (Hepatology 1987;7:660) This classification is commonly used to grade severity of cirrhosis. It is used to varying degrees in clinical studies and in assessing surgical risk. The system is presented in Table 1.11 (Brit J Surg 1973;60:646). To use the system, encephalopathy must be graded. Encephalopathy is called Grade 3 if there is somnolence to semistupor, confusion, and gross disorientation. It is called Grade 4 if coma is present. In Grades 1-2, mental status changes are less severe (Aliment Pharmacol Ther 1996;10:681).

Chapter 2

Esophagus

2.1 Gastroesophageal Reflux Disease

GE 2008;135:1383; Am J Gastro 2005;100:190; Am J Gastro 1999;94:1434

Cause: Episodes of gastroesophageal reflux occur normally in asymptomatic individuals. However, excessive duration and frequency of reflux events lead to a symptomatic illness referred to as gastroesophageal reflux disease (GERD).

Epidem: Lack of a gold standard for GERD makes epidemiologic studies difficult to perform, and data are limited (Digestion 1992;51:24). In the general population, reflux sx occur monthly in 15-44%, weekly in 10-14%, and daily in 4-7%. Reflux sx occur with equal frequency in males and females, though Barrett's esophagus (p 41) is more frequent in males. The prevalence of endoscopic esophagitis is about 1.1%. The incidence of GERD rises steadily after 40 yr of age. The mortality is low at 0.10 per 100 000 per yr (excluding adenocarcinoma from Barrett's) (World J Surg 1992;16:288).

Pathophys:

- Transient relaxation of the lower esophageal sphincter (LES) is an important cause of reflux events both in normals (J Clin Invest 1980;65:256) and in pts with esophagitis (Nejm 1982;307:1547). Newer evidence suggests that the frequency of these transient relaxations is not higher in GERD pts than normal but that when relaxations occur they are more likely to be associated with reflux of acid in GERD pts (Am J Gastro 2001;96:2569). Transient relaxation is not the mechanism of GERD in hiatus hernia (GE 2000;119:1439).
- Some episodes of reflux are due to abrupt increases in intra-abdominal pressure that overcomes LES pressure (Nejm 1982;307:1547). This is probably a greater factor in pts with more severe grades of esophagitis than in those with mild disease (Gut 1995;36:505).
- Hiatal hernia has been convincingly implicated as a contributor to reflux. The right diaphragmatic crus, which encircles the LES, augments LES pressure, particularly with sudden increases in abdominal pressure that occur with coughing and inspiration. Hiatal hernia interferes with this increased LES pressure, and the larger the hernia, the smaller the benefit of the crus in preventing reflux (Ann IM 1992;117:977).
- About 30% of pts with heartburn severe enough to require self-medication with antacids have sensitivity to esophageal acid infusion or balloon distension despite normal endoscopies and pH probes. A lower threshold for esophageal pain may play a role in this subgroup of pts (Am J Gastroenterol 1999;94:628).

- Delayed gastric emptying is an important mechanism for GERD in a small subgroup of pts (GE 1981;80:285).
- In progressive systemic sclerosis (scleroderma), impaired esophageal acid clearance due to poor motility in the distal esophagus and a hypotensive esophagus are the primary defects (Dig Dis Sci 1992;37:833).
- Emotional stress (caused by stressful tasks like playing video games and doing math problems!) increases the subjective severity of reflux sx but not the actual number or duration of reflux events. The data suggest that pts who are anxious or subjected to stress may perceive minimal esophageal reflux as major symptomatic events.
- Reflux in smokers is most often due to the combination of a decreased resting LES pressure and the abrupt increases in intra-abdominal pressure associated with coughing and deep inspiration (Gut 1990;31:4).
- Obesity is associated with GERD sx, and even moderate weight gain is associated with worsened sx (Nejm 2006;354:2340).
- *H. pylori* infection limited to the antrum might worsen reflux by increasing acidity, but more commonly (especially in the developing world), Hp gastritis infects the antrum and body of the stomach, and the resultant gastritis reduces acid production and reduces the incidence of GERD (Am J Gastro 2004;99:1222). There is a strong inverse relationship between Hp infection and severe forms of GERD such as Barrett's esophagus (Am J Gastro 2004;99:1213).

Sx: Frequencies of sx are difficult to establish because of the lack of a clear gold standard defining GERD and the lack of population-based studies. Important sx include:

- *Heartburn* (a retrosternal burning sensation) is the most common sx, for which pts will use many synonyms, including indigestion and sour stomach.
- *Gross regurgitation* of gastric contents, particularly after bending or with recumbency, is often incorrectly reported by pts as vomiting. It is distinguished from vomiting by the lack of the intense nausea that generally precedes vomiting, the lack of force, and the seemingly spontaneous nature of the sx. Minor episodes might only leave a bitter, hot taste in the mouth, especially upon awakening.
- *Dysphagia*, the sensation that food sticks in the chest (p 6), is one of the most helpful clues to a dx of GERD if pts have primarily high epigastric pain or nausea.
- *Odynophagia*, painful swallowing, is less common than dysphagia and suggests the possibility of infections (candida, herpes) or pill esophagitis, especially if sx are of sudden onset.
- *Belching* is a frequent cause of reflux events in normal pts.
- *Nausea* is not rare, and intractable nausea can be the primary presenting complaint (Ann Intern Med 1997;126:704).
- *Chest pain* may occur with or without other typical reflux sx and may be difficult to distinguish from cardiac chest pain by hx alone (p 54).
- *Hoarseness*, repetitive throat clearing, sensation of fullness in the back of the throat (globus sensation), and chronic cough are associated with GERD (Gastrointest Endosc 1995;43:225; Clin Gastroenterol Hepatol 2003;1:333).
- *Asthma* is frequently found in association with GERD with up to half of pts in asthma clinics having symptomatic GERD and up to 80% of asthma pts having abnormal pH probes (Chest 1998;114:275).
- *Water brash*, the abrupt, episodic filling of the mouth with large volumes of saliva, is an uncommon sx.

Si: Usually none.

Crs: GERD is a chronic illness, and chronic rx is needed except in mild disease. Erosive esophagitis has a relapse rate of 50-80% in 6-12 months without maintenance (Arch IM 1996;156:477).

Cmplc: Esophageal stricture (see p 44) and Barrett's esophagus (see p 41).

Diff Dx: The dx is usually made on the basis of the H&P. With a wide variety of presenting sx, the diff dx for GERD can be quite broad. For typical sx (heartburn, regurgitation, dysphagia), consider PUD, especially with secondary reflux due to gastric outlet obstruction, esophageal infection (expect some odynophagia/dysphagia), gastroparesis, nonulcer dyspepsia, massive hiatal hernia, esophageal cancer, achalasia (fermenting food debris in esophagus), angina, and biliary tract disease.

Lab:

- *Technique for pH probe:* (Am J Med 1997;103:130S; GE 1996;110:1982). In ambulatory pH probe studies, a pH probe is passed through the nostril and positioned 5 cm above the manometrically determined LES. The pH is recorded every 6-8 seconds. The accurate placement of the probe is crucial. The extra step of determining the location of the LES with manometry is necessary because determining the LES location by fluoroscopy, endoscopy, or seeing the step-up in pH that occurs when the catheter is pulled back from stomach to esophagus is not reliable (GE 1996;110:1982). Pts usually find the probe tolerable, though not pleasant. It is attached to a recorder worn by the pt. The pt indicates the occurrence of events such as meals, sleeping, or sx (heartburn, chest pain, cough) by pushing an event marker on the device and by means of a diary. Pts who pull the probe out after an hour because they cannot stand it are also providing their physicians with valuable information about their tolerance of discomfort. A wireless system using a pH telemetry device placed endoscopically (Bravo pH System) is an alternative to an indwelling catheter that is usually better tolerated (Am J Gastro 2003;98:740). Longer recording periods (48 hr) give the wireless system greater sensitivity (Clin Gastroenterol Hepatol 2005;3:329). Reflux episodes are defined as drops in pH to below a value of 4.0. Commercial probes provide information on percent total time pH <4, percent upright time pH <4, percent recumbent time pH <4, total number of episodes, and number of episodes longer than 5 min. The most important of these is percent time pH <4, which discriminates between abnormal and physiologic reflux. Most of the clinical application of pH probe is in the correlating of sx with reflux episodes.
- *Indications for pH probe:* Only a tiny proportion of pts with reflux need pH probe as part of their evaluation. A pH probe is indicated for (1) proving abnormal reflux prior to sending a pt with a negative endoscopy to antireflux surgery, (2) evaluating recurrent reflux sx in pts who have had antireflux surgery, (3) evaluating sx that persist despite a month of a PPI, (4) evaluating noncardiac chest pain or throat sx that do not resolve with a PPI trial, and (5) evaluating whether reflux episodes are associated with adult-onset nonallergic asthma (GE 1996;110:1981).
- *Intraluminal impedance monitoring:* This technique measures electrical impedance between pairs of electrodes attached to a plastic catheter in the esophageal lumen. During reflux of liquid, impedance falls rapidly; during reflux of gas, it rises rapidly. Thus impedance monitoring can provide information about reflux unrelated to acidity and may be of value in evaluating pts with sx unrelieved by PPIs or with atypical sx. Its clinical application has yet to be clearly defined (Am J Gastro 2007;102:187).

- *Omeprazole test:* The response of sx to a 14-day trial of omeprazole 40 mg daily in pts with sx suggestive of GERD has a positive predictive value of 68% and a negative predictive value of 63% when compared to pH probe as a gold standard (Am J Gastroenterol 1997;92:1997). The fact that this number is not higher reflects problems using pH probe as a gold standard. As a practical matter, if it sounds like GERD and gets better with omeprazole, it is probably GERD.
- *Indications for EGD:* Pts with typical GERD sx who respond to a course of rx usually do not benefit from endoscopy (Gastrointest Endosc 1999;49:834). EGD is clearly indicated in pts with **dysphagia** so that strictures can be found and dilated. EGD is needed in pts who show evidence of GI blood loss, iron deficiency, or sx suggestive of malignancy, such as weight loss. Many physicians offer EGD to pts with sx of several years' duration because they are at a higher risk of developing Barrett's esophagus. The benefit of this widely used approach is unproven (see Barrett's esophagus p 41). Endoscopy is also appropriate for pts whose sx do not respond to a course of rx. Endoscopy in this group may demonstrate esophagitis, stricture, or Barrett's, or there may be an alternative explanation of sx, such as PUD, gastric outlet obstruction, gastroparesis with retained food, malignancy, candida, or herpetic esophagitis.
- *Grading of esophagitis:* Several grading systems for esophagitis exist and serve as important tools for clinical studies. Grades are commonly used in endoscopy reports. The Savary-Miller system (Gastrointest Endosc Clin N Am 1994;4:677) and the Los Angeles classification (Gut 1999;45:172) are 2 common grading systems.
- *Endoscopic bx:* Bx should be performed in pts with endoscopic esophagitis if they are immunosuppressed (Nejm 1994;331:656). Bx is less likely to be helpful if there is visible erosive change in a normal host. Erosions may obscure the presence of Barrett's mucosa that may be detected by bx. Pts with grossly normal esophageal mucosa may benefit from bx. If bx shows convincing histologic evidence of reflux, the pt may be spared a pH probe for definitive dx. Intraesophageal eosinophils are perhaps the most useful diagnostic findings in reflux, though basal zone thickness and height of papillae are also helpful if specimens are properly oriented (Gastroenterol Clin North Am 1990;19:631).

X-ray: UGI series may show evidence of free reflux, a patulous gastroesophageal junction, esophageal fold thickening due to esophagitis, esophageal ulcer, or stricture. However, UGI series is not a sensitive test for GERD, and the mere occurrence of reflux during an exam is not specific. Therefore, UGI series is rarely useful for dx in pts with GERD.

Rx:

- *Patient teaching:* There is no simple therapeutic recipe appropriate for all pts with GERD. The most common error is failing to appreciate the severity and chronicity of a pt's complaints and offering inadequate rx. Rx begins by teaching pts the basic pathophys of GERD so that they understand why their sx are likely to be chronic without appropriate rx. Most physicians suggest diet and lifestyle modifications despite the lack of critical evidence that such measures change outcomes (Am J Gastroenterol 2000;95:2692). Pts should be selectively advised to (1) avoid large meals, (2) avoid eating within 3 hr of bedtime, (3) stop smoking, (4) lose weight, and (5) elevate the head of the bed by 6 inches if nocturnal sx are problematic. Diet can be modified to minimize high-fat foods, chocolate, caffeine, citrus, alcohol, and tomato products (Mayo Clin Proc 2001;76:1002). Coffee produces reflux more than tea containing equal caffeine concentrations. Decaffeination reduces the

reflux caused by coffee, probably by removing substances in coffee other than just the caffeine (Aliment Pharmacol Ther 1994;8:283). The milder the GERD sx, the more likely that these modifications will make an impact on the need for drug therapy.

- *Drug rx:* There are 2 approaches to drug rx. In some cases, it is best to start with a PPI for rapid sx relief and to switch to an H2RA after sx are completely relieved. Alternatively, one can begin with H2RA and intensify rx if sx are not relieved. Severity of sx and cost of rx are major factors.
  - *Histamine-2 blockers:* There are 4 available H2RAs in the U.S. (Table 2.1). For pts with mild to moderate sx, H2RAs are often effective for sx control. Because they do not suppress acid production completely, the H2RAs are less effective for healing esophagitis, especially if the esophagitis is high grade (Jama 1996;276:983). **Ranitidine** and **famotidine** are currently the most sensible choices. They are available generically, thus reducing cost, and do not have the many drug interactions seen with cimetidine. H2RAs are usually given twice a day, before breakfast and before supper. They can be supplemented with antacids as needed.
  - *Proton pump inhibitors:* There are 6 PPIs available in the U.S. (Table 2.2). PPIs should be offered to pts who require the most rapid relief, to those with advanced degrees of esophagitis, and to those with strictures. Little differentiates the drugs clinically, and cost (often a function of the pt's insurance) is frequently the deciding factor in choosing an agent. The availability of generic and OTC PPIs (omeprazole as OTC and generic; pantoprazole and lansoprazole as generic) has made PPIs much more affordable, especially to the uninsured.

Meta-analysis suggests that esomeprazole (the S-isomer of omeprazole) is slightly more effective than other PPIs in producing mucosal healing and symptom relief (Clin Gastroenterol Hepatol 2006;4:1452). This difference is only likely to be important in the more

Table 2.1 Histamine-2 Receptor Antagonists

Drug	U.S. Trade Name	Rx Dosage	OTC Dosage
Cimetidine	Tagamet	400 mg po bid	200 mg po bid
Ranitidine	Zantac	150-300 mg po bid	75-150 mg po bid
Famotidine	Pepcid	20-40 mg bid	10-20 mg po bid
Nizatidine	Axid	150 mg po bid	75 mg po bid

Table 2.2 Proton Pump Inhibitors

Drug	U.S. Trade Name	Formulations	Usual Total Daily Dose
Omeprazole	Prilosec, Zegerid	10, 20, 40 mg	20-40 mg
Lansoprazole	Prevacid	15, 30 mg	30-60 mg
Rabeprazole	Aciphex	20 mg	20-40 mg
Pantoprazole	Protonix	40 mg	40-80 mg
Esomeprazole	Nexium	20, 40 mg	20-80 mg
Dexlansoprazole	Kapidex	30, 60 mg	30-60 mg

severe grades of esophagitis. High-dose dexlansoprazole MR, with a dual-delayed-release formulation, is more effective than standard-dose lansoprazole for higher grades of esophagitis (Aliment Pharmacol Ther 2009;29:731).

Correct dosing instructions are crucial. The PPIs are prodrugs that require an acidic environment for binding (GE 2000;118:S9). This occurs when the parietal cell is activated by the stimulation of meals. PPIs are most effective after an overnight fast when levels of the proton pump on canalicular membranes are highest. Therefore, single doses should be taken 30 min to 1 hr ac breakfast. Dexlansoprazole MR does not require the same dosing restrictions as other PPIs and can be taken with food. This high-dose formulation first releases drug in the proximal small intestine and later in the distal small intestine to give 2 plasma peaks of drug. Acid suppression is equal for the drug taken with or without eating (Aliment Pharmacol Ther 2009;29:731). PPIs should not be given concomitantly with H2RAs or prostaglandins that will reduce PPI binding. Steady state occurs in a few days and bid dosing may be useful in the first few days. If a second dose is needed, it should be given 30 min to 1 hr ac supper. The PPIs can be expected to heal esophagitis in 80% or more of pts (versus about 50% with H2RAs) and free pts of heartburn in a similar proportion (GE 1997;112:1798). If one PPI fails, it is worthwhile trying another, because individual response varies.

- *Promotility agents:* Promotility agents are appealing in theory because they more directly address the pathophysiology of reflux. Delayed gastric emptying, inadequate LES pressure, and esophageal acid clearance are all potentially reversible with the ideal agent. As first-line rx, cisapride (Propulsid) was shown to be as effective as H2RAs for mild disease (Arch IM 1995;155:2165), and it was used in maintenance rx (Nejm 1995;333:1106). However, cisapride was withdrawn from the U.S. market because it caused life-threatening arrhythmias related to drug interactions and because of the drug's effect in prolonging the QT interval. Metoclopramide (Reglan) should be avoided because of its limited effectiveness and the possibility of serious irreversible movement disorders (mostly tardive dyskinesia) (Arch IM 1989;149:2486).
- *Sucralfate:* This agent binds to ulcer bases and binds to pepsin and bile salts. It has efficacy similar to H2RAs in some trials (Am J Med 1991;91:2A). Its most frequent use may be in pregnant pts where its minimal absorption is perceived as a possible benefit.
- *Maintenance therapy:* GERD is a chronic disorder that usually requires chronic therapy. Maintenance rx is sensible (1) to control sx of relapsing disease or (2) to prevent complications of erosive esophagitis. For pts with symptomatic disease but minimal endoscopic esophagitis, intermittent rx with either omeprazole or ranitidine works well for about half of pts (BMJ 1999;318:502). Rapid recurrence of sx or slow response to retreatment should lead to continuous maintenance rx with the lowest dose of an antisecretory agent that controls sx.

  The first step in tapering rx is to reduce PPI use to once daily. Most pts requiring multiple-dose PPIs can be tapered to single-dose rx with good relief (Am J Gastro 2003;98:1940). If daily PPI rx is well tolerated a couple of months, the pt can switch to ranitidine 150-300 mg bid or famotidine 20-40 mg bid. This can be tapered further if sx remain well controlled. If sx recur with the taper, therapy with the previously effective agent at the previously effective dose is resumed.

  For pts with endoscopic esophagitis, a very strong argument can be made for maintenance rx to prevent symptomatic relapses and complications (Arch IM 1995;155:1465). It is intuitive, though not well proven, that preventing the relapse of erosive esophagitis might

prevent progression to the more severe complications of stricture and Barrett's esophagus. For erosive disease, the PPIs are clearly superior to H2RAs, and if one chooses to control esophagitis rather than sx, then chronic PPI rx is rational (Arch IM 1999;159:649; Ann Intern Med 1996;124:859; GE 1994;107:1305).

- *PPI safety:* PPIs are generally safe and well tolerated. Because of decreased gastric acidity, pts may be more susceptible to small intestinal bacterial overgrowth (Gut 1996;39:54) or acute infectious gastroenteritis. PPI therapy appears to be a risk for C. *diff* colitis (CMAJ 2004;171:33) and community-acquired pneumonia (Jama 2004;292:1955). Long-term PPI is associated with a greater risk of hip fracture (Jama 2006;296:2947) perhaps by decreasing calcium absorption. Because hip fracture is an infrequent event, the absolute hip fracture risk for an individual pt on long-term PPI therapy is an increase from 0.18% to 0.4% annually (GE 2007;132:2063). Ensuring adequate dietary calcium seems sensible.

  There is an increased risk of atrophic gastritis (and therefore theoretically gastric cancer) in pts infected with Hp and maintained on omeprazole, though dysplasia associated with atrophy is rare (GE 2000;118:661). This risk has prompted many clinicians to test for and eradicate the organism if a long-term PPI is used. A recent trial of eradication of Hp in pts on long-term PPI rx (for an unspecified mix of indications) showed that pts who had Hp treated had improved sx and used less healthcare resources, adding additional incentive to eliminate Hp in long-term PPI users (Aliment Pharmacol Ther 2007;25:585).

  B_{12} malabsorption may occur (Ann IM 1994;120:211), though it is usually not a clinically evident problem and can usually be prevented with an oral B_{12} supplement.

  There has been recent concern that PPIs may reduce the effectiveness of the antiplatelet agent clopidogrel (Plavix). Some studies show reduced effectiveness of clopidogrel after acute coronary syndrome when PPIs are used (Jama 2009;301:937). Other studies suggest that this may not be a class effect and that use of esomeprazole and pantoprazole is not associated with a reduced response to clopidogrel (Am Heart J 2009;157:148 e1). Additional studies are underway to clarify the issue.

- *Refractory GERD sx:* Some pts will not respond to conventional once-a-day dosing of PPIs with the relief of sx. In this case the dx should be carefully reconsidered. Malignancy, esophageal infection, gastroparesis, achalasia, and heart disease must be excluded. The most common reason for PPI failure is improper timing of doses.

  If a bid PPI is ineffective, a pH probe on rx should be done to determine if the pt has inadequate pH control despite rx. For the small minority who will turn out to have inadequate pH control, a pH probe will be cheaper than increasing PPI doses for months on end. For those without good control by pH probe, a dx of ZE syndrome should be considered (p 86), and surgery or higher-dose PPIs are the rx choices. Many pts on bid PPIs will have nocturnal periods of intragastric pH drops below 4.0 lasting more than an hour. This has been called nocturnal acid breakthrough (Aliment Pharmacol Ther 1998;12:1231). These pH drops in the stomach are associated with reflux events. The proportion of pts with refractory sx who have nocturnal acid breakthrough is unknown. The addition of ranitidine 300 mg qhs (GE 1998;115:1335) is effective in reducing nocturnal acid breakthrough. This is more effective than a bedtime dose of a delayed-release PPI, perhaps because the meal-stimulated acid secretion necessary for PPI binding does not occur, or perhaps because histamine is more important in nocturnal acid secretion. Bedtime administration of immediate-release omeprazole (Zegerid) is another effective treatment for nocturnal reflux (Aliment Pharmacol Ther 2005;22 Suppl 3:31).

Some pts have persistent sx due to reflux of nonacidic gastric contents. In some of these pts, gastroparesis has not been recognized as the major problem and a gastric emptying scan may be helpful for dx (p 77).

In some pts with typical sx and normal endoscopies and pH probes, esophageal hypersensitivity may be the primary problem. When these pts are refractory to acid-blocking rx, there may be a role for other therapies (eg, antidepressants) to modulate the hypersensitivity, but this approach has not been well studied (Ann Intern Med 1996;124:950).

- *Surgical therapy for GERD:* While medical rx offers excellent relief of sx for the majority of pts, surgical rx is a consideration in several circumstances. Surgery should be considered in (1) pts whose sx are not adequately controlled by medical rx or (2) pts whose sx are well controlled by PPIs but who are intolerant of them or (3) pts who would rather have surgery than take medications chronically and who are willing to accept the greater risks of surgery.

The most common surgical approach has been the **Nissen fundoplication**, in which a portion of the mobilized gastric fundus is passed posteriorly to the esophagus and wrapped around the GE junction. The procedure was first performed by open laparotomy but is now widely being performed by the laparoscopic approach (World J Surg 1999;23:356). The laparoscopic method has a higher risk of dysphagia (by RCT [Lancet 2000;355:170]) but is associated with reduced morbidity and shorter hospital stay (Ann Surg 2004;239:325). In pts with poor motility, a 270-degree wrap (the Toupet fundoplication) can be used. In pts with foreshortened esophagus, the Collis gastroplasty (creating a tube of stomach as a neoesophagus) can be used. In pts with severe obesity, a transthoracic approach may be preferred. There is no single operation appropriate for all pts, and the choice of operation needs to be tailored to the anatomy of the pt (J Thorac Cardiovasc Surg 1995;110:141).

Based on a large academic series, the following short-term results might be expected with laparoscopic Nissen fundoplication in expert hands (Ann Surg 1996;223:673): (1) relief of heartburn 93%, (2) elimination of atypical sx 87%, (3) minor complications 6%, (4) major complications 2%, (5) reoperation 2%, and (6) fundoplication failure 2%. Mortality in large series is about 0.2% (Surg Laparosc Endosc 1997;7:17). Outcomes from community-based practice suggest that fundoplication is less effective than might have been hoped, with a third of pts taking medicines for heartburn and more than half of pts with new sx of dysphagia, bloating, or excessive abdominal gas (Am J Med 2003;114:1).

Dysphagia is reported in 3-24% of pts undergoing fundoplication and can usually be treated by dilatation, except in those pts with a slipped fundoplication or in those pts who have had second operations (Am J Gastroenterol 1996;91:2318).

Upper endoscopy should be performed in all pts prior to fundoplication. If EGD shows erosive esophagitis, then surgery may be one of the appropriate choices. A 24-hr pH probe is unnecessary if EGD shows erosions. If EGD is normal and the dx is in doubt, then pH probe may be helpful in determining the certainty of the dx and the appropriateness of surgery. Motility testing (manometry) will change the operative approach in the 10% of pts in whom poor esophageal motility is found and an incomplete wrap is performed. Many experts use manometry in all pts prior to fundoplication.

There is a learning curve in laparoscopic fundoplication. This curve is at least 20 cases for an individual surgeon and 50 cases for a small group working together. The rates of complications, reoperation, and conversion to open procedures are all higher on the

early portion of the learning curve (Ann Surg 1996;224:198). Causes of failure of antireflux procedures include disruption of initial repair (46%), repair around the stomach instead of esophagus (23%), a too-tight or too-long repair (10%), unrecognized esophageal motor disorder (9%), herniation (6%), and gastric denervation (6%) (Am J Surg 1996;171:36).

- *Endoscopic treatment of GERD:* A variety of endoscopic methods have been tried as alternatives to surgical fundoplication or medical therapy. Studied techniques have included suture plication of the proximal fundic folds, injection of biopolymers into the GE junction, radiofrequency energy delivery to the LES, and the use of bioprostheses. Trials have been characterized by small numbers, short follow-up, and safety problems. At present, endoscopic therapy for GERD is not indicated (GE 2006;131:1313).
- *Extraesophageal reflux:* Cough, hoarseness, asthma, and laryngitis are associated with GERD but are not specific to it. It is uncommon to have an extraesophageal sx without an esophageal sx of GERD. Given the lack of accurate tests for GERD as a cause of these extraesophageal sx, a trial of a PPI can be considered. However, if a PPI trial is ineffective, alternative causes of the atypical sx should be sought (GE 2008;135:1392). In pts who have persistent ENT sx despite effective suppression of acid (as proven by pH probe), Nissen fundoplication is of no benefit (Clin Gastroenterol Hepatol 2006;4:433).
- *Reflux during pregnancy:* First-line rx for symptomatic pts with GERD should include antacids or sucralfate. Cimetidine and ranitidine are the preferred H2RAs for pregnant pts (Gastroenterol Clin North Am 1998;27:153). Meta-analysis suggests that PPIs can be safely used in pregnancy (Am J Gastro 2009;104:1541).

2.2 Barrett's Esophagus

Am J Gastro 2008;103:788; Am Fam Phys 2004;69:2113; Nejm 2002;346:836

Epidem: The mean onset of Barrett's is probably 40 yr of age; the mean age of dx is 55-60 yr. M:F ratio is 4:1. It occurs 10-20 times more frequently in whites than blacks. It is more frequent in smokers and the obese. The prevalence in the Swedish adult population is 1.6%, only 40% of whom have GERD sx (GE 2005;129:1825). It is found in 8-12% of pts having endoscopy for GERD sx (Arch IM 1996;156:2174).

Pathophys:

- Barrett's esophagus is most commonly defined as a change in the esophageal epithelium of any length that is shown on bx to have intestinal metaplasia. Intestinal metaplasia is recognized by the presence of goblet cells on bx. Earlier definitions have required a length of >3 cm without the necessity for intestinal metaplasia. However, since intestinal metaplasia has been thought to be the risk factor for adenocarcinoma, this widely adopted definition makes intestinal metaplasia with goblet cells the cornerstone (Am J Gastroenterol 1998;93:1028). Recent studies have challenged this definition by demonstrating that metaplastic columnar epithelium without goblet cells has a similar frequency of DNA content abnormalities as epithelium with intestinal (goblet cell) metaplasia (Am J Gastro 2009;104:816).
- There is convincing evidence that Barrett's is a consequence of GERD. Pts with Barrett's have high levels of acid exposure on pH probe, low resting LES pressures, and poor esophageal motility (Scand J Gastroenterol 1993;28:193). It is not clear which components of

the refluxate are important in the development of Barrett's. Acid and pepsin are thought to be the most important, but biliary and pancreatic secretions, and perhaps saliva, may play a role in the metaplastic change (Arch IM 1996;156:2174).

- **Short-segment Barrett's esophagus** is a length of intestinal metaplasia of less than 3 cm. Its prevalence on diagnostic EGD is an astounding 8-32%. It is associated with reflux sx, but pts have less severe acid exposure and better motility. The magnitude of the cancer risk associated with short-segment Barrett's is unknown, but cancer is much less commonly seen in short-segment than in long-segment disease (metaplasia of greater than 3 cm in length) (J Clin Gastroenterol 1997;25:480).
- Barrett's is more common in pts with severe esophagitis on barium study (eg, stricture, ulcer, severe esophagitis), in those with GERD sx >5 yr, and in those with scleroderma (Arch IM 1996;156:2174). EGD to detect Barrett's will have a higher yield in this group.

Sx: Sx are those of GERD, though pts with Barrett's tend to have a longer duration of sx, earlier age of onset of sx, and more frequently have GERD complications such as stricture (Am J Gastroenterol 1997;92:27). Up to 40% of pts who develop adenocarcinoma (presumably from Barrett's) have no GERD sx (Nejm 1999;340:825).

Cmplc: Adenocarcinoma complicates Barrett's in less than 0.5% of pts per yr (GE 2000;119:333). Prior overestimates due to publication bias fuel the current aggressive approach to screening. The RR of cancer in Barrett's is 30-125 compared to that of the general population. However, only a small proportion of pts with Barrett's esophagus will ultimately die of adenocarcinoma. In a series of 155 pts who did not undergo surveillance but who were followed up at a mean of 9.3 yr, only 2.5% died of adenocarcinoma of the esophagus (Gut 1996;39:5). Survival in Barrett's pts is similar to that seen in age- and sex-matched controls (Gut 1989;30:14). Adenocarcinoma is more likely to develop in those with long segments of Barrett's, in those with hiatal hernia >3 cm, and perhaps in those with frank ulcers in Barrett's mucosa of the esophagus (Am J Gastroenterol 1999;94:3416).

Diff Dx: Intestinal metaplasia of the cardia of the stomach has an identical histologic appearance to that of Barrett's esophagus. Bx taken close to the apparent GE junction may actually be sampling stomach and be wrongly interpreted as showing Barrett's. Since short-segment Barrett's and intestinal metaplasia at the GE junction cannot always be distinguished, some experts offer surveillance to the pt with both conditions (GE 2004;126:567).

Endoscopy: Barrett's epithelium is suspected at endoscopy by the gross appearance of reddish to pink velvety mucosa in the distal esophagus, which generally stands out well against the more gray color of the squamous mucosa. Its presence, however, can only be proven by bx showing columnar metaplasia (see previous definition of Barrett's). Active esophagitis can make Barrett's more difficult to detect. If a first endoscopy in GERD pts shows esophagitis but no Barrett's, a second endoscopy will reveal Barrett's in 9.9% (Am J Gastro 2008;103:1892).

Rx:

- Pts with Barrett's should have medical rx for their underlying GERD. PPIs are usually needed for adequate symptom control in these pts. However, control of sx is not synonymous with normalization of acid exposure. Some authors have gone so far as to suggest that proving adequate acid suppression by pH probe in Barrett's pts is necessary. However, guidelines call for control of sx alone (Am J Gastro 1999;94:1434). Surgery is no more likely than medical rx to prevent progression of Barrett's to cancer (Am J Gastro 2003;98:2390).

- The compelling reason to consider endoscopic surveillance for Barrett's is the poor prognosis of adenocarcinoma found in symptomatic pts. Cancers found in surveillance programs do tend to be found at earlier stages and are thus more curable (Am J Gastroenterol 1998;93:1028; GE 2002;122:633). However, there are no convincing data to demonstrate that surveillance, as it is currently practiced, saves lives. Skeptics of the current approach to screening GERD pts for Barrett's and subsequent surveillance (Clin Gastroenterol Hepatol 2004;2:861) point out that (1) adenocarcinoma of the esophagus is uncommon while the number of GERD pts is enormous, (2) many pts with esophageal cancer never have GERD sx, and (3) surveillance is very costly. Updated guidelines reflect this view by concluding that screening for Barrett's in the general population cannot be recommended and that screening targeted to high-risk groups is of uncertain utility (Am J Gastro 2008;103:788).

  The first decision to be made with the pt is whether to begin a surveillance program. The data on cancer risk, the low chance of death from cancer, and the unknown benefit of surveillance should be discussed. Pts with significant comorbid illnesses are unlikely to have their lives improved by surveillance of unproven merit. Additional risk factors for cancer include a length of Barrett's >8-10 cm and presentation with esophageal ulcer (Arch IM 1996;156:2174; Gut 1996;39:5), and these pts may be more likely to benefit.
- Pts undergoing surveillance typically have bx taken from 4 quadrants of the esophagus, in intervals of less than 2 cm, for the entire length of the visibly abnormal epithelium. Where available, a jumbo bx forceps passed through a large-channel endoscope is preferred by some authors (GE 1993;105:40) so that larger samples can be obtained.
- Biopsies are obtained to look for dysplasia or cancer. Dysplasia is graded as negative, indefinite, low grade, high grade, and carcinoma. Interobserver agreement in the classification of dysplasia is a disappointing 72-85% among expert pathologists (Am J Gastroenterol 1998;93:1028). This makes decision-making more difficult, and a second pathologic opinion is mandatory before major interventions.
- If no dysplasia is found, the ACG protocol is to use a 3-yr interval of surveillance after 2 endoscopies within a year are negative for dysplasia (Am J Gastro 2008;103:788).
- If low-grade dysplasia is found, then endoscopy is repeated within 6 months with intensive rx of the associated GERD. If dysplasia does not progress beyond low grade, endoscopy is then repeated yearly. If no dysplasia is found in 2 consecutive endoscopies, then the interval of surveillance returns to q 3 yr. In only 25% of pts surveyed does low-grade dysplasia persist (GE 2004;127:1233).
- The management of high-grade dysplasia is evolving. High-grade dysplasia should be confirmed by an expert pathologist. Repeat endoscopy with more extensive bx and resection of nodular areas should be done to exclude cancer. If only high-grade dysplasia is present, then the choices are (1) continued endoscopic surveillance, (2) endoscopic ablation therapies, and (3) esophagectomy. The local expertise, the pt's medical condition, and the pt's wishes are important factors in the choice of rx. Surgical rx and endoscopic rx appear to have similar outcomes (GE 2007;132:1226).
- Esophagectomy had been the standard therapy based on study showing a 43% incidence of occult carcinoma in resection specimens of pts sent to surgery for high-grade dysplasia (Ann Surg 1996;224:66). However, in a recent series of 15 pts with high-grade dysplasia, 8 progressed and 7 regressed in endoscopic follow-up over 3 yr (Am J Gastroenterol 2000;95:1888).

In a series of 72 veterans followed for almost 20 yr with yearly endoscopy because of high-grade dysplasia, adenocarcinoma developed in only 13 pts (GE 1998;114:1149). Ten of these 13 pts underwent curative surgery, and 1 who was not compliant with the yearly follow-up had metastatic disease and was not resected. In another series of 28 pts who had surgery for cancer or high-grade dysplasia, endoscopic bx reliably separated the cancers from the high-grade dysplasias (GE 1993;105:40).

- On the basis of the research presented here regarding treatment of Barrett's, intensive surveillance is an alternative to esophagectomy. The ACG guidelines recommend surveillance every 3 months for these pts. The conventional 4 jumbo bx every 2 cm is not adequate for this group (missing half the cancers that develop), and 4 bx every cm is suggested (Am J Gastroenterol 2000;95:3089).
- Ablative therapies are now considered an excellent alternative to surgical resection or watchful waiting for high-grade dysplasia. Ablation can be accomplished with laser, multipolar electrocoagulation, argon plasma coagulation, or photodynamic rx (Gastro Endosc 2003;58:760; Gastro Endosc Clin N Am 2005;15:377). The choice of method is dependent on the experience of the endoscopist.
- Endoscopic therapy to ablate nondysplastic Barrett's epithelium has been proposed. There are inadequate data to support the widespread adoption of this practice (Am J Gastro 2009;104:805).

2.3 Benign Esophageal Strictures and Rings

J Clin Gastroenterol 1998;27:285

Pathophys: Esophageal strictures are a common problem and are generally due to acid reflux. Rings are less commonly a clinical problem. Some of the rings detected by barium swallow turn out to be GERD-related strictures. Rings and strictures are distinguished by their thickness. Narrowings with a thickness less than 3 mm are called rings, and those thicker than 3 mm are called strictures (J Clin Gastroenterol 1998;27:285). Most strictures are reflux-related, presumably due to cycles of acid-induced inflammation and healing with scar formation. Strictures can also be caused by pill esophagitis, caustic ingestion, radiation, sclerotherapy, and esophageal surgery. The cause of rings is unclear. Some of the lower rings are reflux-related and may evolve into frank strictures. They are unlikely to be congenital since they present after age 40 yr. Lower esophageal rings (Schatzki's rings) are associated with hiatal hernia. It has been suggested that as reflux-related inflammation shortens the esophagus (and lengthens the hernia), the ring is formed from pleated esophageal mucosa (Dig Dis 1996;14:323).

Sx: Intermittent solid food dysphagia is the hallmark (see detailed sx description on p 6). Pts usually do not have dysphagia unless the luminal diameter of the stricture is less than 13 mm. Pts often do not report their dysphagia sx episodes unless specifically asked.

Crs: The typical pattern is one of an increasingly frequent, intermittent dysphagia to solids, which may progress over months to years. Strictures commonly recur, and repeated dilatation may be required.

Cmplc: Food impaction requiring endoscopy for removal (see Foreign Bodies, p 47).

Diff Dx: See diff dx of dysphagia in Table 1.3.

X-ray: Strictures can be demonstrated with a barium swallow using a 13-mm barium tablet. The tablet is helpful in reproducing sx and demonstrating more subtle strictures. Not all pts with dysphagia require barium studies. Pts with intermittent, mild to moderate dysphagia should undergo EGD without x-ray.

Endoscopy: Strictures and rings are visible at careful endoscopy if adequate care is taken to insufflate the esophagus. Bx is indicated to rule out malignancy in new strictures and may reveal histologic evidence of associated reflux.

Rx: The mainstay of rx is dilatation using mechanical dilators or balloons. A **mercury-filled dilator** (eg, the tapered Maloney dilator) passed blindly into the esophagus without aid of a guidewire is safe and effective for simple strictures or rings.

More commonly used are the polyvinyl **Savary dilators** that are passed over a guidewire placed endoscopically into the stomach. Fluoroscopy is used by some endoscopists but is often unnecessary, especially if the scope can be advanced to the antrum to deploy the wire and keep it in a fixed position (Am J Gastroenterol 1993;88:1381). Typically, 3 dilators are passed sequentially in a single session with an eventual goal of dilating to at least 15 mm (in multiple sessions if needed). Bx and dilatation can be completed in the same session. For narrow strictures, several sessions spaced at intervals of 1-2 weeks are used until the target is reached.

Through the scope (TTS) balloons are the other popular method of dilatation. Balloon dilatation offers the theoretical advantage of applying only radial force to the stricture, and balloons may be better tolerated by pts than the passage of 3 dilators. However, in practice, there is convincing evidence that the outcomes are the same no matter which method is chosen (Gastrointest Endosc 1999;50:13). Operator preference and expense (Savary dilators are reusable) are the major determinants of the method selected.

The most feared complication of dilatation is perforation, which occurs at a rate of 1 per 500 dilatations (Gastrointest Endosc Clin N Am 1996;6:323). Much higher rates have been reported for the dilatation of caustic strictures (Radiology 1998;209:741). Bleeding and bacteremia are very uncommon complications (Gastrointest Endosc Clin N Am 1996;6:323).

There are case series of using electrocautery to cut esophageal rings as an alternative to dilatation on refractory cases (Gastrointest Endosc 1993;39:616). In strictures that rapidly recur, injection of intralesional corticosteroids appears to be effective (Gastrointest Endosc 1995;41:596; Gastro Endosc 2002;56:829). In the past, monthly dilatations and self-dilatations were needed for those with severe disease. With the advent of PPIs, frequent dilatations are rare. It is clear that all pts with reflux-related strictures should have lifelong PPI rx (or surgery). Pts who receive PPIs after dilatation have better relief of dysphagia and need fewer dilatations than those placed on H2RAs (GE 1994;106:907). Pts with Schatzki's rings have lower risks of recurrence after dilatation if they are kept on PPI rx (Am J Gastro 2005;100:1929). In pts whose strictures recur rapidly, high-dose PPI rx may be needed, and 24-hr pH probe may be cost effective in choosing an effective dose.

2.4 Eosinophilic Esophagitis and the Ringed Esophagus

Am J Gastro 2008;103:2635; Clin Gastroenterol Hepatol 2004;2:523

Epidem: Eosinophilic esophagitis (EE) is an uncommon disorder affecting children and adults for which limited epidemiologic data are available. The disease is often unrecognized though it is likely more prevalent in children than Crohn's disease (Nejm 2004;351:940). There is a strong male predominance.

Pathophys: Eosinophils infiltrate the mucosa and probably the muscle layers of the esophagus by both allergic (IgE-dependent) and IgE-independent mechanisms. The allergens are not clearly known, but pediatric pts have responded to elemental diets. Longstanding eosinophilic inflammation presumably leads to the gross changes seen at endoscopy in advanced cases.

Sx: Dysphagia to solids, often presenting as food impaction. Most pediatric pts have associated allergic sx (asthma, food allergy, atopy), but these findings are less frequent in adult presentations.

Crs: In adults followed for >10 yr, the illness is chronic with continued dysphagia (GE 2003;125:1660). The disease remains confined to the esophagus and is not associated with malignancy. The course in children (many of whom will outgrow their atopic/allergic conditions) is unknown.

Cmplc: Perforation occurs more frequently because the dx goes unrecognized and dilatation to large diameters is improperly attempted.

Diff Dx: See Dysphagia (p 6). Eosinophilia on esophageal bx can be seen in GERD (though typically it is in the distal esophagus and only a few eosinophils per high-powered field). A variety of other uncommon illnesses may be associated with esophageal eosinophils (J Clin Gastro 2000;30:242). Some cases presenting with rings and stenosis may be congenital stenosis (see p 47), and some authors suggest that the ringed esophagus can result from GERD (Am J Gastro 2001;96:984).

X-ray: In advanced cases, barium swallow may show a narrow-caliber esophagus with rings or strictures.

Endoscopy: Subtle findings include loss of the vascular pattern, vertical furrows, and a speckled pattern of whitish exudate that looks like candida but is actually eosinophilic infiltrations. More obvious findings include narrow caliber, the appearance of multiple rings, or a corrugated appearance. A dominant stricture in the distal esophagus may be seen. Bx of the middle and lower esophagus makes the dx.

Rx: Elimination diets may be useful, especially in children (Gastroenterol Clin North Am 2003;32:949). Some experts suggest allergy testing and elimination diets for adults as well (Mayo Clin Proc 2007;82:1541). Oral steroids are effective but potentially toxic. Fluticasone propionate 220 mcg/puff bid for 6 weeks provides relief for up to 4 months. Some experts use higher doses, up to 4 puffs bid, after breakfast and supper (Clin Gastroenterol Hepatol 2005;3:299). The drug is swallowed, given without a spacer, and the mouth is rinsed with water after use (Mayo Clin Proc 2003;78:830). A minority of pts improve with PPIs given for what is likely secondary reflux. Dysphagia improves with dilatation but is risky, with long linear tears frequently occurring. Reinspection with endoscopy after the passage of each dilator or use of

a balloon dilator for continued visualization seems prudent. Several sessions of dilatation may be needed to reach an adequate diameter (Am J Gastro 2008;103:2635).

2.5 Congenital Esophageal Stenosis and the Ringed Esophagus

Am J Gastroenterol 2000;95:32

Epidem: Some reputed adult cases of congenital esophageal stenosis are probably misdiagnosed ringed esophagus (see Section 2.4). The incidence is estimated to be 1 per 25 000 live births (Dig Dis Sci 1993;38:369).

Pathophys: Stenosis occurs due to tracheobronchial rings that presumably arise from sequestration of tracheobronchial precursor cells in the esophageal wall (Dig Dis Sci 1993;38:369).

Sx: Dysphagia to solids that usually goes back as far as the pt can remember. Pts usually have had multiple episodes of food impaction and are slow eaters.

Crs: Chronic dysphagia.

Cmplc: Perforation occurs more frequently because the dx goes unrecognized and dilatation to large diameters is improperly attempted.

Diff Dx: See Dysphagia (p 6) and Section 2.4.

X-ray: The proximal esophagus is dilated. In the upper esophagus, there is a long stenotic segment with multiple fine rings visible within it. This appearance has been called "funnel esophagus."

Endoscopy: The proximal esophagus is dilated. In the stenotic segment, numerous cartilagenous rings, which have been described as having a coiled spring appearance, are seen (Dig Dis Sci 1993;38:369).

Rx: Treat esophagitis if present. Dilate with caution to a diameter the pt can live with and emphasize to the pt the need for careful chewing.

2.6 Foreign Bodies

Gastro Endosc 2002;55:802; Gastrointest Endosc 1995;41:33

Comment: This discussion does not cover FBs above the cricopharyngeus. Guidelines for management of very young children may be different than guidelines presented here.

Epidem: Most FB ingestions occur in children from 6 months to 3 yr. In adults, the majority of the FBs are food impactions from esophageal pathology. Ingestions are also associated with psychiatric illness and mental retardation. Prisoners may ingest FBs for secondary gain.

Pathophys: FBs may impact in the esophagus in areas of stricturing and in normal anatomic areas of narrowing or angulation, such as cricopharyngeus, aortic arch, left mainstem bronchus, pylorus, duodenal sweep, ileocecal valve, and anus. Most objects pass spontaneously, but sharp objects create a risk of perforation.

Sx: Most pts will clearly describe the sensation of an FB in the esophagus, though their perception of the exact location may not be correct. A complete obstruction due to an esophageal

FB usually presents as pain and the inability to handle oral secretions. Objects that pass beyond the esophagus are usually asymptomatic unless perforation or obstruction occur. The type of suspected FB (eg, food, pin, toothpick) should be established.

Si: The exam is unhelpful unless perforation occurs, in which case there may be crepitus in the neck or findings of peritonitis.

Crs: About 80-90% of objects pass spontaneously, 10-20% require endoscopy, and less than 1% require surgery (Gastrointest Endosc 1995;41:39).

Cmplc: Perforation, obstruction.

X-ray: Radiopaque objects may be localized with plain films, but many ingested objects are not radiopaque. Contrast studies should be avoided because of the risk of aspiration.

Endoscopy: Endoscopy is indicated in some specific instances for FB removal (see Rx). A variety of instruments (snare, basket, retrieval nets, rat tooth forceps, alligator forceps, overtubes, endoscope hoods) may be required. Rigid endoscopy has a higher complication rate and should be used in the esophagus only if a flexible scope fails (Gastrointest Endosc 1993;39:626).

Rx: The characteristics of the object and its location in the GI tract determine management. **Food boluses** impacted in the esophagus should be removed promptly if there is evidence of distress or inability to handle secretions. If the pt is comfortable, the procedure can be delayed in case the bolus passes spontaneously, but it should be removed within 12-24 hr of ingestion. The bolus is usually removed with a snare or basket through a flexible scope with conscious sedation. An overtube can facilitate multiple passages of the scope and offers airway protection. Some experts blindly but gently push boluses into the stomach and fragment them with a snare, if need be, to promote passage (Gastro Endosc 2001;53:178). Barium studies should be avoided since they make endoscopy difficult. Glucagon can be given, but there are no controlled data to support its use (Emerg Med Clin N Am 1996;14:493). **Blunt objects** such as coins should be removed urgently if they are in the esophagus on plain film. However, if they reach the stomach, they are likely to pass spontaneously and should be managed conservatively (BMJ 1991;302:1321). These objects can be followed with weekly radiographs, and if they do not progress beyond the stomach, endoscopic removal is performed at 4 weeks. **Long objects** such as pens and toothbrushes should be removed since they will have difficulty passing the duodenal sweep. **Sharp, pointed objects** should be removed endoscopically. These dangerous objects often require the use of an overtube, or rubber hood over the endoscope, and in some circumstances endoscopy is done with general anesthesia. The sharp edge should be trailing to minimize the risk of puncture. Dry runs with similar objects can be helpful in selecting an instrument for grasping the object (Gastrointest Endosc 1995;41:39). **Button batteries** are managed differently because of the risk of damage from electric current or leak of alkali (Peds 1992;89:747). Batteries in the esophagus should be removed promptly, usually with a retrieval basket. If the battery is in the stomach, it should be removed only if it is large or if it fails to pass the pylorus within 48 hr. **Narcotic packets** should be left alone while the pt is observed in the hospital and should not be removed endoscopically because of the risk of rupture and fatal overdose. If packets fail to progress on radiographs, or if a toxic screen suggests leakage, they should be removed surgically (Post Grad Med J 1990;66:659).

2.7 Esophageal Cancer

Nejm 2003;349:2241; Ann Oncol 1998;9:951

Epidem: The vast majority of esophageal cancers are either squamous cell or adenocarcinomas. There has been a dramatic rise in the proportion of adenocarcinomas to squamous cancers (33% adenocarcinoma in 1988 to 43% adenocarcinoma in 1993). Incidence varies widely through the world from a low of 4 per 100,000, to a high of 130 per 100,000 in endemic areas of China and Iran (Ann Oncol 1998;9:951; Semin Oncol 1994;21:403). There are a disproportionate number of (1) low-socioeconomic-status pts with this cancer (15% of esophageal cancer versus 10% for all other cancers), and (2) African Americans with this cancer (17% of esophageal cancers versus 8.2% for all other cancers).

Pathophys: The major risk factors for **squamous cell cancer** (see Brit J Surg 1996;83:1174; Semin Oncol 1994;21:403) are (1) smoking (5-fold risk of smoker vs nonsmokers, 10-fold risk for heavy smokers vs nonsmokers), (2) alcohol (20-50 times increased risk for heavy drinkers compared to nondrinkers), (3) nutritional deficiency (in endemic areas of China, Iran, and South Africa, diets are rich in wheat and corn and are low in carotene and vitamins), (4) dietary toxins (nitrosamines in pickled vegetables, barbecued food, and salted foods, and mycotoxins in moldy foods), (5) chronic irritation (from spicy and hot foods, achalasia, lye strictures), and possibly (6) infectious agents (papilloma virus, fungi, bacteria) (GE 1992;103:1336) and environmental factors and pollutants. The major risks for **adenocarcinoma** are (1) Barrett's esophagus, (2) symptomatic GERD (Nejm 1999;340:825), (3) obesity (J Natl Cancer Inst 1998;90:150), (4) alcohol, and (5) the use of LES-relaxing drugs (Ann IM 2000;133:165). There may be **protective** benefits of aspirin and NSAIDs in both histologic types of esophageal cancer (GE 2003;124:47).

Sx: Dysphagia to solids, retrosternal discomfort, and weight loss.

Si: Cachexia, supraclavicular adenopathy.

Crs: The crs is similar for squamous and adenocarcinomas and depends on stage. Five-yr survival for stage I disease is 42% and falls to 3% for stage IV disease. Only 25% of those with stage IV disease will survive a year (Cancer 1996;78:1820).

Tumors are divided into 4 stages based on a TNM system. Stage I tumors are limited to submucosa. Stage IIA tumors are deeper but have no evidence of local nodes. Stage IIB tumors have local nodes. Stage III lesions invade adventitia or local structures and have positive nodes. Stage IV lesions have distant mets.

Cmplc: Esophageal obstruction, tracheoesophageal fistula, blood loss, and malnutrition.

Diff Dx: Usually dx is not difficult. Diagnostic confusion can arise in distinguishing benign from malignant strictures. Cancer needs to be considered if an apparently benign stricture rapidly recurs or is unusually difficult to dilate.

X-ray: Barium swallow generally reveals exophytic mass, nodularity, or stricture, all of which lead to endoscopy for dx. CT scanning of chest and abdomen is useful for detecting distant metastatic disease but has an overall staging accuracy of only 67%. MRI is sensitive but not specific (Chest 1998;113:107S). PET scanning is superior to CT scanning in identifying distant disease, and its use may prevent about 20% of pts from having surgery for unresectable disease (Ann Thorac Surg 1997;64:770).

Endoscopy: EGD reveals lesions that range from subtle nodularity to exophytic lesions that ulcerate. Dx is made by bx with at least 6 bx obtained. Cytology may pick up some lesions missed by bx, but a high degree of cytologic expertise is needed. EUS has a staging accuracy of about 80% in experienced hands, but is operator dependent. Overstaging occurs in about 14%, and understaging occurs in up to 28% early on the learning curve and much less so (3%) with experience (Gastrointest Endosc 1996;44:58).

Rx:

- Surgical resection is the rx of choice for pts who are fit for surgical rx and who do not have evidence of distant disease. Lymphadenectomy and esophageal resection offer cure in about 20% of pts. Though cure is the goal for these pts, palliation is usually what is achieved. The choice of the surgical technique is based on location of the tumor and preference of the surgeon (Surg Clin N Am 1997;77:1169). En bloc esophagectomy may improve survival and certainly improves staging (Surg Oncol Clin N Am 1999;8:295). The data for lymphadenectomy involving cervical, mediastinal, and abdominal nodes (called three-field lymphadenectomy in the literature) also suggests improved survival compared with retrospective controls, and further prospective study seems warranted (Ann Oncol 1998;9:951). With esophagectomy, death occurs in 5%, MI in 1%, pulmonary embolus in 1%, arrhythmias in 10%, anastamotic leak in 7%, and vocal cord paralysis is seen in 4% of pts. High-volume centers have better outcomes (Dis Esophagus 2004;17:310).
- Minimally invasive staging with thoracoscopy, mediastinoscopy, and laparoscopy are available, but their place in preoperative evaluation is not yet clear. However, minimally invasive surgical staging is more accurate than endoscopic US (J Thorac Cardiovasc Surg 1997;114:817).
- Because of the poor outcome with surgery alone or with radiation and chemotherapy given postoperatively, attention has turned to multimodality rx with preoperative chemotherapy and/or radiation rx (Surg Clin N Am 2002;82:729). Unfortunately, in pts with squamous carcinoma (despite more than 30 randomized controlled prospective trials with conflicting results), there is no increased resectability rate, and survival rate and postoperative mortality rate appear higher (Brit J Surg 1999;86:727). The results are not convincingly different for adenocarcinoma (Gastroenterol Clin North Am 1997;26:635) despite some encouraging individual trials (Nejm 1996;335:462). A recent meta-analysis suggests a possible survival advantage with preoperative chemotherapy, but the data are inconclusive (Cochrane Database Syst Rev 2006;3:CD001556). A strong argument can be made to offer multimodality rx, if at all possible, in the setting of a clinical trial.
- In pts who are treated nonsurgically, combined chemotherapy and radiation appears more effective than radiation alone (Cochrane Database Syst Rev 2006;CD002092).
- Endoscopic palliation of dysphagia can be achieved with a variety of modalities: (1) esophageal dilatation, (2) self-expanding metal stents (SEMS), (3) Nd:YAG laser, (4) photodynamic therapy (application of laser light after administration of a photosensitizing material to create tumor-destroying oxygen free radicals), (5) BICAP tumor probe (which destroys tissue by direct heat), and (6) injection of ethanol or polidocanol to ablate tumor. Dilatation is inexpensive and technically easy, but a short duration of relief and a perforation rate of up to 5% limits its utility (Surg Clin N Am 1997;77:1197). SEMS have replaced plastic stents, which have unacceptable complication rates and limited efficacy. There are many types of stents, and technical evolutions are seemingly continuous.

Immediate complications of stent placement are chest pain in 6%, bleeding in 0.2%, perforation in 1%, and stent migration in 2%. Late complications are expected in 10-30% and include bleeding (which can be fatal), stent migration, tumor ingrowth, and food impaction. Despite their limitations, SEMS have largely displaced the other techniques listed previously for palliation of dysphagia. They are also the rx of choice for tracheoesophageal fistula (Chest Surg Clin N Am 1997;7:623).

2.8 Caustic Ingestion

J Clin Gastro 2003;37:119; Gastroenterol Clin North Am 1991;20:847; Spechler S, Taylor M. Caustic ingestions. In: Taylor M, ed. Gastrointestinal Emergencies. Baltimore: Williams Wilkins, 1997:19

Cause: Intentional ingestion of caustic substance by adults in suicide attempts and accidental ingestion of household caustics in children. Lye (a mixture of sodium and potassium hydroxide) is the most common ingestion. More dilute forms of lye, such as liquid drain cleaners that contain <10% lye, have replaced solid lye and highly concentrated liquid solutions, but are still strong enough to cause visceral perforation. Crystalline drain cleaners are 50% lye, but pain usually limits their ingestion. Most household ammonia solutions, household bleach, and detergents are weaker caustics, and catastrophic injury is uncommon. Strong acids may be encountered in swimming pool cleaners, toilet bowl cleaners, and batteries, but their accidental ingestion is much less common in the Western Hemisphere.

Epidem: Bimodal peak of incidence with children under 5 yr of age and adults 20-30 yr, with about 80% of cases in children. About 5000-15,000 per yr in the U.S. (Am J Gastroenterol 1992;87:1).

Pathophys: Damage from lye has been experimentally studied and is divided into 3 phases. Initial injury occurs within seconds by a process of liquefactive necrosis accompanied over the next few days by vascular thrombosis and inflammation. Over the next 10 days, the necrosis sloughs and granulation tissue develops. Over the following months, reepithelialization occurs and strictures may develop. Ingestion of lye in concentrations of >25% is associated with gastric injury 95% of the time, but these concentrations are not readily available in the U.S. (Am J Gastroenterol 1992;87:337).

Acid produces coagulation necrosis, which may limit its depth of penetration. The esophagus is more resistant to acid injury than to alkali injury, but significant injury may occur to the esophagus and severe gastric injury may occur.

Sx: Caustic ingestion causes burning mouth pain. Cough, wheezing, and stridor are seen if aspiration occurs. In large ingestions, vomiting, chest pain, dysphagia, drooling, and epigastric pain may be seen.

Si: Oral burns (lack of oral burn does not rule out esophageal injury), wheezing, findings of peritonitis in advanced cases.

Crs: The acute phase is the initial 5 days, with si and sx described earlier. There is a latent phase of 10 days when pt may do deceptively well. Scarring occurs in third phase with 10-30% of pts developing strictures if esophageal injury occurred and 80% of those becoming symptomatic within 8 weeks. During this phase strictures may progress rapidly, and prompt evaluation and

rx are needed (Gastroenterol Clin North Am 1991;20:847). Gastric outlet obstruction can occur as a late finding 4-6 weeks or even years later. With Grade 2b injuries (see Endoscopy), strictures develop in 70%. Grade 3a injuries are associated with complications requiring surgery in 25%. Grade 3b pts have a 70% incidence of acute complications with a mortality of 65%.

Cmplc: Esophageal or gastric perforation, esophageal stricture. Gastric outlet obstruction occurs as often in acid as in alkali ingestion, with a rate of about 5% in children requiring hospitalization (Pediatr Surg Int 1999;15:88). Squamous cancer of the esophagus is a late complication with a thousand-fold RR of cancer. In a series of 63 pts, the mean latent period was 41 yr (Cancer 1980;45:2655). These pts seem to have a better prognosis, perhaps because the cancer develops in the scar, preventing its dissemination. The ASGE recommends surveillance 15-20 yr after ingestion at intervals of not more than 1-3 yr, with prompt evaluation of sx.

Diff Dx: Usually the distinction between accidental and intentional ingestions is clear. Consider the ingestion of other substances in suicide attempts and consider that the pt may still be suicidal.

Lab: In suicide attempts, toxic screen for other ingested substances is indicated.

X-ray: CXR, abdominal series in suspected perforation or pneumonitis.

Endoscopy: EGD should be performed promptly if the pt is stable and without evidence of perforation or severe hypopharyngeal burns. The most risky period for EGD is 5-15 days after ingestion due to wound softening. The endoscope can be advanced until a circumferential ulceration is seen (J Clin Gastro 2003;37:119). Endoscopic findings are staged as follows:

- Grade 1: erythema, edema consistent with sloughing superficial mucosa
- Grade 2a: friability, hemorrhage, blisters, erosions, shallow ulcers implying extension down to muscularis propria
- Grade 2b: Grade 2 findings that are circumferential
- Grade 3a: brown-black or gray discoloration with deep ulcers, implying possible transmural injury with erosion into adjacent structures
- Grade 3b: severe involvement of 3a findings

Rx: All pts should be brought to the emergency room. Emesis should *not* be induced. The airway should be assessed and endotracheal intubation performed if needed. There is no point to neutralizing alkali or acid in the stomach. If the pt is stable and there is no evidence of perforation clinically, EGD should be performed. Pts without injury may be discharged unless psychiatric or child safety concerns prevent it. Pts with Grade 1 or noncircumferential Grade 2 burns should be watched for 72 hr for evidence of perforation and then discharged with the assurance the strictures are unlikely. Circumferential burns need close follow-up for strictures that may develop and progress rapidly without rx. Steroids have been used to prevent stricture formation but are ineffective (Nejm 1990;323:637). Antibiotics do not appear to prevent strictures and should be used only for specific indications. Orally placed rigid esophageal stents have been used in pts who failed dilatation in the first 8 weeks with 70% success (J Pediatr Surg 1996;31:681). Symptomatic strictures are dilated, but perforation rates are higher and early recurrences are greater than with peptic strictures (Gut 1993;34:1498). Strictures with an esophageal wall thickness of greater than 9 mm by CT are very difficult to keep dilated and require multiple sessions (Gastrointest Endosc 1995;41:196). Surgical interposition may be required and carries significant mortality of 4-15% and high morbidity due to leaks and late stricturing (Pediatr Surg Int 1998;13:336).

2.9 Achalasia

Am J Gastro 1999;94:3406; Jama 1998;280:638

Cause: Unknown.

Epidem: Uncommon disorder with incidence of 0.5-1.2/100 000/yr. Incidence peaks at age 20-40 yr, with a second peak in the 70s. Seen in all races and equally in the sexes.

Pathophys: The defining feature of achalasia is loss of esophageal peristalsis and failure of the LES to relax appropriately. The inhibitory neurons in Auerbach's that mediate LES relaxation are greatly reduced in number perhaps on an autoimmune or infectious basis. This results in unopposed cholinergic stimulation of the LES with inadequate relaxation.

Sx: Dysphagia, usually insidious in onset. Dysphagia is to liquids and solids, but the problems with solids may be more apparent to the pt than problems with liquids. Pts may describe a variety of maneuvers (drinking large volumes, raising arms over heads, jumping, straightening the back) to relieve sx (Jama 1998;280:638). Heartburn may occur due to fermenting, retained food in the esophagus. Chest pain is frequent and may be more prominent in younger pts. Weight loss is usually mild if present. Aspiration is uncommon.

Si: Usually none, but cachexia and pneumonia may be seen.

Crs: Slow, progressive dysphagia.

Cmplc: Squamous cancer of esophagus due to stasis (RR = 16) (Gut 1992;33:155). The NNT for annual surveillance EGD to detect 1 cancer is 406 for men and 2200 for women (Jama 1995;274:1359). Rx may lower risk.

Diff Dx: Pseudoachalasia due to destruction of neurons by cancers mimics achalasia. Other considerations are Chagas disease, nonspecific motility disorders, and esophageal stricture.

Lab: Esophageal manometry is diagnostic when showing low-amplitude, simultaneous contractions and failure of the LES to relax. A variant with high-amplitude, simultaneous contractions called vigorous achalasia can be identified at manometry.

X-ray: Plain films may show esophageal air fluid level. KUB may show absence of gastric air bubble. Barium swallow shows dilated esophagus, delayed passage of barium, and a bird beak of barium leading to the closed LES.

Endoscopy: May show retained food or esophagitis due to fermentation of retained debris. The sudden give of the endoscope as it pushes through the closed LES can also provide a clue, but often EGD is unrevealing.

Rx: The goal of rx is to reduce LES pressure and to allow gravity to empty the esophagus, because contractions are still not effective. There are 4 options for rx:

- Nifedipine and nitrates are 50-80% effective in relieving sx by lowering LES pressure. However, side effects limit their use, and long-term results are such that their use is reserved for those pts who are not candidates for more invasive rx (J Clin Gastroenterol 1999;28:202).
- Forceful disruption of the LES with a single session of pneumatic dilatation is effective for about 70% of pts over a 5-yr follow-up (Jama 1998;280:638). Additional dilatations improve that figure to about 80-90%. It is possible that there is lower morbidity in beginning with

a 30-mm size and increasing to 35 mm and then 40 mm for dilatations that fail at smaller diameters (Am J Gastroenterol 1993;88:34). The duration of inflation is not critical; a 6-second inflation is as effective as a 60-second inflation (Am J Gastroenterol 1998;93:1064). The perforation rate should be in the range of 3%, though this figure varies widely in published studies. Gastrografin swallow is sensitive for the detection of perforation. Pts treated surgically for a promptly recognized perforation undergo repair of the perforation and completion of the myotomy with a morbidity and outcome similar to morbidity and outcome of elective thoracotomy and Heller myotomy (Dig Dis Sci 1993;38:1409).

- Intrasphincteric injection of botulinum toxin results in inhibition of acetylcholine release from nerve endings. It is effective short-term rx for achalasia. About 60-70% of injected pts have a good response for 6 months (Gut 1997;41:87; Nejm 1995;332:774). However, the response rate falls to 30% at 1 yr (Gut 1999;44:231). This rx is an option for high-risk pts.
- Several surgical approaches to myotomy are available. The Heller myotomy, done through an abdominal incision, has been the most widely performed. Relief of dysphagia can be expected in more than 90% of pts, although reflux sx reduce the proportion of pts with an excellent result to 60% at 15-20 yr (Ann Thorac Surg 1994;58:1343). Transthoracic and thoracoscopic approaches are no longer commonly used (Surg Clin N Am 2002;82:763). Currently, laparoscopic Heller myotomy with loose fundoplication is the favored surgical approach with excellent relief of dysphagia (90%) and a hospital stay of only 3-5 days (Am J Surg 1997;174:709; Ann Surg 1997;225:655). Surgery should be considered for (1) very young pts, given the likelihood of repeated dilatations over a lifetime; (2) failures of nonsurgical rx; (3) pts at high risk for dilatation due to tortuous esophagus, prior GE junction surgery, or esophageal diverticula; and (4) pts who prefer a surgical approach given the better chance of long-term sx relief (J Clin Gastroenterol 1999;28:202).

2.10 Noncardiac Chest Pain

J Clin Gastro 2002;34:6; Am J Gastro 2001;96:958

Epidem: About 30% of pts who undergo cardiac catheterization have exams negative for coronary disease. This implies an annual U.S. incidence of noncardiac chest pain of about 180,000 cases (GE 1997;112:309).

Pathophys: Some of the pts with pain of esophageal origin will have structural esophageal disease, with perhaps 10-15% having esophagitis endoscopically (Am J Gastroenterol 1999;94:2310) and another 20-30% having nonerosive, occult GERD. The cause of pain for the remaining 60-70% is functional. Though many manometric abnormalities have been described in pts with noncardiac chest pain, no manometric pattern correlates well with sx (J Clin Gastroenterol 1999;28:189). Esophageal sensory function and CNS abnormalities are seen in pts with functional pain. These pts have lower pain thresholds with balloon distension (Ann Intern Med 1996;124:950) and a lower CNS threshold for perception of esophageal stimuli (Gut 1992;33:298).

Sx: Dysphagia, gross regurgitation, heartburn, and pain after meals may suggest GERD. Esophageal pain comes in frequent, long episodes usually without associated dyspnea, lightheadedness, palpitations, or diaphoresis. Pain radiation to the back is not uncommon. Be very cautious about implicating the esophagus in pain that radiates to the jaw, neck, or arms. Infrequent

attacks of spontaneous pain are more suggestive of cardiac disease than esophageal disease (J Clin Gastroenterol 1985;7:477).

Si: Unhelpful, except to assess pt for signs of cardiac disease or musculoskeletal causes of pain.

Crs: Follow-up at a mean of 21 months shows that pts continue to have pain, though those with a specific esophageal dx are less likely to require physician visits or be disabled by the pain (Am J Gastroenterol 1987;82:215). Pts with chest pain and a normal angiogram have 96% 7-yr survival (J Am Coll Cardiol 1986;7:479).

Cmplc: Repeated medical evaluations, including repeat cardiac catheterization and emergency room visits. Disability secondary to pain and fear that pain is cardiac in origin.

Diff Dx: The diff dx is broad, and most of these other disorders are readily excluded prior to GI evaluation. Angina is the most important differential point. Esophageal chest pain from GERD and angina frequently coexist. Chest wall pain may occur from costochondritis, rib fracture, arthritis, fibromyalgia, or zoster (prior to rash). Pulmonary causes include pulmonary embolus, pneumonia, and pneumothorax. Biliary pain, pancreatitis, and peptic disease usually are not sources of confusion. Psychiatric causes include anxiety disorders, panic attacks, depression, somatoform disorders, and fixed delusions. Psychiatric disorders are more common in pts with chest pain associated with motility disorders (Nejm 1983;309:1337).

Lab: A 24-hr pH probe is the most useful test for differentiating reflux-associated pain from other causes of pain. A 24-hr pH probe is more helpful than manometry, acid perfusion (Bernstein test), or edrophonium challenge test (trying to reproduce pain with a cholinesterase inhibitor that stimulates motility) (Am J Med 1991;90:576). The edrophonium test is considered positive when a pt's sx of chest pain is reproduced. This is a relatively specific test in that it rarely provokes pain in healthy controls or in those with IBS (Dig Dis 1998;16:198). A strong argument can be made to use an empiric trial of a PPI just as would be done in other cases of clinically suspected reflux (GE 1998;115:42). This strategy is likely to reduce cost and to result in fewer diagnostic tests. Manometry is not routinely indicated in suspected esophageal chest pain (GE 1994;107:1865). It should be considered for pts with chest pain and dysphagia with a negative endoscopy (to identify those with true esophageal spasm or achalasia, for which there is specific rx). It may be of value in selected pts by establishing the presence of a nonspecific motility disorder. Pts who receive a specific dx are less likely to be disabled by their pain and less likely to have repeated physician evaluations. A 24-hr ambulatory esophageal manometry is technically possible but of uncertain value (Dig Dis 1995;13:145).

X-ray: Selective use of CXR, rib films.

Endoscopy: EGD reveals esophagitis in 10-15% of pts.

Rx: Therapy for GERD should be tried as outlined and continued if appropriate. Pts with initial responses and later relapses should be evaluated with pH probe rather than be committed to long-term GERD rx, because there might be an initial placebo response to any intervention. Trazodone 100-150 mg daily (GE 1987;92:1027) or imipramine 50 mg po qhs (Nejm 1994;330:1411) may be effective treatment for those with visceral hypersensitivity. Oral nifedipine reduces contraction amplitude in pts with high-amplitude peristaltic contractions (the nutcracker esophagus), but it is no more effective than placebo at relieving sx (GE 1987;93:21). Oral diltiazem decreased pain in a small study (Am J Gastroenterol 1991;86:272).

Botulinum toxin injection has been associated with short-term benefit (Dig Dis Sci 1996;41:2025). Surgery to treat spastic conditions of the esophagus has been performed but seems unwarranted (Int Surg 1997;82:113).

2.11 Diffuse Esophageal Spasm and Related Spastic Disorders

Lancet 2001;358:823; Gastroenterologist 1997;5:112

There are 4 named disorders that are usually discovered in the evaluation of pts with chest pain or dysphagia. The clinical relevance of these diseases defined by manometry is unclear. Chest pain syndromes associated with these abnormalities can be treated as outlined in section 2.10. These disorders are:

- *Diffuse esophageal spasm* (DES), a disorder dx in <2% of pts referred for manometry. It is defined by the presence of simultaneous (and therefore nonperistaltic) contractions in the body of the esophagus. This is the spastic disorder most likely to cause severe sx. Some pts with DES go on to develop achalasia.
- *Nutcracker esophagus*, defined manometrically as the presence of peristaltic contractions of high amplitude (>180 mm Hg).
- *Hypertensive lower esophageal sphincter*, defined as a resting LES pressure >45 mm Hg with normal LES relaxation and normal peristalsis.
- *Nonspecific esophageal motility disorder*, defined by nontransmitted contractions, low-amplitude contractions, prolonged contractions, triple-peaked contractions, or nonperistaltic contractions (Am J Gastroenterol 1992;87:825).

2.12 Mallory-Weiss Tears

Am J Gastroenterol 1997;92:805; Am J Gastroenterol 1993;88:2056

Epidem: Mallory-Weiss tears represent about 5% of cases of UGI bleeding (Am J Gastroenterol 1993;88:2056).

Pathophys: These lesions are linear tears in the mucosa of the GE junction. They are often seen in association with vomiting, regurgitation, during endoscopy, during PEG lavage for colonoscopy (Am J Gastroenterol 1993;88:1292), or with other causes of increased abdominal pressure, but at times these tears occur without obvious cause. They were first described at autopsy in alcoholics with fatal hematemesis after an alcoholic debauch. Many tears are of little clinical consequence and go undiagnosed. However, massive bleeding can occur, especially in those with coagulopathies or portal HTN (Hepatology 1990;11:879).

Sx: Hematemesis, melena, or hematochezia, often after a vomiting illness.

Si: Volume depletion.

Crs: Rebleeding, usually within 24 hr, was seen in 7% of pts in a large series (Am J Gastroenterol 1997;92:805). Pts with coagulopathies, hematochezia, or hemodynamic instability at presentation were most likely to rebleed. Mortality has been reported at up to 12%, in association with multisystem organ failure (Am J Gastroenterol 1993;88:2056).

Endoscopy: Endoscopy excludes other causes of bleeding and helps to assess risk. Clean-based tears and tears with adherent clot are at low risk for rebleeding. Pts with bleeding at index EGD are most likely to rebleed (Am J Gastroenterol 1997;92:805).

Rx: General supportive measures for UGI bleeding are begun (p 25). If there is active bleeding, endoscopic rx is appropriate, but there are limited data regarding the best technique. Endoscopic band ligation and endoscopic placement of hemoclips are both highly effective methods (World J Gastroenterol 2008;14:2080). Multipolar cautery reduced the need for transfusion and surgery in a small RCT (Nejm 1987;316:1613). Sclerotherapy was effective in 13 pts with active bleeding from a tear, but was associated with a perforation (Am J Gastroenterol 1994;89:2147). Epinephrine injection and heater probe have been effective in small series (Am J Gastroenterol 1997;92:805).

2.13 Boerhaave's Syndrome

Post Grad Med J 1997;73:265; ANZ J Surg 2003;73:1008

This rare condition is spontaneous rupture of the esophagus. It is named after the physician who described a case of esophageal rupture that killed the Grand Admiral of Holland 18 hr after self-induced vomiting. The classic presentation is vomiting, severe lower chest pain, and sc emphysema. However, atypical presentations are the rule, and the dx is frequently missed. Mortality climbs sharply if the dx is delayed more than 12 hr. The dx can usually be made with CXR, limited UGI series (starting with water-soluble contrast to try to keep large volumes of barium out of the chest), or CT scan in some cases. Treatment is surgical.

2.14 Zenker's (Hypopharyngeal) Diverticulum

Laryngoscope 1997;107:1436; Ann Otol Rhinol Laryngol 2003;112:583

Epidem: 50% of cases in 7th and 8th decades of life. More common in men.

Pathophys: The diverticulum forms in the Killian triangle, which is an area of scant muscular fibers between the horizontal fibers of the cricopharyngeal muscle and the oblique fibers of the inferior constrictor muscle in the dorsal wall of the most caudal part of the hypopharynx (Ann Otol Rhinol Laryngol 1994;103:178). The diverticulum forms in this weakness as a result of resistance to outflow from the pharynx (Gastrointest Endosc 1999;49:126).

Sx: Dysphagia (80%), regurgitation (50%), aspiration, coughing, throat clearing (30%), pneumonia (14%), hoarseness (5%), weight loss, halitosis, neck pain. Pts may describe coughing up food that is several hours old. GERD is frequently associated.

Si: A palpable mass may be felt in the neck.

Crs: Continued slow enlargement of the diverticulum with progressive sx.

Cmplc: Diverticular perforation may occur due to endoscopy, NG tube, or foreign bodies. Squamous cancer was observed in 0.5% in a series of 1249 pts (Hepatogastro 1992;39:109).

Diff Dx: Other causes of dysphagia need to be considered, but barium swallow eliminates diagnostic doubt.

X-ray: Barium swallow most often reveals the diverticulum posteriorly and to the left of the esophagus.

Endoscopy: Generally not indicated and is risky due to possibility of perforation.

Rx: Therapy is surgical or endoscopic, and the choice largely is determined by local expertise. Diverticulectomy with cricopharyngeal myotomy has been the standard rx in the U.S. This can be complicated by pharyngocutaneous fistula (3-13%), wound infection (3% or higher), mediastinitis, stenosis, bleeding, or death. Several procedures do not violate the esophageal mucosa and lead to fewer infections and more rapid recovery. These include diverticulopexy (where the tic is suspended by suturing it to the prevertebral fascia), imbrication (in which the tic is dissected free and inverted into the lumen of the esophagus), and myotomy alone (Laryngoscope 1997;107:1436). In the endoscopic method, the muscular bar that separates esophageal lumen from diverticulum is divided. In experienced hands, excellent pt satisfaction and low morbidity are seen (Ann Otol Rhinol Laryngol 1994;103:178). A technique with flexible endoscopy, conscious sedation, and a needle-knife papillotome has been described (Gastrointest Endosc 1999;49:93), but the safety data are lacking (Gastrointest Endosc 1999;49:126).

2.15 Epiphrenic Diverticulum

World J Surg 1999;23:147; Ann Thorac Surg 1993;55:1109

Epiphrenic diverticula are found in the distal third of the esophagus and are associated with motility disorders (Ann Thorac Surg 1993;55:1109) or trauma (Am J Surg 1996;62:973). They present with regurgitation or dysphagia. They can be complicated by aspiration, squamous cancer from stasis, or *Candida* infection. Surgery can be considered for pts with severe sx, but mortality is significant at 9% in some hands (Ann Thorac Surg 1993;55:1109), though not in others (World J Surg 1999;23:147). Minimally invasive surgical treatments are being developed (Am Surg 2003;69:465).

2.16 Rumination Syndrome

J Postgrad Med 2007;53:203; Peds 2003;111:158; Mayo Clin Proc 1997;72:646; GE 1995;108:1024

Epidem: This disorder is found in 6-10% of people who are institutionalized with mental retardation. It also occurs in pts of normal intelligence, usually young adults, with a F:M ratio of 3:1.

Pathophys: The mechanism by which pts ruminate is unclear since retrograde contraction does not occur in the human esophagus. Not all episodes are associated with increased intra-abdominal pressure. It is thought that rumination in adults of normal intelligence is a learned adaptation of the belch reflex, in which there is prolonged LES relaxation (GE 1995;108:1024).

Sx: Repetitive regurgitation of partially undigested food, usually within 10 min of eating and lasting 1-2 hr postprandially. Weight loss is common, presumably because of spitting out the regurgitated boluses. Bulimia nervosa is present in a subgroup who spit out the refluxed boluses to control weight.

Crs: Over 3-yr follow-up, most pts remain symptomatic. The severity of sx decreases with time.

Diff Dx: GERD, gastroparesis, vomiting, obstruction, or pseudo-obstruction. The early onset after eating is a clue to rumination rather than gastroparesis, in which vomiting is delayed.

Lab: If performed, gastroduodenal manometry can show simultaneous spikes in pressure at all recording levels (called R waves) as artifact of a sudden increase in intra-abdominal pressure.

X-ray: UGI series, if done to exclude other causes, is normal. Gastric emptying scan may be needed to exclude gastroparesis.

Rx: Education, reassurance, or multidisciplinary rx as an eating disorder in adults of normal intelligence. Biofeedback has been used (J Clin Gastroenterol 1986;8:115). Behavior modification techniques have been used in the mentally retarded.

2.17 Candida Esophagitis

Curr Treat Options Gastroenterol 2003;6:55; GE 1994;106:509

Cause: *Candida albicans*, less commonly other *Candida* species.

Epidem: Most often a disease of the acutely or chronically immunocompromised pt; much less common in the population at large.

Pathophys: Defects in lymphocyte function (HIV pts), defects in granulocyte function (chemotherapy pts), altered microbial flora (such as after antibiotics), and structural (diverticula, strictures) or motility abnormalities (scleroderma) of the esophagus predispose to colonization followed by infection (GE 1994;106:509).

Sx: Dysphagia or odynophagia (see p 6) are the presenting sx in 60-80% of pts.

Si: Oral thrush may be present in one-third, but the presence of thrush does not guarantee *Candida* in the esophagus and the absence of oral lesions does not rule it out.

Crs: Usually responds to rx but may become chronic or recurrent in the immunocompromised.

Cmplc: Esophageal stricture, disseminated candidiasis, esophageal perforation.

Diff Dx: See Dysphagia and Odynophagia (p 6).

Lab: Budding yeast, hyphae, and pseudohyphae are seen on histology, cytology, or KOH prep.

Endoscopy: Candida is suspected when discrete raised whitish lesions are seen. In mild cases, the lesions are small and discrete, but they increase in size and ultimately coalesce and ulcerate in more severe cases. The lesions should be brushed as well as biopsied, since bx alone has a substantial miss rate (Am J Clin Path 1995;103:295).

Rx: (Clin Infect Dis 2004;38:161) Esophageal candida is treated systemically rather than topically. Empiric rx is reasonable in circumstances where the dx seems very probable. Fluconazole (200 mg po to load followed by 100 mg po qd) or itraconazole solution (200 mg po qd) are first-line choices. Therapy is continued 14-21 days depending on rapidity of response. Fluconazole resistance is most likely in severely immunosuppressed pts and in pts who have long prior exposure to azole rx (J Infect Dis 1996;173:219). Fluconazole failures can be treated with itraconazole (dose above), voriconazole (200 mg po bid), or caspofungin (50 mg iv qd). IV amphotericin B deoxycholate (0.3-0.7 mg/kg qd) is used in refractory disease. Esophagectomy has been described for transmural necrosis with perforation (Ann Thorac Surg 1999;67:231).

2.18 Herpes Simplex Esophagitis

Curr Treat Options Gastroenterol 2003;6:55; GE 1994;106:509

Cause: Herpes simplex virus (HSV).

Epidem: Seen sporadically in healthy hosts, HSV esophagitis is largely a disease of the immunocompromised pt. Associated conditions include HIV infection, hematologic malignancy, transplantation, chronic steroid use, and diabetes (Am J Gastroenterol 1986;81:246). Orogenital sexual transmission has been reported (Gastrointest Endosc 1999;50:845).

Pathophys: Primary HSV infection often occurs in childhood and is followed by a latent period of HSV infection of nerve ganglion cells. Reactivation is probably the dominant mechanism.

Sx: Classically, pts present with sudden onset of severely painful swallowing associated with retrosternal burning chest pain. GI bleeding, gross or occult, may also be a presenting sx (Am J Gastroenterol 1986;81:246). However, up to half of pts have neither odynophagia nor chest pain (Gastrointest Endosc 1991;37:600). Unexplained nausea and vomiting is a common presentation of HSV in bone marrow transplant pts (Transplantation 1986;42:602).

Si: Oral HSV lesion in approximately 30% of pts.

Crs: Self-limited infection with several days of sx in healthy host; may be prolonged or recurrent in immunocompromised pt.

Cmplc: Esophageal hemorrhage, herpes pneumonia, disseminated infection, tracheoesophageal fistula, and esophageal perforation.

Diff Dx: See Dysphagia and Odynophagia (p 6).

Lab: Viral culture from brushings and bx of ulcer edges. Histology shows multinucleated giant cells, intranuclear inclusions. Immunochemical staining is of value.

Endoscopy: 1- to 3-mm vesicles are the earliest lesion and are rarely seen. These develop into sharply demarcated ulcers with raised yellow edges. The ulcerations later coalesce and can develop inflammatory pseudomembranes. In a minority of cases, only inflammatory changes without discrete ulcers are seen (Gastrointest Endosc 1991;37:600).

Rx: Acyclovir 200-400 mg orally 5 times daily × 2-3 weeks. IV acyclovir (250 mg/m^2 iv q 8 hr × 7-14 days) in moderate to severe cases or if pt is unable to take po. Foscarnet or famciclovir may be needed in pts with acyclovir resistance (Curr Treat Options Gastroenterol 2003;6:55). Small doses of 2% lidocaine provide sx relief.

2.19 Cytomegalovirus Esophagitis

Curr Treat Options Gastroenterol 2003;6:55; GE 1994;106:509

Cause: Cytomegalovirus (CMV).

Epidem: Peak ages of primary infection are preschool age and young adulthood.

Pathophys: CMV is typically acquired perinatally, in infancy, or through sexual contacts in adulthood. Primary infections are asymptomatic or present as a mild mononucleosis-type illness in adults without prominent GI effects. After primary infection, the virus enters a latent phase.

Most symptomatic disease is reactivation that is seen in immunocompromised hosts (Ann IM 1993;119:924).

Sx: Because CMV is systemic, sx of nausea, vomiting, diarrhea, weight loss, and fever are common. This distinguishes CMV from other viral causes of esophagitis. Odynophagia occurs in 60% of pts (GE 1994;106:509).

Si: Fever.

Crs: Self-limited in healthy hosts but can be chronic/relapsing in immunocompromised pts.

Cmplc: Stricture has been described (J Clin Gastroenterol 1991;13:678).

Diff Dx: See Dysphagia and Odynophagia (p 6).

Lab: Culture of bx of ulcer base is most sensitive. Histology shows large cells in subepithelial lining with intranuclear and cytoplasmic inclusions (the latter specific to CMV).

X-ray: Barium swallow is nonspecific; may be normal or show ulcerations or large flat ulcers several centimeters long.

Endoscopy: Early lesions are discrete ulcerations with raised borders. These progress to long, generally shallow ulcers. CMV infects the fibroblasts and endothelium, not squamous mucosa, so bx should be in base of ulcer.

Rx: Ganciclovir and foscarnet are the 2 equally effective drugs that inhibit CMV DNA polymerase. A randomized trial in HIV-infected pts of foscarnet (90 mg/kg iv bid) vs ganciclovir (5 mg/kg bid) (diluted in 750-1000 mL NS to reduce risk of renal toxicity) for 21 days has shown symptomatic response in about 80% of pts and endoscopic improvement in 70% of pts. Ganciclovir-resistant strains can often be treated with foscarnet (Am J Gastroenterol 1998;93:317).

2.20 Esophageal Manifestations of HIV Infection

Compr Ther 2000;26:163

Cause: The most common causes of dysphagia in HIV pts are: (1) *Candida*, (2) cytomegalovirus, (3) idiopathic esophageal ulcer, and (4) *Herpes simplex* virus. GERD is uncommon in these pts.

Pathophys: Opportunistic infection generally begins when CD4 counts drop below 100/μL. The cause of IEU is unknown (Ann Intern Med 1995;123:143).

Sx: Dysphagia to solids more than liquids. Odynophagia suggests an esophageal ulcer. Nausea, vomiting, and systemic sx suggest CMV.

Si: Oral thrush is a helpful clue, but many pts may have more than 1 infection.

Crs: Prior to effective antiretroviral rx, relapses of candida were typical within 3 months (GE 1994;107:744). CMV esophagitis usually does well with rx (Am J Med 1995;98:169).

Diff Dx: See Cause. The broader differential of dysphagia should be considered if CD4 counts are >200/μL (see Dysphagia and Odynophagia, p 6).

Lab: CD4 count.

Endoscopy: May show findings of candida, CMV, herpes, or IEU. Culture and histology should be obtained as described in earlier sections. IEU shows well-circumscribed ulcers similar to CMV.

Rx: Empiric fluconazole (200 mg po loading dose followed by 100 mg qd × 10 days) is a reasonable first step. In pts who do not respond, EGD is done to make a specific dx. CMV is treated with ganciclovir or foscarnet (J Infect Dis 1995;172:622), HSV with acyclovir, IEU with prednisone (Am J Med 1992;93:131), or thalidomide (AIDS Res Hum Retroviruses 1997;13:301).

2.21 Esophageal Leiomyoma

Chest Surg Clin N Am 1994;4:769

Cause: Esophageal leiomyoma is the most common benign tumor of the esophagus, but its frequency is only 1% of the frequency of esophageal malignancy. It is a smooth muscle tumor usually found as a submucosal mass in distal esophagus. It is usually asymptomatic but can cause dysphagia. Barium swallow shows a crescent-shaped filling defect that usually does not obstruct the lumen and that on EUS is a well-circumscribed, hypoechoic mass with fine internal echoes arising in muscularis propria (Gastrointest Endosc Clin N Am 1994;4:791). Surgery is considered when the pt is symptomatic or when malignancy is suspected. Enucleation is the safest approach for most lesions and can be done by a thoracoscopic approach (Surg Endosc 1997;11:280).

2.22 Esophageal Papilloma

Am J Gastroenterol 1994;89:245; Am J Surg Pathol 1993;17:803

This benign squamous epithelial tumor is typically found incidentally at EGD. It is usually <1.0 cm, and malignant degeneration is a rarity. It may form in response to mucosal irritation, but HPV is found by PCR in more than half the cases. It can be removed endoscopically, though it is not clear that this is necessary.

2.23 Esophageal Intramural Pseudodiverticulosis

J Clin Gastro 2001;33:378; Thorax 1985;40:849

This rare disorder is defined by the presence of numerous small diverticula (dilated mucous glands) contained within the wall of the esophagus. Barium swallow shows many 1- to 4-mm, flask-shaped (ie, narrow-necked) sacs projecting at right angles to the esophagus. There may be associated motor disorders, candidiasis, or esophagitis, and pts may present with dysphagia or, rarely, bleeding.

2.24 Esophageal Inlet Patch

Am J Gastro 2004;99:543

An inlet patch is a small area of heterotopic gastric mucosa in the cervical esophagus. It is thought to be congenital and is usually asymptomatic. It is a common finding (prevalence <1%, often missed at EGD). Some pts develop dysphagia, hoarseness, cough, or strictures from acid produced in the patch. Malignant transformation is very rare.

Chapter 3

Stomach and Duodenum

3.1 Gastritis

Terminology for gastritis is difficult to follow and in its current state is of little clinical value. No satisfactory system that correlates endoscopic appearance, histologic findings, and clinical sx exists. What the endoscopist calls gastritis often bears no relationship to what the pathologist calls gastritis, which in turn often bears no relationship to the pt's clinical complaint. More than 80% of cases of histologic gastritis are caused by Hp (Endoscopy 1991;23:289). Other causes include autoimmune gastritis, drugs, allergy, Crohn's, sarcoid, vasculitis, and radiation, as well as other bacteria, viruses, or fungi. The Sydney system is currently the most widely used classification system for histologic gastritis. It was developed by European pathologists. It separates gastritis into 3 categories: (1) nonatrophic, (2) atrophic, and (3) special (Am J Surg Pathol 1996;20:1161). A second system that is frequently used in the literature classifies gastritis as: (1) type A (atrophic gastritis of the body, often autoimmune associated with pernicious anemia), (2) type B (diffuse antral gastritis usually associated with Hp), (3) type AB (atrophic gastritis involving body and antrum and a known risk for gastric cancer), and (4) type C (chemical gastritis). The term gastritis should probably be considered only a histologic dx given the lack of correlation between endoscopy, histology, and the pt's sx (Gut 1994;35:1172).

3.2 *Helicobacter Pylori*

Am J Gastro 2007;102:1808; Nejm 2002;347:1175; Jama 1995;274:1064

Cause: *Helicobacter pylori* (Hp). Humans are the major reservoir of Hp, though human isolates can infect cats and cause gastritis (Helicobacter 1998;3:225). Fecal–oral transmission has been hypothesized but is difficult to prove (Am J Med 1996;100:12S). Hp has been recovered from stool (BMJ 1997;315:1489) and from drinking water (GE 1996;110:1031). Oral transmission from stomach contents seems plausible. Oral–oral transmission from a mouth reservoir in adults is not easy to demonstrate. Dentists (at risk for oral exposures) do not have an increased prevalence (Scand J Infect Dis 1995;27:149; Am J Gastro 1992;87:1728), but endoscopists do (presumably from infected endoscopes, pH probes, etc) (Am J Gastro 1994;89:1987) and nurses do (at risk for both oral and fecal exposure) (Arch IM 1993;153:708).

Epidem: Hp is found worldwide, but prevalence varies widely and is greatest in developing countries. Risk factors for infection include crowded or unsanitary conditions. In developing countries, the infection is probably acquired in childhood, and childhood prevalence is very high. In developed countries such as the U.S., the prevalence is <20% in those under age 50 yr, but rises abruptly after that. This suggests that childhood acquisition was likely in those infected prior to 1950 and that since 1950, the infection has been slowly acquired through life (Jama 1995;274:1064). In the U.S., the prevalence is greater in blacks and in those with less education. However, there is a large geographic variation that has not been well explained by socioeconomic status alone (Am J Med 1996;100:12S). Smoking has little, if any, effect on prevalence. A dose-dependent, protective effect of alcohol has been observed. Drinking coffee is associated with a greater prevalence (BMJ 1997;315:1489).

Pathophys: Hp survives in the acidic gastric environment by metabolizing urea into ammonia. This creates an alkaline microenvironment. The bug attaches to the surface mucus-secreting cells and lives in the mucus layer, thereby escaping normal clearance by the immune system (Jama 1995;274:1064). The organism produces toxins that damage the mucosa and induce the inflammatory mediators that cause the gastritis. More virulent strains secrete vacuolating cytotoxin A (vacA), a cytotoxin that causes vacuolization of gastric epithelium. Some of the same virulent strains (about 60% of the total) possess the cytotoxin-associated gene A (cagA) that is associated with more severe inflammation and risk of subsequent development of ulcer, gastric cancer, and atrophic gastritis (Nejm 1996;334:1018).

Sx: Acute infection (rarely diagnosed) causes dyspepsia or is asymptomatic. Chronic sx arise from complications of Hp infection. These complications are DU, GU, MALToma, gastric cancer, and possibly nonulcer dyspepsia.

Crs: Acute infection (documented by investigators intentionally infecting themselves! [Am J Gastroenterol 1987;82:192]) causes a dyspepsia-like illness, followed by achlorhydria, and a histologic gastritis with neutrophils. A period of 10-15 yr of chronic active gastritis follows, during which there is inflammation, but the stomach remains acidic. At the end stages, achlorhydria and atrophic gastritis develop. Of those infected, DU occurs in <1% per yr. Only 20% of pts will ultimately develop a clinical consequence of infection (Lancet 1997;349:1020).

Cmplc: There have been 4 convincingly demonstrated consequences of Hp infection:

- *Duodenal ulcer:* The most convincing evidence for the role of Hp as a cause of DU is the marked reduction in ulcer recurrence following eradication of Hp with antibiotics (eg, Lancet 1994;343:508; Nejm 1993;328:308). Until that evidence was available, causality was difficult to establish because of the lack of an animal model and because of the high prevalence of Hp compared to DU. It was also difficult initially to establish why an infection that is predominantly in the antrum causes DU (Jama 1994;272:65). However, it is likely that the Hp resides in areas of gastric metaplasia in the duodenum and induces ulceration by the inflammation induced by Hp cytotoxins. Acid hypersecretion is also likely the result of Hp infection, which reduces the number of somatostatin-producing cells in the antrum. This in turn lessens negative feedback on gastrin secretion, resulting in higher gastrin levels and greater acid output (Jama 1995;274:1064).
- *Gastric ulcer:* The pathogenic role of Hp in GU is not as clear as its role in DU. However, Hp eradication speeds GU healing, reduces ulcer recurrence, and heals ulcers refractory to healing with acid suppression alone (Gut 1994;35:19).

- *Gastric cancer:* Gastric cancer is more common in pts infected with Hp. Data from case control studies nested within prospective cohorts suggest a RR = 5.9 for noncardia gastric cancer in Hp-infected pts (Gut 2001;49:347). In a large Japanese cohort, gastric cancer was seen only in those with Hp infection and was most likely in those with atrophy, corpus gastritis, or intestinal metaplasia (Nejm 2001;345:784). Long-term Hp infection in Mongolian gerbils causes adenocarcinoma, adding strong support to this connection (GE 1998;115:642). Screening and treating Hp might be cost effective in preventing gastric cancer (Lancet 1996;348:150).
- *Mucosa-associated lymphoid tissue (MALT) lymphoma:* Gastric mucosa does not ordinarily contain organized lymphoid tissue. However, in response to Hp infection, lymphoid follicles develop and may evolve into low-grade B-cell lymphoma. About 90% of gastric MALTomas are associated with Hp infection, and Hp eradication cures the subset of pts with superficial and distal tumors (Ann IM 1999;131:88).
- *Nonulcer dyspepsia (NUD):* Between 30% and 60% of pts with NUD have Hp infection. However, properly performed population-based studies do not show a consistent association between Hp and NUD, and there is no convincing evidence of an effect of Hp on gastroduodenal motor or sensory function (GE 1997; 113:S67). The 2 best trials of rx have yielded conflicting results. One trial showed a benefit of Hp eradication (21% vs 7% sx relief at 1 yr [Nejm 1998;339:1869]). The other trial showed no benefit (26% vs 31% sx relief at 1 yr [Nejm 1998;339:1875]). However, the studies are similar in that the sx of NUD are not relieved in 75% of pts in whom Hp is eradicated, suggesting a limited role for Hp in NUD. Most clinicians treat Hp-positive pts with NUD.
- *Other questionable associations:* Recent data suggest an association between Hp infection and iron deficiency, but the cause and effect relationship is unproven. The argument has been made to test pts with unexplained iron deficiency for Hp and to treat if positive (Am J Gastro 2005;100:453). The ready availability of serologic tests seems to have inspired authors to search for non-GI–associated manifestations of Hp infection. Preliminary associations have been made between Hp infection and CAD, cerebrovascular disease, HTN, Raynaud's phenomenon, migraine, sudden infant death syndrome, and ITP. However, the quality of the data is limited, and these associations remain uncertain, and in some cases biologically implausible (Arch IM 1999;159:925).

Diff Dx: Most infections are asymptomatic; the clinical diff dx is usually that of dyspepsia (p 2).

Lab: (Am J Gastro 1998;93:2330)

- *Whom to test:* It only makes sense to test those pts who will be treated if the test is positive. Pts with DU, GU, and MALTomas should be tested. Gastric polyps in an Hp-infected stomach may disappear with Hp rx, so that group should be tested (Ann IM 1998;129:712). The data are conflicting on the utility of eradicating Hp in NUD, but most clinicians test and treat the positive pts. Some consider testing those with a family hx of gastric cancer, but the value of that is speculative. Testing may be considered prior to long-term NSAID use (p 71) or prior to long-term PPI use (p 39). No large group has yet endorsed screening and treating asymptomatic pts, but that day may come. The choice of test depends on the clinical circumstances.
- *Urease tests of bx specimens:* These tests depend on the urease activity in endoscopically obtained bx and show positive results by a color change in an indicator when the urease is present. The 3 FDA-approved tests are Clotest, Pyloritek, and Hp-fast. Sensitivity is 88-95%,

and specificity is 95-100%. Sensitivity is reduced by prior use of PPIs (Aliment Pharmacol Ther 1996;10:289), H2RAs, bismuth, antibiotics, and alcohol consumption (Am J Gastroenterol 1997;92:1310). Bx from the antrum during active GI bleeding greatly reduces sensitivity of urease testing (Gastrointest Endosc 1999;49:302), so breath testing or serology should be used instead. Serology should also be used if testing is necessary in a pt who has been on antibiotics, PPIs, or H2RAs within the last month. Two antral bx are usually sufficient (Gastrointest Endosc 1994;40:342), but sensitivity can be improved using an additional bx from the body in pts on H2RAs or PPIs (Am J Gastro 1997;92:1310).

- *Histology:* With this method, both the presence of Hp and the inflammation can be detected. If there is no gastritis histologically, then Hp infection is reliably excluded. Specialized stains such as Giemsa or immunostains (J Clin Pathol 2000;53:756) can be used if H&E is negative and gastritis is present. The same conditions decrease sensitivity for histology as for urease bx testing (see previous bullet item). The sensitivity is 93-96%, and specificity is 98-99%. One strategy to reduce cost and maximize sensitivity is to run urease testing first and to proceed with histology only if urease is negative.
- *Urea breath tests:* (Am J Gastro 1998;93:2330; Gut 1994;35:723) The pt swallows a small amount of ^{13}C (nonradioactive) or ^{14}C (radioactive) urea. Hp urease converts the urea to bicarbonate and ammonia. The bicarbonate is converted to CO_2, which is recovered in a breath sample and detected on mass spectroscopy (^{13}C) or scintillation counting (^{14}C). In the U.S., the FDA has approved a ^{13}C test (Meretek) and a ^{14}C test (Tri-Med). The ^{14}C has the advantage of lower expense and the disadvantage that it cannot be given to children or pregnant women because of the radioactivity. Both tests perform well, with sensitivity of 90-96% and specificity of 88-98%. Antibiotics lower sensitivity, and the test should be performed at least 4 weeks after completion of eradication rx. PPIs may reduce sensitivity for 2 weeks, and H2RAs do so for 5 days (Ann IM 1998;129:547).
- *Fecal antigen test:* These tests identify bacterial antigens in stool that suggest active infection. Both polyclonal and monoclonal tests are available, and the latter may be more specific when performed posttreatment (Helicobacter 2004;9:347). The tests have similar limitations to breath testing regarding recent use of PPIs, antibiotics, and bismuth. Overall, they work about as well as breath testing (regarding sensitivity and specificity) but have the difficulties associated with handling stool.
- *Serology:* IgG for Hp by ELISA is 86-94% sensitive and 78-95% specific. It is readily available and is useful in detection when endoscopy is not being performed, but it does not distinguish remote from active infection. A fall in titer after rx is not consistent enough to be useful for determining response to rx, unless the titer falls to zero (Jama 1998;280:363). The positive predictive value of serology is low in populations with a low pretest probability of infection, and breath testing or fecal antigen testing is preferred.
- *Culture:* Culture is not readily available in many hospital labs and is not commonly used in clinical practice. It is 80-98% sensitive, 100% specific. Its major use would be for detecting resistant strains in pts who have failed rx. As a practical matter, an alternative rx is chosen without sensitivity information.
- *Whole blood tests:* These tests were designed for office use and have reduced sensitivity (67-88%), reduced specificity (75-91%), and reduced cost compared to serum-based ELISA testing. It does not seem worthwhile to use them given the small cost savings at the expense of accuracy.

Endoscopy: There are no endoscopic features that identify Hp. A grossly normal stomach at endoscopy can be infected, and bx are mandatory if Hp infection is to be diagnosed or excluded.

Rx: (Curr Gastroenterol Rep 1999;1:518; Am J Gastroenterol 1998;93:2330; J Gastroenterol 1998;33:48; Gut 1997;41:8; Am J Gastro 2007;102:1808)

- Pts with a positive test should be treated if the test was obtained for an appropriate clinical reason. Since rx morbidity is minimal and the World Health Organization has called Hp a class 1 carcinogen, it becomes difficult not to treat the positives even if the test was obtained for inappropriate reasons. However, it has been argued that rx of all strains of Hp is premature since not all strains cause clinical disease (Lancet 1997;349:1020).
- *Characteristics of best therapies:* A bewildering 1409 Hp rx arms have been identified in a meta-analysis of Hp rx (GE 1997;113:S131). In screening the literature for appropriate regimens, one needs to look for rx that is >80% effective in intent-to-treat analysis and >90% effective in per-protocol analysis, with reproducible results from different geographic areas. It should be well tolerated, simple, and cost effective. Regimens that are bid have greatly enhanced compliance. The regimens in the following list are all oral and use omeprazole 20 mg bid or lansoprazole 30 mg bid. Pantoprazole 40 mg po bid or rabeprazole 20 mg bid are probably equally effective (Aliment Pharmacol Ther 1999;13:741). Esomeprazole 40 mg qd is another alternative. PPIs are used to increase concentration of antibiotics in gastric juice, to lessen the viscosity of the mucus layer and to increase the stability of the antibiotics that act locally in the mucus layer (Am J Gastro 2009;104:26).

  Unfortunately, resistance to rx is increasing and regimens are often less effective in practice now than when they were originally described. Guidelines from the ACG suggest (Am J Gastro 2007;102:1808):

  - For pts not allergic to penicillin who have not previously received a macrolide antibiotic: *PPI + amoxicillin 1000 mg + clarithromycin 500 mg bid × 2 weeks*. This is commonly called **clarithromycin-based triple therapy**.
  - For pts allergic to penicillin or who have previously received a macrolide antibiotic: *Bismuth subsalicylate (Pepto Bismol) 525 mg qid + metronidazole 250 mg qid + tetracycline 500 mg qid for 10-14 days + acid suppression with PPI (qd or bid) or ranitidine 150 mg po bid*. This is commonly called **bismuth quadruple therapy**.
  - For pts allergic to penicillin who have not previously received a macrolide antibiotic or who don't tolerate bismuth quadruple therapy: *PPI + metronidazole 500 mg + clarithromycin 500 mg po bid × 2 weeks*.
  - For pts not allergic to penicillin who have previously received a macrolide antibiotic and who don't tolerate bismuth quadruple therapy (unless intolerance was due to metronidazole): *PPI + amoxicillin 1000 mg + metronidazole 500 mg po bid × 2 weeks*.

- *Sequential first-line therapy:* Because of the high frequency of failure of standard clarithromycin-based triple therapy (especially in Europe), sequential therapy was devised. In this rx, the first 5 days are treatment with a bid PPI and 1000 mg bid of amoxicillin. This is followed by 5 days of clarithromycin 500 mg bid and metronidazole 500 mg bid. Success rates are high (Am J Gastro 2008;103:2220) but U.S. data are lacking.

- *Treatment failures:* (Am J Gastro 2007;102:1808) Pt compliance and antibiotic resistance are likely important factors in treatment failures. Unfortunately, antibiotic susceptibility data are not readily available in most pts with treatment failure. Bismuth quadruple therapy × 7-14 days (see above) would be the first choice for pts who have failed clarithromycin-based therapies. Levofloxacin triple therapy with a bid PPI, amoxicillin 1 gm bid, and levofloxacin 500 mg qd for 10 days is a third-line regimen that is better tolerated and may be more effective than bismuth quadruple therapy (Am J Gastro 2006;101:488) but for which U.S. data are lacking.
- *Post-rx follow-up:* Confirmation of eradication 4 weeks after completion of rx is recommended in pts with MALToma, ulcer disease, and early gastric cancer after resection. Follow-up testing should also be done in pts with persistent dyspepsia despite rx as part of the "test-and-treat" approach to dyspepsia (p 2). Its importance in other pt groups is less well established. Breath testing is ideal unless endoscopy is needed for another reason.

3.3 Peptic Ulcer

Lancet 2002;360:933; Am J Gastro 1997;92:1255

Cause: Hp infection (see Section 3.2) and NSAIDs account for the vast majority of cases.

Epidem:

- *GU:* Incidence estimated at 0.1%/yr; much higher in NSAID users. About 3% of GUs turn out to harbor malignancy (Nejm 1995;333:32).
- *DU:* M:F incidence ratio is 2:1 (confounded by a higher smoking rate in men); higher in smokers, RR = 2.2 (J Clin Gastroenterol 1997;24:2), though not confirmed in a large prospective study (Epidemiology 1997;8:420); higher in those with a family hx of DU (J Clin Gastroenterol 1995;20:104). It is unlikely that caffeine or alcohol are important risk factors (Epidemiology 1997;8:420). The literature on psychological risks for DU is a quagmire, with purported risks ranging from life events stress (J Clin Gastroenterol 1995;21:185; GE 1986;91:1370) to a personality that prompts one to sport a half-mustache on the upper lip (J Clin Gastroenterol 1992;15:96). It seems unlikely that psychological factors are of major, definable, clinical relevance. Diet plays no clear role, and the traditional suggestion of a bland diet is not made on solid ground (especially with the suggestion that chili is protective for DU! [Dig Dis Sci 1995;40:576]).

Pathophys:

- *GU:* GU results when gastric mucosal defenses are overwhelmed by the harsh, intraluminal gastric environment rich in acid and pepsin. Gastric epithelium remains intact in the stomach by a series of prostaglandin-dependent defenses, including (1) the semipermeable mucus layer, (2) bicarbonate in an unstirred water layer, and (3) regeneration and repair (Gut 1997;41:425; Gut 1993;34:580). Hp infection causes epithelial injury by production of cytotoxins, urease, and other factors that cause cell injury and death, leading to ulceration. NSAIDs inhibit mucosal cyclooxygenase, thereby reducing prostaglandin production, inhibiting mucus and bicarbonate production, and decreasing mucosal blood flow. This prevents cell replication and leads to ulcer formation.
- *DU:* The initiating event in most DU is Hp infection. Antral gastritis from Hp infection results in a decrease in somatostatin-producing cells (D cells), whose role is to inhibit

gastrin-producing G cells. This in turn leads to the increased parietal cell mass (perhaps also increased due to genetic or other environmental factors) that results in the increase in acid secretion seen in DU pts. Areas of intestinal metaplasia form, possibly in response to increased acid, and these are subsequently colonized by Hp. Duodenitis results from release of inflammatory mediators from Hp, and in the presence of acid, an ulcer forms. NSAIDs presumably cause ulceration by reducing mucosal prostaglandin-mediated defenses. The foregoing theory does not account for DU that is seen in Hp-negative pts not taking NSAIDs. A meta-analysis of rigorously designed U.S. trials demonstrated 20% ulcer recurrence rate in pts cleared of Hp, suggesting that in a subset of DU pts, Hp infection is not the critical factor (Am J Gastroenterol 1998;93:1409). These so-called "idiopathic ulcers" may be more difficult to treat and may be more likely to result in complications (Am J Gastro 2002;97:2950).

Sx: There is no sx complex diagnostic for GU or DU, and sx do not reliably distinguish DU from GU or from non ulcer dyspepsia (GE 1993;105:1378). PUD often presents with epigastric pain, sometimes described as burning, aching, or as a hunger pain. Classically it is described as postprandial and may be relieved with antacids, but these features are highly variable. GU, especially NSAID-induced, can be asymptomatic or present with a complication such as bleeding or perforation in the absence of prior pain (Am Fam Phys 1997;55:1323). If the ulcer is near the pylorus, poor gastric emptying may result in reflux sx, vomiting, or early satiety. Sudden severe sx may indicate perforation, and constant pain may suggest penetration. Weight loss is more common with giant GU (>3 cm).

Si: Epigastric tenderness.

Crs:

- *GU:* The vast majority of GUs will heal with initial rx. A small subgroup refractory to H2RAs will heal with a PPI (Aliment Pharmacol Ther 1996;10:381). If NSAIDs are eliminated and Hp is cured, recurrence is low. Chronic GU should lead to investigation for a missed gastric malignancy (adenocarcinoma or lymphoma) or surreptitious NSAID use.
- *DU:* Before the advent of rx for Hp, DU was a chronic relapsing illness. With clearance of Hp, DU recurrence is uncommon (eg, Lancet 1994;343:508; Nejm 1993;328:308). However, recent analysis of U.S. trials suggests that the proportion of pts who relapse after Hp eradication may be as high as 20% (Am J Gastroenterol 1998;93:1409). At one time it was thought that ulcer disease largely burned itself out, but long-term follow-up studies of pts dx in the pre-Hp era show that 50% remain symptomatic (Gut 1996;38:812).

Cmplc: Bleeding, gastric outlet obstruction, perforation, penetration into adjacent structures without free perforation.

Diff Dx: See Dyspepsia (p 2). The diff dx of an endoscopically identified ulcer includes gastric adenocarcinoma, lymphoma, and Crohn's disease.

Lab: CBC, CMP, amylase, lipase aid in diff dx. Testing for Hp is usually done at EGD for GU but may be done by serology or breath testing if DU was diagnosed by UGI rather than EGD.

X-ray: UGI barium x-ray can establish dx but is highly operator dependent and is much less sensitive and specific than EGD. A variety of radiographic signs have been proposed to separate the benign from the malignant GU. However, if the pt is medically fit, EGD should be performed to rule out malignancy if UGI shows GU (Jama 1996;275:622). UGI should generally be discouraged in the evaluation of dyspepsia unless EGD is thought unsafe or

unavailable. UGI should not be used to dx DU (because it is a poor negative). However, if a DU is found on UGI, then EGD is not mandatory since the cancer risk in typical DU is negligible.

Endoscopy: EGD is the gold standard for dx of ulcers. Ulcers are directly visualized, and features that predict risk for bleeding can be identified (p 75). A clean, punched-out appearance of a GU suggests that the ulcer is benign. At least 6 bx should be obtained to rule out malignancy. The endoscopic gross appearance is not a reliable negative, and 3 bx detect only 70% of cancers (GE 1982;82:228). Many experts believe that all GUs should be followed to healing by EGD (not UGI) to prove benignity by healing. Some have advocated foregoing follow-up EGD because initial EGD and bx is 99% accurate (Dig Dis Sci 1993;38:284). However, the yield of finding a curable cancer at follow-up EGD is high enough (1 cancer per 250 endoscopies [Scand J Gastroenterol 1991; 26:1193]) that the practice is felt appropriate by many (Dig Dis Sci 1994;39:442). DUs are usually identified in the first portion of the duodenum (often called the bulb or cap). Since they are at a very low risk for malignancy, follow-up EGD to document healing is rarely indicated.

Rx: (Jama 1996;275:622)

- *Suppression of acid:* Though excess acid is not the primary cause of GU, acid suppression heals ulcers, and about 90% of ulcers will be healed in 12 weeks. Acid suppression relieves sx. Cimetidine (800 mg qhs) or ranitidine (300 qhs) are cheaper but not as rapidly effective as PPIs. Consider initial use of a PPI at a high dose (eg, omeprazole 40 mg daily) in large or complicated ulcers (Am J Gastro 1996;91:2516). About 90-95% of DUs heal by 8 weeks with acid suppression, and GUs typically take 12 weeks because healing is slower and GUs are often larger.
- *NSAID ulcer:* Stop NSAIDs. If NSAIDs are stopped, then an H2RA is appropriate rx unless the ulcer is very large. If NSAIDs cannot be stopped, the dosage might be reduced. If NSAIDs are continued, a PPI (eg, omeprazole 20-40 mg po qd) rather than an H2RA should be used to treat the ulcer (Nejm 1998;338:719).
- *Eradication of* Helicobacter: (p 63).
- *Refractory ulcer:* Consider malignancy, ongoing NSAID use (surreptitious or otherwise), and ZE syndrome (p 86) as causes. High-dose lansoprazole (60 mg) results in >80% healing of GU not cured with 6 weeks of H2RA (Aliment Pharmacol Ther 1996;10:381), and cure can be maintained by 30 mg po qd. Consider surgery.
- *Giant GU:* Giant GU is defined as GU >3 cm. Historically, these were treated with early surgery because of perceived higher risk with medical rx. However, in the era after introduction of H2RAs, it became evident that these ulcers usually heal with medical rx. They more frequently present as emergencies, often relapse without maintenance (though data on Hp status are lacking), and are a marker for poor general health. The mortality rate from associated medical illness is high, though subsequent risk of cancer is low (Am J Gastro 1999;94:3478). A PPI would be appropriate medical rx.
- *Hp-negative, NSAID-negative ulcers:* (Am J Gastro 2009;104:190) The most important point in management is to make sure that these pts truly have Hp- and NSAID-negative ulcer disease. Malignancy, Crohn's disease, bisphosphonate use, mastocytosis, and ZE syndrome may need to be considered. These pts often require higher doses of PPI for healing and a PPI for maintenance.

- *Prevention of ulcer recurrence:* In uncomplicated Hp-infected GU or DU, maintenance is not warranted. In Hp-infected pts with an ulcer complication, maintenance rx might be continued until Hp eradication is confirmed. In Hp-negative pts with a hx of recurrent or morbid complications, maintenance rx with an H2RA or PPI is reasonable, though data are limited. The typical maintenance dose of an H2RA is half the initial dose (eg, ranitidine 150 mg po qhs reduces endoscopic recurrence to 20-25%), but full-dose or PPI rx may be warranted if the initial event was highly morbid.
- *Surgical rx:* Most surgery for PUD is now done emergently for complications. It becomes a matter of clinical judgment as to when to send a pt with a refractory ulcer to surgery. Indications for surgery include refractory sx, suspicion of malignancy, uncontrolled bleeding, and obstruction. Exclude ZE (p 86) prior to surgery. The need to exclude ongoing NSAID use by random salicylate or other NSAID levels (pts do lie sometimes!) is critical. Relatives should be questioned. A series of 30 pts from 1 center with postsurgical recurrence of ulcer due to aspirin use (half of it surreptitious) had a high incidence of stenosis, multiple operations, and a poor outcome (GE 1998;114:883).

  Surgery with wedge resection of GU is just as effective as more extensive resections with vagotomy to reduce acid, presumably because excess acid plays little role in the pathogenesis of the ulcer. Mortality in GU is substantial (6.9% all comers, lower electively, higher in those with cardiovascular disease), and ulcer recurrence is still 5% (Am Surg 1996;62:673).

  For DU, the operation of choice for intractable pain and perforation is proximal gastric vagotomy (aka parietal cell vagotomy) (Surg Clin N Am 1992;72:335). This more limited vagotomy causes less postoperative morbidity than a truncal vagotomy. However, individual experience, the nature of the ulcer complication, and judgment are important factors in selecting the best operation. If a pt has an intractable DU, then medical noncompliance or NSAID use is likely, and operation should be approached with great caution.
- *Postgastrectomy syndromes:* (Surg Clin N Am 1992;72:445) About 20% of pts have postgastrectomy syndromes after ulcer operations. With a proximal gastric vagotomy, the incidence is only 5%. **Dumping syndrome** is one of the most common syndromes and is due to the rapid emptying of hyperosmolar, carbohydrate-rich food. Dumping syndrome causes GI sx of distension, cramping, nausea, vomiting, and explosive diarrhea. It causes vasomotor sx of diaphoresis, weakness, dizziness, flushing, and palpitations. It is treated by eating small meals, avoiding concentrated carbohydrates, and taking liquid 30 min after meals. Operative treatment is sometimes required. Other postgastrectomy syndromes include postvagotomy diarrhea, gastroparesis, problems with a small gastric remnant, alkaline reflux, and several syndromes related to the jejunostomy.

3.4 NSAID Gastropathy

Am J Gastro 2008;103:2890; Am J Gastro 2008;103:2908; GE 2001;120:594; Am J Gastro 1998;93:2037

Epidem: Of the U.S. population, 1.2% use NSAIDs on a daily basis (Am Fam Phys 1997;55:1323). Of these, 1-2% per yr will be hospitalized for GI complications of bleeding or perforation, at an annual cost approaching $1 billion. Overprescribing of NSAIDs for pain rather than joint inflammation contributes greatly to the number of avoidable complications (Ann IM 1997;127:429). The major **risk factors** for the development of serious complications are (Am J Gastro 1998;93:2037) (1) prior peptic ulcer or bleed (RR = 2.74); (2) age >60 yr

(RR = 5.52); (3) high dosage, >2 times normal (RR = 10.1); (4) concurrent corticosteroids (RR = 4.4); and (5) concurrent anticoagulants (RR = 12.7), (6) *Helicobacter* infection (Aliment Pharmacol Ther 2005;21:1411), and (7) multiple NSAIDs or (8) aspirin plus an NSAID. Gender, smoking, and alcohol are *not* independent risks. Complications are more likely to occur within the first 3 months of rx.

Pathophys: Prostaglandins protect the gastric mucosa by promoting secretion of gastric mucus and bicarbonate and by increasing mucosal blood flow and ultimately cell replication. NSAIDs inhibit prostaglandin production by inhibiting cyclooxygenase. Minor toxicity from NSAIDs occurs because of local effects of these weak acids on gastric mucosa that result in erosions (small, shallow mucosal breaks). More important are the systemic effects of these agents that can cause gastroduodenal injury even if given by the rectal or iv route.

There are 2 isoforms of cyclooxygenase that NSAIDs may inhibit. COX-I isoforms maintain mucosal integrity, and COX-II isoforms induce inflammation. A newer class of NSAIDs that selectively inhibits COX-II and thus does not reduce mucosal prostaglandins has become available. Two first-generation agents in this class, celecoxib (Celebrex) and rofecoxib (Vioxx), appear to be associated with a low risk of ulcer complications (Lancet 1999;353:307). However, this class is associated with an increased risk of cardiovascular events and only celecoxib remains on the U.S. market after the others were withdrawn. The older non–COX-II selective drugs may also increase cardiovascular risk but to a much lesser degree. Naproxen may have the lowest cardiac risk of the nonselective NSAIDs (Am J Gastro 2008;103:2908). The use of ibuprofen appears to reduce the cardioprotective effect of aspirin (Med Lett Drugs Ther 2004;46:61).

Of the older non–COX-II selective drugs, ketorolac and piroxicam have the highest GI toxicity; naproxen, indomethacin, ketoprofen, and diclofenac are intermediate in GI toxicity; ibuprofen is less toxic (Arch IM 1996;156:1623). Nabumetone is probably the least toxic of the older agents, but at the expense of reduced anti-inflammatory activity (Am J Gastro 1996;91:2080).

The role of Hp infection in the genesis of NSAID ulcers has been difficult to sort out. A prior hx of ulcer is a risk factor for subsequent NSAID ulcers, and Hp is strongly associated with ulcers. It is tempting to hypothesize that Hp infection is a cofactor in NSAID ulcer rather than unrelated to NSAID ulcer development, but studies have been conflicting. However, meta-analysis suggests that eradication of Hp reduces the overall incidence of ulcer disease (Aliment Pharmacol Ther 2005;21:1411).

Sx: Dyspepsia may occur with NSAIDs but does not predict endoscopic ulcer. Most pts with NSAID gastropathy are asymptomatic. Up to 60% will remain so until they present with bleeding or perforation (Lancet 1986;1:462). Only about 1 in 10 NSAID-induced ulcers bleed.

Crs: Reversible illness upon withdrawal of NSAID, but mortality may occur.

Cmplc: Bleeding; perforation; death, especially in elderly women (Ann IM 1997;127:429).

Endoscopy: EGD is appropriate if there is suspicion of an ulcer complication. Erosions are common, especially early in a course of NSAID use.

Rx: (Am J Gastro 2008;103:2890; Am J Gastro 2008;103:2908; GE 2008;134:1240)

- *Assess risk vs benefit, eliminate Hp:* The first step in prevention is to make sure that the pt has an indication for an NSAID and that it is given for the shortest time possible.

Hp should be eradicated if present. The strategy for therapy then depends on an evaluation of both GI and cardiac risk.

- *Drugs that prevent NSAID ulcer:* (Am J Gastro 2008;103:2890; Am J Gastro 2008;103:2908; GE 2008;134:1240) Pts at **high risk** for NSAID gastroduodenal toxicity can be treated with (1) a nonselective NSAID plus misoprostol, (2) a nonselective NSAID plus PPI, or (3) a COX-II selective agent (a "coxib"). **Misoprostol** in a dose of 200 mcg po qid reduces GI complications up to 40% compared with placebo (Ann IM 1995;123:241). Diarrhea is an intolerable problem in up to 20% of pts. This sx can be reduced by changing the dosage to bid or tid, but this approach is less effective in protecting against GU (Ann IM 1995;123:344). The drug may also be better tolerated if begun at a low dose (100 mcg) and slowly increased to the target dose. **PPIs** are better tolerated than misoprostol and are used more frequently. Omeprazole 20 mg po qd or lansoprazole 30 mg po qd are effective choices when combined with a nonselective NSAID for pts at high risk. For pts at **very high risk** (prior NSAID ulcer bleeding) the combination of a coxib and a PPI is much more effective than a coxib alone in preventing ulcer bleeding (Lancet 2007;369:1621). Conventional-dose H2RAs are ineffective as prophylaxis against GU and therefore should not be used for prevention.
- *NSAID ulcer prevention in pts at low cardiovascular risk:* In pts with average GI risk for NSAIDs (none of the risk factors listed in Epidemiol), a nonselective NSAID can be used. In pts with a moderate increase in GI risk, a nonselective NSAID and a PPI (or misoprostol) can be used. In pts with very high GI risk (such as prior bleeding ulcer, multiple GI risk factors), a coxib and a PPI (or misoprostol) can be used.
- *NSAID ulcer prevention in pts at high cardiovascular risk:* As a practical matter, these pts are all on aspirin, which increases their GI risk. If the pt has no additional GI risk factors, then naproxen with a PPI (or misoprostol) is an option. If the pt has additional GI risk factors and cannot take a coxib because of cardiac risk, then NSAIDs should not be used. In the unusual circumstance that an NSAID is still thought essential in a pt with very high GI risk, naproxen with a PPI (or misoprostol) would be less dangerous to the heart than a coxib, but would still be a very high-risk therapy.

3.5 Stress Ulcer

Drugs 1997;54:581

Epidem: In the modern ICU, the incidence of bleeding from stress ulcer steadily declined from 20-30% in the 1970s to 1.5-14% in 1995 (Am J Gastro 1995;90:708).

Pathophys: (Am J Gastro 1995;90:708) Stress ulcer is a term used to refer to gastroduodenal ulcers or diffuse erosive disease that occurs in critically ill pts in an ICU setting. Erosions and superficial mucosal hemorrhage are seen in 70-90% of critically ill pts and progress to confluent ulcers in a smaller subgroup. Ulcers in pts with burns and head injury are probably due to gastrin-stimulated acid production. Mucosal ischemia is probably important in many other groups at risk. In a large study weighted to cardiac surgery pts, the 2 major risks for bleeding were mechanical ventilation for more than 48 hr (15 times risk) and coagulopathy (4-fold risk)

(Nejm 1994;330:377). Prior GI bleeding or ulcers within a year is another major risk (Am J Health Syst Pharm 1999;56:347). Other risk factors include shock of any cause, multiple trauma, major organ failure, burns of >35% body surface area, head trauma, sepsis, steroid use, ICU stay longer than 7 days, and quadriplegia. The risk of bleeding rises markedly if there are 3 or more risk factors.

Sx: Hematemesis, melena, NG aspirate with coffee grounds or frank blood.

Si: Hypotension.

Crs: Usually dictated by the underlying medical illness rather than stress ulcer itself.

Cmplc: Bleeding. Perforation is much less common than bleeding in stress ulcer.

Diff Dx: Acute bleeding from preexisting upper tract lesions, including PUD and malignancy (see GI Bleeding, p 21).

Lab: Hgb (look for drop of >2 gm to suspect important bleeding); PT/INR, PTT, platelets; DIC screen if DIC is suspected clinically on basis of initial labs or multiple bleeding sites.

Endoscopy: EGD is performed in these critically ill pts if there is ongoing bleeding for which endoscopic rx may be needed. Usually EGD is unnecessary in pts with evidence of bleeding (ie, coffee grounds in NGT) without hemodynamic consequences.

Rx: The rx of stress ulcer is that of bleeding peptic ulcer (p 75). The greatest focus has been on prevention. The cornerstone of prevention is the optimal management of the underlying illness. Improvements in ICU care are probably responsible for some of the decline in stress ulcer bleeding. Prophylaxis should be given in pts with any of the major risk factors above and considered in those with minor risk factors (especially if multiple risk factors are present). Several agents can be considered to prevent bleeding:

- *H2RAs:* These agents have been shown in meta-analysis to reduce risk of clinically important bleeding, and a trend suggests that they are more effective than sucralfate. This reduction in bleeding may come at the risk of a trend toward increased risk of nosocomial pneumonia (Jama 1996;275:308). However, a prospective study of 1200 ventilated pts confirmed the benefit of ranitidine over sucralfate in prevention of clinically important bleeding (1.7% vs 3.8%) but did not show a higher pneumonia risk in the ranitidine group (Nejm 1998;338:791). While continuous infusion of H2RAs results in better acid suppression, it does not translate into less bleeding and is not necessary (Am J Gastro 1995;90:708).
- *Sucralfate:* The argument for using sucralfate has been the apparent lower pneumonia rate and a reduced mortality rate (Jama 1996;275:308). This may be especially important in pts undergoing prolonged mechanical ventilation who are not enterally fed (Drugs 1997;54:581). In such pts the apparent lower efficacy of sucralfate in preventing bleeding may be offset by a lower risk of pneumonia.
- *PPIs:* Though PPIs are widely used for stress prophylaxis, the data are limited. Immediate release omeprazole oral suspension is no less effective than iv cimetidine (Crit Care Med 2005;33:760). Other high-quality studies are not available.
- *Antacids:* While antacids appear to lower the risk of bleeding, they must be given q 1-2 hr with close monitoring of gastric pH and dosage titration. Thus, they are infrequently used for stress ulcer prophylaxis.

3.6 Treatment of Bleeding Peptic Ulcer

Nejm 2008;359:928; Surg Clin N Am 1996;76:83; Nejm 1994;331:717

Endoscopy: Endoscopy identifies the cause of bleeding and predicts risk of rebleeding in the first week. Endoscopy is performed after volume resuscitation and stabilization of the pt. If the endoscopist identifies active arterial spurting from the ulcer, the chance of rebleeding in the first week is 80% without rx. If a nonbleeding visible vessel is seen (generally a red or bluish lesion of a few mm sticking up in the ulcer bed), the rebleed rate is 50%. An adherent clot has a 30% risk, a flat black spot carries a 10% risk, and a clean, exudate-covered ulcer base has a risk of less than 5%.

Rx:

- *Intravenous PPIs:* Treatment with iv omeprazole or pantoprazole at high doses appears to lower the risk of ulcer rebleeding, urgent surgery, and death (Aliment Pharmacol Ther 2005;21:677). Continuous therapy with omeprazole or pantoprazole (80 mg to load followed by 8 mg/hr continuous infusion × 72 hr) appears to be more effective intermittent bolus therapy (Crit Care Med 2002;30:S369).
- *Endoscopic therapy:* (Clin Gastroenterol Hepatol 2009;7:33) Endoscopic rx reduces the risk of rebleeding by 40%, the need for surgery by at least 60%, and mortality in acute bleeding by 60% (GE 1992;102:139). Bleeding can be treated by direct application of thermal energy to coagulate blood vessels, by application of hemostatic clips, or by injection of various substances into the vessel and surrounding tissues. Endoscopic rx is clearly indicated for actively bleeding ulcers and for those with visible vessels. Endoscopic therapy may be appropriate for ulcers with adherent clots after epinephrine injection and careful removal of the clot (GE 2002;123:407), but the additional benefit of endoscopic rx in this group is uncertain when iv PPIs are used.
    - **Thermal energy** is applied with a BICAP probe or a heater probe. Pressure is applied directly onto the vessel until bleeding stops. This squeezes the opposite walls of the vessel together and allows highly effective coagulation. There is no convincing evidence that one device is better than another. The difficulty can be getting *en face* to the vessel so that pressure can be directly applied, because many ulcers can only be approached tangentially. Long, low-energy bursts of current are applied (Surg Clin N Am 1996;76:83).
    - **Injection rx** can be carried out with 1:10,000 diluted epinephrine, alcohol, thrombin, or other sclerosants. The beauty of injection rx is that the device is inexpensive, the technique easy to master, and it can be used to treat an ulcer that can only be approached tangentially. Epinephrine is safe, simple, and effective. Generally 10-20 mL total are injected in several sites. The vasoconstriction and tamponade effect of the large volume stop bleeding. The initial success rate is >90% (BMJ 1997;314:1307), but injection alone is inferior to the combination of epinephrine with a second method. Therefore, epinephrine injection should not be used as the sole modality of endoscopic rx (Clin Gastroenterol Hepatol 2009;7:33). Sclerosant therapies

and fibrin glue are also effective. The disadvantage of sclerosants and alcohol is the perforation risk, because extensive tissue necrosis may occur (Brit J Surg 1996;83:461).

- **Combination therapy** with injection of epinephrine followed by a thermal method is widely used following a trial from a respected center showing effectiveness (BMJ 1997;314:1307). The concept is that epinephrine controls immediate bleeding and the second modality prevents later rebleeding.
- Endoscopic application of **metal clips** to bleeding ulcers is effective, but results of trials comparing it to thermal methods are conflicting (compare Am J Gastro 2002;97:2250 to Gastro Endosc 2001;53:147).

- *Surgery and interventional radiology:* **Failures of endoscopic rx** are best managed with a second attempt at endoscopic rx (Nejm 1999;340:751). Endoscopic retreatment reduces the need for surgery without increasing the risk of death and has fewer complications than surgery. The purpose of surgery is to control bleeding when endoscopic methods and a PPI fail rather than to cure the underlying ulcer disease. Angiography with embolization of vessels is an alternative, especially in poor surgical candidates or if the bleeding site has not been localized (Nejm 2008;359:928).

3.7 Nonulcer Dyspepsia

GE 2004;127:1239; Nejm 1998;339:1376; GE 1997;112:1448

Epidem: The prevalence of dyspepsia is about 15% in the adult population. The majority of these pts have normal endoscopies and could potentially be labeled as having nonulcer dyspepsia (NUD).

Pathophys: (Mayo Clin Proc 1999;74:1011) NUD is defined as persistent or recurrent pain centered in the upper abdomen that lasts more than 3 months and is not associated with a biochemical or anatomic abnormality. A variety of causes of NUD have been proposed, including (1) Hp infection, (2) histologic gastritis or duodenitis, (3) GERD with a negative EGD, (4) heightened visceral sensitivity, (5) gastroparesis, (6) impaired gastric accommodation to a meal, (7) other motility abnormalities, or (8) a psychiatric disorder. None of the data are convincing for a single etiology. Clinicians should not think of this as a single disease, for it is really a sx with multiple elusive causes.

Sx: By definition, NUD is pain in the upper abdomen. There can be associated nausea, bloating, early satiety, or postprandial fullness. Subtypes have been identified (refluxlike, dysmotility-like, ulcerlike, and nonspecific) but are not helpful in choosing empiric rx (GE 1992;102:1259).

Cmplc: None by definition.

Diff Dx: The diff dx is that of dyspepsia (p 2). To truly make a dx of NUD, there are a large number of exclusions that must theoretically be made. However, exhaustive testing is often unnecessary, and testing should be tailored to the severity and persistence of the complaint.

Lab: Normal by definition.

X-ray: Normal by definition.

Endoscopy: Normal by definition.

Rx:

- *Treatment of* Helicobacter: Between 30 and 60% of pts with NUD have Hp infection. The 2 best trials of rx in NUD with Hp infection have yielded conflicting results. One showed a benefit of Hp eradication (21% vs 7% sx relief at 1 yr [Nejm 1998;339:1869]). The other showed no benefit (26% vs 31% sx relief at 1 yr [Nejm 1998;339:1875]). However, the studies are similar in that sx of NUD are relieved in 25% of pts in whom Hp is eradicated. Since rx is quite benign, and since Hp is a risk for gastric cancer and future peptic disease, it is reasonable to treat Hp in the setting of dyspepsia.
- *Trial of a PPI:* Since a large number of pts with GERD have a normal EGD and not all pts with GERD have typical retrosternal sx, a trial of a PPI is warranted (p 37). PPIs are more effective than placebo in rx of NUD (Clin Gastroenterol Hepatol 2007;5:178). If the pt has a good response, an attempt to taper rx to an H2RA or stopping it entirely is reasonable. If sx relapse, a dx of GERD may be entertained. If confirmation is felt mandatory, a pH probe could be considered.
- *Trials of H2RAs, sucralfate, simethicone, and antacids:* (Cochrane Database Syst Rev 2006; CD001960) H2RAs are more effective than placebo, but PPIs seem a better choice to treat the undiagnosed GERD pts in the NUD group. Antacids and sucralfate are not more effective than placebo. Simethicone 105 mg po tid is more effective than placebo, and about half of pts call the response "very good" (Aliment Pharmacol Ther 2002;16:1641).
- *Trial of a prokinetic agent:* It has been common practice to try a promotility agent, especially if pts have sx of bloating or postprandial fullness. These agents appear to be about 40% better than placebo. The withdrawal of cisapride from the U.S. market has made this approach less desirable. Metoclopramide, an alternative agent, is often poorly tolerated. Domperidone is not available in the U.S. but may be a useful trial where available.
- *Psychotropic drugs and psychotherapy:* In the absence of a specific psychiatric dx, there are no data to support the use of psychotropic agents in NUD. However, because anxiety and other psychiatric disorders may coexist with dyspepsia and make the sx less tolerable, many clinicians offer pts rx for the psychiatric disorder. There is insufficient evidence to conclude that psychological rx is effective (Am J Gastro 2004;99:1817), though data on the possible benefits of hypnotherapy are intriguing (GE 2002;123:1778).

3.8 Gastroparesis

Am J Gastro 2006;101:1129; GE 2004;127:1592

Cause: Acute gastroparesis (<3 months) can be seen postoperatively. It can also be caused by viral agents, hyperglycemia, hypokalemia, hypothyroidism, and drugs including narcotics, calcium channel blockers, and anticholinergics.

Chronic gastroparesis is most commonly caused by diabetes or is idiopathic. It can also be caused by gastric surgery (Am J Surg 1996;172:24), Parkinson's disease, cancer (especially lung and pancreas), hypothyroidism, anorexia nervosa, scleroderma, amyloid, polymyositis/dermatomyositis, chronic pseudo-obstruction, porphyria, and other CNS disease.

Pathophys: The stomach stores ingested food, mixes it with digestive juice, grinds it, and releases it in a controlled fashion into the small intestine. Emptying of solids occurs after a lag phase

during which food is moved from proximal stomach to the antrum, where it is ground up. After this initial lag phase, emptying of solids is linear, with about half of solids emptying in 60-100 min. A wide variety of motor abnormalities with poor coordination and hypomotility result in poor emptying.

Sx: Early satiety, nausea, and vomiting are the hallmarks of gastroparesis. Gastroparesis is probably an overlooked cause of postprandial abdominal pain and heartburn (Am J Gastro 1999;94:1029). Diabetics may exhibit sx of poor glycemic control. Sx do not correlate well with emptying times.

Si: Rarely, a succussion splash is heard from retained gastric contents. This is demonstrated by placing the stethoscope over the stomach and rocking the pt side to side.

Crs: The course is generally chronic, but pts whose illness is associated with features suggesting a viral illness (sudden onset, fever, vomiting, cramps, and diarrhea) seem to improve with time (Am J Gastro 1997;92:1501).

Cmplc: Malnutrition, aspiration, GERD.

Diff Dx: The sx of gastroparesis are nonspecific, so the differential is broad and includes GERD (p 33), PUD (p 68), nonulcer dyspepsia (p 76), gastric cancer (p 81), rumination syndrome (p 58), and other causes of upper abdominal pain (p 2) and nausea (p 7).

Lab: Appropriate labs include CBC, CMP, Hgb A_1c, and TSH to look for correctable causes or clues to other disorders in the diff dx.

X-ray: Scintigraphic gastric emptying studies are the gold standard for the dx of gastroparesis. Pts are given a meal of solids, typically eggs, laced with a radioisotope. Studies are typically reported as the time to empty half the isotope (normal is 60-100 min), or as proportion emptied at 100 min. The variation for repeat studies in individuals is about 15% (GE 1998;115:747).

Endoscopy: EGD is generally indicated to make sure that there is no mechanical cause of poor emptying (gastric outlet obstruction due to PUD or tumor).

Rx: General measures include rx of electrolyte disorders, small frequent meals, low-fat meals, and avoidance of high-fiber and nondigestible solids (peels, fruit pulp, etc). It may be helpful to replace solids with liquids. Glycemic control in diabetics should be optimized. Drugs for symptomatic pts include metoclopramide, erythromycin, and domperidone. Response is highly variable. Cisapride 10-20 mg po qid was the drug of choice until it was withdrawn from the U.S. market for its association with cardiac arrhythmias. Erythromycin, a motilin agonist, can be helpful but is not always well tolerated and tachyphylaxis can be a problem (Aliment Pharmacol Ther 2008;27:724). Metoclopramide 5-10 mg po ac and qhs is effective but is often poorly tolerated because of CNS side effects such as anxiety, restlessness, somnolence, and depression. In addition, irreversible tardive dyskinesia is an important long-term risk. Domperidone 40-80 mg daily in divided doses can be useful but is not readily available in the U.S., and the quality of the data supporting its use is limited (Am J Gastro 2007;102:2036; Clin Gastroenterol Hepatol 2008;6:726). In refractory cases, a jejunal tube feeding may be needed. A venting gastrostomy may provide sx relief. Gastrectomy is a last-resort intervention. Gastric pacemakers may have a role in refractory pts, but data showing benefit are very limited (Am J Gastro 2003;98:2122). There had been interest in therapy with botulinum toxin injected into the pylorus, but a recent randomized trial did not show benefit (Am J Gastro 2008;103:416).

3.9 Hiatal Hernia

Postgrad Med 1990;88:113

Epidem: Prevalence rate of 0.8-2.9% of all pts undergoing barium studies.

Pathophys: There are 3 commonly recognized types of hiatal hernia. In the **sliding hiatus hernia**, the GE junction is in the chest above the diaphragmatic hiatus, and the GE junction is the lead point of the hernia. This is by far the most common type of hernia. It is strongly associated with endoscopic esophagitis (Dig Dis Sci 1979;24:311) and sx of reflux. The diaphragmatic crus contributes substantially to the antireflux barrier at the normal GE junction, and this benefit is lost when the GE junction is displaced into the chest. In a **paraesophageal hernia**, the GE junction stays fixed, and the fundus and sometimes the body of the stomach migrate into the posterior mediastinum. The stomach may later rotate in the chest, causing obstruction (Arch Surg 1986;121:416). Very rarely the stomach may herniate through an entirely separate defect in the crus. In **mixed hernias**, the GE junction is in the chest, and a large portion of the stomach slides up to be beside the esophagus in the chest. Linear gastric erosions in the portion of stomach at or near the diaphragm commonly occur in pts with substantial sliding hernias. These ulcerations are often multiple, are seen on the crests of the folds, and may be blood covered (GE 1986;91:338). They are a well-recognized cause of iron deficiency and are referred to as Cameron ulcers (Gastrointest Endosc Clin N Am 1996;6:671).

Sx: Most pts with small or moderate sliding hiatal hernia are asymptomatic or have sx of GERD. In massive hernias and paraesophageal hernias, mechanical sx predominate and include the sudden onset of chest or epigastric pain, vomiting, and dysphagia (J Thorac Cardiovasc Surg 1998;115:828). Chronic reflux sx are also present in over half of pts. A sense of dyspnea may develop in massive hernias. In paraesophageal hernia, sx of postprandial chest pain dominate complaints of heartburn (Dig Dis Sci 1992;37:537). Acute incarceration can present as a surgical emergency with severe pain, fever, and sx of esophageal or gastric obstruction.

Si: None except in those presenting with incarceration who may be febrile and appear toxic.

Crs: Most pts with hiatal hernias have a benign course. There are no adequate data on the course of untreated massive hernias or paraesophageal hernias. Recent series suggest that sx progression is slow and that high-mortality emergent operations are less common than had been originally feared (Surg Clin N Am 2008;88:959).

Cmplc: Bleeding, usually occult, is common in large hernias. Incarceration, strangulation, and perforation are feared but rare except in massive and paraesophageal hernias.

X-ray: UGI series shows gastric mucosa above the diaphragm.

Endoscopy: The diaphragm can be seen endoscopically and moves with respiration. Hernia is diagnosed when the end of the tubular esophagus and apparent GE junction is above the diaphragm. The retroflexed view often makes the defect more obvious.

Rx:

- *Surgery:* (Semin Thorac Cardiovasc Surg 1997;9:163) Absolute indications for surgery include (1) severe obstruction that occurs when a large amount of stomach is in the chest and a volvulus results, (2) necrosis from incarceration, and (3) malignancy in the hernia. Other

indications for operations are less clear. It used to be a surgical dictum that all pts with a paraesophageal hernia needed operation because of the perception that these pts were at very high risk of dangerous complications (Arch Surg 1986;121:416). However, watchful waiting has become much more common since learning that the mortality of emergent operation is not as high as previously thought (Ann Surg 2002;236:492). Some pts may have surgery for chronic iron deficiency, though most such pts respond to medical rx. Sx from intermittent volvulus of the herniated stomach or symptomatic incarceration manifest by postprandial chest pain or fullness are relative indications for surgery. In surgery the distal esophagus is restored to an intra-abdominal position, a fundoplication is usually created, and the defect in the diaphragmatic hernia is fixed. Laparoscopic repair can be carried out in experienced hands (J Am Coll Surg 1998;186:428).

- *Medical therapy:* Most hernias require no specific medical rx except when associated with GERD or iron deficiency. In pts with iron deficiency, the blood loss is so slow that often iron supplementation alone is adequate. When iron is stopped, anemia recurs. The lesions do not heal with iron rx alone, but do frequently heal with short courses of H2RAs or PPIs. Maintenance with H2RAs or PPIs has not been well studied. It seems reasonable to treat with H2RAs or PPIs and iron and attempt to stop iron after stores are repleted. This is the preferred course if pts have associated reflux sx. However, long-term iron supplementation alone is usually effective (Am J Gastro 1992;87:622).

3.10 Gastric Volvulus

Gastroenterologist 1997;5:41

Epidem: Seen in young pts with congenital defects and in older pts associated with hiatal hernia.

Pathophys: A gastric volvulus is a 180-degree or greater rotation of the stomach out of its normal position. This occurs when the ligaments that hold the stomach in place are disrupted. This is associated with paraesophageal hernias in adults and congenital hernias in children, or it may be a primary event without any other evident defects. An **organoaxial volvulus** is created when the body of the stomach rotates on its long axis (a line connecting cardia and pylorus). Think of the stomach as a washcloth being wrung out. Twists occur in the proximal and distal stomach where the blood supply becomes compromised, and the clinical presentation is acute. There is also a chronic presentation in which the twist is not severe enough to obstruct or compromise the vasculature. A **mesenteroaxial volvulus** is created when the stomach folds upon itself around a line drawn from the mid-lesser to the mid-greater curve. There is no highly obstructing twist and no immediate threat to the vascular supply, so the clinical presentation is chronic.

Sx: **Acute** volvulus presents with the triad of sudden onset pain, vomiting followed by retching, and inability to pass an NG tube. **Chronic** volvulus has a nonspecific presentation with vague upper abdominal pain, bloating, and early satiety.

Cmplc: Perforation or bleeding in the acute presentation.

Diff Dx: For **acute** volvulus, the other differential points are the causes of sudden acute severe epigastric pain, notably perforated ulcer disease, pancreatitis, and, less likely, cholecystitis or other intra-abdominal catastrophe. For **chronic** volvulus, the differential is even broader

given the vague sx and includes peptic disease, gastric malignancy, gastroparesis, GERD, chronic pancreatitis, chronic mesenteric ischemia, and biliary colic (p 201).

X-ray: Barium studies are diagnostic, and this is one of the situations in which x-ray is more informative than EGD (shudder!). In organoaxial volvulus, the stomach looks upside-down with the greater curve above the lesser curve and the cardia and pylorus on the same plane. Mesenteroaxial volvulus is harder to visualize. The stomach may just be a distended sphere, or the antrum may be seen above the body. There are usually 2 gastric bubbles on plain film, 1 for the fundus and 1 for the antrum, with nothing in between where the fold is located.

Endoscopy: EGD may show the twist of organoaxial volvulus and the inability to intubate the pylorus. Otherwise the endoscopist just notes the odd anatomy and orders the barium study!

Rx: Acute volvulus is a surgical emergency. The volvulus is reduced, resection may be needed if there is necrosis, and the predisposing defects are fixed. In chronic volvulus, rx can also be surgical, but endoscopic reduction of the volvulus (Am J Gastro 1990;85:1486) and placement of 2 PEG tubes to anchor the stomach in place is an alternative (Am J Surg 1998;64:711).

3.11 Gastric Cancer

Lancet 2003;362:305; Am Fam Phys 2004;69:1133; Nejm 1995;333:32

Epidem: Wide variation of rates throughout the world with high-incidence areas in Japan, China, South America, and eastern Europe (30-80 cases/100 000/yr), and much lower incidence in western Europe and the U.S. (10 cases/100 000/yr). M:F ratio is approximately 2:1. In the U.S., incidence is more frequent in nonwhites than whites. Incidence declined steadily from 1930 to the 1970s. The incidence of adenocarcinoma of GE junction is rising rapidly. In the U.S., the mean age at dx is 70 yr (Ann Surg 1993;218:583).

Pathophys: Two types of adenocarcinoma are seen. The **intestinal type** is made up of gland-forming epithelium that results in discrete masses that ulcerate and are most often found in the distal stomach. This type of adenocarcinoma accounts for the greatest percentage of cases in high-incidence countries. In the **diffuse type**, cells have minimal cohesion and infiltrate the gastric wall without forming a discrete mass. This is more often seen in the proximal stomach, more often in younger pts, and has constant incidence throughout the world.

Early gastric cancer (EGC) is a cancer confined to the mucosa or submucosa regardless of lymph node involvement. In Japan, EGC has a 90% 5-yr survival rate, which makes screening more attractive. Perhaps 40% of Japanese cancers are EGC, but the rate is much lower in the West. For unknown reasons, survival is much better in Japanese pts with EGC than in Western pts (Gut 1997;41:142).

Conditions predisposing pts to gastric cancer include (1) chronic atrophic gastritis with intestinal metaplasia, (2) gastritis associated with pernicious anemia or gastric resection, (3) Hp infection (p 63), (4) Ménétrier's disease (p 90), and (5) adenomatous gastric polyps. DU lowers risk (Nejm 1996;335:242). **Genetic factors** may be important since gastric cancer clusters in families, in HNPCC pts, and in FAP pts, and is more common in blood group A pts. **Environmental factors** that are associated with increased risk include

smoking and diets rich in salted, smoked, pickled, or poorly preserved food. Lower risk is seen in people with diets rich in fresh fruits and vegetables. The role of nitrates and nitrites is unclear.

Sx: Only half of pts have abdominal pain. Other sx include weight loss (62%), nausea (34%), anorexia (32%), and less often dysphagia, melena, and early satiety. It can be difficult to distinguish GU from cancer in the elderly pt by hx. Of gastric cancer pts, 25% have a hx of GU (Ann Surg 1993;218:583).

Si: Abdominal mass, supraclavicular node (Virchow's node), periumbilical nodules from peritoneal spread (Sister Mary Joseph's node), enlarged ovary (Krukenberg tumor), mass in the cul-de-sac, and ascites.

Crs: The disease is staged by a complex TNM system into 4 stages based on tumor penetration, regional nodes, and distant mets. Involvement of intra-abdominal lymph nodes other than perigastric nodes puts pts into the unresectable stage IV. For all stages combined, 5-yr survival is 18% (CA Cancer J Clin 1995;45:8). In the U.S., 5-yr survivals are 50% for stage I, 29% for stage II, 13% for stage III, and 3% for stage IV. Survival is 40% higher for stage I and II tumors in Japan.

Diff Dx: Gastric lymphoma, leiomyosarcoma, PUD.

Lab: Anemia (40%), hypoproteinemia (26%), abnormal LFTs (26%), and positive FOBT (40%). Tumor markers (CEA, AFP, CA 19-9) are not helpful in early dx.

X-ray: If malignancy is suspected, endoscopy rather than UGI should be done. If UGI is done and shows questionable cancer or ulcer, EGD should be done.

Endoscopy: EGD may reveal an ulcer, a mass, or a diffuse infiltrative appearance in a nondistensible stomach. Multiple bx and brushings should be performed.

Rx: **Preoperative staging** is crucial, since pts with stage IV disease do not benefit from surgery in the absence of a sx to palliate such as bleeding or obstruction. Laparoscopy prevents laparotomy in up to one-fourth of pts by finding intra-abdominal lymph nodes or other mets not seen on CT (Nejm 1995;333:1426). Laparoscopic US may provide additional data on T and N staging. EUS is useful in initial T staging. Those with apparent T1 or T2 tumors should have resection, but those with T3 or T4 tumors should have laparoscopy (with possible laparoscopic US) to look for advanced nodal disease, which would place the pt in the unresectable stage IV (Semin Oncol 1996;23:347).

Resection of the primary tumor and the adjacent lymph nodes is the only chance for cure. Unfortunately, most pts in the West present with relatively advanced disease. If preoperative staging reveals no distant disease, surgery is undertaken. At operation, lymph node dissection can be of varying degrees. A D1 resection removes lymph nodes within 3 cm of the tumor en bloc with the stomach and greater omentum. A D2 resection additionally requires the resection of celiac nodes to the aorta, hepatoduodenal and retroduodenal nodes, splenic nodes, and retroperitoneal nodes. In practice, D2 operations often require distal pancreatectomy and splenectomy and dissection of the major vascular pedicles down to the aorta. In Japan, D2 resections are typically carried out except in the very elderly (Brit J Surg 1996;83:836), with survival about 30% better in stage II and III disease than in Western pts (Cancer 1999;86:1657). However, in Western countries, increased morbidity and mortality after D2 resections seems to negate any survival benefits of more extensive lymphadenectomy

(Lancet 1996;347:995). It is not clear if this is due to differences in disease biology, pt age, or surgical skill between the 2 regions. There is a survival advantage to adjuvant or perioperative chemotherapy with or without radiotherapy (Cancer J 2007;13:168). Palliative chemotherapy is a consideration for stage IV disease (Ann Oncol 2007;18 Suppl 2:ii17).

3.12 MALT and Other Gastric Lymphomas

Am J Gastro 2003;98:975; Br J Haematol 1998;100:3; Gastroenterologist 1996;4:54

Epidem: Gastric lymphoma is an uncommon disease. Lymphoma represents 3% of all gastric malignancies, and up to half may be of the MALT type (J Clin Gastroenterol 1999;29:133).

Pathophys: The stomach does not ordinarily have lymphoid tissue. Mucosa-associated lymphoid tissue (MALT) in the stomach is made up of nonneoplastic lymphoid follicles. These follicles arise in response to chronic antigenic stimulation, typically due to Hp infection. **MALT lymphoma** (MALToma) arises from malignant transformation of a clone of B cells. The B cells respond to signals from Hp-specific T cells (Lancet 1993;342:571), and the tumor tends to stay localized in the stomach by virtue of a homing mechanism in the B cells. However, MALTomas can transform into higher grade lesions and disseminate into lymph nodes and bone marrow (Br J Haematol 1998;100:3). Most other primary gastric, **non-Hodgkin's lymphomas** are diffuse, large-cell lymphomas of B-cell origin. About 60% of gastric lymphomas arise in chronic gastritis.

Sx: Epigastric pain, weight loss, anorexia, vomiting, melena, hematemesis, back pain, and nausea.

Si: Epigastric tenderness, positive FOBT.

Crs: MALT lymphoma is generally an indolent disease, often remaining localized for years without rx, with a 5-yr survival of 82% (Br J Haematol 1998;100:3). For other gastric lymphomas, 5-yr survivals vary widely, but overall survival runs about 40% (Gut 1995;36:679). Five-yr survival is closer to 88% in pts whose disease does not spread into other intra-abdominal organs or outside the abdomen (Eur J Surg Oncol 1994;20:525).

Cmplc: Bleeding and perforation may occur, especially with chemotherapy, but are not as common as once feared.

Diff Dx: Gastric cancer, benign GU, gastric Crohn's, gastric TB, gastric sarcoid, syphilis (Nejm 1995;332:1153), and the broad diff dx of dyspepsia (p 2).

Lab: Histologically, MALTomas appear as lesions in which gastric glands and crypts are invaded and partially destroyed by abnormal lymphocytes (Br J Haematol 1998;100:3). Confusion with Hp gastritis can be a problem for the pathologist, and sampling error may be a problem. Bone marrow bx is done as part of staging.

X-ray: CT scan may show thickening of the stomach or nodal involvement. Staging is done with CT of chest, abdomen, and pelvis.

Endoscopy: EGD may demonstrate a malignant-appearing mass or ulcer, thickened folds, or nonspecific gastritis. EUS can identify disease that is beyond the submucosa.

Rx: For **MALT lymphoma**, a trial of Hp rx (p 67) should be the first line for pts with disease confined to mucosa and submucosa. A response rate of 60% is expected but may take months

to occur (Ann IM 1995;122:767). Pts with disease beyond the mucosa and submucosa at EUS do not respond to antibiotic rx alone (GE 1997;113:1087), but elimination of Hp is still worthwhile. Chemotherapy and radiation are considerations for pts who do not respond or who relapse after antibiotics. Surgery is now generally reserved for those with localized residual disease or complications after medical therapy.

For non-MALT lymphomas, gastric resection was once the mainstay of rx (Br J Haematol 2007;136:521). This operation was performed to make a tissue dx, to stage, and to cure the cases in which the disease was confined to the stomach. It was thought that gastric resection would prevent future hemorrhage or perforation when pts received chemotherapy. However, surgery is usually not needed for dx, understaging is a moot point if systemic chemotherapy is used, and the incidence of perforation and bleeding may be lower than the morbidity of surgery. Therefore, as in MALT lymphoma, surgery is largely reserved for disease persisting after medical rx (Ann Surg 2004;240:28).

3.13 Gastric Polyps

Arch Pathol Lab Med 2008;132:633; Endoscopy 1995;27:32

Epidem: Autopsy prevalence of gastric polyps is 0.12-0.8% (Am J Gastro 1995;90:2152). They are found at about 2% of endoscopies. Adenomatous gastric polyps are uncommon under the age of 50 yr; fundic gland polyps, hyperplastic polyps, and inflammatory polyps are more common in women (Endoscopy 1994;26:659).

Pathophys: A recent large series showed several histologies in the 6% of EGD pts who had polyps (Am J Gastro 2009;104:1524). **Fundic gland polyps** were seen in 77%. Histologically they are glandular cysts found in body and fundus, and endoscopically they are small and hemispherical. The presence of somatic mutations suggests that theses are neoplastic lesions. They are of no clinical consequence unless they are associated with FAP or attenuated FAP (GE 2003;125:1462). They are often seen as a consequence of PPI rx. **Hyperplastic polyps** were seen in 17%. Hp infection may be etiologic in that clearance of Hp causes regression of polyps (Ann IM 1998;129:712). There are reports of large hyperplastic polyps harboring carcinoma (Gastrointest Endosc 1993;39:830) and reports of the development of focal carcinoma in hyperplastic polyps (Am J Gastro 1995;90:2152). However, this is rare enough that most practitioners consider them harmless (Endoscopy 1995;27:32) unless they bleed or obstruct the pylorus. **Adenomatous polyps** (0.69% of the total) are neoplastic lesions typically seen in the antrum, in which malignant transformation occurs about 10% of the time (Am J Gastroenterol 1998;93:2559). Other infrequent lesions include polypoid adenocarcinoma, inflammatory polyps, carcinoid, Brunner's gland heterotopia, pancreatic rests, xanthoma/xanthelasma, Peutz-Jeghers, GISTs (p 85), Cronkite-Canada, and juvenile polyps.

Sx: Usually none unless they bleed or prolapse through pylorus and cause pain and vomiting (Endoscopy 1996;28:452).

Cmplc: Bleeding, malignant transformation, obstruction of pylorus.

Diff Dx: Gastric epithelial polyps may be confused with subepithelial lesions such as GIST, leiomyoma, or lipoma. However, in these entities, bx of the overlying mucosa is normal.

Endoscopy: Fundic gland polyps are shiny and generally small (mean 4 mm) so that they can be plucked like grapes with a bx forceps. Hyperplastic polyps are soft and often have an eroded surface. Eroded surfaces can also be seen in inflammatory polyps and polypoid cancers. Because endoscopic appearance is not diagnostic, a forceps bx is always indicated (Endoscopy 1994;26:659).

Rx: All gastric polyps should undergo bx. If an adenoma is detected, the polyp should be excised and follow-up should be done. The American Society for Gastrointestinal Endoscopy (ASGE) recommends repeat EGD in a year and every 3-5 yr thereafter. If hyperplastic polyps are found, Hp should be sought and eliminated (Ann IM 1998;129:712). Routine follow-up EGD thereafter seems like overkill. However, some authors recommend excision of large hyperplastic lesions (because they are more likely to harbor cancer), and a minority excise all such polyps and perform follow-up endoscopy (Am J Gastro 1998;93:2559). Consider FAP or attenuated FAP (p 146) if a large number of fundic gland polyps are found in a younger pt. Bleeding or obstructing lesions should be excised.

3.14 Subepithelial Gastric Lesions

GE 2006;130:2215; Gastro Endosc 2002;56:S43; GE 2004;126:301

Cause: Most subepithelial lesions of the stomach are found incidentally at upper endoscopy and may arise from any of the layers of the stomach (not just the submucosa). The most common of these is the gastrointestinal stromal tumor (GIST), which is potentially malignant (Gastro Endosc 2003;58:80). Older literature is confusing because GISTs were previously thought to be leiomyomas, leiomyoblastomas, or sarcomas. Other malignant or potentially malignant subepithelial gastric lesions include carcinoids, lymphoma, glomus tumors, and metastatic disease. Lipomas are the second most common subepithelial tumor. Other benign causes of subepithelial gastric lesions include extrinsic compression, varices, pancreatic rests (ectopic pancreatic tissue), true leiomyomas, neural origin tumors (including Schwannomas, neuromas), duplication cysts, and inflammatory fibroid polyps.

Epidem: GISTs typically present in pts over 50 yr. The incidence is unknown with estimates of up to 6 000 new cases/yr in the U.S., with up to 30% of these malignant in behavior.

Pathophys: **GISTs** are believed to arise from the interstitial cells of Cajal, which are pacemaker cells important in normal motility (Hum Pathol 2002;33:456). They are defined by immunohistochemical staining for CD-117 (aka c-kit protein), a cell membrane receptor with tyrosine kinase activity. All GISTs appear to have malignant potential, and it is not possible to classify them as simply benign or malignant. Recent classification schemes use size and mitotic count of excised specimens to define risks (Hum Pathol 2002;33:459). Lesions under 1 cm are almost always benign in behavior, and those under 2 cm with low mitotic counts are very low risk. Risk increases with size, and lesions >5 cm are very high risk. **Glomus tumors** are lesions that arise from modified vascular smooth muscle cells. They are uncommon and are usually, but not always, benign. They can ulcerate or bleed. **Gastric carcinoids** are usually associated with atrophic gastritis and present as small lesions in the body or fundus found incidentally at endoscopy. They can also be seen in ZE syndrome (p 86). These 2 groups of

pts have elevated gastrin levels. Carcinoids can also be sporadic (in which pts have normal gastrin levels), and these pts have a high incidence of mets and carcinoid syndrome. **Lipomas** are almost always unimportant except in rare instances where they cause bleeding or obstruction.

Sx: Usually none unless they bleed, obstruct, or metastasize.

Cmplc: Bleeding, malignant transformation, obstruction of pylorus.

Diff Dx: The identity of a subepithelial lesion is determined by EGD, EUS, or other imaging modalities.

Endoscopy: (GE 2004;126:301) Subepithelial lesions are evaluated for size, consistency, color, and shape. The overlying mucosa is biopsied and some submucosal elements may be sampled. GISTs are usually firm and immobile. Lipomas are often yellowish, compress like a pillow with a forceps, and are usually mobile. Varices are usually bluish in color. Pancreatic rests are often antral and may have a central umbilication. Changing pt position may help to define extrinsic compression.

If the cause of the lesion is not evident at EGD, it should be evaluated with EUS, which can determine the size and the layer of origin, identify features suggestive of malignancy, and often establish a dx. Fine-needle aspiration (FNA) with immunohistochemical staining is used to attempt to separate GISTs from leiomyomas, glomus tumors, and neural tumors. Mitotic activity of a GIST (one of the predictors of malignant behavior) cannot be determined on aspirated samples. Endoscopic subepithelial resection and core needle bx are evolving approaches to dx and rx.

Rx: Lipomas, duplication cysts, pancreatic rests, inflammatory polyps, and neural origin tumors require no intervention or follow-up. Extrinsic compression, metastatic disease, lymphoma, and varices are evaluated and treated as clinically appropriate. GISTs under 3 cm can be followed or resected depending on the wishes and medical fitness of the pt. For GISTs ≥3 cm, surgical excision is warranted. Metastatic GIST can now be treated with imatinib, a tyrosine kinase inhibitor that targets the specific molecular abnormality seen in GISTs (Lancet 2001;358:1421). Carcinoids in pts with normal gastrin levels are prone to metastatic disease and should be resected.

3.15 Zollinger-Ellison Syndrome

Annu Rev Med 1995;46:395

Cause: Gastrin-secreting tumor.

Epidem: Incidence about 0.1-3/million/yr. Mean age of onset is 50 yr with a range of age 7-90 yr. Incidence greater in men than in women.

Pathophys: Gastrinomas secrete gastrin, which causes gastric acid hypersecretion. The hyperacidity results in PUD in most cases or in sx of severe GERD. Diarrhea is caused by direct damage to small intestinal mucosa, inactivation of lipase by acid, and precipitation of bile salts (Nejm 1987;317:1200). The tumors (which can be multiple) can be difficult to find. They are usually located in the gastrinoma triangle, bounded by the junction of cystic duct with common bile duct superiorly, the junction of 2nd and 3rd portions of duodenum inferiorly, and the junction

of the body and head of pancreas medially. Metastatic disease most often involves the liver and is the usual cause of death.

Sx: Epigastric pain is the usual presenting sx, and 90% of pts will have PUD at some point. Up to 60% of pts will have sx of GERD, often severe. Diarrhea can be the sole sx in 20% of pts.

Crs: The growth of the tumor can be very slow and the course protracted. The survival of all pts with gastrinoma is about 60% at 5 yr and 50% at 10 yr. Ten-yr survival is very high (90-100%) when no tumor is found at surgery and much lower (20-40%) in pts with unresectable metastatic disease.

Cmplc: Complications of ulcer disease with bleeding, perforation, or obstruction may occur.

Diff Dx: ZE must be distinguished from simple recurrent PUD. The latter is quite uncommon in the setting of rx for Hp and cessation of NSAIDs. ZE should be ruled out when pts present with recurrent ulcers despite rx. Severe diarrhea, especially if associated with PUD, should raise consideration of ZE. A strong family hx of ulcer or the combination of ulcer with hyperparathyroidism raises the question of ZE and multiple endocrine neoplasia (MEN type 1 [Ann IM 1998;129:484]). MEN type 1 is present in 10-50% of pts with ZE, and ZE occurs in 20-70% of MEN type 1 pts (Medicine 2004;83:43).

ZE is not the only cause of high gastrin. High gastrin can be caused by achlorhydria (due to pernicious anemia, PPIs, or atrophic gastritis), G-cell hyperplasia, postvagotomy state, renal failure, gastric outlet obstruction, and retained gastric antrum after surgery. These can be distinguished by provocative lab tests.

Lab: Serum gastrin is highly sensitive and is typically obtained by fasting pts for 3 days, because serum levels can fluctuate. A value of >100 pg/mL raises the question of ZE, but typically levels are much higher. Achlorhydria as a cause of elevated gastrin is excluded by verifying that the stomach produces acid by gastric sampling. A variety of provocative tests in which tumors are stimulated to produce gastrin by the infusion of secretin, calcium, or other substances have been used. The secretin test is preferred. An increase in the gastrin levels of >200 pg/mL within 2-15 min of secretin infusion is diagnostic (Surg Clin N Am 1995;75:511). PPIs can cause a false positive secretin test (Clin Gastroenterol Hepatol 2009;7:600).

X-ray: Localizing the tumor is difficult, but it is crucial to the outcome. Multiple imaging tests (combinations of CT, MRI, angiograms, portal venous gastrin sampling, and labeled octreotide analog scans) are typically required since no single test is sensitive for both the primary lesion and metastatic disease (Clin Radiol 1994;49:295). The purpose of imaging is to identify lesions for a cure, to identify multiple lesions if present, and to find hepatic or other mets that may preclude surgery or require resection (Surg Clin N Am 1995;75:511).

Endoscopy: EUS may reduce the need for angiograms and portal venous sampling (Gastrointest Endosc 1999;49:19).

Rx: PPIs are the drugs of choice for suppression of acid in the pts who are not cured by surgery. The drug dosage is titrated to lower the basal acid output (BAO) to <5 mmol/hr for pts with intact stomachs and to <1 mmol/hr for postgastrectomy pts who need higher levels of acid suppression (Aliment Pharmacol Ther 1996;10:507).

All pts should undergo laparotomy unless substantial hepatic mets are found. In expert hands, short-term cure is 80% and long-term cure is 30% (Ann Surg 1992;215:8). In pts with persistent or recurrent disease after a first operation, a reoperation cures 30% of pts and

should be considered if imaging studies show the tumor (Surgery 1996;120:1055). Pts with MEN type 1 have tumors that are small and multifocal, and cure is rare. Some experts suggest operation only if tumor is found on preoperative imaging studies (Surg Clin N Am 1995;75:511).

3.16 Bezoars

Gastrointest Endosc Clin N Am 1996;6:605

Epidem: Trichobezoars are typically found in girls. Phytobezoars are more common in middle-aged men.

Pathophys: A bezoar is swallowed material that fails to clear from the stomach and forms into a mass or concretion. Most bezoars form in pts with prior gastric surgery, gastroparesis, or unusual ingestions on a psychiatric or behavioral basis. The most common type is a vegetable matter bezoar **(phytobezoar)**. Excessive vegetable fiber intake and poor mastication may be important, but prior gastric surgery seems to be the biggest risk (Brit J Surg 1994;81:1000). Unripened persimmons frequently cause bezoars from a coagulum caused when the fruit pulp is exposed to acid. Less common are hair bezoars **(trichobezoars)** typically found in children who compulsively pull and eat their hair (Mayo Clin Proc 1998;73:653). A large number of foreign substances, such as cement, shellac, cotton, paper, and a variety of pills can develop into bezoars. These foreign substance bezoars are most frequently found in psychiatric or institutionalized pts with pica.

Sx: Abdominal pain, nausea, bloating, early satiety, halitosis, and weight loss.

Crs: Because the underlying disease is usually still present, bezoars frequently recur.

Cmplc: gastric ulcer, perforation, bleeding.

Diff Dx: Dx is usually not a problem when the investigation of a nonspecific sx leads to a diagnostic UGI, CT, or EGD.

X-ray: UGI or CT shows a freely mobile mass.

Endoscopy: Needed for definitive dx. Phytobezoars are amorphous masses. Trichobezoars are usually black, slimy, and have visible hairs.

Rx: A few days of a liquid, low-residue diet may be sufficient in mild cases. Papain (a proteolytic enzyme) or cellulase is 80% successful in dissolving phytobezoars (Am J Gastro 1993;88:1663). Underlying gastroparesis should be treated to prevent recurrence, and foods high in fruit pulp and vegetable fiber need to be avoided. Trichobezoars are challenging to remove endoscopically (Gastrointest Endosc 1993;39:698). Surgery may be needed if bezoars have caused perforation or are too large for endoscopy (Mayo Clin Proc 1998;73:653).

3.17 Gastric Antral Vascular Ectasias

Gut 2001;49:866; J Clin Gastroenterol 1992;15:256

Epidem: Uncommon disorder, true incidence unknown. Predominance in women, with age range of 50-90 yr in most series (Am J Clin Pathol 1998;109:558).

Pathophys: The dx of gastric antral vascular ectasia (GAVE) is made when intensely red stripes of mucosa are seen in the antrum radiating from the pylorus in a pt with evidence of chronic GI bleeding. Bx, if done, shows features of vascular ectasia, intravascular thrombi, and vascular hyperplasia, but is not specific or diagnostic. This disorder is more frequent in pts with chronic liver disease and in pts who have undergone bone marrow transplant (Gastrointest Endosc 1996;44:223). The pathogenesis is unknown, and theories have postulated roles for portal HTN, antral motility disorders, and humoral factors (Gastrointest Endosc 1996;44:355).

Sx: Those of the anemia associated with chronic GI blood loss and intermittent melena.

Crs: Chronic GI blood loss without rx.

Diff Dx: Two areas of confusion may arise. The first is distinguishing GAVE in pts with liver disease from severe portal hypertensive gastropathy (p 256). This distinction usually is made on the basis of the endoscopic appearance, with the latter involving the more proximal stomach and being more diffuse. Histology may aid in the distinction. The other endoscopic confusion might be in separating mild GAVE from stripes of antral inflammation.

Lab: Iron deficiency.

Endoscopy: As described in Diff Dx.

Rx: Argon plasma coagulation is the endoscopic therapy of choice (Best Pract Res Clin Gastroenterol 2008;22:313). Antrectomy is effective but is not generally necessary if endoscopic rx is available (GE 1984;87:1165).

3.18 Dieulafoy's Ulcer

Gastrointest Endosc Clin N Am 1996;6:739; Am J Gastro 2001;96:1688

Epidem: An uncommon cause of UGI bleeding representing 1.5-2% of all cases of massive upper bleeding. Mean age of incidence is 60 yr, with a large age range and predominance in men.

Pathophys: A Dieulafoy's ulcer is a tiny mucosal ulcer that forms over a very large submucosal blood vessel. It has been proposed that the ulcer forms because the mucosa is compromised by mechanical effects of the large blood vessel close to the surface. Dieulafoy's ulcers are most often seen in the proximal stomach (75%), distal stomach (13%), or proximal duodenum (12%), but have also been reported elsewhere in the small intestine and colon (J Clin Gastroenterol 1998;27:169).

Sx/Si: The sx and si are those of acute massive UGI bleeding (p 21).

Crs: After initial hemostasis is achieved by endoscopic means, recurrent bleeding is uncommon (Endoscopy 1997;29:834). Episodes of rebleeding years later have been recorded (Gastrointest Endosc 1999;50:762).

Cmplc: Perforation due to endoscopic rx is uncommon.

Diff Dx: The diff dx is that of UGI bleeding (p 21). However, the lesion should be listed high on the differential when there is a substantial acute bleed and the initial EGD shows no cause or shows minor abnormalities that do not adequately explain a massive bleed.

X-ray: Arteriography cannot make a dx unless there is active bleeding, and it is of little value.

Endoscopy: EGD shows the tiny ulcer, sometimes with the tip of a protruding vessel poking out. There is little if any surrounding inflammatory reaction. Good air insufflation is needed. The dx is made at initial EGD only half the time, and multiple EGDs may be needed. Sometimes if an exam is done within a few hours of the bleeding, some clot remains in the ulcer, which makes it easier to spot.

Rx: Endoscopic rx is successful on the first attempt in about 85% of cases. In other cases, a second endoscopic attempt or surgery is needed. There is no science to guide the selection of the method of endoscopic rx. Heater probe, BICAP, sclerotherapy, hemoclipping, band ligation, and laser all seem effective (Endoscopy 1997;29:834). When endoscopic rx fails, surgery with limited wedge resection using intraoperative endoscopic guidance is appropriate (J Am Coll Surg 1994;179:182).

3.19 Ménétrier's Disease

This is a rare condition characterized clinically by giant gastric folds, usually in body and fundus, by low gastric acid secretion even when stimulated, and by protein loss from hyperplastic gastric mucosa (Ann Surg 1988;208:694). Pathologically, there is hyperplasia of the surface of the mucosa and atrophy of the glandular component in the body. Surgery is the definitive rx (Ann Surg 1988;208:694), but response to medical rx including anticholinergics, acid blockers, and prednisone have been reported (J Clin Gastroenterol 1991;13:436). Response to rx with a monoclonal ab to epidermal growth factor receptor has been reported (Nejm 2000;343:1697). Octreotide has been used successfully (Dig Dis Sci 2009;54:1403). Gastric carcinoma may complicate the illness.

Chapter 4

Inflammatory, Functional, and Other Intestinal Disorders

4.1 Irritable Bowel Syndrome

Am J Gastro 2009;104 Suppl 1:S1; GE 2002;123:2105; Nejm 2003;349:2136

Epidem: In a large U.S. householder survey, the prevalence of irritable bowel syndrome (IBS) sx was 9.4% (Dig Dis Sci 1993;38:1569). In a large U.S. county survey, the prevalence of IBS sx was 17% (GE 1991;101:927). In contrast, only 2.9% of the population reports a medical dx of IBS, because most people with sx of IBS do not become *pts* with IBS (GE 1990;99:409). Women are more than twice as likely to have IBS sx and even more likely to seek care for IBS sx (GE 1991;100:998). Sx reporting decreases with age, suggesting the benign course of these sx (Scand J Gastroenterol 1994;29:102). There are no differences between the physical or psychological sx of men and women, but there are few studies of sx in men (Am J Gastro 2000;95:11). The economic cost is huge. Pts with IBS lose twice as many work days due to illness, require greater numbers of physician visits for GI and non-GI sx (Dig Dis Sci 1993;38:1569), and undergo many more appendectomies, cholecystectomies, hysterectomies, and back surgeries (GE 2004;126:1665).

Pathophys:

- *Definition of IBS:* A working definition of IBS is needed to conduct sound clinical studies. This has proved to be difficult. The most widely used criteria to define IBS are referred to as the Rome criteria, which were published in 1992 and then substantially revised (Gut 1999;45[suppl 2]:II43). Given the limited number of GI sx possible with any gut disorder, it is impossible to develop a definition, based on clinical sx, that will distinguish IBS from other bowel diseases (Am J Med 1999;107:5S). As a practical matter, IBS is considered when a pt presents with abdominal pain and disordered defecation for more than 3 months in the absence of structural disease.
- *Abnormal motility and IBS:* Resting motility is similar in IBS and non-IBS pts, but IBS pts have increased motility in response to stimuli such as food or psychological stress. The severity of pain does not correlate with abnormal motility (Gastroenterologist 1994;2:315).
- *Abnormal visceral perception and IBS:* (Gut 2002;51[suppl 1]:i67) There is a body of evidence suggesting that enhanced visceral sensitivity is a factor in IBS pathophysiology. IBS pts

perceive pain from balloon distension of the rectum or ileum at pressures and volumes much lower than controls do. The mechanisms of enhanced sensitivity are unclear. It is thought that multiple inciting factors (genetic factors, chronic inflammation, psychological stresses, peripheral nerve irritation) alter afferent pain pathways to the brain and leave them permanently revved up long after the inciting stimulus goes away. In a sense, the IBS pt develops a pain memory that causes stimuli, which an ordinary subject would not perceive, to be experienced as pain. These stimuli are further modulated by the CNS in ways that might further enhance the perception of pain. Serotonin is an important signaling molecule within the GI tract and enteric nervous system (GE 2007;132:397), and effective serotonergic drugs have been developed for rx of IBS.

- *Psychosocial factors and IBS:* Up to 60% of IBS pts have psychosocial difficulties, including major psychiatric disorders, personality disorders, stressful life events, a hx of physical or sexual abuse, and chronic pain behaviors. These psychosocial factors distinguish IBS pts from pts with IBS sx who do not seek medical attention. Psychosocial factors play a major role in explaining why the IBS pt experiences sx as being more severe than the individual who has the same IBS sx and copes without medical evaluation. These psychosocial problems translate into worse outcomes (measured by more disability days, more physician visits, and more medicines). A hx of sexual or physical abuse is one of the strongest predictors of poor outcome. Those with the most severe IBS have the greatest psychosocial stressors (Am J Med 1999;107:41S).
- *Food intolerance:* A subgroup of pts have sx of IBS in response to specific foods. These intolerances have been verified with blinded administration of the offending foods through an NG tube. The mechanism does not appear to be allergic, but it does provide a rational basis for the use of food and sx diaries in pts with moderate sx. Some clinicians have pts pursue strict exclusion diets to find the offending food (Lancet 1982;2:1115).
- *Bacterial overgrowth:* Bacterial overgrowth may be an important factor in subgroups of pts with diarrhea or bloating as evidenced by the response to antibiotic therapy (see Rx).

Sx: Since IBS cannot be defined by any test or structural abnormality, it is recognized by its sx. Three sx patterns are recognized. The patterns require different diagnostic workups and respond differently to rx (Am J Med 1999;107:20S). Common to all 3 subtypes are that: (1) the pts have pain or closely related noxious sx; (2) the sx are chronic, typically lasting years; (3) the sx typically begin insidiously in young adulthood; and (4) there are no findings to suggest structural diseases (ie, no weight loss, bleeding, fever, etc). Sudden-onset sx, especially in older pts, are usually not IBS. Sx that awaken pts from sleep are less common but do not rule out IBS. The recognized sx patterns are:

- *Diarrhea-predominant IBS:* The pts have pain associated with loose, watery BMs and great urgency. Pts often describe the stools as explosive, and typically several will be passed in a short period requiring several trips to the toilet. The BMs often cluster in the morning. Pts are usually well once the flurry of activity passes. Sometimes bouts are directly related to stressful events (taking tests, job-related stress, Monday morning).
- *Constipation-predominant IBS:* These pts have crampy lower abdominal pain associated with infrequent BMs. The stool is hard and looks like it is composed of individual pellets packed together. There is a sense of incomplete evacuation and straining at stool. Pain is relieved by passage of a BM. Interestingly, such constipation-predominant pts are more likely to have dyspepsia, musculoskeletal pain, poor sleep, and sexual dysfunction (Am J Med 1999;107:20S).

- *Mixed-diarrhea/constipation IBS:* This group presents with complaints of constipation alternating with diarrhea. These pts have crampy pain and go days without BMs. Eventually they pass hard, dry BMs. After the initial hard, dry stool has passed, a number of looser BMs may follow and the pt may complain of diarrhea. The pt then may be without sx for a day or 2 and the pattern often repeats.
- *Pain/discomfort-predominant IBS:* This group presents with complaints of generalized discomfort/pain, usually associated with bloating, a perception of abdominal distension, and a sensation of gas. Their sx may or may not be related to meals, and the relief with BMs is variable. They tend to experience sx over a greater part of the day. The distension is often thought by physicians to be imaginary, but increases in abdominal girth are seen in IBS pts compared to controls without a clearly defined mechanism (Gut 1991;32:662).

Si: PE is useful only for detecting structural diseases by palpation of masses, detection of blood, and identification of abdominal wall pain. No positive finding on physical exam makes IBS more likely or predicts clinical outcome or response to rx (Am J Med 1999;107:33S).

Crs: Combining results of observational studies, it is evident that more than 50% of pts have improvement in their sx over the course of years. Complaints vary in severity over time but tend not to change in their quality. Psychological distress and a long duration of complaints correlate with poorer outcome (Scand J Gastroenterol 1998;33:561).

Diff Dx: One approach to diff dx in IBS is to list all disorders known to humankind that cause diarrhea, constipation, or abdominal pain. This can lead to a lengthy list and the compulsion to rule out each dx on the list with a specific test. In practice, such a complete diff dx and subsequent workup is unnecessary. It is more fruitful to consider a short diff dx for the specific set of pt complaints, taking into account the age of the pt and the duration and severity of sx.

For pts with **diarrhea** as a predominant sx routine, celiac disease testing (p 119) should be considered. The prevalence of celiac disease in pts meeting diagnostic criteria for IBS is substantially increased (Arch IM 2009;169:651). Other conditions to consider include lactose intolerance (p 102), drug-induced diarrhea, bacterial overgrowth (p 169) sorbitol ingestion (p 11), surreptitious laxative use, and IBD. Infections are uncommon if the sx are long standing, except in areas endemic for parasitic infections. The malabsorptive diseases, such as pancreatic insufficiency, rarely present with the crampy lower abdominal pain typical of diarrhea-predominant IBS. Uncommonly, collagenous colitis and selective bile salt malabsorption are considerations. Only in refractory cases does a more extensive diff dx for chronic diarrhea need to be considered (p 17).

For pts with **constipation**-predominant sx, age and duration of sx guide testing. In those with a short-duration sx and in those >40 yr of age, colonic obstruction due to malignancy is a consideration. The reader should review the discussion of constipation (p 11).

The diff dx for pts with **pain/discomfort**-predominant IBS is more complex. Consider lactose intolerance (p 102), sorbitol ingestion (p 11), partial mechanical obstruction (p 123), Crohn's disease (p 105), pseudo-obstruction (p 126), malabsorption (p 19), gastroparesis (p 77), and bacterial overgrowth (p 169).

Lab: A CBC and CMP are commonly performed to find clues to more serious illness. Stool testing for FOBT is reasonable. TSH should be done for specific reasons such as diarrhea or constipation. Stool studies for infectious causes are of very low yield if the sx are long

standing and not recently changed. Stool testing can be considered in areas endemic for parasitic infection or in pts with recent exacerbation of diarrheal sx. In refractory diarrhea, a 72-hr stool collection for weight and fat can help identify those with a structural cause of diarrhea by demonstrating stool weight >300 gm/day or malabsorption of fat (p 19).

X-ray: CT enterography or SBFT is indicated if Crohn's disease is suspected or if there are other clues to mechanical obstruction. CT colonography or ACBE in combination with sigmoidoscopy can be used in the small number of pts in whom obstructing neoplasm must be ruled out. However, colonoscopy would be the test of choice in pts over the age of 50 yr, who might have the secondary benefit of the most effective screening for polyps.

Endoscopy: Endoscopy is not indicated in the vast majority of pts with IBS. The threshold to perform colonoscopy to evaluate possible IBS sx should be lower in older pts, in pts with sudden-onset sx, and in pts with refractory diarrhea. The yield will be higher in these pts, and they gain the additional benefit of clearing the colon of polyps as a means of preventing future CRC. Sigmoidoscopy should not be part of the routine workup of IBS but should be done for specific clues that pathology is within reach of the sigmoidoscope.

Rx:

Initial approach:

- *Evaluation of the pt's complaints can be therapeutic:* Pts with long-standing complaints seek care for a variety of reasons. Many are concerned that they may have a dangerous underlying illness, while others simply seek relief of sx. It is important to know the pt's reason for seeking care. A detailed hx, obtained with empathy, is crucial to demonstrate to the pt that the physician takes the complaints seriously and is competent to evaluate them. A cursory hx and blind reassurance on that basis can be destructive even if the physician is entirely correct with the dx. Explain to the pt the diff dx being considered and the planned evaluation to rule out structural illness. Reassure the pt that if he/she fails to respond to the initial therapeutic approach and if the initial testing is unrevealing, further testing and rx will be carefully considered. However, it is important to not create unrealistic expectations about the goals of rx or the extent of diagnostic testing needed.
- *Dietary fiber:* Establish the importance of diet in the pt's sx with a detailed dietary hx. Estimate the pt's daily fiber intake in grams by determining the pt's intake of whole-grain bread, cereal, beans, fruits, and vegetables (Am Fam Phys 1995;51:419). A fiber intake of 25 gms will generally improve pts with constipation and helps some with diarrhea-predominant IBS. Its use in diarrhea-predominant pts is controversial, given limited evidence of efficacy (Am J Med 1999;107:27S). Some pts will experience bloating as fiber is increased due to fermentation/degradation, so the amount of fiber should be increased gradually. Fluid intake should be increased as dietary fiber is increased. As an alternative, fiber supplements containing psyllium seed, methylcellulose, or polycarbophil can be used (p 13), but diet should be tried first in those who are willing.
- *Trial of lactose exclusion:* Establish the daily intake of lactose-containing products. In pts with diarrhea or bloating, a therapeutic trial of exclusion of lactose (for 7-14 days) is worthwhile. Some authors do breath testing for lactose intolerance instead. This spares some pts an unneeded trial but does not answer the question as to whether lactose intolerance is responsible for sx (p 102).

- *Exclusion of excessive sorbitol:* In pts with diarrhea or bloating, determine the intake of sorbitol. Sorbitol is not absorbed and is then fermented by bacteria, causing distress or diarrhea. It can be found in sugarless gum, breath mints, some hard candy, apples, pears, peaches, prunes, and foods sweetened for diabetics.
- *Legumes:* Determine the intake of beans, cabbage, broccoli, and cauliflower. For pts with bloating and gas, consider a trial of exclusion or of an alpha-galactosidase preparation such as Beano (J Fam Pract 1994;39:441).
- *Fatty foods:* In IBS there can be abnormal motility in response to a variety of triggers, and for some pts this includes fatty foods.

In pts without a good response to the initial approach, consider:

- *Rethinking of the dx:* If pts do not improve with initial management, the physician should rethink the dx and workup. For example, failure of constipation to respond to a high-fiber diet might prompt excluding obstruction. Failure of diarrhea to improve after excluding milk and sorbitol may cause reconsideration of other causes of chronic diarrhea (p 17), especially celiac disease or IBD.
- *Antidiarrheal agents:* Loperamide is effective in treating chronic diarrhea due to IBS. It reduces diarrhea and diminishes urgency but may not improve pain. The dosage should be gradually increased from 2 mg to a max of 16 mg daily in 4 divided doses. Pts should be cautioned about the risk of impaction with excessive loperamide. A second-line agent is cholestyramine, which may relieve the diarrhea due to the malabsorption of bile salts that occurs frequently in pts with functional diarrhea and treats those with the uncommon disease of idiopathic bile salt malabsorption (Am J Med 1999;107:27S). A dosage of 4 gm tid can be used as a trial. Some pts prefer 1-gm colestipol hydrochloride tablets when low doses are required.
- *Smooth muscle relaxants:* In the U.S., dicyclomine (10-20 mg po qid prn) and hyoscyamine (0.125-0.25 mg po qid prn or as a timed-release preparation [eg, Levsinex] 0.375 mg po q 12 hrs) are widely used for relief of pain in IBS. There are limited data to support their use due to methodological limitations in the available trials. A meta-analysis of smooth muscle relaxants in IBS showed that they achieved some benefit in control of pain and resulted in global improvement (Aliment Pharmacol Ther 1994;8:499). Peppermint oil appears to be effective, but data are limited (BMJ 2008;337:a2313).
- *Antibiotics:* Treatment with the nonabsorbable antibiotic rifaximin improves sx of IBS, especially diarrhea and bloating (Am J Gastro 2009;104 Suppl 1:S1; Ann IM 2006;145:557). Presumably, some of the pts who respond have bacterial overgrowth. A course of 400 mg po tid for 10-14 days may give relief for 3 months, but recurrence is common. There are no data on long-term use.
- *Probiotics:* Probiotics appear to be effective in IBS, but the degree of benefit and the most effective agents and strains are unknown (Gut 2008 Dec 17 Epub ahead of print; PMID 19091823). Bifidobacterium infantis was effective in a large study of women with a mix of subtypes of IBS (Am J Gastro 2006;101:1581). It is commercially available in the U.S. OTC as Align.
- *Antidepressants:* Tricyclic antidepressants are appropriate for pts whose sx are persistent over months, especially if there is associated depression or anxiety. They probably work centrally as analgesics. Doses needed for IBS are often lower than doses needed for depression (10-25 mg of amitriptyline, 50 mg of desipramine). Trials of 2-3 months seem

appropriate, and a second agent should be tried if the first fails, as success will be seen about 50% of the time on a second trial (Aliment Pharmacol Ther 1994;8:409). Selective serotonin reuptake inhibitors (SSRIs) also appear to be effective, but data are limited (Gut 2009;58:367).

- *Alosetron:* Alosetron is a 5-HT3 receptor antagonist that improves pain and BM frequency in pts with **diarrhea-predominant IBS** (Lancet 2000;355:1035). It was temporarily withdrawn from the U.S. market because of a possible association with cases of ischemic colitis. It has been re-released under a special prescribing program for use in women with severe sx of diarrhea-predominant IBS.
- *Lubiprostone:* Lubiprostone is a chloride channel activator that is effective in idiopathic constipation. Low-dose therapy (8 mcg po bid) improves sx in pts with **constipation-predominant IBS** with a low incidence of side effects (Aliment Pharmacol Ther 2009;29:329).
- *Tegaserod:* Agonists of the 5-HT4 receptors appear beneficial in **constipation-predominant IBS**. Tegaserod (2-6 mg po bid) improves sx of pain and constipation (Aliment Pharmacol Ther 2001;15:1655). Unfortunately, it was withdrawn from the market in 2007 for a 0.11% rate of adverse cardiovascular events.
- *Chinese herbs:* Chinese herbal remedies reduce sx but are not readily available or standardized (Jama 1998;280:1585; Jama 1998;280:1569).

If pts are refractory to anything on the preceding list:

- *Reconsider the diagnosis:* At this point if the pt has refractory sx, especially if they are long standing and constant, the dx is likely secure. Additional testing is unlikely to be needed. However, pts with IBS are not prevented from coming down with serious unrelated illnesses, and the physician should guard against failing to listen to the pt's sx.
- *Review the abuse history:* Hopefully, long before this point in rx, the physician will be able to establish whether there is a hx of verbal, physical, or sexual abuse. However, because this hx is so depressingly common in pts with refractory sx (Ann Intern Med 1995;123:782), the physician must reexplore this area.
- *Refer for psychological rx:* (Arch IM 2003;163:265) A variety of modalities are available, which may be of benefit to pts whose sx are more severe and substantially affect their quality of life (Ann IM 1995;123:688). These include stress management, psychotherapy, behavioral rx, hypnotherapy, and biofeedback/relaxation training. Choice of rx is usually made by the mental health professional on the basis of pt's needs and resources.

4.2 Physical and Sexual Abuse and GI

Ann IM 1995;123:782

Pts with chronic, functional GI complaints have a distressingly high (44%) incidence of prior physical or sexual abuse (Int J Colorectal Dis 1995;10:200; Ann IM 1990;113:828). Most of these pts never report these tragic life experiences to their physicians. A large number of factors that suggest a hx of abuse have been identified (Ann IM 1995;123:782). The link between abuse hx and GI sx may be that chronic or traumatic stimulation increases sensitivity of visceral afferent receptors (Am J Med 1994;97:105). As a simple rule of thumb, always consider physical or sexual abuse in pts with functional complaints that do not respond readily to routine measures and in pts who have seen multiple providers for the same complaint.

Eliciting a hx of abuse can be easily done in the routine office setting. Sometimes the pt may make a veiled reference to prior difficulties in life that open a door of inquiry. At other times a supportively phrased question is most helpful. For example, say, "Many pts I have seen with difficult or long-lasting belly pain have told me that they have been sexually or physically abused in their lifetimes—has that ever happened to you?" Most pts are surprised at the question, and most have never been previously asked about abuse by a physician. Most pts will respond well to a supportive inquiry. In an academic center, only 3% of pts required urgent counseling after the inquiry (Ann IM 1995;123:782). It is then useful to go on to explain the possible connection between chronic GI complaints and the abuse hx and to reassure pts that many others have had similar difficult experiences. For pts who answer affirmatively to an abuse hx, it is often sensible to limit testing and to try to work with dietary and other therapies while the process of counseling is initiated. The pt is followed along with mental health clinicians until the picture improves. Occasionally, the inquiry throws a schedule into disarray, but there is greater satisfaction in steering such a pt to expert help than in being on time for the next endoscopy.

4.3 Food Allergy

Am J Gastro 2003;98:740; Lancet 2002;360:701; BMJ 1998;316:1299

Cause: The most common causes of true food allergy are cow's milk, hen's eggs, cod (and other fish), shrimp (and other shellfish), peanuts (and other nuts), soybeans, wheat, and food additives. Those allergic to pollen may have reactions with a variety of foods.

Epidem: The confirmed prevalence of food allergy in adults is only 1.4-2.4% compared with a 20% pt-perceived prevalence (Lancet 1994;343:1127). Rates of true allergy are higher in children.

Pathophys: Adverse reactions to food can be (1) IgE-mediated allergy (involving basophils and mast cells [GE 1992;103:1075]); (2) delayed non-IgE-mediated immunologic reactions (eg, eczema from milk); (3) nonallergic food intolerance (eg, scromboid fish poisoning due to high histamine levels, reaction to monosodium glutamate in Chinese food); and (4) food aversion. The last category is the most common, and sx are nonspecific and cannot be confirmed by blinded food challenge. Food additives (benzoates, sulfites, tartrazine, food colorings, and salicylates) may cause a nonimmunologic, harmless, contact urticaria.

Sx: Pts develop specific and reproducible sx or si involving the mouth, gut, skin, and respiratory systems. At least 2 of these systems should be involved. Sx include oral itching and swelling, nausea, vomiting, abdominal pain, diarrhea, asthma, cough, rhinitis, atopic dermatitis, or anaphylaxis. In a subgroup, sx develop only after exercise.

Si: Angioedema, urticaria.

Crs: About one-third of children and adults lose clinical reactivity to food allergens, though lab testing can remain positive for years.

Cmplc: Anaphylaxis.

Diff Dx: Food aversion is the major differential point and is much more common than allergy. Reactions to additives and other intolerances can be difficult to separate from allergy.

When sx suggest allergy, the dx is confirmed by lab testing followed by eliminating and then rechallenging (under medical supervision) with the offending food.

Lab: Antigen-specific IgE to water-soluble extracts of food antigens can be evaluated in serum. Many clinically insignificant cross-reactivities create false positives. Skin prick testing with food extracts is the alternative.

Rx: Rx is food avoidance. Epinephrine should be available to the pt at home, along with a user-friendly delivery device (eg, EpiPen). Anti-IgE and immunomodulatory therapies are being developed. Methods are being developed to produce hypoallergenic foods (GE 2005;128:1089).

4.4 Colonic Diverticulosis and Diverticulitis

Lancet 2004;363:631; Am J Gastro 1999;94:3110

Epidem: Rare in children. In Western countries, the prevalence of diverticula is <10% in those under age 40 yr, 20-30% in those over age 50 yr, and >50% in those over age 80 yr. Rare in rural Africa and Asia. Based on prevalence of data and hospitalization data, only 0.5% of pts are hospitalized for diverticular disease.

Pathophys: (Gastroenterologist 1994;2:299) Left-sided diverticula are pseudodiverticula that contain only mucosa and submucosa rather than all layers of bowel. They form between the longitudinal muscle layers of the colon that are present in 3 bands called the tenia coli. Diverticula form between the mesenteric and the 2 antimesenteric tenia, where the nutrient arteries pierce the circular muscle layers. These arteries create weak points where herniation can occur. The association of each diverticulum with a nutrient artery predisposes to diverticular hemorrhage.

In Western countries, 90% of pts have left-sided disease, and in Asia, right-sided disease dominates. The number of diverticula can range from a few to hundreds and are usually 5-10 mm in diameter. Resected specimens with diverticular disease show a shortening of the tenia, thickening of the colon wall, and deposition of elastin in teniae, though not true muscular hypertrophy. The thickening of the circular muscle folds is due to shortening of the tenia (Gastroenterologist 1994;2:299). The colon in pts with diverticular disease appears to be less elastic and pliable. New diverticula may be formed when dysmotility causes high-pressure segments to develop within the sigmoid.

Because of the epidemiology, it was hypothesized that diverticulosis was a fiber deficiency disease. Fiber increases the bulk of stool, increases luminal diameter, and decreases intraluminal pressure. A high-fiber diet reduced the risk of symptomatic diverticular disease (RR = 0.63) in the prospective U.S. Health Professionals Study (J Nutr 1998;128:714). Nut and popcorn consumption was associated with a lower risk of diverticulitis in this cohort (Jama 2008;300:907). A study of 1800 rats also demonstrated a protective effect of a high-fiber diet (Am J Clin Nutr 1985;42:788).

Diverticulitis is the result of a small perforation of a diverticulum. This is thought to occur when undigested food debris blocks the neck of the diverticulum. This results in bacterial fermentation and mucus secretion in a closed space, which increases pressure in the diverticulum. The vascular supply becomes compromised and perforation occurs. Most of these perforations are walled off by the mesocolon or appendices epiploicae (Nejm 1998;338:1521). The walled abscess (stage I) may lead to other intra-abdominal or pelvic

abscesses (stage II), or to peritonitis from rupture of the abscess (stage III). Bowel contents do not spill into the abdomen in stage III because the diverticulum is swollen shut at its neck. In stage IV disease there is a large hole in the colon that allows free spillage of stool into the abdomen with its attendant morbidity and mortality.

Diverticular bleeding is arterial. Thus, it tends to be fairly large volume and abrupt in onset. Bleeding occurs from the rupture of the artery in the diverticulum as it courses over the dome of the diverticulum. Inflammation is not part of the picture histologically (GE 1976;71:577). It is not clear what predisposes an artery to thinning. NSAID use is associated with diverticular hemorrhage (Dig Dis Sci 1997;42:990).

Sx: Most pts with diverticular disease have no sx. A subgroup will present with abdominal pain without evidence of diverticulitis. It is not clear if the pain is related to the diverticulosis. The pain is typically crampy, LLQ, associated with bloating, and has features similar to IBS, though in many cases the hx is of recent-onset pain (Am J Clin Nutr 1985;42:788). **Diverticulitis** typically presents as sudden onset of LLQ pain and fever, usually associated with a change in bowels. There may be minor bleeding or pain elsewhere in the belly. Pneumaturia suggests colovesical fistula, and feculent vaginal discharge may indicate colovaginal fistula. Dysuria and frequency may occur from inflammation of the bladder. **Diverticular bleeding** presents as a sudden, large-volume bleed, usually reddish bloody stool with clot, as would be expected from rupture of an artery. Intermittent, chronic, small-volume hematochezia should not be attributed to diverticular bleeding. Melena from bleeding right-sided diverticula is rare.

Si: Tenderness to palpation is almost universal in diverticulitis and is usually in the LLQ. Percussion tenderness and localized or diffuse peritoneal signs are variably present and reflect the severity of the episode. Fever is usually present. A palpable mass may be evident in more severe cases. FOBT may be positive, but gross bleeding is rare in diverticulitis.

Crs:

- *Diverticulitis:* The risk of recurrence after a first attack of diverticulitis managed medically is about 25%, but the rate reported in the literature does vary widely (Am J Gastro 1999;94:3110). Older case series suggested that if a second attack occurs, it is much less likely to respond to medical rx, more likely to have complications such as abscess, and more likely to require surgery in 2 stages (BMJ 1969;4:639). More recent data suggest that 80% of pts with diverticulitis are never hospitalized again with the illness and only 5-7% undergo colectomy (J Am Coll Surg 2004;199:904). Diverticulitis recurs in 10% of pts treated surgically and requires reoperation in 3%, especially if the anastomosis is to distal sigmoid rather than rectum.
- *Diverticular hemorrhage:* Bleeding stops spontaneously in 80% of pts. It recurs in 22-38% of pts, and the chance of a third bleed after a second bleed may be as high as 50% (Am J Gastro 1999;94:3110). Pts who require less than 4 units of blood per 24 hr usually stop spontaneously (Ann Surg 1994;220:653).

Cmplc: Pylephlebitis (inflammation or infection of the portal vein and/or its tributaries); fistulae to bladder, vagina, or skin; intra-abdominal abscess.

Diff Dx: Many causes of acute abdominal pain need to be considered (p 1). The most important differential considerations for diverticulitis are (1) ischemic colitis (in which there is usually prominent bloody stool and crampy pain is prominent); (2) CRC (where the hx of sx is usually longer); (3) Crohn's or ulcerative colitis (where extraintestinal manifestations and

chronic diarrhea may be a clue); (4) appendicitis (especially if diverticulitis is right sided); (5) pain from an ovarian source (cyst, abscess, or torsion); (6) ectopic pregnancy; (7) bacterial colitis, including *C. diff* (where diarrhea is prominent); and (8) perforated ulcer disease. The diff dx for diverticular hemorrhage includes brisk UGI bleeding, bleeding from angioectasias, cancer, or ischemia (p 21).

Lab: In diverticulitis severe enough for hospitalization, the wbc is usually elevated, but may be normal (Surgery 1994;115:546).

X-ray: An abdominal series to look for free air under the diaphragm is indicated in pts in whom perforation is suspected. However, since diverticulitis is really an extraluminal disease, the best imaging test is CT scan. CT with oral and, if needed, rectal contrast can reveal thickening of the colon, infiltration of the pericolonic fat (so-called "greying" of the fat), abscess, or air or contrast outside the bowel wall. If abscess is seen, CT can be used for percutaneous drainage. In addition, CT may show an alternative dx. False-negative rates for CT vary widely and are reported in 2-21% of pts (Nejm 1998;338:1521). Contrast enemas are often nondiagnostic (since the disease is outside the bowel), but force the dx to be reconsidered if there are no diverticula seen. US has its advocates but is very operator dependent, and studies on its use have been small (Am J Gastro 1999;94:3110).

Endoscopy: Endoscopy should be avoided in acute diverticulitis for fear of creating free perforation from the air or the instrument. Limited sigmoidoscopy is appropriate acutely if there is strong diagnostic concern for IBD or infectious colitis and stool studies are negative. After the pt recovers from a clinically diagnosed bout of diverticulitis, the entire colon should be evaluated (generally with colonoscopy). This is typically done several weeks after recovery from the acute bout. Diverticular inflammation can be an incidental finding in asymptomatic pts that does not require treatment (Am J Gastro 2003;98:802).

Rx: (Am J Gastro 1999;94:3110; Dis Colon Rectum 1995;38:125)

- *Diet and exercise:* A high-fiber diet is reasonable for pts with asymptomatic diverticular disease with the hope of reducing the risk of diverticulitis. Nuts and popcorn do not need to be restricted. Vigorous physical activity is associated with a lower risk diverticulitis and might be considered.
- *Medical rx of diverticulitis:* Mild to moderate episodes in otherwise healthy pts can be treated on an outpatient basis with oral antibiotics. Severity is judged by fever, wbc count, physical exam, and reported sx severity. Pts must be well enough to be hydrated orally and be in a safe setting in case they become more ill. A 10-day course of oral antibiotics with aerobic and anaerobic coverage is prescribed. There are many acceptable choices, including amoxicillin-clavulanate (500 mg po tid × 10 days); trimethoprim-sulfamethoxazole (1 DS tab po bid) plus metronidazole (500 mg po tid); or ciprofloxacin (500 mg po bid) plus metronidazole. Because the majority of pts who recover from their first attack of diverticulitis never have a recurrence, surgery should not be offered after a single uncomplicated bout.
- *Surgical rx of recurrent uncomplicated diverticulitis:* For years it has been argued that each attack of diverticulitis makes it more likely that another attack will occur and less likely that the next attack will respond to medical rx. This theory has led to consideration of surgery after a second bout of diverticulitis. However, these recommendations are based on data from small case series. Decision analysis based on more recent larger studies suggests that delaying surgery until after a fourth episode lowers cost, death rate, and

the need for colostomy. There are no hard-and-fast rules, and the decision should be individualized. The medical fitness of the pt for an operation, the severity of the attack, the response to medical rx, and the desires of the pt all factor into the decision. If pts are treated while not acutely ill, they can undergo resection of the diseased segment and anastomosis in a single operation (primary anastomosis). A 1-stage operation may not be possible in complicated disease.

- *Complicated diverticulitis:* Abscess, fistula, free perforation, and obstruction define complicated diverticulitis. All pts with complicated diverticulitis should be offered surgery unless the medical risk is prohibitive. Small pericolic abscesses may resolve with antibiotics (Surgery 1994;115:546). Larger abscesses can be drained with CT-guided drainage or surgery. If CT drainage is successful, the pt can usually have a 1-stage operation with primary anastomosis. If CT drainage is not possible or is unsuccessful, laparotomy with resection is done. If contamination is substantial, a Hartmann procedure is done. In this operation, the diseased segment is resected, an ostomy is created for the portion of bowel still in the fecal stream, and the free end of the defunctionalized bowel is closed. In the fit pt who makes a good recovery, a reanastomosis can be performed (a 2-stage operation). Pts with obstruction often respond to medical rx initially and can undergo resection with primary anastomosis electively. Pts with free perforation should have resection with colostomy. This group has high morbidity and mortality (6-35%).
- *Diverticulitis in the young:* Some authors have suggested that diverticulitis in young pts is a more virulent disease that requires surgery more than 70% of the time (Am J Surg 1994;167:562). However, other series suggest that the rate of perforation and the need for urgent surgery are not increased in a first episode of diverticulitis in the younger pt (J Am Coll Surg 1994;179:156). There does not appear to be compelling evidence to change the therapeutic approach in young pts.
- *Diverticular hemorrhage:* The approach to suspected lower GI bleeding is outlined on p 23. In suspected diverticular bleeding, an anorectal cause should be excluded by anoscopy. Upper endoscopy may be needed to exclude an upper source. If the pt is bleeding actively, a tagged rbc scan or CT angiogram is obtained to try to localize the bleeding site. If the site is localized and bleeding does not stop, angiographic rx or a surgical **resection** is performed. Some centers offer urgent **angiography** with selective embolization as therapy. Angiography can be diagnostic and therapeutic but is associated with a high incidence of complications, requires more vigorous bleeding than a rbc scan requires for visualization (≥0.5 mL/min), and surgery is still frequently required (GE 2000;118:978). If bleeding stops or slows enough for a colonoscopy prep, the pt should undergo colonoscopy to look for a treatable cause of the bleeding. Some authors advocate urgent colonoscopy following vigorous bowel prep with polyethylene glycol lavage. The purpose is to stratify the pt's risk of rebleeding (by identifying those with active bleeding, visible vessels, and adherent clots) and to treat high-risk lesions endoscopically. **Endoscopic rx** includes injection of the base of the actively bleeding diverticulum with 1-2 mL of 1:20,000 epinephrine in 4 quadrants and bipolar electrocoagulation for visible vessels. Endoscopic clips can be used (Gastro Endosc 2004;59:433). A nonrandomized trial suggests benefit (Nejm 2000;342:78), and a small RCT showed no effect on outcomes (Am J Gastro 2005;100:2395). A large, randomized, multicenter trial is needed to assess the safety and efficacy of this approach. Retrospective data suggest a high risk of recurrence for those treated endoscopically (Am J Gastro 2001;96:2367).

4.5 Lactose Intolerance

Aliment Pharmacol Ther 2008;27:93; Am Fam Phys 2002;65:1845; Postgrad Med 1998;104:109

Cause: Low levels of lactase, a small intestinal enzyme.

Epidem: The prevalence of adult lactase deficiency is low in northern Europeans (2-7%) and U.S. Caucasians (6-22%) and is higher in Hispanics (50-80%), African Americans (60-80%), Native Americans (80-100%), and Asians (98-100%). The prevalence rises with age (Dig Dis Sci 1994;39:1519).

Pathophys: Lactase is normally present in the brush border of small intestinal epithelial cells. At birth, levels of the enzyme are high but decline rapidly after weaning in most populations. In some groups, especially northern Europeans, single nucleotide polymorphisms in the lactase gene cause levels of lactase to remain abnormally high into adulthood. Thus the normal condition is to become lactase deficient after weaning, but mutations have allowed some populations to remain lactose tolerant into adulthood. In some cases, lactase deficiency is acquired due to infection (eg, *Giardia*), drugs, or other diseases of the bowel. When dietary lactose is not appropriately broken down into glucose and galactose, it passes unabsorbed into the colon. In the colon, bacteria ferment lactose, producing gas and other metabolites that cause net fluid secretion into the colon. Not all pts who maldigest lactose become symptomatic; some live blissfully with their deficiency. Most of the sx are associated with the gas production. Sx from less than 12 gm lactose (1 cup of milk) are minimal to nonexistent, and sx increase in a dose-related fashion thereafter (Aliment Pharmacol Ther 1995;9:589).

Sx: Abdominal pain, bloating, flatulence, and diarrhea after the consumption of lactose.

Si: Distension is usually not detectable clinically.

Crs: Surprisingly, sx can improve with continued lactose exposure in pts who are lactase deficient. This occurs not by improved lactose digestion but by colonic adaptation (Am J Clin Nutr 1993;58:879).

Diff Dx: Since the sx of lactose intolerance are similar to those of IBS, the 2 conditions are easily confused. Lactose intolerance is as common in IBS as in the general population.

Lab: Several tests are available for the dx of lactase deficiency. The most widely used is the breath hydrogen test that measures the amount of hydrogen produced after the ingestion of lactose. Breath hydrogen is produced by intestinal bacteria that ferment the malabsorbed lactose. If breath hydrogen rises more than 20 ppm, lactase deficiency is diagnosed. False-negative results can occur in up to 20% of pts with recent antibiotics or if the pt's flora uses the available hydrogen to produce methane. Small bowel bx is the gold standard but is largely a research tool. Other serum tests have been described (Scand J Gastroenterol [suppl] 1994;202:26). There is controversy regarding which pts to test for lactase deficiency. Since not all pts with lactose maldigestion have sx and some pts have sx without proven maldigestion, it seems reasonable to do a trial of exclusion of lactose without a diagnostic test. However, this approach risks making a dx of a lifelong condition with a trial of questionable validity (Aliment Pharmacol Ther 1995;9:589). If this

approach is taken, a rechallenge with lactose should be considered after the pt has been asymptomatic for some time.

Rx: (Postgrad Med 1998;104:109) Rx is for the control of sx. The mainstay is the avoidance of lactose-containing foods. Most pts tolerate the amount of lactose in less than 1 cup of milk daily. Foods highest in lactose include milk, ice cream, cottage cheese, and yogurt. Yogurt is often well tolerated because of the lactase found in live cultures. Calcium supplements may be needed in those who avoid dairy products. In pts who do not respond to exclusion of the obviously offending foods, it is possible that lactose added to other foods or used as a carrier in pills is causing sx. However, it is more likely that the pt's sx are not related to lactose. A variety of oral lactase supplements are available (eg, Lactrase, Dairy Ease, LactAid), and they are helpful for most pts who wish to use milk products moderately. Different preparations may have different efficacies (Am J Gastro 1994;89:566), but large comparative studies are lacking. Reduced lactose milk is available but has a sweet taste not acceptable to many.

4.6 Appendicitis

Nejm 2003;348:236; Am Fam Phys 1999;60:2027

Epidem: (Am J Epidemiol 1990;132:910) This common illness affects 8.6% of men and 6.7% of women over a lifetime, though 12% of men and 23% of women have appendectomy! The peak incidence is in pts aged 10-20 yr, but it can occur at extremes of age where dx is more difficult. It is 1.5 times more likely to occur in whites, and incidence peaks in summer. For unknown reasons the incidence declined 15% between 1970 and 1984.

Pathophys: The appendix is long, tubular, and lined with lymphoid follicles. It can be up to 20-cm long and can thus cause pain anywhere in the abdomen. Most often it is behind the cecum (60%), but it may lie below, in the pelvis, anteriorly or posteriorly to the ileum, or up in the RUQ behind the liver. These variations result in varied sx and physical findings. Appendicitis results from luminal obstruction that is most commonly caused by lymphoid hyperplasia (due to any number of infectious illnesses), by fecaliths, or more rarely by parasites, tumors, or Crohn's.

Sx: (Jama 1996;276:1589) Abdominal pain is the cardinal sx of appendicitis and is usually of less than 36-hr duration on presentation. It is usually located in the RLQ but may occur in the flank, RUQ, or elsewhere depending on appendiceal anatomy. About half the time pain begins diffusely in a periumbilical location before localizing. Anorexia and nausea are common but do not help much in the diff dx. Vomiting is a clue if it occurs after the pain, but if it precedes the pain, an alternative dx should be sought.

Si: (Am Fam Phys 1999;60:2027) Tenderness occurs in the RLQ unless the appendix is in an unusual location. Tenderness is to direct palpation and often to percussion. Suggestive positive signs include percussion in the LLQ causing RLQ pain and localizing pain with cough. A positive psoas sign (pain on extension of the right thigh with the pt lying on the left side) may occur when the appendix is retroperitoneal. A tender rectal exam may occur in a pelvic appendix. A positive obturator sign (pain on internal rotation of the flexed right thigh) may also

indicate a pelvic appendix. Low-grade fever is common. A pelvic exam should be done since this is the major differential point in women.

Crs: Appendicitis is usually an acute illness, but there are data to suggest that about 6% of pts who come to appendectomy have had recurrent bouts of a similar pain, and that the pain is relieved by appendectomy (recurrent appendicitis) (Brit J Surg 1997;84:110).

Cmplc: Perforation, with resultant intra-abdominal sepsis, is the most important complication and is seen in 18% of cases (Am J Epidemiol 1990;132:910). The perforation rate climbs to 50% in those over 65 yr of age, indicating the greater difficulty of dx in this age group. About 4% of pts present with abscess or phlegmon. The initial management of this group is nonsurgical in most cases. While some pts undergo "interval appendectomy" after the acute illness resolves, many are managed without appendectomy with only a 7% risk of recurrence (Ann Surg 2007;246:741).

Diff Dx: (Emerg Med Clin N Am 1996;14:653) The differential is long for this common illness. In women, ruptured ovarian cyst, ectopic pregnancy, pelvic inflammatory disease, endometriosis, ovarian torsion, and tubo-ovarian abscess are important considerations. Diverticulitis, Crohn's, perforated viscus, Meckel's diverticulitis, gastroenteritis, and a plain old bad tummy ache are the GI considerations. Renal stones, pyelonephritis, UTI, psoas abscess, and rectus sheath hematoma are only a partial list of remaining considerations.

Lab: (Emerg Med Clin N Am 1996;14:653) The wbc is elevated in 80% of pts, often with a left shift, but this finding is nonspecific. An elevated C-reactive protein (>0.8 mg/dL) is also common. The absence of all 3 of these lab parameters (an elevated wbc, a left shift, and elevated C-reactive protein) argues strongly against appendicitis. A pregnancy test should be obtained in females. A urinalysis may be helpful in the diff dx.

X-ray: (Am Fam Phys 1999;60:2027) **Plain films** of the abdomen are useful in ruling out obstruction or free air but of little specific value in diagnosing appendicitis. **US** is helpful in pts with equivocal clinical findings. It is most helpful in female pts to look for pelvic pathology and in pediatric or pregnant pts to avoid radiation. A negative US is one in which the appendix is seen and is less than 6 mm. US is less sensitive, less specific, and more operator dependent than CT, but is less expensive. **Helical CT scan** (Radiol Clin North Am 1999;37:895) is the most sensitive and specific test for equivocal cases. Best results are reported when a gastrografin-saline enema is given, but even standard CT is probably better than US. It is superior in its ability to assess the inflammatory process around the appendix. Some have advocated the routine use of appendiceal CT after a prospective trial showed that it lowered cost for pts admitted to hospital for suspected appendicitis by preventing unnecessary appendectomy and unnecessary observation days (Nejm 1998;338:141).

Rx: Appendectomy is the rx of choice, and negative appendectomy rates of 22% for women and 9% for men can be expected (Can J Surg 1999;42:377). There is a need for a large, RCT to determine if laparoscopic appendectomy is superior to the open approach. A meta-analysis suggests that by using the open approach, operating time is shorter, hospital stay is unaffected, but return to normal activity takes longer (Can J Surg 1999;42:377).

4.7 Crohn's Disease

Am J Gastro 2009;104:465; Nejm 2002;347:417

Cause: No causative agent has been identified.

Epidem: The incidence of Crohn's disease has a bimodal distribution. The first peak occurs in the early 20s, and a second peak occurs in the 50s. The incidence in women is about 20% higher. U.S. blacks and whites have similar incidences and disease courses (Am J Gastro 2000;95:479), but African blacks have a lower incidence, suggesting an environmental influence. Jews have a higher incidence, and U.S. Hispanics have a low incidence (GE 1992;102:1940). The disease is more frequent in higher socioeconomic status populations, urban populations, and in those with sedentary occupations. The annual incidence varies greatly with location, with high rates in Scandinavia and northern Europe (3.6-9.8/100,000) and in North America (up to 15/100,000, and with low rates in southern Europe (0.3-3/100,000), Asia, and Africa (GE 1999;116:1503). Great variation in incidence within regions suggests the importance of local environmental factors. For obscure reasons, the incidence has rapidly risen in the last 30 yr. Smoking doubles risk of developing disease (Dig Dis Sci 1989;34:1841) and worsens the clinical course (Gut 1992; 33:779). First-degree relatives of Crohn's pts have 15 times the risk.

Pathophys: Crohn's disease represents a failure of the immune system to control or down-regulate an inappropriate inflammatory process in the intestinal mucosa. The ongoing immune response is probably driven by the normal intestinal flora and defects in the intestinal mucosal barrier and mucosal immune system (Nejm 2002;347:417; Nejm 2009;361:2066). There is strong evidence for a genetic predisposition (GE 2003;124:521). The high concordance in twins, the increased risk of a family hx, ethnic and racial variations, and the association of Crohn's with other rare genetic illnesses all suggest a genetic predisposition. Unlike the case in simple Mendelian disorders, where a single mutation causes disease, multiple gene defects are required in Crohn's disease. There is also a large environmental component (suggested by the epidemiology) that any model of Crohn's pathogenesis must explain.

The inflammatory mediators produced in Crohn's disease are presumably a response to antigenic stimulation and result in mucosal inflammation, ulceration, and ultimately fibrosis. The structural abnormalities created result in the diarrhea, obstruction, bleeding, and fistula formation seen in the disease. To produce these effects, the inflammatory process must be initiated and then be inappropriately perpetuated. Environmental factors such as viral or bacterial infections or toxins could be the antigens that act as initiators. Some data implicate *Mycobacterium paratuberculosis*, measles, or *Listeria* infections, but a single-agent cause is unlikely. Chronic antigen stimulation in the gut from other bacterial antigens or toxins or from a leaky mucosal barrier may be important. There are differences in the presentation of antigens to the immune system by intestinal epithelial cells in normal versus diseased individuals (GE 2000;118:S68). The role of exogenous factors such as excess dietary sugar and cigarettes, both associated with increased risk, is not yet defined (J Clin Gastroenterol 1992;14:216). No matter what the underlying events turn out to be, there is an imbalance created between proinflammatory and anti-inflammatory mediators.

Many of the important proinflammatory and anti-inflammatory mediators have been identified in animal models of IBD, and drug rx can be targeted to those mediators (see Rx).

The interleukins (especially IL-1), the leukotrienes, and tumor necrosis factor (TNF) are important mediators of inflammation that can be targeted by drugs. Autoimmunity (the failure to recognize normal host antigens as self) is probably not a major factor in Crohn's disease, though a variety of autoantibodies have been described (Inflamm Bowel Dis 1999;5:61).

Sx:

- *Gut sx:* Crohn's disease can present clinically in many ways since it can involve the gut from esophagus to anus and has many extraintestinal manifestations. Disease is limited to the distal ileum in 30% of pts, is limited to the colon in 20% of pts, and is seen in large and small bowel in 50% of pts. Gastroduodenal disease is uncommon, and esophageal involvement is rare. Sx vary with disease location. The nature of the sx will be different depending on whether the pt has fistulizing or perforating disease, fixed obstruction due to fibrosis, or primarily inflammatory changes of the mucosa. Pts with distal ileal disease commonly present with RLQ pain, diarrhea, and weight loss. Gross bleeding is uncommon. Sometimes, obstruction from the inflamed ileum is more prominent, and pts have crampy, postprandial pain, and bloating and diarrhea may not be prominent. A subgroup will have minimal sx until they present with near complete small bowel obstruction. Crampy lower abdominal pain, diarrhea, minor bleeding, and weight loss are common in colonic disease. Pts with gastric and/or duodenal involvement present with epigastric pain that may be suggestive of PUD. Diffuse jejunoileal Crohn's is uncommon, but such pts are usually quite ill with pain, weight loss, and diarrhea (Gut 1993;34:1374).
- *Perianal disease:* About one-third of pts will have perianal sx of fissures, fistulas, or abscess that may be the dominant sx or may precede the bowel sx by years. A hx of perianal disease can be an important clue in dx.
- *Extraintestinal disease:* (Gastroenterol Clin North Am 1999;28:255) Joint sx are common, especially arthritis. A nondestructive peripheral arthritis involving large joints (15-20%), ankylosing spondylitis (3-5%), or sacroiliitis (9-11%) may be seen. In the skin, erythema nodosum presents as red, painful nodules, especially on the shins (in up to 15%). Pyoderma gangrenosum is a skin lesion that causes deep sterile ulcers and is usually seen on the legs or on the abdomen near stomas after colectomy (1-2%). Iritis may present as a red, painful eye with a halo of erythema outside the cornea. Sclerosing cholangitis (1%) is the important hepatic manifestation (p 233). Aphthous ulcerations of the mouth are common. Gallstones and renal diseases are extraintestinal manifestations seen in Crohn's but not in UC. Fistulas, ureteral obstruction, oxalate stones, amyloid, and other urologic abnormalities may complicate Crohn's (Am J Gastro 1998;93:504). A variety of uncommon, steroid-responsive lung diseases have been reported (Medicine [Baltimore] 1993;72:151).
- *Fistulas:* Fistulas may develop because Crohn's is a disease of the entire thickness of the bowel, not just the mucosal surface. Fistulas may develop from bowel to bladder (enterovesical) and cause multiorganism UTIs or pneumaturia. Fistulas between loops of bowel (enteroenteric) can present as masses or abscesses. Fistulas to skin (enterocutaneous) present as feculent drainage and are most common around the anus. Rectovaginal fistula is an uncommon event.

Si: Low-grade fever is common, but temps >101°F usually represent a complication such as abscess. There may be findings of cachexia. A mass may be palpable, either because of inflamed loops of bowel matted together or because of abscess. FOBT may be positive. Skin findings as in the previous list.

Crs: Dx is delayed an average of 3 yr in small intestinal disease (Digestion 1985;31:97). The course is unpredictable. Based on the placebo arm of 2 drug trials, it can be expected that 30-60% of placebo-treated pts with active disease enter remission within 4-5 months, and half of these will stay in remission for 2 yr (Digestion 1985;31:97; GE 1979;77:898). Postoperative recurrence is common, with endoscopic recurrence rates of >70% at 3 yr. More than 30% of surgically treated pts ultimately required a second resection (see Rx).

Cmplc:

- *Colorectal cancer:* Pts with Crohn's colitis are at increased risk for CRC, but the magnitude of risk is not as well defined as it is in ulcerative colitis. A well-performed, population-based study showed an absolute cancer risk of 8% at 22 yr and an RR of 18 in pts with more than a decade of extensive colitis (Gut 1994;35:651). Many of the prior studies that failed to show an association were flawed because they failed to account for the cancer-preventing effects of resective surgery and failed to examine cancer rates in those still at risk (Gut 1994;35:1507). Malignancy is most likely in long-standing extensive disease, strictures, and fistulizing disease. Surveillance strategies for Crohn's and ulcerative colitis should probably be similar since the risks are of the same magnitude (Am J Gastro 1996;91:434).
- *Other malignancies:* Small intestinal malignancy is more common in Crohn's pts than in the general population, but the magnitude of the risk is unclear and surveillance does not seem justified. Lymphoma appears to be associated with Crohn's, but the cause of the association is not clear cut (Am J Gastro 1996;91:434). Immunomodulator rx is associated with increased lymphoma risk (Gut 2005;54:1121).
- *Osteoporosis:* Pts with Crohn's disease commonly have osteopenia or osteoporosis. Malabsorption, inflammation, and corticosteroid rx all contribute, and specific strategies for prevention and rx have been proposed (Am J Gastro 1999;94:878; GE 2003;124:795).

Diff Dx: The differential varies with the major presenting sx. Usually, chronic diarrhea is the predominant sx, and Crohn's must be distinguished from IBS, ischemic colitis, ulcerative colitis, infectious diarrhea, and other dietary and drug causes of chronic diarrhea (p 17). Short duration and abrupt onset of diarrhea usually argues against IBD as the cause. When disease is confined to the ileum, appendicitis and other causes of bowel obstruction may be the major differential points. Gastroduodenal Crohn's is confused with PUD.

Often the major diagnostic problem is determining whether pts have Crohn's colitis or ulcerative colitis. Crohn's is diagnosed by the presence of small bowel involvement, by its tendency to spare segments of bowel (skip areas, especially sparing the rectum), by its endoscopic features, and by histology (see Endoscopy). In 5-10% of cases of colitis, a convincing dx cannot be made (indeterminate colitis).

Lab: A CBC should be obtained to look for anemia and leukocytosis. Sometimes pts with active inflammation can have very high wbc counts (above 20 000/mm^3) due to the inflammatory process and steroid rx, even in the absence of abscess. CRP is another useful marker of inflammation. CMP is appropriate to assess electrolytes, renal function, and liver function. Elevations of alk phos may be a clue to sclerosing cholangitis as a complication. Several serologic tests have been developed for IBD testing. These include (1) antibodies to *Saccharomyces cerevisiae* (ASCA), (2) antibodies to outer membrane porin C (anti-ompC), (3) atypical perinuclear cytoplasmic autoantibodies (pANCA), and (4) antibodies to

bacterial flagellin Cbir 1 (anti-Cbir1). These tests can be combined into test panels of reasonable sensitivity and specificity, but they have low predictive value if used to screen pts with a low pretest probability of IBD (Clin Gastroenterol Hepatol 2007;5:545).

X-ray: Imaging the small intestine is appropriate in all cases to assess the extent and activity of small bowel disease. SBFT is commonly used and is most often positive for disease in the distal ileum where narrowing of the bowel lumen, mucosal ulceration, and fistula might be detected. CT enterography, which uses large volumes of water as oral contrast medium, can give an excellent evaluation of mucosal detail and bowel wall thickness as well as detect abscesses (Dig Dis 2004;22:56). MRI enteroclysis is not widely available but is sensitive and does not carry the radiation risk of repeated CT scans (BMJ 2008;336:273). BE can demonstrate mucosal abnormalities or strictures in Crohn's and can be used to visualize strictures that cannot be traversed with an endoscope. However, where Crohn's is suspected, colonoscopy is preferred for more certain dx. CT scanning with barium or iodine-based oral contrast is helpful to identify abscess, can often detect bowel wall thickening indicative of inflammation, and can help distinguish Crohn's from appendicitis in some cases. However, CT with conventional oral contrast is not highly sensitive for mucosal disease alone.

Endoscopy: Colonoscopy is used for initial dx and to survey for dysplasia on long-standing disease. It is also used to assess disease activity and distribution in pts with established Crohn's disease in situations where knowledge of the endoscopic findings would change the drug or surgical rx. Colonoscopy should not be used to assess response to steroid rx, because it adds nothing to clinical sx in determining when a steroid taper can begin or in predicting outcome (GE 1992;102:1647). Colonoscopy is valuable for monitoring for postoperative recurrence and assessing the efficacy of rx for maintenance postoperatively (see Rx). Capsule endoscopy is more sensitive than radiographic tests for the detection of mucosal changes of Crohn's disease (Am J Gastro 2006;101:954), but there is a substantial risk of the capsule becoming stuck in a stricture. The role of capsule endoscopy in Crohn's is not yet fully defined.

In Crohn's colitis the rectum is often normal. The involvement with the inflammatory process is usually discontinuous. Aphthous ulcers in a background of normal mucosa, deep linear ulcers, and cobblestoning are common. The diffuse friability and granularity of UC is uncommon in Crohn's (Med Clin N Am 1990;74:51).

Bx is useful in establishing the dx. Bx may show evidence of inflammation with lymphocytes and plasma cells and distorted crypt architecture. Granulomata, often not seen in endoscopic bx, help distinguish Crohn's from ulcerative colitis when present. Histologic features help distinguish acute self-limited colitis due to infection from a first presentation of IBD (Scand J Gastroenterol 1994;29:318).

Rx: (Am J Gastro 2009;104:465; GE 2006;130:935)

- *Assessment of disease severity and distribution:* In order to choose rx, it is essential to know the severity and distribution of the disease. Colonoscopy and small bowel imaging are generally performed to determine which segments of bowel are affected. Severity is assessed by the clinical features, diarrhea, weight loss, abdominal findings, ability to maintain nutrition, and laboratory parameters such as anemia, hypoalbuminemia, and functional status. Based on severity of illness, rx is chosen as indicated.

- *Mild to moderate disease:* These pts are ambulatory, carry out most of their usual activities, tolerate an oral diet, and do not have severely disruptive sx or signs. For pts whose disease is confined to the ileum or right colon, a course of **Budesonide** 9 mg po daily is emerging as the preferred rx. It is a steroid with high topical potency and rapid first-pass metabolism in the liver; it is as effective as prednisone for disease in the ileum and proximal colon but with less toxicity (GE 1998;115:835; Nejm 1994;331:836). Budesonide (available in the U.S. as Entocort EC) is typically given at 9 mg for 8 weeks followed by a taper to 6 mg and then 3 mg if sx are well controlled. Budesonide is not effective for long-term maintenance, and a 5-ASA or immunomodulator is needed for maintenance. For disease outside the reach of budesonide the **5-aminosalicylates** (5-ASA), such as mesalamine compounds are commonly used. Several formulations of 5-ASA compounds are available, but data to support their efficacy are limited. Typical choices of mesalamine formulation in the U.S. would include Asacol 800-1600 mg po tid or Pentasa 1000 mg po qid. **Metronidazole** is an alternative regimen and is given in doses of 250-500 mg po tid for 12 weeks, with about a 50% response rate (Gut 1991;32:1071). **Ciprofloxacin** with or without metronidazole (Can J Gastroenterol 1998;12:53) appears to be effective in 50-70% of pts, though adverse reactions to long courses of antibiotics are common. Often antibiotics are added in pts who are not doing well with 5-ASA products alone but who are not ill enough for steroids.
- *Moderate to severe disease:* These pts have often failed 5-ASA and antibiotics or have more severe disease at presentation with fever, malnutrition, and sx of diarrhea and pain preventing normal activities. These pts are usually treated with corticosteroids, which are effective in about 70% of pts within 4 weeks (BMJ 1999;319:1480). **Prednisone** 40-60 mg po qd is used initially and is tapered after substantial improvement occurs. The drug is tapered by 5-10 mg a week until a dose of 20 mg is reached and then further tapered at 2.5-5 mg per week until stopping. Sometimes in tapering, a flare of sx will occur, and the dose is boosted by 10-15 mg until sx improve. The major concern with steroid rx is toxicity. Side effects include hyperglycemia, HTN, adrenal suppression, osteoporosis, aseptic necrosis of the hips, increased risk of serious infection, sweats, proximal myopathy, depression, insomnia, impaired wound healing, and growth retardation. In addition to the concerns about side effects, about half of pts will be unable to stop steroids or will become steroid resistant (Gut 1994;35:360).

The immune modulators **azathioprine (AZA)** or **6-mercaptopurine (6-MP)** should be considered if a pt is ill enough to have required a course of prednisone and especially if prednisone cannot be tapered. The anti-TNF antibodies are also a consideration (see below). Azathioprine is a prodrug that is metabolized to 6-MP and ultimately to the active metabolite, 6-thioguanine (6-TG), which is cytotoxic to lymphocytes. The onset of action is slow, possibly taking 3 months before the benefits are fully evident, and steroids are often needed as a bridge. Azathioprine doses are usually 2-3 mg/kg, and 6-MP is dosed at 1-1.5 mg/kg. Typically, 50 mg of either agent is used to start and if tolerated, the dose is increased to the weight-based target dose a couple of weeks later. Metabolism of these drugs requires the enzyme thiopurine methyltransferase (TPMT). About 90% of pts have high levels of TPMT, but 10% have reduced levels, and 0.3% have little or no activity. Measurement of TPMT levels prior to beginning rx guides dosing and identifies the rare pt with absent activity who will certainly develop toxicity (Ann IM 1998;129:716).

The correlation between 6-TG levels and remission is weak. However, measurement of 6-TG levels in nonresponders can identify pts who are noncompliant and those who preferentially metabolize 6-MP to the inactive 6-methylmercaptopurine (6-MMP) metabolite (Am J Gastro 2004;99:1744). Pts who preferentially form 6-MMP can be treated with allopurinol and reduced doses of AZA/6-MP to boost 6-TG levels (Aliment Pharmacol Ther 2005;22:441). Side effects of these agents include nausea, rash, pancreatitis, hepatitis, and bone marrow suppression. CBC is typically monitored weekly during the period of dose adjustment and every 1-3 months thereafter. LFTs are also periodically checked, but the optimal frequency has not been established.

The **anti-TNF monoclonal antibodies** are expensive, effective agents for the treatment of moderate to severe disease that has not responded to steroids and immunomodulators. The available agents include **infliximab**, (Remicade), **adalimumab** (Humira), and **certolizumab pegol** (Cimzia). Infliximab was the first of these agents developed and is the agent for which there is the most data. It is a mouse-human chimeric antibody to TNF-α, an important mediator of inflammation in Crohn's. It is indicated to induce remission in moderate to severe disease unresponsive to conventional rx and in fistulizing disease with enterocutaneous or perianal fistulas. Infliximab alone or combined with AZA is more effective than AZA alone in pts who have failed steroids and 5-ASA rx (GE 2006;130:940). Because of its potency and rapid onset of action, it may also be beneficial in hospitalized pts with severe disease who have not failed all conventional rx. It also appears beneficial in pts with extraintestinal manifestations such as ankylosing spondylitis, sacroiliitis, arthritis, and pyoderma gangrenosum.

A single infusion of 5 mg/kg in pts with disease resistant to other modalities results in remission in 65% (Nejm 1997;337:1029). The commonly used (and FDA approved) method of inducing remission is to infuse 5 mg/kg at 0, 2, and 6 weeks because it appears to be more effective and may reduce subsequent infusion reactions (Am J Gastro 2002;97:2962). Repeated infusions of 5-10 mg/kg every 8 weeks help maintain remission and maximize the chance of discontinuing steroids (Lancet 2002;359:1541). Infusion reactions and loss of efficacy are associated with the development of antibodies to infliximab (Nejm 2003;348:601). The concomitant use of 6-MP/AZA reduces that risk, as does the use of hydrocortisone 200 mg iv prior to infliximab infusion (GE 2003;124:917). Loss of efficacy in maintenance rx can be treated by dose escalation from 5 up to 10 mg/kg. Infusion reactions are not decreased by scheduled infusions (GE 2004;126:598).

Infliximab is costly and is associated with serious side effects. The cost of a single 5-mg/kg infusion for a 70-kg pt is upwards of $3000. In a reported series of 500 pts, 6% had a serious adverse reaction, including acute infusion reactions (3.8%), serum sickness illness (2.8%), drug-induced lupus, multiple sclerosis, serious infection, and death (0.8%). Serious infection and demyelinating diseases are contraindications to rx. A causal relationship between infliximab and malignancy (seen in 1%) is uncertain, but the report of young males developing hepatosplenic T-cell lymphomas taking combination rx with AZA/6-MP has raised concerns about long-term combination therapy. A variety of opportunistic infections have been described. The incidence of tuberculosis is much higher than that of other opportunistic infections, and screening for latent tuberculosis is indicated prior to rx (Nejm 2001;345:1098). PPD testing is limited by the high incidence of anergy; obtaining a hx of tuberculosis risks and CXR may be of great importance (Clin Gastroenterol Hepatol 2004;2:309). Postmarketing surveillance has also raised concerns about cytopenias and liver function abnormalities.

Adalimumab is effective in pts with moderate to severe disease who have never been treated with an anti-TNF drug (GE 2006;130:323) or who previously could not tolerate or failed infliximab (Ann IM 2007;146:829). Induction dosing is 160 mg sc followed by 80 mg 2 weeks later. Maintenance of remission is maintained by 40 mg every other week or weekly if needed (Gut 2007;56:1232). The sc dosing and lack of delayed hypersensitivity reactions may be an advantage over infliximab. Safety concerns are the same as for infliximab.

Certolizumab pegol is effective in inducing remission at a dose of 400 mg sc given at 0, 2, and 4 weeks (Aliment Pharmacol Ther 2009;29:605). It is effective in maintenance of remission in a dose of 400 mg sc q 4 weeks (Nejm 2007;357:239). Reinduction can be used for pts who flare on maintenance. Delayed hypersensitivity reactions do not occur. The q-4-week sc dosing may be an advantage over other agents. Safety concerns are the same as for infliximab.

In pts who do well only after anti-TNF rx is added to AZA/6-MP, the question arises as to whether long-term combination therapy is worth the risk. Withdrawing immunomodulators in stable pts does not appear to have an impact on effectiveness in the short term (GE 2008;134:1861).

In pts who have never received corticosteroids, the question has been raised as to whether "top-down" therapy with infliximab and AZA is preferable to a step-up approach that begins with steroids to induce remission, adds AZA to maintain it, and uses infliximab for failures. The top-down approach has demonstrated some promise in an open label trial (Lancet 2008;371:660). However, when there is close adherence to step-up guidelines, outcomes are good and morbidity is low without the added expense of the indiscriminate use of biologics (Clin Gastroenterol Hepatol 2009;7:323).

It is not yet known whether pts who initially respond to infliximab can be effectively transitioned to AZA in the long term.

- *Severe disease:* These pts are unable to tolerate oral feeding and medicines and require hospitalization. They often have evidence of obstruction, malnutrition, and fever. They are treated with iv steroids (eg, methylprednisolone 60-80 mg iv daily in divided doses or by continuous infusion) or anti-TNF drugs. Infectious causes of diarrhea, especially *C. diff*, are sought, and CT scanning is considered to look for abscess. Antibiotics such as metronidazole or ciprofloxacin are added empirically. Surgery is considered depending on the clinical course and response to steroids.
- *Other biologic therapies:* Natalizumab is a humanized monoclonal ab to alpha-4 integrin, which blocks leukocyte adhesion. It is an option for pts who have failed steroids, immunomodulators, and anti-TNF therapy (GE 2007;132:1672). However, it has been associated with the fatal reactivation of the JC polyoma virus in a disease called progressive multifocal leukoencephalopathy (PML) (Nejm 2005;353:362). A bewildering number of biologic therapies are under development for use in IBD (GE 2009;136:1182). These drugs are largely recombinant human proteins (cytokines, growth factors) and monoclonal antibodies. Many are in FDA phase II and III of development.
- *Other medical therapies:* In pts who do not achieve excellent control of disease with 5-ASA, steroids, or AZA/6-MP, other agents can be considered. **Methotrexate** is effective in 40% of steroid-dependent pts but has substantial toxicity (Nejm 1995;332:292). **Cyclosporine** has short-term efficacy (Scand J Gastroenterol 1993;28:849), but the lack of durable response and toxicity make its use minimal in clinical practice.
- *Maintenance of medical remission:* The 5-ASA agents are marginally effective in maintaining remission (Aliment Pharmacol Ther 1996;10:1). 5-ASA are often selected in the hope of

avoiding the side effects of immunomodulators. In those cases attempts to maintain the remission are made with whatever 5-ASA preparation was used in inducing remission at a dose not lower than 2.4 gm daily. Meta-analysis shows that AZA and 6-MP are effective in maintenance of remission (Ann IM 1995;123:132). These agents are used to maintain remission when they are part of the initial rx that induced remission or in pts who required steroids for remission. The maintenance dose is the same as that used to induce remission. Stopping AZA in pts in remission for >3.5 yr is associated with a substantially increased risk of relapse (GE 2005;128:1812), suggesting that the drug needs to be continued indefinitely. The anti-TNF drugs can be used for maintenance of remission as discussed above.

- *Surgical therapy:* Surgery is considered in 2 settings. The first is in those pts with acute complications such as obstruction, bleeding, or abscess not amenable to radiological drainage that are not responding to medical rx. The second is in pts who remain chronically ill despite medical rx. It is especially sensible to consider surgery early in medically refractory pts with a limited extent of disease. Prolonged courses of ineffective, toxic medical rx must be avoided.
- *Prevention of postoperative recurrence:* (Am J Gastro 2000;95:1139; Am J Gastro 2008;103:1029). Endoscopic postoperative recurrence usually occurs at the neoterminal ileum, the surgically created distalmost small bowel. The mechanism for this pattern is unknown. Smoking increases the risk. Endoscopic recurrence is 28% at 1 yr and 77% at 3 yr and is not initially clinically evident. Clinical recurrence rates are lower, but ultimately >30% of pts require a second resection within 10 yr. Mesalamine reduces risk in most studies, but the magnitude of risk reduction is only 13% (GE 1997;113:1465). AZA/6-MP appear moderately beneficial in maintaining remission especially if given with an initial 3-month course of metronidazole (GE 2008;135:1123). Recently infliximab has been shown to be effective for postoperative maintenance at 1 yr (GE 2009;136:441). A strong argument can be made for planned colonoscopic evaluation of the effectiveness of any therapy chosen. If colonoscopy shows active disease, additional therapy can be used that might spare the pt a second surgery.
- *Nutrition:* Enteral feeding is effective in inducing remission in Crohn's disease but is difficult and expensive. Polymeric and elemental diets are of equal efficacy (Am J Gastro 2000;95:735). They may be of greatest use in childhood and adolescence, when growth retardation of steroids is the greatest concern (Aliment Pharmacol Ther 1997;11:17). In pts with partially obstructive disease, a low-residue diet may reduce sx.
- *Cigarettes:* Smokers are more likely to develop Crohn's, to need surgery, to require immune-modulating drugs such as 6-MP, and to relapse than nonsmokers are (Am J Gastro 2000;95:352). Smokers should be counseled and helped to quit.
- *Perianal disease and fistulas:* (Semin Gastrointest Dis 1998;9:10) Fissures, fistula, and abscesses occur in one-third of pts with Crohn's. When there is pain or fluctuance, imaging studies (eg, CT scan) and surgical drainage may be needed. In the absence of pain or fluctuance, antibiotics are the first line of rx for fistulas, though controlled data are lacking. Choices include metronidazole 250-500 mg po tid, ciprofloxacin 500 mg po bid, or clarithromycin 500 mg po bid. Relapse is 70% when rx is stopped. AZA/6-MP is helpful in two-thirds of pts. The strongest evidence supports the use of infliximab (5 mg/kg iv at 0, 2, and 6 weeks). It is effective in closing fistulas in two-thirds of pts with a median duration of response of 3 months (Nejm 1999;340:1398). This should be tried when the less expensive measures fail or when the faster healing and greater chance of benefit with infliximab is

desired despite the cost. Surgical rx is needed to control sepsis and to treat refractory sx (Semin Gastrointest Dis 1998;9:15). Surgery should generally be avoided for treatment of skin tags, hemorrhoids, and fissures because of poor healing and risk of complications (GE 2003;125:1503).

- *Osteoporosis prevention:* Osteoporosis is common in Crohn's even when corticosteroids are not used. Most pts need calcium (1.5 gm daily) and vitamin D supplementation (800 IU daily). Prophylactic regimens to reduce steroid-induced bone loss should be instituted (GE 2003;124:791).
- *Psychosocial issues:* Psychosocial factors do not cause Crohn's but are as important to evaluate and treat as other sx of the disease. Assessing the psychosocial factors will improve compliance, minimize misunderstandings between pt and physician, and improve the pt's health status (Gastroenterol Clin North Am 1995;24:699).
- *Pregnancy:* Most pts whose disease is well controlled can expect nearly normal fertility and an uncomplicated pregnancy. The 5-ASA agents and steroids can be used in pregnancy. Metronidazole and ciprofloxacin should be avoided. The use of AZA/6-MP is controversial (Dig Dis 1999;17:201). Infliximab might be an option after a careful weighing of risks and benefits with the pt (Am J Gastro 2009;104:1575).

4.8 Ulcerative Colitis

Am J Gastro 2004;99:1371; Lancet 2002;359:331

Cause: No causative agent has been identified.

Epidem: (Gastroenterol Clin North Am 1995;24:467) The epidemiology of UC is similar to that of Crohn's. The incidence is bimodal, with peaks in the 3rd and 6th decades. In contrast to Crohn's, men with UC outnumber women with UC by 20%. Incidence is higher in urban areas, industrialized countries, and in those of higher socioeconomic status. Like Crohn's, UC is more common in northern latitudes (eg, incidence 15/100,000/yr in Norway and 2/100,000/yr in Spain), but in contrast to Crohn's, incidence has been stable over time. Smokers have half the risk of nonsmokers, and former smokers are at even greater risk than nonsmokers (GE 1994;106:807). First-degree relatives have 15 times increased risk of UC but not of Crohn's. Though at one time, UC was thought to be primarily a psychiatric disorder, there appears to be no greater frequency of psychiatric dx in UC pts than in controls (Dig Dis Sci 1982;27:513).

Pathophys: UC and Crohn's share many common epidemiologic and clinical features, and the pathophysiologies must be closely related. UC results from a failure of the immune response to be appropriately down-regulated (Gastroenterol Clin North Am 1995;24:475). The inappropriate immune response results in lymphokines (especially interleukins 4 and 10) that mediate mucosal inflammation in the colon. Colonic inflammation causes the diarrhea and bleeding that characterize the disease. The nature of the stimulus that initiates the immune response and the factors that perpetuate the response are unknown. Both genetic factors (BMJ 1993;306:20) and environmental factors contribute. UC, like Crohn's, is likely a group of closely related disorders that share final common pathways of inflammation. Current models cannot account adequately for the distribution of UC, the high frequency of autoantibodies in the disorder, or its extraintestinal manifestations.

Sx: Chronic bloody diarrhea is the hallmark of UC. It is usually associated with a sense of urgency with BMs, a sense of incomplete evacuation, and an uncomfortable sensation of rectal spasm (tenesmus). The distribution and severity of the colitis affects the clinical presentation. Pts with **proctitis** (disease confined to the rectum) may present with relatively formed BMs once or twice daily interspersed with multiple trips to the toilet to evacuate bloody mucus. With greater lengths of involved bowel (proctosigmoiditis, left-sided colitis, or pancolitis), the pt has more diarrhea, crampy lower abdominal pain, and is generally more ill. Weight loss and fever reflect more severe inflammation or a greater extent of disease. The **extraintestinal manifestations** of UC are less numerous than those of Crohn's. Acute arthropathy occurs in 10-15% of pts and typically involves single large joints or multiple small joints symmetrically. Other manifestations include sacroiliitis (9-11%), ankylosing spondylitis (1-3%), uveitis and episcleritis (5-15%), erythema nodosum (10-15%), pyoderma gangrenosum (1-2%), and sclerosing cholangitis (2-7%) (Gastroenterol Clin North Am 1999;28:255).

Si: Depending on the severity of illness, the pt may have fever, cachexia, and abdominal tenderness. Distension raises the possibility of toxic megacolon.

Crs: Most pts have a chronic relapsing illness. About 10% of pts will have a single unrelenting attack or a single attack with prolonged remission. Pts with systemic sx such as fever and weight loss are most likely to relapse. A pt in remission has a 20% chance of relapse of disease the following year, and those with active disease have a 70-80% chance of relapse in the following year (GE 1994;107:3). Those with proctitis develop disease outside the rectum about 12% of the time over the course of 10 yr and have a low risk of colectomy (3-5%) (Scand J Gastroenterol 1977;12:727).

Cmplc:

- *Colorectal cancer:* (Curr Gastroenterol Rep 1999;1:496; J Clin Gastro 2005;39:S66) The CRC risk for pts with UC is about 7-14% at 25 yr. Older studies from referral centers overestimated the risk. The risk appears to rise after 8 yr of disease and increases 0.5-1% per yr of disease duration. A family hx of CRC or concurrent sclerosing cholangitis increases risk, while 5-ASA rx (Am J Gastro 2005;100:1345) and regular medical care decrease risk. Dysplasia, which can be defined as neoplasia confined to the mucosa, precedes invasive cancer. Pathologists classify dysplasia as low-grade, high-grade, or indefinite. Colonoscopic surveillance to detect dysplasia is widely performed, but there are several practical problems with cancer prevention by surveillance for dysplasia, including the following: (1) pathologists frequently do not agree on the determination of dysplasia, (2) not all resected colon specimens with cancer show dysplasia elsewhere in the specimen, (3) surveillance samples a tiny portion of the mucosa, (4) cancer can be seen within a year or 2 of surveillance, and (5) surveillance has never been conclusively proven to save lives. Despite these limitations, the U.S. Multi-Society Task Force has recommended surveillance colonoscopy with bxs q 1-2 yr for pts with more than 8 yr of pancolitis or more than 12-15 yr of left-sided disease (GE 2008;134:1570). Many bxs are needed to lower sampling error risk, and the ASGE guideline specifies 4 quadrant bxs every 10 cm for a minimum of 32 bxs (Gastro Endosc 2006;63:558).

  The finding of dysplasia of any grade (confirmed by a second expert pathologist) is considered an indication for colectomy. An area of confusion is the management of dysplasia-associated lesions or masses, or so-called DALMs. Some of these lesions are

probably garden variety sporadic adenomas unrelated to colitis (Am J Gastro 1999;94:1746). Those DALMs that look like resectable discrete polyps in healed mucosa can be managed by endoscopic polypectomy, bx of the surrounding mucosa, and surveillance (Gastro Endosc 2006;63:558).

- *Osteoporosis:* Like pts with Crohn's, pts with UC are at increased risk (Am J Gastro 1999;94:878).
- *Toxic megacolon:* This is a condition in which the colon becomes dilated (>6 cm) in the presence of severe colitis and systemic toxicity. Morbidity and mortality are high. Management includes rx of the colitis, avoidance of narcotics and anticholinergics, colonic decompression, and close observation for complications requiring surgery (Am J Gastro 2003;98:2363).

Diff Dx: The most common difficulty in dx is distinguishing acute, self-limited infectious colitis from UC. An abrupt onset is the most useful piece of hx suggesting an infectious cause. Stool studies should be obtained to rule out bacterial pathogens (p 155) and in some regions amebiasis (p 164). *C. diff* is common in IBD pts but tends not to be so bloody. Ischemic colitis, CMV colitis, drug-induced colitis (especially gold), and radiation colitis round out the differential. Crohn's disease is usually distinguished from UC by the tendency of Crohn's to involve noncontiguous portions of bowel (skip lesions) and to spare the rectum, by its histologic features, or by small bowel involvement. About 5-10% of pts cannot be cleanly classified as having UC or Crohn's and their cases are called indeterminate colitis.

X-ray: BE is too insensitive to be useful in UC. CT, if done for other reasons, may show thickened colon. Plain abdominal films are useful for the detection of toxic megacolon.

Endoscopy: Colonoscopy shows evidence of colitis beginning in the rectum and found in a continuous and circumferential pattern to the point of transition to normal mucosa. The colitis is characterized by granularity, friability, ulceration, and inability to visualize the underlying normal vasculature (loss of the vascular pattern) (Med Clin N Am 1990;74:51). Histology shows acute and chronic inflammation in the lamina propria and distortion of the normal architecture (eg, gland atrophy, branching). Histologic features help distinguish acute self-limited colitis due to infection from a first presentation of IBD (Scand J Gastroenterol 1994;29:318).

Rx: (GE 2004;126:1582; Am J Gastro 1997;92:204; Gastroenterol Clin North Am 1999;28:297)

- *Proctitis:* Proctitis is most effectively treated with mesalamine supps (Canasa 1000 mg pr qhs) for a period of 4-8 weeks, depending on severity of disease and response to rx and response. For a first mild episode it is reasonable to stop rx and wait for relapse. Maintenance rx is individualized with a single supp every 2nd or 3rd night. Hydrocortisone supps or foam are alternatives. A rare pt may require oral steroids.
- *Proctosigmoiditis:* For pts who are ambulatory and with no signs of toxicity, mesalamine enemas 4 gm pr qhs are effective, expensive, and work more rapidly than oral 5-ASA preparations. Steroid enemas are an alternative, but systemic steroid absorption does occur. For pts who prefer oral rx, the aminosalicylates and related agents are appropriate. There are several formulations of **mesalamine** available in the U.S. These formulations use various means to carry mesalamine (5-ASA) to the colon (where it acts locally) without excessive small intestinal absorption. Mesalamine preparations include (1) Asacol (400-mg tabs) and Asacol HD (800-mg tabs) 800-1600 mg po tid, (2) Pentasa

1 gm po qid, and (3) Lialda 1.2-gm tablets 2-4 tabs po daily as a once-daily dose. Another extended-release mesalamine, Apriso, is only indicated for maintenance rx at a dose of four 0.375-mg tablets once daily. The weight of the evidence suggests that mesalamine doses of at least 4 gm/day should be used to induce remission in pts with moderately active disease (Aliment Pharmacol Ther 2006;24 Suppl 1:10). Another aminosalicylate is **balsalazide** (Colazal 2.25 gm po tid). Balsalazide is carried to the colon where bacterial enzymes cleave off the active 5-ASA molecule. A 6.75-gm daily dose releases 2.4 grams of 5-ASA in the colon. Studies comparing mesalamine to balsalazide are too limited by methodologic problems to conclude that any agent is superior (Am J Gastro 2002;97:2939). **Sulfasalazine** 2-4 gm daily in 2-4 divided doses is a less expensive alternative that is associated with many more side effects. These are mostly caused by the sulfapyridine portion of the sulfasalazine molecule that is released when the parent drug splits off the active 5-ASA molecule in the colon. One gram of sulfasalazine releases 400 mg of 5-ASA in the colon. If sulfasalazine is used, then folate 1 mg po qd should be given to treat impaired folate absorption caused by sulfapyridine. **Olsalazine** (Dipentum), a 5-ASA dimer, is effective but is used less often because of diarrhea as a side effect.

- *Disease beyond the sigmoid:* Delivery of topical rx outside the sigmoid is less reliable, and oral rx is often needed. Mesalamine and balsalazide are common choices as previously described. Topical rx with a mesalamine enema can be added to oral rx for more rapid sx control.
- *When 5-ASA is not enough:* (GE 2006;130:935) Pts with extensive colitis, weight loss, and anemia and those who are more disabled by their sx should be treated with prednisone from the outset. In addition, pts who are not as ill but have failed attempts at maximal 5-ASA rx should receive prednisone. Prednisone is given at doses of 40-60 mg daily. The oral 5-ASA can generally be stopped at high doses of prednisone, though topical rx can still be helpful for sx relief. When sx improve, the prednisone is tapered by 5 mg per week. The 5-ASA is resumed when the prednisone dose is reduced to 20 mg or so, but there is little science to guide the practice. Sometimes the taper must be slowed (eg, 2.5 mg a week) when the prednisone dose drops below 20 mg. For those with an inadequate response to oral steroids or for those who relapse with tapering and become steroid dependent, AZA/6-MP should be considered (p 109). Infliximab (p 110) is an appropriate next step if these measures fail. Surgery is a curative alternative that needs to be considered in this group of refractory pts. There is limited evidence that fish oil (as Max-EPA 6 caps po tid) is beneficial (Ann IM 1992;116:609). Rosiglitazone 4 mg po bid has some efficacy, but its place in therapy is uncertain (GE 2008;134:688).
- *Severe disease:* IV steroids and hospitalization are needed in pts who have signs of systemic toxicity, those who fail to improve with oral steroids, or those who are too ill to maintain hydration and nutrition. Methylprednisolone 60-80 mg in divided doses or by continuous infusion is begun. ACTH can be used in a first attack but has little apparent advantage, and adrenal hemorrhage is a risk. In these ill pts, concomitant 5-ASA or iv antibiotics may be used. In general, narcotics, antidiarrheals, and anticholinergics are avoided for fear of precipitating toxic megacolon. If pts fail to turn the corner in a week, then surgery needs to be considered. Infliximab may be a rescue option in these severely ill pts (GE 2005;128:1805). Cyclosporine can be given iv, but in

some cases it may forestall rather than prevent colectomy. It is best used in centers with expertise in its use (Am J Gastro 1997;92:1424).

- *Surgery:* (Gastroenterol Clin North Am 1999;28:371) Surgery can be urgently required for hemorrhage, bleeding, and in pts who remain ill despite 7-10 days of maximal medical rx. Surgery is also indicated in pts who are steroid dependent or intolerant despite AZA/6-MP/infliximab, or those who do not achieve a good quality of life on medical rx. Pts who have endured a prolonged attempt at medical rx rarely express regret after colectomy, despite the life changes. If surgery is required urgently, a subtotal colectomy (sparing the rectum) is less dangerous than a total colectomy, especially in medically high-risk pts. Completion proctectomy (with ileostomy or ileoanal anastomosis) can be achieved at a later date. For those having elective surgery, the choice is between total proctocolectomy with ileostomy versus ileal pouch-anal anastomosis. For proctocolectomy with ileostomy, 25-50% have leakage problems, 10-25% require a stoma revision, 15% will develop bowel obstruction, and 5% of men will become impotent.

  Ileoanal anastomosis was initially offered only to the young and fit, but it is now being offered to greater numbers of pts. Most surgeons perform the procedure in 2 stages. The first is abdominal colectomy, rectal mucosectomy (leaving the rectal muscular cuff and anal sphincter), creation of an ileal pouch as a fecal reservoir, ileal-anal anastomosis, and temporary diverting ileostomy. The ileostomy reduces dehiscence and pelvic infection and requires closure in a second operation 8 weeks later. Some surgeons skip the diverting ileostomy in low-risk pts. The functional results are good. The chief morbidity is bowel obstruction and infection. The failure rate requiring permanent ileostomy is 5-10%. Pts can expect an average of 6 BMs daily, including a nocturnal one. The major late complication is pouchitis (15%), an inflammatory condition of the ileal pouch of unknown cause, which responds to antibiotics (Gastroenterol Clin North Am 2001;30:223).
- *Maintenance rx:* Pts whose distal disease comes into remission with 5-ASA enemas can be maintained on these agents given q 2-3 days. Those who come into remission with an oral 5-ASA can usually be maintained on a lower dose of 5-ASA. The evidence suggests that the equivalent of ≥2 gm 5-ASA daily is most likely to maintain remission (Aliment Pharmacol Ther 2006;24 Suppl 1:17). If relapse occurs on lower dose 5-ASA rx, the dose can be increased to the higher doses used to induce remission. The available 5-ASA formulations are discussed previously. Those who cannot taper steroids without relapse or those who require a second course of steroids after failing high-dose maintenance 5-ASA are usually considered for AZA or 6-MP rx (GE 2006;130:935). The use of these agents is discussed on p 109. Maintenance AZA/6-MP is long term since stopping the drug is associated with a high risk of relapse (Am J Gastro 2009;104:2760). Those whose disease required infliximab for induction of remission are usually maintained with q-8-week dosing.
- *Survey for CRC:* As discussed in Cmplc.
- *Osteoporosis prevention:* Osteoporosis is common in IBD even when corticosteroids are not used. Most pts need calcium (1.5 gm daily) and vitamin D supplementation (800 IU daily). Prophylactic regimens to reduce steroid-induced bone loss should be instituted (GE 2003;125:937).

4.9 Collagenous Colitis

Mayo Clin Proc 2003;78:614; Gastroenterol Clin North Am 1999;28:479

Cause: The cause is unknown, though a link to NSAIDs has been hypothesized (Gut 1992;33:683).

Epidem: Population-based data suggest an incidence of 5/100 000/yr (Clin Gastroenterol Hepatol 2008;6:35). There is a 9:1 predominance in women, and a peak incidence in the eighth decade (Gut 1995;37:394).

Pathophys: The pathophysiology of the disorder is poorly understood (Dig Dis Sci 1991;36:705). Collagenous colitis is considered 1 of the 2 subtypes of **microscopic colitis**. Some have hypothesized an autoimmune etiology since there is a strong association of collagenous colitis with autoimmune disorders (like thyroiditis, Sjögren's, and rheumatoid arthritis). The collagen itself does not explain the diarrhea, which probably results from the inflammatory process. The most favored hypothesis is that the disorder is an inflammatory response to an uncommon, luminal infectious agent (Dis Colon Rectum 1996;39:573).

Sx: Chronic watery diarrhea and diffuse, crampy abdominal pain that waxes and wanes and has often been present for years prior to dx.

Crs: About two-thirds of pts remit with or without rx, and the remainder have a waxing and waning course. The disorder is an annoyance rather than a debilitating illness and does not have an impact on life expectancy.

Cmplc: None.

Diff Dx: The disorder should be considered in any older pt with chronic watery diarrhea. Most of these pts will be thought to have IBS until endoscopic bxs make the dx clear. The full diff dx is discussed under Chronic Diarrhea (p 17).

Lab: Fecal leukocytes are seen in 55%, but no other routine lab studies are of diagnostic help (Mayo Clin Proc 1995;70:430).

Endoscopy: At colonoscopy the mucosa is normal, or nonspecific erythema is seen. Histology is the defining feature, with features of colitis (acute and chronic inflammatory cells in lamina propria) associated with an increase in the thickness of the subepithelial collagen band (from a normal of 3 mm to an average of 15 mm) (Mayo Clin Proc 1995;70:430). The dx can usually be made at sigmoidoscopy since the vast majority of pts have involvement in the distal left colon (Mayo Clin Proc 1995;70:430).

Rx: There are few randomized trials to guide rx. The initial approach can be symptomatic. Exclusion of caffeine, lactose (p 102), and sorbitol (p 17) should be tried. Loperamide is often effective. Some pts respond to cholestyramine, metronidazole, or bismuth subsalicylate (8 tabs in 3 divided doses for 8 weeks [Gastroenterol Clin North Am 1999;28:479]). When pts remain symptomatic, 5-ASA preparations (eg, sulfasalazine 2-4 gm daily or mesalamine 2.4-4.8 gm daily in 3 divided doses) are tried. Budesonide has been effective in randomized trials (eg, Gut 2003;52:248), but relapse is common and the toxicity of long-term therapy is unclear. Rarely, prednisone and surgery have been used.

4.10 Lymphocytic Colitis

This disorder has clinical features similar to collagenous colitis and a histology that is similar except for the absence of the subepithelial collagen layer. It is considered a subtype of **microscopic colitis**. Some have wondered if it is a precursor lesion to collagenous colitis or part of the spectrum of 1 illness (Am J Gastro 1995;90:1394). Lymphocytic colitis does not have the striking predominance in women seen in collagenous colitis, suggesting it may be a different disorder. The therapeutic approach is the same as for collagenous colitis.

4.11 Diversion Colitis

This is an inflammatory process that occurs in segments of bowel that have been diverted from the fecal stream (pts with a Hartmann's pouch or mucous fistula) (J Clin Gastroenterol 1992;15:281). Pts may present with pain or bloody mucoid discharge. Reestablishing the fecal stream cures the disorder. Fatty acid enemas can be tried in pts who are not candidates for surgery, but no benefit was seen in a small RCT (Dis Colon Rectum 1991;34:861).

4.12 Celiac Disease

(Gastroenterology 2006;131:1977) Lancet 2003;362:383; Nejm 2002;346:180

Cause: Sensitivity to gluten, the protein fraction of wheat, rye, and barley.

Epidem: (BMJ 1999;319:236) The prevalence of disease used to be quoted as lower than 1/1000, but the recognition of asymptomatic or latent disease detected by serologic screening has put the prevalence in the 1:80 to 1:140 range. The disease can occur at any age, though childhood disease is declining. Peak incidence is in the 5th decade, with a predominance of 3:1 in women. First-degree relatives of celiac pts have a disease prevalence of about 10%. Several disorders are associated with an increased prevalence of celiac disease. These include iron deficiency anemia (2-5%), osteoporosis (1.5-3%), type 1 diabetes (2-5%), Down's syndrome (8%), Turner's syndrome (6%), autoimmune thyroid disease (3%), and IBS (~3% (Arch IM 2009;169:651)). Other associated disorders include IgA deficiency (2%), Sjögren's, pancreatitis (Clin Gastroenterol Hepatol 2007;5:1347), ataxia, and seizures. Celiac disease is associated with an increased risk of liver diseases including acute hepatitis, fatty liver disease, PBC, PSC, and cirrhosis (Clin Gastroenterol Hepatol 2007;5:63). Cigarette smoking appears to be protective (sigh!) (Gut 1996;39:60).

Pathophys: (GE 2000;119:234) Gluten, the trigger of celiac disease (aka celiac sprue, aka gluten-sensitive enteropathy) is the material that makes dough sticky and allows the making of bread. Gliadin, the alcohol-soluble fraction of gluten, contains proteins that are rich in glutamine and proline and toxic to celiac disease pts. These toxins are present in high concentrations in wheat, rye, and barley and in small concentrations in oats (which may be tolerated by some pts). The toxic proteins are absent in corn, millet, and rice. These toxic proteins resist digestion in the upper intestine (Nejm 2003;348:2573). They are deamidated by

the enzyme **tissue transglutaminase**, which appears to be the autoantigen in celiac disease. The deamidated proteins ultimately bind to the HLA-DQ2 or -DQ8 molecules and are recognized by T cells. These activated T cells produce cytokines, which produce an immune response with hyperplasia of the mucosal crypts followed by atrophy of the small intestinal villi. The villous atrophy causes the characteristic clinical syndrome, though not all pts with abnormal mucosa develop sx. The disease begins in the proximal small intestine, and the length of involvement affects the development of sx. Genetic factors are important, with a 70% concordance in monozygotic twins and strong associations with the HLA-DQ2 or -DQ8 antigens. However, genetics are not the entire explanation, and environmental factors, yet unidentified, are probably important.

Sx: The classical presentation of sprue is that of diarrhea due to malabsorption and subsequent weight loss. The diarrhea is associated with bloating, borborygmi, and relatively little pain. There has been a shift toward diagnosing pts with milder sx such as indigestion, fatigue, or iron deficiency. Associated sx may include peripheral neuropathy, ataxia, infertility, aphthous ulcerations of the mouth, sore tongue, generalized weakness, and arthritis. In severe cases, vitamin deficiency syndromes may occur. Dermatitis herpetiformis is a blistering skin disease characterized by pruritic, papulovesicular skin lesions (Nejm 1991;325:1709) that is considered a manifestation of celiac disease. About 75% of pts with this lesion have villous atrophy, and the rash responds to diet.

Si: In severe cases there is wasting, glossitis, and malnutrition. FOBT-positive stools are common (Nejm 1996;334:1163).

Crs: The vast majority of pts do well with dietary rx and become asymptomatic. Relapses are usually due to dietary exposure to gluten (often unintentional). A small group of pts do not respond to diet and are diagnosed with refractory or unclassified sprue. This is a heterogeneous group with a poor prognosis, and many are ultimately found to have T-cell lymphomas (GE 2000;119:243).

Cmplc: Celiac disease is associated with lymphoma of the small intestine (RR = 77), cancer of the mouth and pharynx (RR = 23), and cancer of the esophagus (RR = 12). This risk appears to be reduced to normal after 5 yr of a gluten-free diet (Gut 1989;30:333). Osteoporosis has been convincingly associated with celiac disease, and bone density should be evaluated (Gut 1994;35:150; Gut 1995;37:639).

Diff Dx: The major problem in dx is failure to consider celiac disease in the diff dx. A missed dx is especially common in the elderly (Gut 1994;35:65). A suggestive hx or a positive screening test leads to small bowel bx, which shows evidence of villous atrophy. A similar bx can be seen in tropical sprue (an infectious illness of uncertain cause [Gut 1997;40:428]), acid hypersecretion from gastrinoma, bacterial overgrowth, lymphoma, and eosinophilic gastroenteritis (Nejm 1991;325:1709). Therefore, the dx is only considered certain when pts respond to a gluten-free diet.

Lab: The autoantigen in CD has been identified as **tissue transglutaminase** (tTG) (Nat Med 1997;3:797), and effective screening tests using ELISA assays are available. Susceptible individuals also develop autoantibodies to reticulin, a constituent of the extracellular matrix. These antibodies are identical to **antiendomysial** (EmA) antibodies, allowing their use as a screening test. However, EmA testing is expensive and cumbersome and is being replaced by tTG testing. IgA antiendomysial and tTG antibodies are >95% sensitive and specific but may miss cases with partial villous atrophy. Since IgA deficiency is common in celiac disease,

an IgG TTG antibody test or IgA levels are selectively considered. Antigliadin antibodies are not considered specific enough to be routinely indicated.

Folate and iron deficiency (both absorbed in the duodenum) are common. Abnormal transaminases are common (Lancet 1998;352:26) and resolve with dietary rx. Because of the pitfalls of serologic dx and the difficulty of the lifelong dietary rx, most pts go on to have small bowel biospy for diagnostic confirmation. This may be unnecessary in symptomatic pts with a positive IgA EmA or tTG (Dig Dis Sci 1996;41:83). HLA testing can be used to exclude celiac disease since the DQ2 or DQ8 alleles are required for the disease. However, the clinical value of these tests is limited because 40% of the general U.S. population is positive.

X-ray: SBFT can be normal in moderate disease. If disease is more advanced, there is loss or thickening of folds. In advanced cases there are featureless, dilated loops of small intestine with rapid transit of barium.

Endoscopy: Endoscopy can be normal or show reduced or absent Kerckring duodenal folds or scalloping of the folds (Nejm 1988;319:741). Bx obtained at endoscopy shows the histologic abnormalities described above. Some pts with latent or mild disease will have only an increase in intraepithelial lymphocytes, but the finding is nonspecific (Am J Gastroenterol 2009;104:142). Endoscopic findings are not sensitive (Am J Gastro 2002;97:933).

Rx: In theory, the dietary rx of celiac disease is straightforward. The pt simply avoids all products with gluten: wheat, barley, and rye. Oats are less toxic and are usually well tolerated (Nejm 1995;333:1033). Many clinicians will add oats to the diet after a period of stability on a diet without oats (though many commercial oat products are contaminated with gluten). The reality, however, is that a gluten-free diet is difficult because modern food processing results in the addition of gluten as an additive in many foods. Consultation with a dietary expert is mandatory, and many lay organizations provide food lists and recipes. In practice, motivated pts often end up the true experts and can be helpful to those newly diagnosed. When pts do poorly, it is most often due to continued gluten ingestion. Other causes of a poor response to rx include wrong dx, lactose intolerance, pancreatic insufficiency, lymphocytic or collagenous colitis, and bacterial overgrowth (Lancet 2003;362:383; Am J Gastro 2003;98:839). Only 50-70% pts are fully compliant with diet (Lancet 1997;349:1755). Pts should receive supplementation with folate, iron, and calcium if needed. They may not tolerate lactose well in the early stages of rx. A tTG ab can be used to look for ongoing gluten ingestion in pts with relapsing sx. However, a negative tTG does not mean the mucosa is fully healed. Evaluation of bone density and screening of first-degree relatives is appropriate. The improved understanding of the pathophysiology of celiac disease is leading to new approaches for rx by detoxifying the detrimental gluten peptides (Gastroenterology 2007;133:1025) or by identifying varieties of wheat that lack toxic sequences (Gastroenterology 2005;129:797).

4.13 Short Bowel Syndrome

Gut 2006;55 Suppl 4:iv1; GE 2003;124:1105; Gastroenterol Clin North Am 1998;27:467

Cause: Extensive surgical resection of small intestine due to mesenteric vascular disease, Crohn's disease, or malignancy. Thrombotic vascular disease may be due to underlying coagulation defects.

Epidem: The epidemiology follows that of the underlying illness leading to the surgery.

Pathophys: The normal adult has about 240 cm of jejunum, 360 cm of ileum, and 160 cm of colon. Enteral nutrition and hydration cannot be generally maintained when massive resection leaves the pt with less than 70-100 cm of small bowel. After resection, there is a phase of intestinal adaptation during which hypertrophy of the mucosa increases absorptive surface area, and there is slowing of intestinal transit. A bewildering number of nutritional and hormonal factors are crucial in the adaptation process. Loss of surface area results in inadequate uptake of calories and protein (causing weight loss), poor absorption of micronutrients (especially fat-soluble vitamins), and electrolytes (especially Ca^{++}, Mg^{++}, and Zn^{++}). Bile salts and fatty acids are malabsorbed and may cause worsened diarrhea in pts with an intact colon by stimulating fluid secretion.

Sx: Diarrhea, weight loss, sx of volume depletion. Specific micronutrient deficiencies may result in a variety of syndromes (Gastroenterol Clin North Am 1998;27:467).

Si: Cachexia and volume depletion.

Crs: The course is generally determined by the length of small bowel remaining. The outcome is better in young pts and in pts with (1) proximal intestinal resections (allowing for bile salt absorption in the distal ileum), (2) an intact ileocecal valve, and (3) an intact colon.

Cmplc: D-lactic acidosis due to fermentation of malabsorbed carbohydrates in the colon may occur (presenting as dysarthria, ataxia, or confusion, with an elevated anion gap). Oxalate kidney stones (due to excessive colonic absorption of oxalate, which is bound to malabsorbed fatty acids) and gallstones may be seen.

X-ray: SBFT may be used to estimate the remaining length of intestine.

Rx: (Gut 2006;55 Suppl 4:iv1; Scand J Gastroenterol 1997;32:289) The initial postoperative management problem is usually massive diarrhea that requires TPN, fluid and electrolyte replacement, and an PPI to minimize gastric acid volume. Early use of tube feeding is indicated, since the intestinal adaptation process requires enteral feeding. Antimotility agents are used (eg, loperamide 16-20 mg daily). Reduction of fat calories may be needed in those with an intact colon to prevent bile salt-induced diarrhea, but is not needed in those without a colon. A mix of long-chain and medium-chain triglycerides are used as a fat source. Pts are given fat-soluble vitamin supplements (A, D, E, and K). Parenteral Mg^{++} replacement may be needed because of diarrhea from oral preparations. Cholestyramine may be used in pts with an intact colon who develop bile salt-induced diarrhea. If the colon is intact, dietary oxalate should be restricted to prevent kidney stones. With this approach, most pts can be gradually transitioned from TPN and enteral feeding to an oral diet.

In pts who do not improve with these measures, continuous tube feeding with a polymeric diet, nocturnal feeds, or TPN may be needed. Those who require long-term TPN are on the slippery slope of complications from infection, TPN-induced liver disease, poor vascular access, and bacterial overgrowth. Operations to create antiperistaltic segments or to increase absorptive surface area have mixed success (Brit J Surg 1994;81:486). Small bowel transplant is a high-risk option that may be needed in those with intractable TPN complications (Lancet 1996;347:1801).

4.14 Bowel Obstruction

Lancet 1999;353:1476; Adv Surg 1997;31:1

Pathophys: Most episodes of bowel obstruction occur in the small intestine, and most of those are due to adhesions. While adhesions can be inflammatory, most of them are postoperative. Nearly one-third of pts undergoing laparotomy are readmitted over the following 10 yr with adhesion-related complications (Lancet 1999;353:1476). Pts having colonic resections and pelvic surgery are at higher risk. Other causes of obstruction include herniae, malignancy, Crohn's, radiation, bezoars, intussusception, gallstone ileus (obstruction by a gallstone), and volvulus. In the colon, malignancy is the most common cause of obstruction.

Obstruction results in distension of bowel loops, edema of the bowel wall, and third spacing of intravascular volume. The distended, edematous bowel is more likely to twist, creating a closed-loop obstruction. This twist occludes the arterial blood supply and causes gangrene of the bowel (strangulation).

Sx: Colicky abdominal pain is the typical presenting sx (70%), though pain may become more steady in nature as obstruction persists (Scand J Gastroenterol 1994;29:715). Anorexia and nausea are frequently seen. Vomiting is common, especially in high-grade or proximal obstructions. Diarrhea may result transiently as the downstream bowel is emptied.

Si: Abnormal sounds and distension are the best physical exam evidence of obstruction. Usually bowel sounds are high-pitched, but if seen late in the illness or if strangulation has occurred, bowel sounds may be diminished or absent. Distension may be absent if the obstruction is proximal. Peritoneal signs (percussion and rebound tenderness, involuntary guarding) suggest the possibility of strangulation. Inguinal, femoral, and abdominal wall hernias should be excluded by exam.

Crs: A large proportion of pts with partial obstruction resolve nonoperatively. Of those with complete obstruction, 8-23% will have strangulation at surgery. Recurrence rates are high (34% at 4 yr, 42% at 10 yr) except if obstruction is due to hernia. Recurrence rates are lower in pts treated operatively (29% vs 53%), and mortality rates range from 2-12% (Arch Surg 1993;128:765).

Cmplc: Strangulation with subsequent perforation, and intra-abdominal sepsis.

Diff Dx: Gastroenteritis (pain, nausea, vomiting), ileus, and pseudo-obstruction (p 125).

Lab: Leukocytosis is usually mild, and wbc >15,000/mm^3 should raise the question of ischemia. Electrolyte abnormalities and azotemia should be sought and corrected.

X-ray: (AJR Am J Roentgenol 1997;168:1171) **Plain films** of the abdomen are routine in suspected bowel obstruction. Air fluid levels in dilated small bowel are diagnostic but are seen in only 50-60% of cases. About 20-30% of films are equivocal, and 10-20% are normal and misleading. The x-ray can be normal if loops are all fluid filled or if the obstruction is proximal. An upright chest film centered on the diaphragm may show free air due to perforation.

CT scan is very helpful in diagnosing obstruction (Clin Gastroenterol Hepatol 2008;6:130). It can be used to visualize air- or fluid-filled loops without aid of oral contrast, which can be difficult to give due to vomiting. IV contrast should be used. Sometimes the point of obstruction can be seen. If the obstruction is caused by an extrinsic process such as mass or

inflammation, CT can identify it. CT may show for evidence of strangulation that may prompt earlier surgery.

Other **radiographic studies** may be needed. An unprepped gastrografin enema is an efficient way to evaluate suspected large bowel obstruction and may be therapeutic if the obstruction is due to fecal impaction. In the acute setting, barium studies (SBFT or enteroclysis) are of limited value but may be of use after an episode of obstruction has spontaneously resolved. CT enteroclysis is an evolving technique. US may be of some value in determining that obstruction exists (seeing dilated loops) but usually does not reveal the cause (Radiology 1993;188:649). It may be of most value in pregnant pts.

Rx: Third space fluid losses and electrolyte abnormalities must be rapidly corrected. Pts with a specific cause of obstruction (such as mass or hernia) and those with no prior surgery that might have led to adhesions should undergo laparotomy. Prompt surgery is needed if there is evidence of compromised bowel (peritoneal signs, toxicity, evidence of perforation). In obstruction due to suspected adhesions, an attempt should be made to avoid operation. An NGT should be placed to decompress the stomach and small bowel. Longer tubes are of no proven additional value (Am J Surg 1995;170:366), though the issue is being revisited as new methods of long tube placement are being developed. Most pts who resolve without operation begin to do so within 24-48 hr, though some experts wait as long as 5 days before giving up and proceeding with laparotomy (Am J Surg 1993;165:121). Those with partial obstructions are at low risk for strangulation. Pts are monitored frequently with physical exam for signs of compromised bowel and undergo laparotomy urgently if they develop. The role of laparoscopy is not yet clear (Surg Endosc 2000;14:154). Intraperitoneal bioresorbable membranes have been used to prevent recurrent adhesions (J Am Coll Surg 1996;183:297).

4.15 Colonic Volvulus

Adv Surg 1996;29:131

Epidem: Incidence is lowest in Western nations (1-3/100,000/yr) and higher in developing nations (12/100,000/yr in Ghana). The mean age of presentation is 60-70 yr in the West and 40-60 yr in developing nations. Institutionalized pts with chronic constipation are at high risk.

Pathophys: A volvulus is an axial twist of part of the GI tract around the mesentery, resulting in a complete or partial obstruction. Most volvuli occur in the sigmoid or the cecum. A redundant sigmoid colon contributes to sigmoid volvulus. A cecal mesentery that is not well attached to the posterior abdominal wall predisposes to cecal volvulus. Volvuli in other segments of colon is rare.

Sx: The presentation is that of bowel obstruction with distension, pain, and constipation. Since the condition may spontaneously revert, pts may have a hx of prior similar episodes.

Si: Distension is striking and is often asymmetric. Peritoneal signs are absent unless ischemia has complicated the volvulus.

Crs: Mortality is high in Western countries (14%) (where volvulus occurs in the medically unfit) and is higher in those needing emergency operations (25%) (Dis Colon Rectum 2000;43:414).

Cmplc: Intestinal gangrene from loss of vascular supply carries a 50% mortality (Dis Colon Rectum 1982;25:494).

Diff Dx: The differential includes mechanical obstruction from malignancy or diverticular disease and pseudo-obstruction (J Am Coll Surg 1996;183:297).

X-ray: Plain films are diagnostic in 80% of sigmoid volvulus, with findings of a distended sigmoid, 2 air fluid levels, and a bird beak deformity. Cecal volvulus can be more difficult to identify. Contrast studies can identify the bird beak deformity and may be therapeutic by decompressing the volvulus.

Rx: In sigmoid volvulus without clinical evidence of perforation or ischemia, sigmoidoscopy is the initial therapeutic approach. As the scope passes by the twist, there is a large and sometimes spectacular rush of gas as decompression occurs. The mucosa is then inspected for evidence of ischemia. A decompression tube is left behind, which may help splint the bowel in place. Surgery is indicated in fit pts because the risk of recurrence is high. Operations that tack bowel down (sigmoidopexy, suturing the sigmoid serosa to the posterior abdominal wall) are associated with higher recurrence rates (30-80%) than those that involve a bowel resection (Dis Colon Rectum 2000;43:414). However, resection carries greater operative risk. Extraperitonealization of the sigmoid without resection has been described as an alternative, with acceptable mortality and low recurrence rate (Dis Colon Rectum 1998;41:381). Cecal volvulus usually requires surgical rx.

4.16 Acute Colonic Pseudo-obstruction

Gastro Endosc 2002;56:789; Annu Rev Med 1999;50:37

Epidem: This disorder (aka **Ogilvie's syndrome**) has been associated with a long list of conditions, notably orthopedic surgery, narcotics, anticholinergics, and chemotherapy. Many neurologic, renal, cardiac, obstetrical, and lung disorders have been described in association with this disorder. Malignancy, metabolic, and endocrine disorders may be present.

Pathophys: In pseudo-obstruction, the radiographs suggest mechanical obstruction, but no mechanical obstruction is present. The pathogenesis of acute colonic pseudo-obstruction is unknown. It is thought to represent an imbalance of sympathetic and parasympathetic stimulation.

Sx: The usual presentation is progressive abdominal distension that occurs over days in a hospitalized pt. Pain, nausea, and vomiting are variable features.

Si: Tympany to percussion and visible distension. Bowel sounds are present and may be high-pitched.

Crs: The course is largely dependent on the underlying illness.

Cmplc: Perforation rates of up to 3% have been reported, and perforation is associated with a 50% mortality.

Diff Dx: The major differential point is that of mechanical obstruction. In pts with a typical clinical background, conservative measures can be employed without further evaluation. In those pts who fail to improve within 24 hr, endoscopy or unprepped, water-soluble contrast enema should be obtained to rule out mechanical obstruction.

Lab: Electrolytes, Ca^{++}, Mg^{++}, PO_4, BUN/Cr, O_2 saturation, and a CBC are routinely obtained. Leukocytosis is a finding worrisome for perforation.

X-ray: KUB shows a distended colon. Cecal diameter should be measured, because the risk of perforation becomes higher when cecal diameter reaches 10-12 cm. KUB is repeated daily until the findings resolve. A water-soluble contrast enema should be considered in all pts prior to the use of neostigmine to rule out a mechanical obstruction (Nejm 1999;341:1622; discussion 1623).

Endoscopy: See Rx.

Rx: (Nejm 1999;341:192) Metabolic abnormalities such as acidosis, hypokalemia, hypocalcemia, hypomagnesemia, and volume depletion should be corrected. Drugs that inhibit motility (eg, narcotics, anticholinergics) should be stopped. Frequent turning of pts (or log rolling, spending 15 min in each of decubitus, prone, and supine positions) can be effective. An NGT and/or a rectal tube is inserted. If the pts fail to improve or worsen in the first 24 hr and if there are no contraindications, neostigmine should be used. A dose of 2 mg iv provides decompression within minutes (Nejm 1999;341:137). It should be given with the pt supine, on the bedpan, and on a cardiac monitor because of the risk of bradycardia, which may require atropine. Abdominal pain, salivation, and vomiting may occur. For pts who relapse or fail to respond to this intervention, colonoscopic decompression with a tube placed in the right colon is usually advocated (Gastrointest Endosc 1996;44:144). Surgery is indicated for those who have clinical evidence of perforation or peritonitis, or who fail all other rx.

4.17 Chronic Intestinal Pseudo-obstruction

Annu Rev Med 1999;50:37; Gut 1997;41:675

Epidem: Rare.

Pathophys: This disorder is defined by the radiographic picture of chronic obstruction in the absence of a mechanical obstruction. A variety of underlying diseases may result in a chronic defect in gut motility. In most pts, the disorder is secondary to diseases such as scleroderma, amyloid, or a paraneoplastic syndrome associated with malignancy. In some pts, there is a defect in enteric smooth muscle (hollow visceral myopathy), and in others there is a defect of the enteric nervous system.

Sx: The predominant sx are pain, distension, vomiting, constipation, and diarrhea. A family hx may suggest one of the primary disorders.

Si: Distension or signs of an associated collagen-vascular or neurologic disease.

Crs: The course in pts with the secondary form depends on the associated disorder. The course in those with primary gut myopathy or neuropathy is that of chronic illness, pain, and malnutrition.

Cmplc: Bacterial overgrowth, malnutrition.

Diff Dx: Mechanical obstruction and mucosal disease such as Crohn's must be excluded.

Lab: A CMP, thyroid studies, Mg^{++}, and CBC are obtained. In specialty centers, motility and transit studies may be performed. Fibrosis and other morphologic abnormalities are seen on full thickness bxs or resected specimens.

X-ray: Plain films show dilated bowel, giving a radiographic impression of obstruction though no mechanical obstruction exists.

Rx: Promotility agents are usually ineffective. Therapy is supportive with nutrition and rx of bacterial overgrowth. Surgery is indicated in severe, symptomatic distension in order to place a decompressive tube enterostomy (Am J Gastro 1995;90:2147). Small bowel transplant is another option. When there is localized pseudo-obstruction, resection or bypass can be performed.

4.18 Intussusception

Ann Surg 1997;226:134; Am Surg 2007;73:1098

In this process, a leading edge of bowel invaginates in the lumen of the bowel distal to it. The lesion is uncommon in adults, and some cases are associated with neoplasia at the leading edge. Most cases of intussusception in children are not associated with an anatomic abnormality. The traditional approach in adults has been surgical exploration. However, with the increased use of abdominal CT, this abnormality is frequently seen as an incidental finding. In a recent large retrospective series, only 8.8% with this CT dx underwent exploration and had a finding at operation that correlated with the CT finding (Am Surg 2007;73:1098).

4.19 Radiation Proctitis and Enteritis

Am J Gastro 1996;91:1309

Cause: Radiation rx for malignancy.

Epidem: Radiation colitis usually occurs in pts undergoing radiation rx for cancer of the uterus, cervix, ovaries, and prostate. In most pts, changes are confined to the rectum. It occurs in 2-5% of such pts (Dig Dis Sci 1991;36:373).

Pathophys: Radiation colitis can be acute or chronic. Acute radiation injury occurs as a result of mucosal cell injury and can last for 3 months after rx has ended. Chronic radiation colitis results from ischemia and fibrosis due to chronic effects of radiation on blood vessels and connective tissue (Dig Dis Sci 1991;36:373). When the blood supply is compromised, pts develop friability, bleeding, ulcers, strictures, or fistulae. The rectum is the most vulnerable because it is in a fixed position in the radiation field (while other bowel loops may move) and is often in closest proximity to the target organ.

Sx: Painful rectal spasms (tenesmus), small-volume stools, and bleeding are the most common acute sx. Fistulae and bleeding are the most common chronic sx.

Si: Blood in stool.

Crs: Most pts who present with mild to moderate sx are likely to improve spontaneously within 2 yr (Q J Med 1983;52:40). In surgical series about 10-15% of pts will have severe, intractable sx lasting years and requiring surgery (Am J Gastro 1996;91:1309), but this probably overestimates the extent of the problem.

Cmplc: Chronic, severe blood loss is the most important complication seen. A small group of pts develop stenosis, fistulae, or perforation.

Diff Dx: Dx is not difficult when there is a hx of radiation and endoscopic findings of neovascularization. Malignancy, infectious or ulcerative proctitis, or solitary rectal ulcer (p 178) are infrequent considerations.

X-ray: If done, a BE might show evidence of stricture or mucosal inflammation, but colonoscopy is more helpful.

Endoscopy: Colonoscopy may reveal mucosal pallor or erythema, friability, or ulceration. Bizarre-looking, telangiectatic blood vessels (neovascularization) may be the only gross finding and are the source of troublesome bleeding. Rectal ulcers or stricture may occur. Histology in the chronic phase shows vascular changes of subintimal fibrosis and telangiectatic vessels.

Rx: Tenesmus and pain are difficult to treat and do not respond well to topical steroids or 5-ASAs (Am J Gastro 1990;85:1537). Sucralfate enemas seem the most effective of the topical medical therapies, but long-term, randomized data are lacking (Dig Dis Sci 1999;44:973). Hyperbaric oxygen has been used but is not readily available (Dig Dis Sci 1991;36:373). Bleeding can be treated with local endoscopic measures such as laser (Gastrointest Endosc 1993;39:641), bipolar cautery (Gastrointest Endosc 1991;37:492), or formalin applied topically (Jama 1994;272:1822). However, argon plasma coagulation has become the most widely used modality. A small, randomized trial of misoprostol rectal supps given during rx showed great benefit in preventing acute and chronic sx (Am J Gastro 2000;95:1961). Surgery, usually with a colostomy, is a last resort and is frequently associated with complications.

4.20 Pneumatosis Intestinalis

This condition is defined by the presence of gas in the bowel wall. Pts with this finding and evidence of bowel obstruction or ischemia need surgery, but many pts with a variety of conditions (recent anastomoses, jejunostomy tubes, IBD, lactulose use, chemotherapy, COPD) recover without surgical intervention (Ann Surg 1990;212:160).

4.21 Typhlitis

Typhlitis is an uncommon disorder of localized inflammation of the cecum and ascending colon seen in neutropenic pts undergoing chemotherapy for malignancy. Surgical intervention may be required (Curr Gastroenterol Rep 2002;4:297).

4.22 Eosinophilic Gastroenteritis

Gut 1990;31:54; South Med J 1996;89:189

Eosinophilic gastroenteritis is a disorder characterized by eosinophilic infiltration of the GI tract. Involvement can be in the mucosal, muscular, or subserosal layers of the gut and can occur from esophagus to colon. Pts with subserosal involvement present with bloating and ascites. Pts with mucosal or muscular involvement may present with seemingly functional sx such as dyspepsia (Dig Dis Sci 1997;42:2327). Common at presentation are nausea, vomiting, diarrhea, weight loss, anemia, protein-losing enteropathy, and intestinal obstruction or perforation (South Med J 1996;89:189). About 50% of pts report a hx of allergy. The dx is suspected with GI sx and eosinophilia, but the eosinophilia may be absent in 25% (Gut 1990;31:54). In these cases, the dx is made when bx shows eosinophilic infiltration, but this can be patchy and the dx missed. In some cases, full-thickness bx may be required. The cause is unknown. Other causes of eosinophilia should be excluded. The response to steroids is usually dramatic (Am J Gastro 1993;88:70). Some experts use allergy testing and exclusion diets as primary therapy.

4.23 Meckel's Diverticulum

Am Fam Phys 2000;61:1037; Gastroenterol Clin North Am 1994;23:21

This abnormality is a diverticulum located on the antimesenteric border within 100 cm of the ileocecal valve and is found in 1-3% of individuals. In half of the pts, the diverticulum is lined by acid-producing heterotopic gastric mucosa. When the diverticulum ulcerates, it can present as lower tract bleeding. Intussusception can occur in adults, with the diverticulum as the leading edge. The gastric mucosa-containing diverticulum may be detected by Tc-99 pertechnetate scanning, but false negatives do occur and dx can be difficult.

4.24 Endometriosis

Endometriosis can involve the gut and can be confused with pain of gut origin. Crampy, nonpelvic pain can be seen in extensive disease, and complaints do not always intensify prior to or during menses. The disease can mimic IBD on barium studies (Arch IM 1995;155:977). It is important to consider this common disorder in women with chronic pain complaints (Obstet Gynecol 2003;102:397).

4.25 Epiploic Appendagitis

J Emerg Med 1999;17:823

The epiploic appendages are fat-containing structures hanging off the outside of the colon. These structures can cause acute abdominal pain if they infarct. The clinical presentation can suggest appendicitis or diverticulitis, but the pt is not ill. The correct dx is

made by CT scanning, which is characteristic with a fat density adjacent to the colon with surrounding inflammatory change. The rx is with analgesia and observation, and sx generally resolve within a week.

4.26 Narcotic Bowel Syndrome

Clin Gastroenterol Hepatol 2007;5:1126

Chronic narcotic use can be associated with an increased perception of visceral pain. Pts with this syndrome have chronic abdominal pain that develops or worsens with chronic narcotic use even as the dose is escalated. It can be seen in pts with no prior GI sx who receive narcotics for painful conditions outside the abdomen and in pts with functional GI pain treated with narcotics. The treatment is to withdraw narcotics under effective medical supervision with medical rx to minimize withdrawal sx.

Chapter 5

Neoplastic Intestinal Disorders

5.1 Colorectal Cancer

GE 2000;118:S115; Lancet 1999;353:391

Epidem: (Gastroenterol Clin North Am 1996;25:717) Colorectal cancer (CRC) is the second-leading cause of cancer death in the U.S. Based on Surveillance Epidemiology and End Results data for 2004-2006, the lifetime incidence of CRC for those born in the U.S. is roughly 5.2% (http://seer.cancer.gov/statfacts). Age-specific incidence increases abruptly at age 40 yr and climbs steadily thereafter. Incidence rates have been declining in whites since the 1970s but not in blacks, perhaps due to poorer access for blacks to colonoscopy and polypectomy (Arch Fam Med 1995;4:849). There is a tendency in the U.S. for African Americans and lower socioeconomic-status whites to present with later stage cancers.

There is a striking geographic variation. The disease is common in the U.S., Scandinavia, western Europe, and Australia, but uncommon in Asia, Africa, and South America. Immigrants to high-incidence areas experience a marked increased incidence, suggesting that environmental factors may be critical in the disease.

About 75% of cancers occur in pts without well-defined risk factors (GE 1997;112:594). There are several well-recognized risk factors, including:

- *Polyposis syndromes:* Familial adenomatous polyposis (FAP) (p 146) represents less than 1% of the total cases, and those with the FAP gene have a near 100% rate of cancer development. Pts with the HNPCC family hx represent about 1-2% of total cases and have a lifetime risk of CRC of about 80% if they inherit an HNPCC gene (p 144). Peutz-Jeghers (p 149), hyperplastic polyposis (p 151), and juvenile polyposis (p 150) are uncommon risk factors.
- *IBD:* Those with ulcerative colitis or Crohn's colitis have an increased rate of CRC after 8-10 yr, and this risk is 7-14% at 25 yr (p 114).
- *Family hx of CRC:* Having a single first-degree relative with CRC appears to confer a lifetime risk of 12-24%. The high-risk end of the range represents people with a first-degree relative with CRC under the age of 45 yr (Gastrointest Endosc Clin N Am 1993;3:715;

Ann IM 1993;118:785). Having 2 first-degree relatives with CRC puts the lifetime risk at 25-35%. The period of greatest excess RR begins under age 45 yr (when rates in the general population are low) (Nejm 1994;331:1669). Therefore, screening such individuals has maximum potential benefit if begun early (eg, age 40 yr). When only a second- or third-degree relative is affected, the risk is increased to only 30-50% above that of the general population, so the screening strategy is not altered (Gastroenterol Clin North Am 1996;25:793).

- *Family hx of adenoma:* Data from the National Cooperative Polyp Study suggests that the RR for CRC for pts whose first-degree relatives have an adenoma is 1.78, and this climbs to 2.59 for siblings of pts whose adenomas were diagnosed before age 60 yr (Nejm 1996;334:82). It has been recently argued that these data are really looking at the risk of adenomas in pts with CRC (Am J Gastro 2009;104:739).
- *Prior CRC:* The risk of a second cancer is low in the first 10 yr after dx but may be as high as 6.3% at 18 yr (Clin Radiol 1984;35:425).
- *Prior colon adenoma:* Pts with villous or tubulovillous adenomas >1 cm have a RR for cancer of 3.6 at a mean of 14 yr of follow-up (Nejm 1992;326:658).
- *Serrated colonic polyps:* Most serrated polyps of the colon are hyperplastic polyps, which have conventionally been regarded as harmless. However, recent lines of evidence suggest that not all serrated polyps of the colon have a benign behavior. The "sessile serrated adenoma" is a serrated polyp that has architectural dysplasia rather than cytologic dysplasia (Am J Clin Pathol 2005;124:380). The polyps are commonly misdiagnosed as hyperplastic polyps. They typically occur in the right colon and can be large. They show a high frequency of the type of mutations found in colon cancers characterized by methylation of DNA (GE 2006;131:1400).
- *Other risks:* Type 2 diabetes mellitus is associated with a RR = 1.43 for CRC in women (J Natl Cancer Inst 1999;91:542). Obesity is associated with a RR = 1.5-2.8 (Am J Gastro 2009;104:739). Cigarette smoking is an often overlooked risk (J Natl Cancer Inst 2000;92:1178). Other risks include prior ureterosigmoidostomy (RR = 10) (J Urol 1990;144:1110), irradiation for gynecologic cancer, acromegaly (Clin Endocrinol [Oxf] 1990;32:65), high intake of red meat (Cancer Res 1994;54:2390), and dietary fat (Nejm 1990;323:1664). Population-based cohort studies do not show a link between breast cancer and CRC, though less methodologically sound studies have suggested an association (J Clin Gastroenterol 1994;19:57).
- *Protective factors:* It has long been thought that **dietary fiber** is protective for CRC after Burkitt hypothesized that the low incidence of CRC in black Africans was related to high dietary fiber. The low risk in black Africans now appears due to low animal product consumption (Am J Gastro 1999;94:1373). The data are not striking for the protective effect of fiber. A large meta-analysis showed benefit (J Natl Cancer Inst 1990;82:650), but several cohort studies show no benefit (Gastroenterol Clin North Am 1996;25:717). Current thinking is that fruit and vegetable fiber are more important than grain fiber. The Nurses Health Study showed a clear benefit of >15 yr of **folate**-containing multivitamin use (RR = 0.25) and a more modest protective effect of dietary folate (Ann IM 1998;129:517).

  There is strong epidemiologic evidence that **aspirin** prevents CRC. Of 11 observational studies done, 10 have shown a protective effect (Ann IM 1998;128:713). The Cancer Prevention Study II, a prospective mortality study of more than 1 million subjects, showed a 40% risk reduction in pts who used aspirin at least every other day (Nejm 1991;325:1593). Similar risk reduction was seen in the Health Professionals Study (50,000 men) after

controlling for a number of confounding variables (Ann IM 1994;121:241). Despite tantalizing epidemiologic data, the only long-term, randomized study showed no differences after 5 yr of randomized aspirin use (J Natl Cancer Inst 1993;85:1220). In a 12-yr follow-up of this cohort (in which subjects self-selected aspirin use or not after 5 yr), CRC was seen as frequently in aspirin users as nonusers (Ann IM 1998;128:713). Aspirin seems most likely to reduce risk if used at high doses for more than 10 yr. The role of aspirin in primary prevention is unclear given the risks of aspirin and the unknown additional benefit of adding aspirin to pts in a screening program (Ann IM 2007;146:365).

Calcium supplementation shows no consistent benefit in epidemiologic studies, but an RCT demonstrated a benefit of supplementation in preventing recurrent adenomas (Nejm 1999;340:101). **Fish oil** is rich in omega-3 fatty acids, and fish oil supplements decrease the synthesis of arachidonate. Fish oil decreases the rectal mucosa proliferation of pts with adenomas (GE 1992;103:883) and is protective in a mouse model of CRC (Nutr Cancer 1991;15:1). Pts who are more **physically active** and leaner have a slightly lower risk of CRC (J Natl Cancer Inst 1997;89:948). **Postmenopausal estrogen** rx is associated with a 20% reduction in risk (by meta-analysis [Am J Med 1999;106:574]). CRC incidence was seen to be decreased in coronary event trials of the **HMG-CoA reductase inhibitors** pravastatin (43% reduction in incidence [Nejm 1996;335:1001]) and simvastatin (19% reduction [Arch IM 1996;156:2085]).

Pathophys:

- *The progression from adenoma to carcinoma:* The molecular mechanisms that cause the formation of adenomas and their degeneration into cancers are quite well understood (Gut 1993;34:289). The common first step is mutation of the adenomatous polyposis coli (APC) gene. This gene (an inherited mutation of which is the defect in FAP [p 146]) appears to be critical in regulating cell proliferation and programmed cell death (apoptosis) (Curr Gastroenterol Rep 1999;1:449). Defects in the APC gene might be inherited or acquired. For example, a subtle mutation in the APC gene (the I1307K mutation) is responsible for inherited cancers in Ashkenazi Jews (Nat Genet 1997;17:79). Adenomas begin as aberrant crypt foci, and their subsequent growth from small adenoma to large adenoma is marked by a series of mutations. Many of these mutations occur in DNA mismatch repair genes (the described defects in HNPCC pts [p 144]). One described defect is the activation of an oncogene, K-ras, while the other defects are primarily loss of tumor suppressor genes. Further transformation to cancer occurs with mutation of the p53 gene, and metastatic disease arises by a series of additional mutations. This sequence does not occur uniformly, and additional mutations are sure to be identified. The time required for this transformation from adenoma to cancer by multiple mutations cannot be precisely known. In the National Cooperative Polyp Study, only 5 of 1418 pts with adenomas developed cancers in 6 yr; all were early stage. Using available data on incidence and prevalence of polyps and data on the average pt age difference at dx of adenoma and cancer, an expert panel estimated that a polyp probably takes an average of 10 yr to transform into a malignancy (GE 1997;112:594). This allows ample chance to interrupt the process by endoscopic polypectomy.
- *Cancers without adenoma:* A small proportion of CRCs appear to arise without a preexisting adenoma. In their early stages, these lesions are entirely flat or minimally elevated, often with a depressed center (Gastrointest Endosc 1995;41:135), and they appear to be capable of invading submucosa. It is difficult to estimate the proportion of cancers that come from such lesions.

- *Cancers from serrated polyps:* About 15% of colon cancers show high levels of methylation of DNA. Current evidence suggests that serrated polyps, rather than adenomas, are the precursors for this type of colon cancer (GE 2006;131:1400).
- **Synchronous cancers** (cancers diagnosed at the same time as the first cancer found) occur in 2-5% of pts, and their dx affects the extent of operation about 10% of the time (Surgery 1997;122:706).
- **Metachronous lesions** (lesions diagnosed later in follow-up) occur in about 2% of pts with a mean lag of 9 yr (Surgery 1997;122:706). The rate of metachronous lesions is higher in pts with HNPCC and in pts who present with synchronous lesions (Dis Colon Rectum 1997;40:935).
- *Location of cancers:* There has been an unexplained trend over time for CRC to be found proximal to the sigmoid colon (Jama 1977;238:1641).

Sx: The location and characteristics of the tumor play a large part in the presenting sx of CRC. A small number of pts will present **without sx** after a positive screening test. Another group will present with visible **rectal bleeding**. These are more often left-sided cancers. A hx of visible rectal bleeding should be sought on ROS in health screening visits. The yield of pursuing visible rectal bleeding is very high in a primary care practice of U.S. veterans (13% polyps, 6.5% cancer, 5% IBD). There were no features on hx or exam that identified a low-risk group, and examination of the entire colon was needed for dx (Jama 1997;277:44). A **change in bowel habits** (eg, change in stool frequency or caliber from an obstructing lesion) is just as important a sx as rectal bleeding and leads to a cancer dx in a similar proportion of pts (Am J Gastro 1993;88:1179). Profound **iron deficiency anemia** without much change in bowels suggests a right-sided cancer and is a common presentation in an otherwise well pt. Those with more advanced disease may present with fatigue or weight loss. Infrequent presentations include complete bowel obstruction requiring urgent surgery, perforation, cancer of unknown primary, and *Streptococcus bovis* endocarditis (Am J Gastro 1995;90:1528).

Si: Usually none but may have mass in abdomen, hepatomegaly if mets, or mass on rectal exam. FOBT is often positive but is not a reliable negative test.

Crs: The prognosis is based on stage of cancer at presentation (Table 5.1). The TNM staging system is preferred, and variations of the older Dukes system are out of favor. Survival correlates with stage (GE 1997;112:594).

Table 5.1 Colon Cancer Staging

Stage	Tumor (T)	Nodes (N)	Metastases (M)	5-Year Survival
I	Tumor invades submucosa (T1) or muscularis propria (T2)	None	None	>90%
II	Tumor through muscularis propria (T3) Tumor through or beyond serosa (T4)	None	None	75%
III	Any T	Positive	None	50%
IV	Any T	Any N	Distant mets	<<10%

Cmplc: Bleeding, perforation, obstruction, mass effects of distant disease.

Diff Dx: The diff dx can be very broad since the sx of CRC are varied and are common to many other gut diseases. In practice, once a sx prompts examination of the colon by imaging or endoscopy, the endoscopic bxs lay the question to rest. The diff dx for masses on BE or CT includes adherent stool (perhaps 50% of masses called questionable on CT are stool); stricture due to ischemia; mass effect from diverticular disease or IBD; and uncommon colonic neoplasms such as lymphoma, carcinoid, and submucosal lesions.

Lab: CBC and CMP are routine. LFTs are not a sensitive indicator of metastatic disease. CEA is a measure of tumor burden and is a possible predictor of tumor recurrence and response to rx. The yield of cures due to CEA monitoring is small compared to the cost (Arch Pathol Lab Med 1995;119:1115).

X-ray: **Barium enema (BE)** is capable of detecting CRC and colonic polyps but is not as sensitive as colonoscopy. A positive BE requires colonoscopy for bx or polypectomy. Sensitivity figures come from a study of 2193 consecutive CRC cases in which records were reviewed for performance of BE or colonoscopy within the 3 prior years (GE 1997;112:17). This comprehensive study, which presumably mirrors general practice in the U.S., showed a sensitivity for ACBE of 85%, single-contrast BE 82%, colonoscopy by gastroenterologists 97%, and colonoscopy by nongastroenterologists 87%. Cancers found at colonoscopy were more likely to be early stage. Colonoscopy outperformed BE in all segments of bowel, and BE did no better on left than right colon. When BE misses cancers, they are usually evident in retrospect (76%) and are typically missed in the barium pool or because of overlapping loops (Gastrointest Radiol 1991;16:123). Strategies to improve the efficacy of BE have been proposed (AJR Am J Roentgenol 1993;160:491), but the gap between the 2 studies is unlikely to close.

CT colonography is a technique in which CT scanning is used to create a 3-dimensional image similar to that seen at colonoscopy (Nejm 1999;341:1496). It is more fully described in the following discussion of screening. It is most commonly used as a replacement for BE in pts who have had failed colonoscopies.

Endoscopy: Colonoscopy is indicated whenever there is a reasonable probability of colorectal neoplasia. If the colon cannot be fully examined, BE or CT colonography can be performed to examine the nonvisualized colon. If colonic sx persist despite a negative colonoscopy, the possibility of a missed lesion needs to be considered.

Rx:

- *Diet and chemoprevention:* It is reasonable to recommend to pts a diet rich in fruit and vegetable fiber and low in fat and animal products; such a diet appears protective for CRC and other illnesses. Diets rich in cereal grains are more useful for treating constipation and preventing diverticular disease but could still be advocated as means of achieving a low-fat intake and for possible beneficial effects in CRC prevention. The data for aspirin are not compelling enough to recommend to the population at large for CRC prevention given the associated risks. Assuming a 50% effectiveness for aspirin in risk reduction, its use would save fewer lives at greater cost than screening colonoscopy (GE 2002;122:78). Further study is needed to define the role of chemoprevention by use of calcium supplements, aspirin, NSAIDs, and other agents (reviewed in GE 2004;126:1423).
- *Detection and removal of adenomas* (see also p 141): It is now well established that the most effective means of preventing CRC is to detect and remove adenomas.

The most convincing data are from the National Cooperative Polyp Study cohort. These 1418 pts had 1 or more adenomas removed and were followed for an average of 5.9 yr. When compared to 3 historic reference groups, the incidence of cancer was 76-90% lower than expected (Nejm 1993;329:1977). Case control studies of screening rigid sigmoidoscopy in a large health plan (Nejm 1992;326:653) and endoscopy with polypectomy in U.S. veterans (Ann IM 1995;123:904) demonstrated a 50% reduction in risk in the screened portions of bowel.

- *Surgery:* All stage I-III cancers should be treated surgically for an attempt at cure. Stage IV lesions are treated surgically to palliate pain, bleeding, or obstruction. The resection involves the primary tumor and its lymphatic drainage with a 5-cm proximal margin and 2-cm distal margin of normal bowel. The extent of bowel resected is usually dictated by the vascular supply of the involved segment. Laparoscopic colectomy improves the immediate postoperative course compared to the open operation and is just as effective for long-term cancer cure as the open operation (Lancet 2004;363:1187; Nejm 2004;350:2050). Pts who present with complete obstruction require a 2-stage operation. They initially undergo diverting loop colostomy (in which a loop of colon is brought out to the skin and an ostomy with 2 barrels is created) until the bowel can be prepped and a cancer operation done.

  Rectal cancers (Gastroenterol Clin North Am 1997;26:103) provide special challenges to the surgeon. When the tumor is in the upper rectum and an adequate margin can be obtained, a low anterior resection with primary anastomosis is performed. Preoperative chemotherapy and radiation is given (see following discussion of chemotherapy). Generally, all tumors outside of the reach of the examining finger can be resected this way. The circular end-to-end stapler revolutionized this operation by making the anastomosis easier to perform (Dis Colon Rectum 1999;42:1369). Pts who have a low anterior resection have a higher risk of anastomotic recurrence and are followed more intensively postoperatively. For those pts in whom a bulky tumor, local spread, or very distal location prevent an anterior approach, an abdominoperineal, or AP, resection of the rectum is performed, and a permanent sigmoid colostomy is created. This procedure is associated with significant sexual dysfunction (45%) and bladder dysfunction (30%). Sphincter-sparing surgery (in the hands of specialists) can be considered if the tumor is 3 cm above the dentate line. Coloanal anastomosis has been described. Local excision may be reasonable for tumors that are within 8 cm of the dentate line, that are mobile, that have moderately or well-differentiated histology, and that are T1 or T2 by endoscopic US.

  Metastatic disease to liver or lung can be approached surgically, especially if there is a solitary lesion. Adequate performance status, good hepatic reserve, and the ability to resect all evident disease are prerequisites. Tumor-free 5-yr survival is 20-30% for resection of hepatic mets, and the results are highly variable for lung mets (Gastroenterol Clin North Am 1997;26:103).

- *Chemotherapy:* (GE 2008;134:1296) The utility of chemotherapy depends on the tumor stage and location. The goal of adjuvant rx is to treat micrometastases not identified at operation (Semin Oncol 1999;26:545). Aspirin shows promise as an adjuvant Rx (Jama 2009;302:688). For **stage III** CRCs, the data currently support the use of 6 months of postoperative fluorouracil, leucovorin, and oxaliplatin. The role of adjuvant rx in **stage II** CRC is uncertain. Randomized trials don't show benefit in this group that already has a good prognosis, but there could be a role for adjuvant rx in higher risk stage II cancers.

For **stage II and III** CRCs, preoperative combined radiation and fluorouracil-based chemotherapy has become the standard of care. For **stage IV** CRC, improvements in therapy have prolonged survival from 6 months to greater than 20 months. The newer agents, which include monoclonal antibodies to inhibit angiogenesis and growth factors, are very expensive.

- *Endoscopic therapy for obstruction:* It is possible to treat acute obstruction with placement of expandable metal stents as a bridge to a single-stage resection or as palliation (Gastrointest Endosc 1998;47:277). Major complications are common, and the value of this approach needs additional evaluation.
- *The malignant polyp:* See p 144.
- *Post-rx follow-up:* About 50% of pts will have a recurrence of CRC after rx, and most of these will happen within 3 yr of surgery. Intensive programs of postoperative surveillance with monitoring of CBC, CMP, CEA, CXR, FOBT, frequent endoscopy, and abdominal CT scanning have been used in various combinations with disappointing results. The European Society for Medical Oncology (Ann Oncol 2008;19 Suppl 2:ii29) suggests options for a menu of more limited follow-up testing. A preoperative or perioperative **colonoscopy** should be done to clear the colon of synchronous lesions, repeated at 1 yr and be repeated every 3-5 yr thereafter. Periodic liver US or CT of chest and abdomen can be considered in pts at higher risk of recurrence. CXR has limited sensitivity. Postoperative CEA can be done q 3-6 months for 3 yr and q 6-12 months. Pts with elevations are evaluated fully for recurrence. About 30% of CRC does not produce CEA, and up to 44% of pts with normal preoperative CEA have elevations with recurrence so CEA testing will have limited value (J Clin Oncol 1999;17:1312). Pts who are treated with a low anterior resection for rectal cancer have higher rates of local recurrence, and sigmoidoscopy or endoscopic US q 3-6 month for 2 yr can be considered (GE 2006;130:1865)

Screening for Colorectal Cancer: (GE 2008;134:1570; Am J Gastro 2009;104:739; Ann IM 2008;149:627)

The Case for Screening Average-Risk Pts: CRC is a disease ideally suited to screening. As detailed earlier, CRC is the second-leading cause of cancer death in the U.S., with a lifetime risk of 5.2%. CRC has a long asymptomatic phase, and progression from adenoma to cancer occurs over a long period in most cases. During this time, precancerous polyps and early stage cancers can be identified and removed. Screening for CRC is a good investment. When measured in dollars per year of life saved, CRC screening (costing $15,000-25,000/yr saved) does well against breast cancer screening ($30,000-35,000), dual airbags in cars ($120,000), and smoke detectors in new homes ($210,000) (Am J Med 1999;106:7S). There are tests currently available to detect prevalent cancers (guaiac-based FOBT testing, fecal immunochemical test for blood [FIT], fecal DNA testing) and tests for cancer prevention (colonoscopy, sigmoidoscopy, CT colonography, BE).

There Are 3 Major Sets of Recommendations: A conservative evidence-based approach is from the **U.S. Preventive Services Task Force**. The task force endorses screening for average-risk pts age 50-75 yr with FOBT, sigmoidoscopy, or colonoscopy. It recommends against routine screening in pts older than 75 yr and suggests that the decision can be individualized. It concluded that there was insufficient evidence to suggest CT colonography or fecal DNA testing as screening modalities (Ann IM 2008;149:627).

A guideline on screening has been published by the **American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of**

Radiology (ACS-MSTF) (GE 2008;134:1570). This document contains a comprehensive review of the data. This group made cancer prevention by polyp detection using colonoscopy, flex sig, or CT colonography the preferred approach. Stool testing for cancer detection was considered to be a less effective option for pts who could or would not have a polyp detection test (Ann IM 2008;149:680). They recommend colonoscopy q 10 yr, flex sig q 5 yr, or CT colonography q 5 yr as acceptable choices. They recommend against using early generation guaiac-based FOBT testing, but endorse annual high-sensitivity FOBT, annual fecal immunochemical testing, or stool DNA testing (interval unstated) as options for detecting prevalent cancers when structural tests were not used.

The **American College of Gastroenterology (ACG)** has made more specific recommendations on the choice of CRC screening from the ACS-MSTF menu of choices (Am J Gastro 2009;104:739). These guidelines make colonoscopy the screening test of choice. For those unwilling or unable to have colonoscopy, flex sig q 5-10 yr or CT colonography q 5 yr were alternatives. If a cancer detection test was chosen, they recommended fecal immunochemical testing. Since these groups reached different conclusions with the same data, it is valuable to understand the background regarding choices of screening tests.

- *Screening colonoscopy:* The effectiveness of colonoscopy as screening has not been established in RCTs or case-control studies. Two lines of evidence support the use of colonoscopy. The first is a case control study that demonstrates that sigmoidoscopy with polypectomy decreases the risk of death from distal bowel cancer by 60% (Nejm 1992;326:653). The second line of evidence comes from the National Cooperative Polyp Study, in which pts who had their colons cleared of adenomas by colonoscopy had a 76-90% reduction in CRC incidence compared to other reference groups (Nejm 1993;329:1977). Colonoscopy does not appear to be as effective in daily practice as predicted by the National Cooperative Polyp Study. Three studies of chemoprevention postpolypectomy had surprisingly high rates of cancer after initial colonoscopy to clear the colon of polyps (GE 2005;129:34). Studies from large administrative databases in Canada suggest that colonoscopy is much more protective for left-sided than right-sided cancers (Clin Gastroenterol Hepatol 2008;6:1117; Jama 2006;295:2366). Colonoscopy may be ineffective because of suboptimal preps, incomplete exams, lack of operator skill/vigilance, incomplete polypectomy, difficulty detecting flat polyps, and tumor biology. Flat polyps are more difficult to detect and have a higher risk of high-grade dysplasia or cancer than polypoid lesions of the same diameter (Jama 2006;295:2366; GE 2006;130:566). Cancers that develop within 5 yr of an apparently negative colonoscopy are 4 times more likely to have mismatch repair gene defects, suggesting a role for tumor biology in rapid cancer development (GE 2006;131:1700). There has been increasing awareness of the great variability in the quality of colonoscopy. The rate at which examiners find adenomas in initial screening exams is highly variable and partially dependent on the time taken examining the colon on withdrawal of the instrument and the technique of examination. Comprehensive recommendations for improving the quality of colonoscopy have been made (Clin Gastroenterol Hepatol 2008;6:506).

  The disadvantages of colonoscopy as a screening modality are the cost and the risk of perforation and/or bleeding from polypectomy. It is likely that there are not enough trained providers and units throughout the country to screen all those pts who would be eligible for screening colonoscopy, but a relatively low acceptance rate has made this less of an issue.

The optimal interval for screening colonoscopy is unknown. In pts with a negative initial colonoscopy, the chances of finding a cancer or pathologically advanced adenoma at 5 yr were 0% and 1.3%, respectively (Nejm 2008;359:1218). Based on rough estimates of the time to develop from adenoma to cancer, and data on the length of time sigmoidoscopy conferred a protective benefit, colonoscopy every 10 yr was initially proposed (GE 1997;112:594).

- *Screening sigmoidoscopy:* Sigmoidoscopy is effective when combined with polypectomy for reducing mortality (Nejm 1992;326:653; J Natl Cancer Inst 1992;84:1572). The major limitation of sigmoidoscopy is that it leaves much of the colon unexamined. Two important studies of screening colonoscopy demonstrate that more than half of the pathologically advanced adenomas were found in pts with no adenomas distal to the splenic flexure (Nejm 2000;343:169; Nejm 2000;343:162). Sigmoidoscopy for CRC can be likened to screening for breast cancer by mammography of 1 breast (Nejm 2000;343:207). Pts screened with sigmoidoscopy will die from preventable CRC. The advantages of sigmoidoscopy are (1) it costs less, (2) it can be performed by primary care physicians, and (3) it does not require sedation. Its use has plummeted since the adoption of full colonoscopy as the most frequently selected option. The optimal interval for sigmoidoscopy has not been determined, but the protective effect may be as long as 10 yr (Nejm 1992;326:653).
- *FOBT:* For the evidence-based purist, **guaiac based FOBT** has the advantage of having been shown effective in 5 RCTs (Am J Med 1999;106:7S). Pts who undergo annual screening with rehydrated FOBT cards (which increases sensitivity and reduces specificity) and have colonoscopy for a positive test have a 33% reduction in mortality over 13 yr of follow-up (Nejm 1993;328:1365). Biennial screening is less effective but reduces mortality by 21% (J Natl Cancer Inst 1999;91:434). Accurate FOBT requires avoidance of raw meats and avoidance of a variety of foods and medicines (Ann IM 1997;126:811). The chief problem with FOBT as a screening strategy is that because of issues of compliance and lack of sensitivity only about 15% of the expected cases of CRC would be prevented in the first 10 yr of screening (Am J Gastro 2000;95:3250). Recent improvements in guaiac-based testing have resulted in more sensitive tests such as Hemoccult SENSA, which demonstrated a 64% sensitivity for cancer and 41% for advanced adenoma in 1 large study (J Natl Cancer Inst 2007;99:1462). There is consensus that when guaiac FOBT testing is chosen, one of the newer enhanced sensitivity tests should be used. **Fecal immunochemical testing** (FIT) detects human globin. It does not require the same dietary restrictions as guaiac-based testing. Because globin is readily digested in the upper gut, false positives from UGI sources of bleeding are much less frequent. FIT appears to be somewhat more sensitive and specific than guaiac-based testing, but there is a wide variation in the performance characteristics of the available tests (Ann IM 2009;150:162).
- *Stool DNA:* Cells from adenomas and cancers are continuously shed into the stool and their DNA can be readily isolated. There is a commercially available stool test that detects DNA alterations known to be associated with adenomas and cancers. Its sensitivity was 52% for the detection of cancer but it detected only 18% of advanced adenomas in 1 large study (Nejm 2004;351:2704). The test detects many but not all of known mutations that occur in CRC.
- *CT colonography:* This technique (aka virtual colonoscopy) is one in which CT scanning is used to create a 3-dimensional image similar to that seen at colonoscopy (Nejm 1999;341:1496). The exam is done with a full bowel prep and insufflation of air into the

colon (not actually a virtual experience). Improvements in hardware and software have resulted in polyp detection rates similar to that of colonoscopy in some studies, but the range of reported sensitivities in recent trials is enormous (Ann IM 2005;142:635). It is not clear which pts with polyps found on CT colonography would be referred for polypectomy (or which pts would be content not to intervene given disclosure of the risk of waiting). While all large polyps would require intervention, polyps in the 6- to 9-mm range cannot likely be ignored since they contain high-grade dysplasia in 2-7% and cancer in nearly 1%. Decision analysis suggests that a wait and watch strategy for 6- to 9-mm polyps will result in more deaths and cancers than doing colonoscopy and polypectomy at the time of initial dx (Clin Gastroenterol Hepatol 2007;5:237). The impact of not removing polyps 5 mm and smaller has not been adequately studied. The radiation risk is a concern. One estimate of risk is an increase lifetime cancer incidence of 0.14% from a single scan (GE 2005;129:328). Though CT colonography has been available for 15 yr, it has had little impact as a primary screening modality (Mayo Clin Proc 2007;82:662).

- *Screening barium enema:* There are limited data on BE in screening. In one trial in which ACBE and sigmoidoscopy were done, BE missed 26% of rectosigmoid adenomas >1 cm and 25% of cancers (Endoscopy 1995;27:159). It is difficult to make the argument that BE is a sensible screening tool (Am J Gastro 2000;95:868).

Recommendations for Average-Risk Pts: It is not realistic to think that physicians will be able to have an in-depth discussion of all these options for colon cancer screening. The approach of the ACG seems the most practical (Am J Gastro 2009;104:739). The screening test of choice is colonoscopy every 10 yr beginning at age 50 yr. The guideline suggests beginning at age 45 yr for African Americans. The interval of 10 yr is not based on any compelling direct data but seems reasonable for a cost-effective risk reduction strategy. Those who have periodic colonoscopy should *not* have annual FOBT testing in the first few years after colonoscopy because most positive tests will be false positives if the pt has had a recent normal colonoscopy. The suggested alternatives (where cost, pt wishes, or available resources prohibit colonoscopy) are flex sig to greater than 40 cm q 5-10 yr, CT colonography, or annual fecal immunochemical test for blood. In time the guidelines may recommend screening at an earlier age in smokers and the obese.

Recommendations for Pts with a Family Hx of CRC: For pts with a first-degree relative with CRC under the age of 60 yr or multiple older relatives with CRC, the risk is increased 3-4 times. Colonoscopy beginning at age 40 yr (or 10 yr earlier than the age at which the relative was diagnosed with CRC) and done every 5 yr is suggested (GE 2008;134:1570). The risk is lower if the relative was diagnosed over age 60 yr (2-fold risk), and the ACS-MSTF guidelines suggest colonoscopy q 10 yr beginning at age 40 yr. It is not clear why the guideline is so different (q 5 yr vs q 10 yr) for a pt whose relative was diagnosed at age 59 yr vs 61 yr. A prospective study supports the use of a 5-yr interval of follow-up (Clin Gastroenterol Hepatol 2003;1:310).

Recommendations for Pts with a Family Hx of Adenomatous Polyp: The ACS-MSTF guideline suggests that a pt with a first-degree relative with an adenoma be considered in the same way as a pt with a first-degree relative with CRC. This is based on data from the National Polyp Study showing an increased risk for relatives of pts with adenomas (Nejm 1996;334:82). The ACG document has recently argued that that data are really looking at the

risk of adenomas in pts with CRC (Am J Gastro 2009;104:739). Since small tubular adenomas are very common in the population, screening all pts with a family hx of 1 or 2 small tubular adenomas would vastly increase the numbers screened early and frequently. Pts with 1 or 2 small tubular adenomas do not appear to be at risk themselves so it is difficult to understand why their relatives should be at increased risk. The ACG suggests that a pt with a first degree relative with a pathologically advanced adenoma under the age of 60 yr be screened in a similar way to those with a first-degree relative with CRC.

Recommendations for Other High-Risk Groups: Specific guidelines are discussed separately for FAP (p 146), HNPCC (p 144), and IBD (p 114), and for those with a personal hx of adenoma (p 141) or CRC (p 137).

5.2 Adenomatous Colonic Polyps

GE 2008;134:1570; GE 2006;130:1872

Epidem: Cumulative incidence of 25% in men by age 50 yr, 40% by age 70 yr. Predominance in men. The prevalence of polyps >1 cm is 15% by 75 yr. Dietary risk factors for the incidence and recurrence of adenomas are similar to those for CRC (p 131) (Ann IM 1993;118:91).

Pathophys: Adenomas are benign colonic neoplasms that are important because of their potential to degenerate into CRCs. The vast majority of CRCs arise from adenomas, and detection and removal of adenomas prevent CRC. The pathologist classifies adenomas as tubular, tubulovillous, or villous on the basis of histology. The endoscopist classifies adenomas by their size, location, and morphology. Polyps on a stalk are called pedunculated and are generally easier to resect completely. Polyps that are flat and broadly attached to the colonic wall are called sessile and are more difficult to remove as they become large. Pedunculated lesions are seen more often in the left colon, presumably due to the traction effect of formed stool on the developing polyp.

Size and histology determine risk for cancer development. Pts with an adenoma larger than 1 cm are 4 times as likely to develop a cancer at another site over a 14-yr period (Am J Gastro 1996;91:448). Severe dysplasia, the precursor of carcinoma, is most likely to develop in older pts with large polyps and in pts whose polyps include a large villous component. A large (>1 cm) villous adenoma in a pt over 60 yr old is 50 times more likely to harbor severe dysplasia than a small tubular adenoma (<5 mm) in a young pt (GE 1990;98:371). Flat and depressed adenomas are more likely to contain high-grade dysplasia and are more difficult to detect at colonoscopy (GE 2006;130:566). Adenomas do not regress but grow at a highly variable rate, with the majority staying stable in size but a minority growing at a rate of 2-4 mm/yr (Am J Gastro 1997;92:1117). Adenomas probably take an average of 10 yr to develop from small adenoma to cancer (GE 1997;112:594).

Adenomas develop from a mutated, monoclonal epithelial stem cell into cancers by a sequence of mutations in tumor suppressor genes and activation of cancer-causing genes (oncogenes) (see Colorectal Cancer, p 131). The National Polyp Study, designed to study surveillance and outcome in pts with newly discovered adenomas, provides data on outcomes after colonoscopic polypectomy. In pts with 1 or more adenomas found at index colonoscopy, 40% will have adenomas by 3 yr of follow-up. However, adenomas with advanced pathologic

features (>1 cm, severe dysplasia, or cancer) were found in only 3% of pts at 3 yr, and only 0.5% were malignant. The rate of advanced adenoma was the same for pts who had 2 colonoscopies (at 1 and 3 yr after index exam) or a single colonoscopy at 3 yr (Nejm 1993;328:901). When these pts were evaluated at a mean of 5.9 yr, there was a 75-90% reduced rate of cancer compared to that in untreated reference groups (Nejm 1993;329:1977). The magnitude of the benefit of colonoscopy has not been as great in actual practice as it was in the National Cooperative Polyp Study (p 138). It is not clear if pts with small tubular adenomas removed at endoscopy have a high risk of CRC in follow-up. In 776 pts with small tubular adenomas (single or multiple) removed at rigid sigmoidoscopy and followed up at a mean of 14 yr, rectal cancer developed in only 4 of 776 pts (Nejm 1992;326:658). However, in the National Cooperative Polyp Study, it was removal of *all* adenomas that resulted in the dramatic decrease in cancer incidence. Given the magnitude of the risk reduction seen in that study, it seems reasonable to continue to survey pts with tubular adenomas unless more convincing evidence of its low yield becomes available. Large sessile polyps (>3 cm) frequently recur (25% in one series), and recurrence may occur after a negative colonoscopic inspection. Carcinoma is common in recurrences (17%), and the risk of metachronous cancer is substantial (4%) (Gastrointest Endosc 1992;38:303).

Sx: Usually none. Large polyps may bleed. Distal polyps may prolapse out of rectum.

Si: FOBT is positive in a minority of adenomas.

Crs: Very few adenomas become cancers, with an estimated annual transformation to malignancy of 2.5 malignancies per 1000 polyps per yr. It probably takes on average 10 yr for a sporadic adenoma to become malignant if it is destined to do so, but there is a likely large variability. Pts with villous, tubulovillous, or adenomas >1 cm have a RR for cancer of 3.6 at a mean of 14 yr of follow-up (Nejm 1992;326:658). This is the rationale for endoscopic surveillance of pts with adenomas.

Cmplc: CRC, bleeding.

Diff Dx: Adenomas (about half of colon polyps) must be distinguished pathologically from other polyps. These include hyperplastic polyps (perhaps 30% of all polyps), which are usually <0.5 cm and frequently in the distal colon. Small hyperplastic polyps are not thought to be a risk factor for CRC unless associated with hyperplastic polyposis (p 151). Serrated adenomas lack the cytologic atypia of adenomas but appear to be an important risk for progression to carcinoma (p 132). Redundant mucosa or tags are polypoid-appearing but have normal colonic mucosa histologically. Lipomas, juvenile polyps, inflammatory polyps, pseudopolyps from IBD, submucosal lipoma, carcinoids, neurofibromas, and Peutz-Jeghers polyps round out the differential. Some polyps that look grossly like benign adenomas turn out to be carcinomas (see The Malignant Polyp, p 144).

Lab: Adenomas are classified according to their histology. Most adenomas are tubular, with glands composed of multiple branching structures. A minority are villous adenomas (about 10%), with long fingerlike glands from the polyp surface projecting into the bowel lumen. These have the greatest risk of subsequent cancer. Some polyps (about 20-30%) contain a mix of tubular and villous elements and are called tubulovillous adenomas. The pathologist will usually describe the degree of dysplasia in the polyp. Severe dysplasia is the equivalent of carcinoma in situ, but as long as all the dysplasia is above the muscularis mucosa, invasive cancer cannot develop. The size of polyps is best estimated when polyps are in the colon rather than after fixation.

X-ray: CT colonography (aka virtual colonoscopy), in which CT is used to create 3-dimensional images of the colon similar in appearance to those seen at colonoscopy, is discussed on p 139. Double-contrast BE is 50-80% sensitive for polyps <1 cm, and 70-90% sensitive for polyps >1 cm. BE has been largely supplanted by CT colonography.

Endoscopy: Colonoscopy is the test of choice for the detection and removal of adenomas. However, it still has limitations (Clin Gastroenterol Hepatol 2008;6:506), as further discussed on p 138.

Polypectomy is achieved by a variety of techniques. Small polyps can be removed with bx forceps. Some endoscopists prefer hot bx forceps for the removal of small polyps. A hot bx forceps has an insulated core for retrieval of a specimen but provides cautery to the polyp base. Its chief disadvantages are the risk of incomplete removal and of cautery injury to the bowel wall, especially in the right colon where the wall is thin (Gastrointest Endosc 1988;34:32). Its use is not recommended. Small polyps can also be removed by snaring them with a wire loop without cautery. Larger polyps are removed by snare cautery in which a wire loop is wrapped around the base of the polyp and cautery applied (Am J Gastro 1987;82:615). Large polyps are easier and safer to resect after injection of a cushion of saline under the polyp. This creates a thermal barrier of colonic mucosa swollen with saline to protect the muscular wall from electric current injury (Am J Gastro 1994;89:305). Complications of endoscopic polypectomy include perforation and bleeding. Bleeding is more likely to occur with large polyps. Bleeding can usually be controlled endoscopically with injection of epinephrine and application of hemostatic clips but may require surgery. Thermal injury can also create the **postpolypectomy syndrome**, in which pts develop pain and localized peritonitis due to a microperforation or serosal burn. Free perforations require surgery, but most pts with postpolypectomy syndrome recover within days with antibiotics (Gastrointest Endosc Clin N Am 1996;6:343).

Rx: Current guidelines for pts with nonfamilial colonic polyps (GE 2008;134:1570) are:

- *Total colonoscopy and endoscopic polypectomy:* When adenomas are detected at sigmoidoscopy, total colonoscopy is generally performed and all adenomas are resected. There is a low yield of finding an advanced adenoma or cancer upon performing full colonoscopy for a single small adenoma found on flex sig in average-risk pts (Ann IM 1998;129:273). However, given the benefit of screening colonoscopy (see Pathophys), it seems reasonable to proceed in most circumstances. Pts who have a hyperplastic polyp found at sigmoidoscopy have a risk of adenomas of the more proximal colon of 18%, though this number is similar in pts who have a sigmoidoscopy without any polyps (GE 1992;102:317). Therefore, hyperplastic polyps on sigmoidoscopy are no more an indication for full colonoscopy than is a normal sigmoidoscopy. If there is uncertainty about the completeness of resection due to polyp size or resection technique, the pt should have colonoscopy in 2-6 months to ensure complete resection, and if complete resection is not achieved after 2-3 sessions, surgery is usually appropriate.
- *Surgical polypectomy:* If adenomas cannot be resected at colonoscopy, colectomy is usually warranted unless the pt is a very poor surgical risk. Laparoscopic-assisted colectomy may allow more speedy recovery without increased complications (Mayo Clin Proc 2000;75:344).
- *Postpolypectomy surveillance:* Full colonoscopy is performed to resect all polyps. If only small hyperplastic polyps are found at colonoscopy, a follow-up exam is done in 10 yr unless a family hx of CRC or advanced adenomas indicates otherwise (p 140). If there is doubt as to the completeness of resection, early follow-up colonoscopy is done and

resection is verified grossly and pathologically. For pts with 2 or fewer tubular adenomas with low-grade dysplasia <1 cm in size, the guidelines call for colonoscopy in 5-10 yr. For those with >2 adenomas, with villous histology, high-grade dysplasia, or an adenoma ≥1 cm, the first follow-up exam is at 3 yr. If the follow-up exam is negative at 3 yr, the surveillance interval is subsequently increased to 5 yr. If there are more than 10 adenomas on a single exam, early follow-up is done. Follow-up should be individualized to the age and life expectancy of the pt.

- *The malignant polyp:* Pathologically, a polyp is malignant when cancer has invaded through the muscularis mucosa into the submucosa (Hum Pathol 1998;29:15). The concern with a malignant polyp is that cancerous lymph nodes may be left in the pt if a colectomy is not done. However, most of these pts are cured by polypectomy, provided that the polyp has 3 favorable features: (1) the polyp is completely excised and recovered and the surgical margin is not involved, (2) the cancer is not poorly differentiated, and (3) there is no evidence of lymphatic or vascular invasion. In pts with polyps with these favorable features, the risk of metastatic disease in pedunculated polyps is 0.3% (GE 1986;91:419). Since the mortality of colectomy is generally higher (0.2% for the very young, >3% for those over age 70 yr, an overall average of 2%), these pts are not operated on and generally do well. The polyp site is inspected in 3 months to ensure complete excision, and then the pt returns to standard cancer surveillance. In sessile polyps with the favorable characteristics described above, the risk may be as high as 4%, so colectomy may be appropriate if the pt is not at undue risk. However, the data are less clear for sessile malignant polyps since not as many large sessile malignant lesions are resected and followed. Large rectal lesions are probably best left to the surgeon or advanced endoscopist, who has a better chance of removing them completely and sufficiently intact to determine if polypectomy alone is curative.

5.3 Hereditary Nonpolyposis Colon Cancer Syndrome

Jama 2006;296:1507

Cause: Inherited mutation of DNA mismatch repair genes.

Epidem: Mean age of onset of cancer 44 yr. No gender predilection. About 1-2% of CRC is HNPCC related (GE 2001;121:1005).

Pathophys: This disorder was first recognized by the study of kindreds that had CRC inherited in a pattern of autosomal dominance with incomplete penetrance. The pathogenesis of HNPCC was suspected when tumors from these pts showed widespread alterations in short, repeated DNA sequences, called microsatellite instability. This suggested that replication errors occurred in tumor development, which led to the identification of inherited mutations in several genes that normally function in DNA mismatch repair. Mutations in the DNA mismatch repair complex (MLH1, MSH2, MSH6, and PMS2) are now considered the defining characteristic of the disorder. Pts with HNPCC do not have large numbers of adenomas, but the adenomas they have occur at a younger age, are more likely to be villous, and grow into cancers at a much faster rate than sporadic adenomas (Gut 1992;33:783). Up to 70% of cancers occur proximal to the splenic flexure.

One of the early sets of clinical criteria used to identify these families were the Amsterdam Criteria. These criteria proposed that HNPCC was an inherited form of CRC that could be identified when (1) 3 or more relatives have CRC and 1 is first degree to the other 2, (2) the cancer involves 2 generations, and (3) 1 of the cases occurs before the pt is 50 yr of age (Dis Colon Rectum 1991;34:424). In addition, some pedigrees will exhibit associated inherited malignancies of endometrium, small bowel, ovary, pancreas, stomach, biliary tree, brain, and transitional cell carcinoma of ureter and renal pelvis (GE 1993;104:1535). About half of families who meet these criteria have a mismatch repair gene defect. Strict application of the Amsterdam means the exclusion of some pts who have the disorder (as defined by the genetic defect). Broader inclusion criteria (called the Revised Bethesda Guidelines) were published (J Natl Cancer Inst 2004;96:261) and indicated that the genetic defect might be strongly suspected and tumors should be tested for microsatellite instability (MSI) when (1) a pt develops CRC before age 50 yr, (2) a pt has 2 HNPCC-related cancers, (3) a single first-degree relative has an HNPCC cancer under age 50 yr, or (4) 2 first- or second-degree relatives have an HNPCC cancer at any age. Histologic reasons to consider that a pt has a mismatch repair gene defect include CRC with a cribiform or signet ring histology, lymphocytes infiltrating the tumor, or a Crohn's-like lymphocytic reaction. These updated clinical criteria for selecting pts for MSI testing still miss cases, and some experts have proposed MSI evaluation of all tumors (Am J Gastro 2008;103:2825). The pedigrees with CRC alone are often referred to as Lynch syndrome I, and those with associated extracolonic cancers as Lynch syndrome II.

About 15% of CRC will show high levels of MSI but are not due to inherited mutations in mismatch repair genes. Many of these cases are due to an acquired mutation in the tumor in the MLH1 or BRAF genes. These are sorted out by laboratory testing.

Some families will have a hx that meets the Amsterdam Criteria but do not have a mismatch repair gene defect. These families have a different disorder with an apparently lower risk of cancer (Jama 2005;293:1979). The screening and surveillance strategies for these kindreds are uncertain.

The **Muir-Torre syndrome** (sebaceous adenomas, sebaceous carcinomas, multiple keratoacanthomas, and colonic adenomas) is a variant of HNPCC (Am J Gastro 1998;93:1572).

Sx/Si: No different than sporadic CRC (see p 131).

Crs: Risk of CRC is roughly 70% by age 70 yr, but it varies with the specific genetic defect. Risk of metachronous cancer is 50% at 15 yr. Risk of endometrial cancer is 40% and ovarian cancer 9% by age 70 yr (Jama 1997;277:915).

Cmplc: Extracolonic malignancies.

Diff Dx: In the absence of a specific diagnostic marker, the dx is usually made by use of the descriptive clinical criteria. HNPCC must be distinguished from FAP (usually easy to do on basis of number of polyps), from attenuated FAP, and from other polyposis syndromes (p 146). The reality is that most HNPCC cases go unrecognized, not because it is difficult to distinguish it from other rare polyposis syndromes but because many clinicians are unaware of its existence.

Lab: Typically the process of identifying a mismatch repair gene defect begins by examining the tumor of the affected relative for MSI, which is present in the tumors in more than 90% of pts with a germline mutation. In addition, immunochemical testing is done looking for loss

of gene products normally made by mismatch repair genes. In pts positive with this initial testing, germline mutation testing is done. If a mutation is identified in the proband, then relatives can be tested. If a relative has a positive result, he or she is at high risk (80% chance of cancer). If a relative is negative with a positive proband, he or she is at average risk. If the proband has negative or ambiguous testing, gene testing for the rest of the family is meaningless because the proband probably has a mutation that cannot be identified by the test. If an affected family member is not available for evaluation, it is reasonable to offer germline mutation testing, but it will only be meaningful if positive. Genetic counseling concerning the positive and negative consequences of a positive or negative test is mandatory (Am J Gastro 1999;94:2344).

Endoscopy: Colonoscopy is the test of choice for suspected gene carriers. Sigmoidoscopy is inadequate, because, unlike pts with FAP, those with HNPCC have few polyps and a tendency for right-sided disease.

Rx: Recommendations for management of HNPCC pts have been made and updated (Jama 2006;296:1507; Jama 1997;277:915). Because of the high risk of development of a second cancer at a later date (a metachronous CRC), subtotal colectomy with ileorectal anastomosis is the operation of choice for pts with CRC in an HNPCC kindred. This gives an excellent functional result, with a short segment of bowel that can be easily surveyed for new adenomas. There are insufficient data to recommend for or against prophylactic hysterectomy and oophorectomy either at the time of colectomy or otherwise, but it can be considered. The 3- to 5-yr intervals typical for surveillance of adenomatous polyps are inadequate for HNPCC pts because cancer frequently develops within 3-5 yr of colonoscopy (10% at 5 yr) (Gut 1992;33:783; Am J Gastro 1994;89:1978). CRC has been reported within 1-2 yr of surveillance exams. Based on observational study evidence, the recommendation is for colonoscopy q 1-2 yr beginning at age 20-25 yr (or 10 yr younger than the earliest cancer in the pedigree, whichever comes first) and then annually after age 40 yr (GE 2008;134:1570). Prophylactic colon resection in those at risk is not recommended. Screening for endometrial cancer is more uncertain. On the basis of expert opinion, annual transvaginal US and/or endometrial aspiration beginning between ages 30 and 35 yr have been proposed, but the benefit is unproven and the sensitivity unknown. Even in known kindreds, there is frequently failure to control cancer because of problems with physician knowledge of HNPCC guidelines and problems with pt compliance (Am J Gastro 1999;94:2344; Dis Colon Rectum 1993;36:254).

5.4 Familial Adenomatous Polyposis and Related Syndromes

Lancet 2004;363:852; Mayo Clin Proc 2000;75:57

Cause: Mutation of the adenomatous polyposis coli (APC) gene and much less commonly mutations in the MYH gene.

Epidem: Frequency of gene mutation 1:5000 to 1:25,000. Prevalence 1:24,500 to 1:43,500. Autosomal dominant inheritance of the APC gene defect results in equal incidence for men and women. The less common biallelic mutations of the MYH gene are inherited in an autosomal recessive pattern. Seen in all races and ethnic groups.

Pathophys: (Q J Med 1995;88:853) In this disorder the pt inherits 1 normal copy of the **APC gene** and 1 mutant copy. This mutation may be inherited from a parent in an autosomal dominant pattern, or the pt may be the first with the germline mutation (and does not have a positive family hx, as occurs in 15-20%). In 80% of pts, the mutation can be identified. In most affected subjects, a frameshift or nonsense mutation results in the production of a truncated protein that can be detected in the lab. Normal APC gene expression seems important in programmed cell death (apoptosis). Disease results when the pt's normal (or wild) APC gene mutates so that the cells have 2 defective copies, 1 germline mutation and 1 acquired (somatic) mutation. Many mutations have been described, and variations in the nature of the mutation partially account for 4 different phenotypic expressions of the APC mutation, which are classic FAP, Gardner syndrome, Turcot syndrome, and attenuated APC.

In **classic FAP**, pts develop hundreds of adenomas that are almost always detectable by age 35 yr and that result universally in cancer by age 50 yr. Adenomas are rare prior to age 12 yr. Congenital hypertrophy of retinal pigment epithelium (CHRPE) is frequently seen and was formerly used in pedigree analysis. Adenomas are seen in stomach and duodenum, especially in the periampullary area, and 5-8% will develop duodenal cancer. Hyperplastic polyps of the stomach and fundic gland cysts are common. Desmoid tumors occur in 4-15% and are benign fibrous tumors that are a major cause of morbidity through intra-abdominal mass effect on bowel and vessels. Tumors of the thyroid (papillary carcinoma, usually in women [2-3%], but as high as 12% in selected series (Clin Gastroenterol Hepatol 2007;5:367)) and hepatoblastomas (age 1-6 yr; occur in <0.5%) are associated, though not common. Adenomas may occur in the ileum after ileoanal anastomosis.

In **Gardner syndrome**, pts show adenomatous polyposis along with multiple osteomas, epidermoid cysts, desmoid tumors, and supernumerary teeth and other dental abnormalities. Sometimes simple FAP and Gardner's coexist in the same pedigree. Pts with **Turcot syndrome** have polyposis with CNS tumors, especially glioblastomas and medulloblastomas. **Attenuated APC** is a syndrome in which fewer than 100 polyps are found, extracolonic sx are uncommon, and there is a large variation in polyp number within 1 pedigree. Some of the pts with clinical features of attenuated APC actually have biallelic mutations in a base excision repair gene called MYH (Clin Gastroenterol Hepatol 2004;2:633). In these families, inheritance of so-called **MYH-associated polyposis** is autosomal recessive.

Sx: The presenting sx are typically rectal bleeding, diarrhea, obstruction, and vague abdominal pain. Pts are often asymptomatic until they present with a cancer.

Si: FOBT-positive, masses from desmoid tumors in the abdomen, CHRPE (see Pathophys), jaw masses, epidermoid cysts.

Crs: Polyps usually develop in the late teens to 20s. Onset of cancer before age 10 yr or after 50 yr is uncommon. In untreated pts, cancer usually develops in the 30s, with death at a mean age of 42 yr. The common causes of morbidity in pts who undergo proctocolectomy are UGI malignancy, desmoids, and operative complications. The proportion of pts dying from CRC has decreased. However, CRC is still the most common cause of death (Dis Colon Rectum 1996;39:384), partially because >20% of pts have no family hx and therefore are not screened, and partially because those at risk often delay surgery or screening for social reasons (Brit J Surg 1997;84:74). Duodenal cancer occurs in 5% (Brit J Surg 1998;85:742).

Cmplc: Bleeding or obstruction from cancer, mass effect from desmoids, extracolonic cancers.

Diff Dx: In its classic form, FAP is not difficult to diagnose once sigmoidoscopy is done. The attenuated form, with fewer than 100 polyps, may cause diagnostic confusion.

Lab: Genetic testing should be offered to those at risk and to those with multiple polyps. Genetic testing allows the pt at risk to determine if he or she carries the gene and to plan accordingly. It also gives relief to those who do not carry the gene. The disadvantages of gene testing are possible effects on future insurability and employment, and survivor guilt in those who prove to be negative for the gene (Am J Gastro 1999;94:2344). Testing begins by looking for the truncated protein (Nejm 1993;329:1982) produced by the mutant APC gene (so-called protein truncation testing, or PTT). If the test is positive in a relative (as it is in 80% of pedigrees), then that relative has the disease. Not all APC mutations result in a truncated protein. Therefore, if the test is negative, an affected family member needs to be tested to see if that kindred makes a truncated protein. Only if truncated protein is found in an affected member of the pedigree is truncated protein a reliable negative test. For those pedigrees that do not make a truncated protein, linkage analysis (requiring at least 2 other family members) can be done with 95% sensitivity. MYH mutation should be considered if APC gene testing is negative (Am J Gastro 2009;104:739).

Endoscopy: Dramatic findings of hundreds to thousands of adenomatous polyps in colon. EGD may show gastric fundic polyps (50%), gastric adenomas (6%), or duodenal/ampullary adenomas (33-90%).

Rx:

- *Surgery:* Surgery should be considered when the pt is in the late teens. There are 3 surgical options: (1) total proctocolectomy with Brooke ileostomy, (2) subtotal colectomy with ileorectal anastomosis, and (3) total proctocolectomy with ileoanal anastomosis (Surg Oncol Clin N Am 1996;5:675). Ileostomy is not widely chosen by young pts. Ileorectal anastomosis has the advantage of being low morbidity, with an excellent functional result and no sexual dysfunction, but it has the disadvantage of the lifelong need for surveillance and the risk of fatal rectal cancer. Ileoanal anastomosis provides elimination of the CRC risk, but the functional results (fecal soilage, stool frequency, nocturnal stooling) are not as good (Ann Surg 1999;230:648). Later conversion to ileoanal anastomosis is associated with substantial morbidity (Dis Colon Rectum 1999;42:903). Most authors prefer ileoanal anastomosis. If rectum is not resected, then postoperative surveillance is difficult because distinguishing small cancers from recurrent adenomas is difficult and because of problems with pt compliance. Postsurgical rectal cancer rates vary widely from 7-32% (Gastrointest Endosc Clin N Am 1997;7:111).
- *Screening those at risk:* (Gut 2008;57:704) Pts at risk for classic FAP should undergo genetic testing. If gene testing is positive, sigmoidoscopy begins at age 10-12 yr and is done q 2 yr until adenomas are detected. When adenomas are detected, colonoscopy is done annually until colectomy is planned. Hepatoblastoma screening is an option until age 6 yr. Pts should undergo annual thyroid exams. In those with equivocal genetic testing, sigmoidoscopy q 2 yr begins at age 10-12 yr, and continues q 2 yr until age 40 yr, then q 3-5 yr until age 50 yr. If the genetic test is unequivocally negative, sigmoidoscopy every few yr is still suggested by some because of the possibility of lab error. In attenuated FAP, surveillance can begin later with full colonoscopy beginning at age 18-20 yr

(because the disease does not always involve distal colon) and continuing q 2 yr. Pts with biallelic MYH mutations are surveyed like those with attenuated FAP.

- *Postcolectomy and EGD surveillance:* If rectal anastomosis is done, surveillance every 6 months is mandatory. If total proctocolectomy is done, the ileal pouch is examined for adenomas q 3-5 yr. EGD with forward and side viewing scopes (to detect ampullary adenomas) is done starting at age 25-30 yr and continued every 1-5 yr thereafter depending on the findings (Brit J Surg 1998;85:742; Lancet 2004;363:852). Sulindac may lower the risk of adenomas if the rectum is retained (GE 2002;122:641) and may be useful when combined with tamoxifen for the treatment of desmoids (Cancer 2004;100:612). Celecoxib may lower the risk of duodenal adenomas, but that class of agents has been associated with cardiac risk (Gut 2002;50:857).

5.5 Peutz-Jeghers Syndrome

Am J Gastro 2000;95:596; Lancet 1999;353:1211

Cause: A germline mutation in STK11, a serine/threonine kinase, the normal function of which has not been fully characterized (Nat Genet 1998;18:38; Nature 1998;391:184). Increased susceptibility comes from the germline defect, and polyps develop when a somatic mutation occurs in the normal copy of the gene from the unaffected parent.

Epidem: Rare disorder with estimated mutation rate of 1/200,000. Inherited as autosomal dominant trait. No gender predilection. Usually presents clinically in the first or second decade of life.

Pathophys: The syndrome is defined by the presence of characteristic melanin pigmentation of the skin and mucous membranes that are associated with GI polyposis. The polyps are hamartomatous (aberrant, but nonneoplastic growths of tissue appropriate to the site) and occur throughout the gut. They are most frequent in the small intestine, less frequent in the stomach and colon. The polyps cause sx by obstruction, intussusception, prolapse, or bleeding.

The association of Peutz-Jeghers with **malignancy** is well established despite the fact that the polyps are not neoplastic. Difficulty in establishing the association is partly due to the heterogeneity of clinical features in different kindreds. In 1 recent series, the RR for cancer of any kind was 19 for women and 6 for men, with a 20 times RR for breast and gynecologic cancers (Ann IM 1998;128:896). Cancer of the pancreas at an early age and the otherwise uncommon Sertoli tumor of the testes are associated cancers (Brit J Surg 1995;82:1311).

Sx: Crampy abdominal pain due to recurrent intussusception, rectal bleeding (80%), hematemesis (10%), and anal extrusion of polyps (Lancet 1999;353:1211).

Si: Characteristic melanin spots, described as small, brown to bluish dark freckles of a few mm in diameter, are most frequently found on the lips and buccal mucosa. They also occur on palms and soles. They may fade with age and vary widely in intensity within kindreds.

Crs: The course is not benign, with obstruction, bleeding, and excess malignancy, but the morbidity is decreasing with effective rx of more recent generations (Lancet 1999;353:1211).

Diff Dx: The combination of pigmented skin lesions and polyp histology usually leaves little doubt as to the dx.

X-ray: SBFT is valuable to identify polyps and plan appropriate surgical intervention.

Endoscopy: Endoscopy reveals polyps of several mm to several cm that are usually lobulated. Polyp histology shows a core of smooth muscle fibers from muscularis mucosa extending up into the mucosa in a branching pattern that makes the polyps appear lobulated. They are covered by normal mucosa. A pattern of pseudoinvasion occurs. In this pattern, mechanical forces drive normal mucosal elements into the submucosa, where they line mucin-filled cystic spaces (Lancet 1999;353:1211).

Rx: The goal is to remove polyps to prevent sx and to reduce the risk of malignancy. The greatest problem is with small bowel polyps outside the reach of the endoscope. All polyps >1.5 cm are removed, often with frequent laparotomies and intraoperative endoscopy. Surveillance guidelines (periodic EGD, SBFT, colonoscopy, surveillance for breast, gonadal, and pancreatic cancer) have been published, but their efficacy is unproven (Am J Gastro 2000;95:596; Clin Gastroenterol Hepatol 2006;4:408).

5.6 Juvenile Polyps and Juvenile Polyposis

Brit J Surg 1995;82:14

Cause: Thus far, 2 identified mutations have been associated with this autosomal dominant disease. Mutations in the gene that codes for a protein called PTEN (Nat Genet 1998;18:12) and mutations in the cancer suppressor gene SMAD4 (a common mutation seen in pancreatic tumors) appear to create alterations in the terrain for epithelial cell growth (Curr Gastro Rep 1999;1:449). There is an association of hereditary hemorrhagic telangiectasia and juvenile polyposis in SMAD4-positive kindreds (Lancet 2004;363:852).

Epidem: This is a very rare disorder. In polyposis registries, it is seen less commonly than FAP. Therefore, gene frequency is probably less than 1:50,000. There are no gender-based differences in prevalence.

Pathophys: A juvenile polyp is a hamartomatous (nonneoplastic) polyp characterized by dilated, cystic spaces lined by columnar epithelium with an inflammatory lamina propria. Solitary juvenile polyps are said to occur in 1% of children. This disorder should be suspected when (1) more than 3-10 juvenile polyps are seen in the colon (Arch Dis Child 1991;66:971), (2) juvenile polyps are seen throughout the gut, or (3) a juvenile polyp is found in a pt with a family hx of juvenile polyposis. The syndrome may present in a severe form in infancy, may be limited to the colon, or may involve the stomach and intestines. Pts develop multiple polyps, which may obstruct or bleed, but the chief concern is the associated CRC risk. An 18% incidence of CRC at a mean age of 37 yr has been reported in one series. The lifetime cumulative risk of CRC is about 50%. Cancer likely arises from the development of adenomatous dysplasia in a juvenile polyp (Cancer 1991;68:889) or from synchronous adenomas. There is an increased incidence of other GI cancers, especially stomach. A family hx is present in 20-50%, and presumably most of the others represent new germline mutations. A large number of extracolonic manifestations have been described in case reports, and it

seems likely that there is a great deal of genetic heterogeneity in the syndrome. The syndrome is autosomal dominant with variable penetrance.

Sx: Bleeding, diarrhea, or obstruction from polyps.

Si: Prolapsing rectal polyps, often FOBT positive.

Crs: Highly variable, depending on number of polyps; cancer risk as in Pathophys.

Diff Dx: Once histology is available, the major differential point is sporadic vs familial polyposis.

X-ray: Polyps on BE or UGI/SBFT, but endoscopy is preferred.

Endoscopy: Colonoscopy reveals polyps of 5 mm to several cm that are red, spherical, or lobulated and often are on a stalk.

Rx: For pts with so many polyps that the colon cannot be successfully cleared, surgery is recommended. Some authors are more aggressive and suggest a surgical approach for all pts, given the 50% cumulative CRC (J Am Coll Surg 1995;181:407). Others believe colectomy is not appropriate if the colon can be cleared and the pt is compliant with surveillance (Arch Dis Child 1991;66:971). Ileorectal anastomosis is the most common approach, but some advocate ileoanal anastomosis given polyp recurrences in the rectum and the need for future surveillance (J Am Coll Surg 1995;181:407). There are few data to guide the intervals of endoscopic surveillance. One approach calls for annual colonoscopy until the pt has 2 negative exams followed by extension of the exam interval (Gastrointest Endosc 1993;39:561). These authors suggest that the upper gut should be surveyed as well, with an interval of 3-5 yr if the exam is negative. Another guideline suggests both upper and lower endoscopy on a q 1- to 2-yr basis to beyond age 70 yr in those affected (Gut 2002;51[suppl 5]:V21).

5.7 Miscellaneous Polyposis Syndromes

Nejm 1994;331:1694

Hyperplastic Polyposis: This rare syndrome is characterized by multiple (>20), large (>10 mm) hyperplastic polyps of the proximal colon often with a smaller number of serrated adenomas (p 132), and mixed hyperplastic/adenomatous polyps (GE 2006;131:30). It is associated with mutations in the MYH gene and carries an increased risk of CRC (GE 2006;131:30).

Cowden's Disease: Also called the multiple hamartoma syndrome, it is characterized by facial trichilemmomas and other mucocutaneous papules, fibrocystic breast disease, goiter, thyroid cancer, and multiple hamartomatous polyps of the GI tract of varying histologies. The polyps are incidental, and there is no associated GI malignancy risk.

Neurofibromatosis: Submucosal neurofibromas that may cause pain or bleeding may be seen throughout the gut (Jama 1997;278:51).

Ruvalcaba-Myhre-Smith Syndrome: Macrocephaly, pigmented penile lesions, and hamartomas of the gut (Pediatr Derm 1988;5:28).

Devon Polyposis Syndrome: Recurrent inflammatory fibroid polyps requiring surgery (Gut 1992;33:1004).

5.8 Carcinoid Tumors of the Gut

Curr Opin Oncol 2002;14:38; Nejm 1999;340:858; Lancet 1998;352:799

Epidem: The incidence is low at 0.5/100 000-2.1/100 000 (Dis Colon Rectum 1997;40:349; Cancer 1997;79:813).

Pathophys: Carcinoids arise from neuroendocrine cells and contain granules rich in hormones and biogenic amines. Serotonin metabolites and other hormones are thought to be responsible for the **carcinoid syndrome** in which there is episodic flushing, wheezing, diarrhea, and eventually right-sided valvular heart disease. Carcinoid syndrome is seen only in pts with liver mets that allow release of hormones directly into the systemic circulation without clearance by the liver. A variety of kinins, prostaglandins, gastrin, somatostatin, glucagon, and other substances can be released from the tumors. The profile of released substances varies with the anatomic site (Dis Colon Rectum 1997;40:349). Serotonin is metabolized to 5-hydroxyindoleacetic acid (5-HIAA), which can be detected in the urine as a marker of the tumor. Carcinoids may occur in several sites. They can be seen as part of the MEN-1 syndrome (Ann IM 1998;129:484). **Gastric carcinoids** are usually associated with atrophic gastritis and present as small lesions in the body or fundus found incidentally at endoscopy. They can also be seen in ZE syndrome (p 86) and sporadically. These 2 groups of pts have elevated gastrin levels. Only the sporadic lesions (in which pts have normal gastrin levels) have a high incidence of mets and carcinoid syndrome. **Small bowel carcinoids** usually arise in the distal ileum and present with obstruction or pain. They can be multicentric and are often associated with carcinoid syndrome. **Appendiceal carcinoids** usually present as incidental findings at appendectomy. In 95% of cases they are <2 cm in size and do not metastasize. Larger lesions may metastasize and cause carcinoid syndrome. **Colonic carcinoids** usually present late as large right colonic masses (Dis Colon Rectum 1994;37:482), and the carcinoid syndrome occurs in <5%. **Rectal carcinoids** are often found incidentally at endoscopy (Dis Colon Rectum 1992;35:717). They typically contain glucagon rather than serotonin and rarely produce the carcinoid syndrome.

Sx/Si: Sx of pain or obstruction may be seen from mass effect of the tumor or mets. Most other sx are related to the **carcinoid syndrome**. Flushing is seen in 90%. In gastric carcinoid, flushing is a prolonged purple hue largely over the face and neck. In small bowel carcinoid, flushing is pink-red and of short duration. Other manifestations include secretory diarrhea (70%), abdominal pain (40%), telangiectasia (25%), wheezing (15%), and valvular heart disease (>30%).

Crs: About 45% of pts present with mets at original dx. The 5-yr survival regardless of site is 50% but is much higher for appendiceal and rectal carcinoid (Cancer 1997;79:813). The course of metastatic disease is highly variable, with some pts having a sx-free survival of many years.

Cmplc: Carcinoid syndrome (see Pathophys and Sx/Si). Carcinoid heart disease occurs in two-thirds of pts with carcinoid syndrome (Nejm 1999;340:858). Fibrotic thickening of the endocardium causes retraction of valve leaflets in the right heart, resulting in tricuspid regurgitation or, less often, stenosis. Less often there is regurgitation/stenosis of the pulmonic or left-sided valves (Circ 1993;87:1188). The cause is unknown. Niacin deficiency (pellagra, dermatitis, diarrhea, dementia) results because the precursor tryptophan is consumed by the tumor.

Diff Dx: The dx is usually considered because of sx suggestive of the carcinoid syndrome. The differential is broad depending on the presenting sx.

Lab: A 24-hr urine test for 5-HIAA is specific for carcinoid (if level >100 mmol/24 hr), though the test requires a variety of dietary and medicine restrictions for accurate performance (Lancet 1998;352:799).

X-ray: CT scan with and without contrast is used to detect hepatic mets. Radiolabeled octreotide scanning can be used to detect mets prior to operation by the binding of somatostatin receptors on tumor cells (Nejm 1990;323:1246). Histologically, these tumors have small cells with well-rounded nuclei. They stain with chromate and with silver. Immunohistochemical stains are diagnostic by confirming the hormone content of the tumor.

Endoscopy: This is the best test for detection of gastric and intestinal lesions within reach of the endoscope.

Rx: Appendiceal carcinoids <2 cm are treated with appendectomy. Those larger than 2 cm or with extension to the base of the appendix are treated with right hemicolectomy. Rectal carcinoids are usually treated with local excision if they are <1 cm and with resection if they are >2 cm. The approach for lesions 1-2 cm in size is individualized because it is not clear that resection is better than local excision for this group. Small bowel lesions are treated with resection. Small gastric lesions can be excised endoscopically, and larger lesions are resected surgically.

In the **carcinoid syndrome**, pts should avoid alcohol, spicy food, and exercise, which may precipitate attacks. Octreotide, a synthetic somatostatin analog injected bid, inhibits serotonin release and is effective in 70-90% of pts if adequate doses are used (Aliment Pharmacol Ther 1995;9:387). Depot octreotide is used because injections can be given monthly. Hepatic mets can be resected in selected pts with long-term sx relief (Am J Surg 1995;169:36) or can be treated by radiofrequency ablation or embolization. Transplant for metastatic carcinoid had a surprising 69% 5-yr survival in a recent French series (Ann Surg 1997;225:355). Chemotherapy is disappointing, and there is little experience with radiation (Nejm 1999;340:858). Radiotherapy targeting peptide receptors is investigational. Antiangiogenesis agents and agents targeted to growth factors have been of little value (Clin Gastroenterol Hepatol 2006;4:526).

Chapter 6

Infectious Intestinal Disorders

Comment: The most frequently encountered infectious causes of diarrhea are summarized in Section 6.1. For a discussion of the diff dx, see Acute Diarrhea (p 14) or Chronic Diarrhea (p 17). General supportive measures are outlined in those sections.

6.1 *Clostridium difficile* Colitis and Antibiotic-Associated Diarrhea

Ann IM 2006;145:758; Nejm 2002;346:334; Am J Gastro 1997;92:739

Cause: *Clostridium difficile* (C. *diff*), an anaerobic, spore-forming bacillus.

Epidem: The reported disease incidence has been rising steadily, probably as a result of better detection, physician awareness, and the emergence of virulent strains. The illness is more common in the elderly, in pts who have been hospitalized, in renal pts, in surgical pts, in IBD pts (Gut 1983;24:713), in pts taking PPIs (CMAJ 2004;171:33) and in those with malignancy. Carriage rates in Europe and the U.S. are 0-3% in healthy adult subjects and 35-65% in healthy neonates. The organism is frequently acquired in the hospital through the ingestion of spores. The spores resist digestion and become vegetative when they reach the colon. Infected pts are a disease reservoir. The organism can be recovered from many surfaces in pt care areas. It is transmitted via healthcare workers' hands or stethoscopes (J Antimicrob Chemother 1998;41[suppl C]:59).

Pathophys: Antibiotic-associated diarrhea is a mild, self-limited illness of unknown mechanism that is associated with many antibiotics, clears with cessation of antibiotics, and causes no structural damage to the colon. C. *diff* causes a spectrum of illness, from diarrhea without obvious macroscopic colitis to more severe forms associated with inflammatory changes in the colonic mucosa. Before the discovery of C. *diff*, this illness was called pseudomembranous colitis because of the endoscopic and histologic findings, and it was thought to be due to *Staphylococcus aureus*. The discovery that 10% of pts given clindamycin developed pseudomembranous colitis led to the discovery that toxins produced by C. *diff* are the cause of the illness (BMJ 1995;310:1375). The use of broad-spectrum antibiotics is the initiating event in the vast majority of cases of C. *diff* colitis. Changes in the normal intestinal flora seem permissive for the proliferation of the organism. The organism is most often acquired

nosocomially from the environment. When the colonized pt is exposed to broad-spectrum antibiotics, there is rapid overgrowth of the organism. Almost all antibiotics have been implicated in C. *diff* colitis, including clindamycin, penicillins, cephalosporins, quinolones, erythromycin, tetracyclines, and sulfonamides. Disease is more likely to follow high-dose, prolonged courses of rx, especially if multiple agents are used.

C. *diff* causes colitis by the elaboration of toxins A and B in the colon lumen. Toxin A causes an inflammatory reaction and fluid secretion. Toxin B is a powerful cytotoxin in tissue culture but not enterotoxigenic in animals (Nejm 1994;330:257). A variety of other virulence factors may be important in promoting colonization and tissue destruction (J Antimicrob Chemother 1998;41[suppl C]:13). From 5% to 25% of strains do not produce either toxin and do not cause diarrhea. The disease has increased in incidence and virulence in recent years with the emergence of an epidemic strain of C. *diff* designated B1/NAP1. This strain is characterized by high production of toxins A and B and other virulence factors (Ann IM 2006;145:758).

Sx: Pts with mild disease usually present with the sudden onset of watery diarrhea during or shortly after a course of antibiotics. However, there may be a delay of many weeks between antibiotic use and illness. Those with more severe illness may have severe diarrhea, substantial abdominal pain, and fever.

Si: In mild disease, there may be mild abdominal tenderness or FOBT-positive stool. In more severe disease, fever, ileus, signs of volume depletion, delirium, and abdominal distension may be seen. Localized peritoneal signs are common in severe illness and usually improve with appropriate rx. A small subgroup will present with fulminant colitis with toxic dilatation, diffuse peritonitis, or signs of perforation.

Crs: Relapse is frequent, occurring in 15-35% of pts (mean about 20%). Most treated ambulatory pts improve over 2-3 days with appropriate rx, and 95% are fully resolved after a 10-day course (Nejm 1994;330:257). However, the disease has become more virulent in the last decade with a dramatic rise in mortality and complications in hospitalized pts (Cmaj 2004;171:468).

Cmplc: Fulminant colitis with peritonitis, gram-negative sepsis, and perforation.

Diff Dx: C. *diff* disease needs to be distinguished from simple antibiotic-related diarrhea. In pts with mild sx, this means stopping the antibiotic and waiting. In pts with moderate illness, stool studies are done for C. *diff*. If these are negative and suspicion is high, endoscopic studies may be indicated. In pts who acquire diarrhea in the hospital, the likely causes are C. *diff*, drugs, or enteral feeding. The yield for other pathogens in hospital-acquired diarrhea is pathetically low, and routine stool cultures are usually wasteful.

Lab: Stool **immunoassays for toxin A and B** are the most widely used tests in the U.S. They are 90% sensitive and vary by brand of test. They are highly specific. A negative test in an affected pt is, therefore, not rare in clinical practice. Ordering a second test on a different day will increase the yield (Ann IM 1995;123:835). Variant strains of toxin can be missed by commercial assays (Ann IM 2001;135:434), and 1-2% of cases involve strains that produce only toxin B (Nejm 2002;346:334). **Tissue culture** is the most sensitive and specific test and is usually reserved for investigating outbreaks when identification of the strain may be important. **Tissue culture for toxin B** is cumbersome and only 90% sensitive. **PCR of stool for toxin B** may have the best combination of sensitivity, specificity, and cost but is not widely available (Clin Gastroenterol Hepatol 2004;2:669). **Latex agglutination** detects a C. *diff* metabolic enzyme, not the toxin (J Clin Microbiol 1991;29:2639). It detects

nonpathogenic strains and has other cross reactivities, making its specificity inadequate. Leukocytosis is common.

X-ray: KUB is usually normal in mild disease, but as disease progresses, there may be radiographic signs of colitis such as thumbprinting (irregularity in the mucosal outline of the colon about the size of a thumbprint) or toxic dilatation. CT scan, often done in severely ill pts before the dx is appreciated, may show thickening of the colonic wall due to colitis.

Endoscopy: In mild disease there is minimal or no gross colitis. When the disease progresses, there is a pathognomonic finding of pseudomembranes at colonoscopy. They are raised, yellowish plaques with a stuck-on appearance, varying from a few mm to more than a cm in diameter. In severe disease they may coalesce into large segments. They are easily stripped off by the endoscope (the origin of the term pseudomembrane) (Am J Gastro 1997;92:739). The intervening mucosa may be nearly normal or edematous, friable, and erythematous, depending on disease severity. In perhaps 10% of pts, the pseudomembranes are confined to the proximal colon and may be missed at sigmoidoscopy (GE 1982;83:1259). These pts may be difficult to dx because they may have less diarrhea given the relatively spared left colon. Neutropenic pts will not have pseudomembranes, because they do not have enough white cells to make them (BMJ 1995;310:1375).

Rx: Whenever possible, antibiotics should be stopped. Some experts suggest that since many cases will resolve spontaneously, antibiotic rx should not be routinely given (Am J Gastro 1997;92:739). However, most clinicians only order a diagnostic test in pts who are significantly affected and rx all positives. Fluid and electrolyte replacement may be needed. Antimotility agents should be avoided since this prolongs the contact of the mucosa with toxin and may worsen the illness.

In pts with mild to moderate disease, oral **metronidazole** 250-500 mg po tid for 7-10 d is the drug of choice based on cost. Some strains are metronidazole-resistant, but this is uncommon. In mild disease metronidazole and oral vancomycin are equally effective, but in severe disease vancomycin is superior (Clin Infect Dis 2007;45:302). In pts with severe disease, who often cannot take oral rx, metronidazole is given as 500-750 mg iv q 6-8 d depending on body weight and severity of illness. Oral **vancomycin** is wildly expensive and should be used when pts do not respond to metronidazole, cannot tolerate metronidazole, have more severe illness, or have a contraindication to metronidazole use (eg, pregnancy). The usual dosage for vancomycin is 125 mg po qid for 7-10 d, but doses up to 500 mg po qid are used in pts with severe illness. The drug can be given by NGT where needed. Oral vancomycin should probably be used concomitantly with iv metronidazole in pts who are critically ill. Vancomycin given by iv does not work because there is inadequate excretion into the colon, where the organism lies. Vancomycin enemas can be given as adjunctive rx in severely ill pts (Clin Infect Dis 2002;35:690), and iv immunoglobulin can be considered in these pts based on anecdotal evidence (Ann IM 2006;145:758).

Cholestyramine or colestipol bind the toxin (and vancomycin!) but are marginal therapies compared to antibiotics. Bacitracin is less effective than vancomycin (GE 1985;89:1038), and a variety of other agents have been used (Aliment Pharmacol Ther 1997;11:1003).

Pts with a substantial symptomatic **relapse** should simply receive a second course of rx with metronidazole, since the cause of relapse is rarely drug resistance. Alternatively, they can be treated with vancomycin. Relapse occurs by germination of spores in the colon, by reinfection in the hospital setting, or due to another course of antibiotics. There is no well-defined approach to pts with multiple relapses. Some experts use a prolonged course of

oral vancomycin; others use intermittent vancomycin (125 mg po q 2-7 d for 1 or 2 months, tapered with a nonscientific flourish). The hope is to kill vegetative forms newly developed from the spores that escape the antibiotic. Other forms of rx include lactobacillus preparations (ineffective by RCT [Mayo Clin Proc 2001;76:883]), oral *Saccharomyces boulardii* (Aliment Pharmacol Ther 1998;12:807; GE 1989;96:981), fecal enemas, donor feces by NGT (Clin Infect Dis 2003;36:580), and iv gamma globulin (Gut 2002;51:456).

Pts with severe disease may require **surgery** for perforation or fulminant colitis with a mortality of 25-67%. Retrospective reviews suggest that pts are more likely to survive if they have subtotal colectomy rather than simple diversion or lesser degrees of colectomy (Am J Gastro 2008;103:3195). Pts with diarrhea should be isolated to **prevent** spread of disease. Hand washing with soap and water is more effective than using alcohol-based hand cleaners, which do not kill spores effectively. The load of spores and vegetative forms is reduced by thorough disinfection of equipment and by cleaning the environment with 10% bleach. Rx of asymptomatic carriers with metronidazole or vancomycin is ineffective (Ann IM 1992;117:297).

6.2 *Campylobacter*

Gastroenterol Clin North Am 2001;30:709; Clin Lab Med 1999;19:489

Cause: Most human *Campylobacter* infections are caused by *Campylobacter jejunii*, but other species, including *C. coli* and any of 12 other subspecies, may cause human disease. The organisms are gram-negative, and are curved or spiral-shaped rods.

Epidem: *Campylobacter* is the most common of the bacterial causes of diarrhea after *C. diff*. There is a bimodal peak of incidence (infants and young adults), but it affects all ages. Sporadic cases are usually associated with undercooked or mishandled poultry and less often with other meats, untreated water, or raw milk. Epidemics are associated with raw milk or contaminated water.

Pathophys: The ingestion of as few as 500 organisms can result in infection. The bug colonizes the distal ileum and colon, where invasion occurs and intestinal absorption is inhibited, resulting in diarrhea.

Sx: The incubation period is 1-5 d. Pts typically present with crampy pain, watery diarrhea (often mixed with blood and mucus), and fever. Headache may be especially prominent and a clue to the etiology.

Crs: The typical course is a 4- to 5-d illness with 1-2 wk for complete resolution. Of those seeking medical attention, 20% have sx for longer than a wk (Am J Gastro 1993;88:1667). The relapse rate is 10-20%.

Cmplc: There is firm serologic and culture-based evidence that *Campylobacter* infection can result in Guillain-Barré syndrome (Clin Microbiol Rev 1998;11:555; Infect Dis Clin North Am 1998;12:173). A syndrome of reactive arthritis in HLA-B27-positive pts may occur (within 1-3 wk) and resolve within 6 months (Arch IM 1983;143:215). Pancreatitis has been reported in 6% of pts sick enough to be hospitalized (Arch IM 1983;143:215).

Lab: Stool culture is the test of choice. Since the organism is fastidious, a single culture may not be adequate (Am J Gastro 1993;88:1667). An experienced observer may be able to pick out the

organism on a Gram stain using carbol fuchsin as a counterstain because it is a curved rod, giving a gull wing appearance. There are no other rapid methods of adequate sensitivity and specificity for commercial use.

Endoscopy: Usually endoscopy is not indicated, but if done, it shows features of a nonspecific colitis with erythema, edema, and loss of the vascular pattern in involved segments.

Rx: Antibiotic treatment shortens the course of illness by about a day and is more effective if given early in the course (Clin Infect Dis 2007;44:696). However, the illness is usually self-limited, and antibiotic resistance is growing. Pts who are slow to recover, who have continued sx of dysentery, or who are immunocompromised should be treated with erythromycin 250 mg po qid for 5 d. In a subgroup of ill pts, rx with a quinolone (eg, ciprofloxacin 500 mg po bid × 5 d) given on presentation before the culture results are available may further shorten the illness (p 16). However, increasing quinolone resistance limits the value of this approach. In Europe and Asia, quinolone resistance ranges from 41-88% and in North America the rate has climbed to over 10% (GE 2000;118:S48). Azithromycin 500 mg daily is an alternative to erythromycin.

6.3 *Salmonella*

Dis Mo 1999;45:268; Am J Gastro 1993;88:1667; South Med J 1978;71:1540

Cause: There are more than 2200 serotypes of *Salmonella*. The species most likely to cause gastroenteritis in the U.S. are *S. typhimurium*, *S. enteritidis*, *S. heidelberg*, and *S. newport*.

Epidem: About 40,000 cases are reported annually in the U.S., representing about 1-5% of the actual total. Transmission is by contaminated water or food, chiefly poultry, eggs, dairy products, and processed meats. Vertical transmission in hen eggs has created an enormous reservoir (Gut 1994;35:726). Fecal–oral spread is easily prevented by hand washing.

Pathophys: The bacteria invade intestinal and colonic epithelium, frequently resulting in bacteremia (5-10%). Pts with sickle cell disease, HIV, and immunosuppression are more prone to bacteremia. Infected pts most commonly develop gastroenteritis and less commonly extraintestinal infections (osteomyelitis, pneumonia, arteritis, and meningitis). Those infected with the typhoid-causing or paratyphoid-causing agents develop enteric fever (not further discussed here). Following acute infection, pts commonly excrete organisms for weeks to months. Pts are said to be chronic carriers if excretion lasts more than 1 yr. This occurs in 1% of pts infected with nontyphoidal *Salmonella*.

Sx: Pts most often present with a mild to moderate illness of crampy abdominal pain and diarrhea. A small subgroup will present with a more severe illness with high fever and bloody diarrhea. The pts with severe illness are more likely to be the very old, the very young, and the immunocompromised.

Si: Fever, abdominal tenderness (sometimes right sided if there is prominent ileal involvement), and blood in stool.

Crs: Usually self-limited illness of several d; prolonged stool excretion, with 1% of pts developing a carrier state (>1 yr of infection).

Cmplc: Extraintestinal infections from bacteremia as listed in Pathophys. Reactive arthritis may occur.

Lab: Stool C&S.

X-ray: KUB, if done, may show evidence of colitis with thick colonic folds and thumbprinting. CT may show evidence of colonic wall thickening.

Endoscopy: If done, shows nonspecific evidence of colitis. Bx shows acute colitis without the distortion of crypt architecture or loss of mucous glands seen in IBD (Gut 1994;35:726).

Rx: Antibiotic rx does not, in general, shorten the course of the illness in otherwise healthy pts with mild to moderate illness. Rx with antibiotics should be reserved for pts with severe sx (such as high fever, bloody diarrhea, or the need to be hospitalized), pts at the extremes of age, or pts who are immunosuppressed. Choices include Tm/S 160/800 mg po bid, ciprofloxacin 500 mg po bid, or norfloxacin 400 mg po bid for 5-7 d depending on the speed of response (Am J Gastro 1997;92:1962). In the small number of pts who develop the chronic carrier state following enterocolitis, rx with a quinolone for 28 d could be considered, but this is by analogy to studies in typhoidal strains rather than by direct evidence (GE 2000;118:S48).

6.4 *Shigella*

Gastroenterol Clin North Am 2001;30:709; Am J Gastro 1993;88:1667

Cause: There are 4 species of *Shigella* organisms—*S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*.

Epidem: The only reservoirs for *Shigella* are humans and apes. In developed nations this is largely a pediatric disease because of person-to-person spread. In the West most infections are with *S. sonnei*, which is less virulent. In contrast, in developing nations, waterborne and foodborne spread is common, and disease is often with the more virulent *S. flexneri* or *S. dysenteriae*.

Pathophys: Small infectious doses are needed and usually resist stomach acid. Clinical illness usually begins within 12 hr as invasion of the small intestine begins. Over the next few d, the colon is invaded and the pt develops lower abdominal pain and in some cases bloody diarrhea.

Sx: The most common sx is large-volume diarrhea (bloody in about half of pts, the classic dysentery). Most pts develop abdominal pain that is crampy and may be severe. Fever and vomiting are common.

Si: Abdominal tenderness, fever, and blood in stool.

Crs: If untreated, the illness usually lasts 1 wk, with a range of 1-30 d. Chronic relapsing sx are rare.

Cmplc: Intestinal obstruction, toxic megacolon, perforation, pneumonia, and HUS have all been described. Reiter's syndrome (arthritis, back pain, urethritis, and conjunctivitis) is seen following 1-2% of cases, most often in HLA-B27–positive pts.

Lab: Stool C&S.

Endoscopy: If done, colonoscopic findings are those of a nonspecific colitis.

Rx: Rx with antibiotics shortens the course of the illness and prevents additional person-to-person spread. Pts with disease acquired in the U.S. should be treated with Tm/S 1 DS tab po

bid × 5 d. Pts whose illness is acquired in foreign travel should be treated with a quinolone such as ciprofloxacin 500 mg po bid, and sensitivities should be confirmed (Am J Gastro 1997;92:1962). Antimotility agents should be avoided in the very ill because they worsen illness (Jama 1973;226:1525).

6.5 *E. coli* O157:H7

Annu Rev Med 1999;50:355; Lancet 1998;352:1207; Ann IM 1995;123:698

Cause: *Escherichia coli* O157:H7, an organism so called because it expresses the 157th somatic (O) antigen and the 7th flagellar antigen. Other Shiga toxin-producing *E. coli* produce diarrheal illness, but their role is not well defined (GE 1993;105:1724).

Epidem: Incidence of 8/100,000/yr in Britain and North America, much higher in South America. Peaks in summer. Healthy cattle are the major reservoir, but it is found in many animals, especially ruminants. The disease is most often transmitted by food or water, but person-to-person spread can be important in some settings, such as a child day-care center. Meat becomes contaminated at slaughter, especially if it is ground in processing. Undercooked ground meat is a frequent cause. Outbreaks have been associated with fresh produce and with drinking or swimming in unchlorinated water. Implicated foods range from fresh-pressed apple cider (Jama 1993;269:2217) to deer meat jerky (Jama 1997;277:1229), emphasizing the need to involve public health authorities in investigation of cases. The infectious dose is very low (50 organisms). Fecal shedding can last for weeks after recovery.

Pathophys: The virulence of this organism is based on its production of Shiga toxins, a virulence plasmid, and on other factors not yet characterized. The organism adheres to the brush border in the colon, and the virulence factors cause cell damage leading to bloody diarrhea. HUS is caused by adherence of Shiga toxins to renal endothelial cells. This probably triggers platelet and fibrin deposition in the renal vessels, causing hemolysis of red cells and renal failure secondary to microvascular occlusion.

Sx: The illness can present as asymptomatic carriage, nonbloody diarrhea, bloody diarrhea, or HUS leading to death. Incubation period is 1-7 d. The illness usually begins as watery diarrhea that turns bloody in 70% of pts. Vomiting is common (60%), but fever is low grade and occurs in only 30% of pts.

Si: Abdominal tenderness may be marked. High fever is uncommon. Neurologic abnormalities may develop in HUS pts.

Crs: Most pts recover within 7 d. However, 3-7% of pts develop HUS. Of these, 9% die, 3% have chronic renal failure or other major sequelae such as stroke or seizures, and 25% have mild renal sequelae (Jama 2003;290:1360).

Cmplc: HUS, which is more common in the very old, very young (younger than 5 yr old), and possibly in those who receive antimotility agents or antibiotics.

Lab: Stool C&S. The organism is presumptively identified because it does not ferment sorbitol. Sorbitol-negative colonies are then tested for the O157 antigen. Leukocytosis is common.

Endoscopy: Endoscopy (which is usually unnecessary) reveals a mucosa that appears hyperemic and congested, with edema and patchy superficial ulceration that is often seen in the right colon. There is no single feature on biospy that is diagnostic. There may be features of ischemic colitis and pseudomembranous colitis seen on bx (Ann IM 1995;123:698).

Rx: Rx is supportive. It seems prudent to monitor for the development of HUS, especially in the very old and very young. Loperamide should be avoided because it may predispose to HUS (J Pediatr 1990;116:589). It is not clear if antibiotics are helpful or harmful. A small prospective cohort study of children demonstrated an increased incidence of HUS in those children who received antibiotics (Nejm 2000;342:1930), but a meta-analysis of 9 studies showed no effect (Jama 2002;288:996). Shiga toxin-binding agents are a new approach, but an RCT of 1 such agent showed no benefit (Jama 2003;290:1337). HUS requires dialysis in 50% of cases. It is crucial that the physician notify public health authorities immediately of confirmed cases or suspected outbreaks. Prompt investigation can lead to prevention of additional cases by rapid identification of the source.

6.6 Cholera and Other *Vibrio* Diseases

Lancet 2004;363:223; Am J Med 1998;104:386; Lancet 1997;349:1825

Cause: *Vibrio cholerae*, a curved gram-negative rod. The O1 and the newly emerged O139 strains cause epidemic disease and others cause sporadic diarrhea. *Vibrio parahemolyticus* causes a diarrheal illness.

Epidem: Cholera is endemic in Asia and Africa. It was reintroduced in epidemic form to Latin America in the 1990s. A newly emerged strain (O139) has caused epidemics in India, Bangladesh, and Southeast Asia. In developed nations, it is usually a disease of returned travelers. Epidemics arise when epidemic strains are introduced into nonimmune populations. Transmission is by water, food, and person-to-person spread. *Vibrio parahemolyticus* occurs from ingestion of undercooked seafood, is common in Japan, and has been seen in coastal areas of the United States.

Pathophys: Cholera is the prototypical enterotoxic, secretory diarrhea. The organism binds to small intestinal epithelial cells and secretes the cholera toxin. The toxin induces adenylate cyclase, increases in intracellular cAMP, which increases chloride secretion, and decreases Na absorption. This causes the massive volume loss that characterizes the disease.

Sx: Massive diarrhea, up to a L per hour.

Si: Volume depletion, stupor.

Crs: Usually resolves within 6 d if vascular collapse is avoided.

Lab: Stool culture. A clinical dx is usually made in an epidemic setting.

Rx: The cornerstone of rx for cholera is rehydration. This is done orally with the World Health Organization oral hydration rx (NaCl, KCl, sodium bicarbonate, and glucose), and with fluids iv in severe cases. Tetracycline, doxycycline, and quinolones shorten the illness. Oral vaccines show promise but may be too expensive for most of those at risk (Lancet 2004;363:223).

6.7 *Yersinia enterocolitica*

Clin Microbiol Rev 1997;10:257

This pathogen is an uncommon cause of illness in North America. It causes an acute enterocolitis, a pseudoappendicitis, or a terminal ileitis suggestive of Crohn's disease. It may be complicated by septicemia with metastatic infection and a variety of other clinical sequelae. The dx is made by C&S, though serology may also be of use. A wide variety of antibiotics are effective.

6.8 Enterotoxigenic, Enteropathogenic, Shiga-Toxigenic, and Enteroinvasive *E. coli*

The strains of *E. coli* that cause diarrhea are very difficult to distinguish from other nonpathogenic *E. coli* in the clinical laboratory. Virulence of these strains is caused by genes that are encoded on plasmids. Only the O157:H7 type discussed in section 6.5 is specifically identified in common clinical practice. The enteropathogenic strain is primarily a disease of infants and may be prolonged. The enterotoxigenic type produces a diarrhea causing enterotoxin and is the major cause of traveler's diarrhea. Antibiotic rx shortens the illness (p 16). The enteroinvasive type causes illness by tissue invasion (Dis Mo 1999;45:268; Am J Gastro 1997;92:1962). The non-O157 Shiga-toxigenic types are being increasingly recognized in outbreaks of illness (Crit Rev Microbiol 2007;33:67).

6.9 *Plesiomonas*

This facultatively anaerobic gram-negative rod causes an illness of diarrhea, fever, and blood in stool. It appears to be an invasive infection after ingestion of uncooked shellfish or travel. Antibiotics (Tm/S or tetracycline) may improve the illness (Ann IM 1986;105:690).

6.10 *Aeromonas*

Aeromonas, a facultatively anaerobic gram-negative rod, is found in fresh and brackish water in the U.S. and is a cause of diarrhea worldwide. Sx can be chronic in adults and acute and severe in children. The diarrhea is probably caused by an enterotoxin. Several antibiotics appear effective (Gastroenterol Clin North Am 2001;30:709).

6.11 Giardiasis

Clin Infect Dis 1997;25:545

Cause: *Giardia lamblia*, a protozoan flagellate.

Epidem: Infection results from ingestion of cysts, which can be viable for months in cool water. Most infections come from contaminated water or less commonly by fecal–oral spread. Although the cysts are often resistant to the chlorine in drinking water, they can be effectively removed by filtration. Campers are at risk from water contaminated by animals (beaver fever). *Giardia* can be endemic in areas where water treatment is inadequate, though most residents of these regions remain asymptomatic.

Pathophys: After cysts are ingested and pass into the duodenum, they change to trophozoites, the vegetative form. Some trophozoites encyst in the ileum and are excreted in stool. Tissue invasion does not occur and no toxin has been identified. The mechanism of diarrhea is not clear, but may be related to disruption of the brush border. Since pts with hypogammaglobulinemia or IgA deficiency have more severe illness, a host antibody-mediated response seems important. Malabsorption commonly occurs. Lactose intolerance is found in 20-40% of pts and may last weeks even after infection is cleared.

Sx: The incubation period is generally 1-2 wk. Most infections remain asymptomatic. Acutely symptomatic pts present with cramping, midabdominal to upper abdominal pain, bloating, flatulence, and loose, foul-smelling stool. Weight loss and anorexia are common. Fever is sometimes seen at the outset of illness. There is no blood found in stools. As infection becomes more chronic, malaise and epigastric pain may predominate and diarrhea lessens.

Si: Distension, very active bowel sounds.

Crs: If untreated, the infection lasts weeks to months, though it usually clears spontaneously in healthy hosts. In multiple relapses, consider recurrent infection (have the well water tested!), hypogammaglobulinemia, HIV, or other immune deficiency states.

Lab: Stool *Giardia* antigen is the test of choice and is highly sensitive and specific. Stool O&P exams are insensitive even with multiple samples. Serologic tests are of little use because they do not distinguish remote from active infection. The string test, in which the pt swallows a capsule attached to a string that is inspected for trophozoites, is cumbersome. Empiric antibiotics seem a sensible alternative.

Rx: Metronidazole 250 mg po tid for 5-7 d is a commonly used rx in the U.S. Tinidazole 2 gm po as a single dose is just as effective and has been released in the U.S. (Clin Microbiol Rev 2001;14:114). Furazolidone (100 mg po qid for 7-10 d), albendazole, and paromomycin are alternatives. Quinacrine is no longer available in the U.S. because of toxicity. Because of the frequency of lactase deficiency, pts should minimize lactose intake and be warned that the lactase deficiency may last for weeks and cause an apparent relapse when pts try to reintroduce milk products.

6.12 Amebiasis

Lancet 2003;361:1025; Clin Infect Dis 1999;29:1117

Cause: *Entamoeba histolytica*, a protozoan parasite. There are several nonpathogenic species, such as *E. dispar*, which is 10-fold more frequent but morphologically identical to *E. histolytica*. There are species of occasional or uncertain pathogenicity, such as *Entamoeba coli* (Lancet 1991;338:254) and *Dientamoeba fragilis* (Dig Dis Sci 1996;41:1811).

Epidem: Infection is endemic in many developing nations and uncommon in nations with well-developed sanitation systems. Each year, 40-50 million cases occur. In the U.S., it is largely a disease of returned travelers and immigrants. Hepatic abscess is 7-12 times more likely in men. Spread is fecal–oral through contaminated food and water.

Pathophys: The parasite is ingested in the cyst form and produces 8 trophozoites, which attach to intestinal mucin glycoproteins and invade host cells. After invasion of the colon, distant sites of infection can develop. The most common is hepatic abscess.

Sx: Some pts remain entirely asymptomatic carriers, especially in endemic areas. Pts with amebic colitis present with the gradual onset of abdominal pain, fever, and diarrhea that becomes bloody. The gradual onset is a hallmark, and weight loss is common. Fever is infrequent in colitis alone. Amebic abscess presents as pain and fever, sometimes with an RUQ mass.

Si: In colitis, blood in stool is common (70%). A mass can be detected in pts who develop a localized segmental mass of granulation tissue called an ameboma (Gastroenterol Clin North Am 1996;25:471).

Crs: The course is usually one of good response to rx, but pregnancy, malignancy, steroid use, malnutrition, and neonatal infection are more likely to result in a fulminant picture (Clin Infect Dis 1995;20:1453).

Cmplc: Extraintestinal disease with abscess of liver, spleen, brain, empyema, or pericarditis; abscesses may rupture; fulminant colitis occurs in <0.5% and can require surgery with a mortality of 50%.

Diff Dx: The diff dx for amebic hepatic abscess is pyogenic liver abscess, echinococcus, and HCC.

Lab: A stool test for *E. histolytica*–specific antigen (Gut 1994;335:1018) is the test of choice because it is 87% sensitive and 90% specific. DNA-based tests are superior but not widely available (Mayo Clin Proc 2008;83:1154). Stool O&P exams miss more than half of infections (unless multiple samples are obtained) and cannot distinguish pathogenic from nonpathogenic species. Serology is a useful adjunct (75-90% sensitive) but does not distinguish recent from remote infection and may be negative early in the course of the illness. In hepatic abscess, alk phos is elevated in 80% of pts.

X-ray: Both CT and US are effective for the dx of abscess.

Endoscopy: Colonoscopy should be done if the cause of colitis is in doubt. Colonoscopy is superior to sigmoidoscopy. The mucosa looks similar to that of IBD with granularity, friability, and ulcerated mucosa. The ulcers may have sharply defined borders and undermining, and are called flask shaped. Scrapings of ulcer bases are examined for trophozoites, and bx are obtained for conventional and immunochemical staining (Gastroenterol Clin North Am 1996;25:471).

Rx: Both the trophozoites and the cysts must be killed to clear the intestinal infection. Metronidazole 750 mg po tid × 10 d kills trophozoites. Tinidazole 2 gm po × 3 d is as effective and is now available in the U.S. Cysts are treated by a course of diloxanide furoate 500 mg po tid × 10 d or iodoquinol 650 mg po tid × 20 d. Asymptomatic cyst passers may be treated without the course of metronidazole. For fulminant colitis, iv metronidazole is used. Other rx is available for pregnant pts and special circumstances (GE 2000;118:S48). For hepatic abscess, initial rx is with metronidazole/diloxanide. Percutaneous drainage or surgery is not needed in most cases.

6.13 Cryptosporidiosis

Nejm 2002;346:1723; Adv Parasitol 1998;40:37

Cause: *Cryptosporidium pavum*, a ubiquitous protozoan parasite.

Epidem: This is a common infection with prevalence rates of under 2% in developed nations and as high as 30% in developing nations (Epidemiol Rev 1996;18:118). It is highly infectious. Human infections come from animals (especially cattle) most often via the water supply. Large outbreaks in cities with good water treatment underscore the difficulty of controlling this agent (Ann IM 1996;124:459). About 4% of pts with HIV infection in the U.S. develop cryptosporidiosis. Other risks include malnutrition and communal living.

Pathophys: The mechanism by which *Cryptosporidia* causes a profuse watery diarrhea has not been established. No toxin has been identified, and overt intestinal destruction is rare.

Sx: After an incubation period of about 6 d, healthy hosts develop a self-limited infection marked by watery diarrhea, anorexia, abdominal pain, and sometimes fever or cough. Some HIV-infected pts have transient illness, but they are more likely to have chronic illness. A minority of immunosuppressed pts will present with a fulminant illness resembling cholera in its ferocity.

Si: Volume depletion, active bowel sounds, sometimes fever.

Crs: It is a self-limited illness of days to weeks in healthy hosts. It is a chronic illness in HIV pts and portends short survival (Q J Med 1992;85:813).

Cmplc: Respiratory infection is common and can cause severe cough and dyspnea. It can be lethal in HIV pts. In HIV pts, biliary infection can cause a sclerosing cholangitis-like picture that improves with sphincterotomy.

Lab: Fluorescent antibody tests are commercially available and are more sensitive than staining techniques (Clin Lab Med 1995;15:307). The modified Ziehl-Neelsen acid-fast stain is an alternative.

Rx: Supportive rx is the most important, since highly effective antimicrobial rx does not exist. Healthy hosts clear the infection. Hosts who appear otherwise healthy and do not improve should be tested for HIV. These otherwise healthy pts with a long illness and pts with HIV infection might benefit from nitaxozanide rx (Cochrane Database Syst Rev 2007;CD004932). For pts with HIV, antivirals are a cornerstone of rx. Loperamide or other antimotility agents should be used, and octreotide can be used as symptomatic rx with some benefit.

6.14 *Cyclospora*

Infect Dis Clin North Am 1998;12:1

Cause: *Cyclospora cayetanensis*, a coccidian protozoan related to *Cryptosporidium* and *Isospora*.

Epidem: The organism is found worldwide. Disease is acquired by the ingestion of oocysts as the result of fecal contamination of water or food. The most notable outbreak in the U.S. was associated with Guatemalan raspberries (Ann IM 1999;130:210). Both outbreak

(Ann IM 1995;123:409) and sporadic cases have been associated with untreated water. Travelers returning from endemic areas are at high risk.

Pathophys: After ingestion, the organism becomes an intracellular parasite of small intestinal epithelium. Understanding beyond these preliminary observations is limited.

Sx: Pts typically present with watery, bloodless diarrhea that can occur in cycles. Fatigue, anorexia, weight loss, and bloating are common. A flu-like illness may precede the diarrhea by a wk.

Si: Weight loss may be demonstrated, but physical findings are nonspecific.

Crs: In immunocompetent individuals, the infection may last for weeks with diarrhea becoming less prominent and fatigue and anorexia persisting. In HIV-infected pts, the illness may be more prolonged and is more likely to relapse.

Lab: The modified Ziehl-Neelsen acid-fast stain is the most widely used detection method. Detection is enhanced by concentration methods, and new detection techniques are emerging (Arch Pathol Lab Med 1997;121:792).

Endoscopy: Bx, if done, may show villous atrophy and crypt hyperplasia (Ann IM 1993;119:377).

Rx: A placebo-controlled trial showed that Tm/S 1 DS tab po bid × 7 d is highly effective (Lancet 1995;345:691). Repeat doses tiw may be needed to prevent relapses in AIDS pts (GE 2000;118:S48).

6.15 *Isospora belli* and Microsporidia

Isospora belli was described as a cause of diarrhea in soldiers in World War I (hence the name). This protozoan is now almost exclusively identified in AIDS pts (Nejm 1986;315:87). Water- or food-bearing oocysts are the presumptive mode of transmission. The organism can be found in small intestinal epithelial cells and causes villous atrophy and crypt hyperplasia. Sx are watery diarrhea with crampy pain and steatorrhea. Dx is made by microscopic detection of oocysts using carbol fuchsin stain. It usually responds to Tm/S 160/800 po qid × 10 d, and regimens to prevent relapse have been described (GE 2000;118:S48).

Microsporidia can cause infection in healthy hosts but is largely a pathogen of AIDS pts. There are many species that can cause a diarrheal illness. They are small and difficult to detect in stool and tissue samples. A modified trichrome stain is used in stool specimens. Albendazole is effective rx for some species (Parasitology 1998;117:S143).

6.16 *Blastocystis hominis*

This protozoan produces an illness of diarrhea and abdominal pain. In many pts with this parasite, a second infectious agent will be found. Its presence indicates that the pt was exposed to contaminated food or water. It is noninvasive and in most cases rx is not needed. Those with persistent sx and in whom no alternative etiology is identified can be offered metronidazole 750 mg po tid for 10 d (J Clin Gastro 1990;12:525).

6.17 *Dientamoeba fragilis*

This protozoan causes an illness of diarrhea and abdominal pain. It is associated with pinworm infection. Rx is diiodohydroxyquin in adults and metronidazole in children (Dig Dis Sci 1996;41:1811).

6.18 Viral Gastroenteritis

Gastroenterol Clin North Am 2001;30:779; Jama 1993;269:627; Nejm 1991;325:252

Viruses are frequent causes of diarrhea. However, the rx for all of the following illnesses is supportive, and a specific dx is rarely required except in the investigation of epidemics. **Rotavirus** is a frequent cause of dehydrating diarrhea lasting 5-7 d in young children. Illness is usually not severe after age 3 yr, and infection is often asymptomatic. It occurs more often in the winter in temperate climates and is easily diagnosed, if desired, by stool antigen testing. **Norwalk-like viruses (caliciviruses)** cause outbreaks of diarrhea, fever, vomiting, and myalgia in children and adults. Infection frequently occurs in settings such as cruise ships, camps, and nursing homes. Outbreaks have been associated with contaminated shellfish, water, or other foods. Illness lasts a day or 2. PCR testing is available in research labs and has enhanced the understanding of these viruses as causes of epidemics. **Enteric adenoviruses** cause prolonged diarrheal illnesses in infants and young children. **Astroviruses** are less well-characterized causes of diarrhea.

6.19 Diarrhea in HIV

GE 1996;111:1724

Cause: Many causes of HIV diarrhea have been identified. These include pathogens that cause illness in healthy hosts such as *Campylobacter, Salmonella, Shigella, C. diff, Giardia*, and *Entamoeba histolytica*. Opportunistic infections such as CMV, *Cryptosporidia, Cyclospora*, microsporidia, *Isospora*, and *Mycobacterium avium* complex cause prolonged diarrhea in HIV-infected pts. Multiple pathogens are seen in up to 29% of pts (Gut 1996;39:824).

Diff Dx: The differential needs to include the causes of diarrhea seen in pts who are not HIV infected (p 17). Diarrhea secondary to drugs is common in HIV-infected pts.

Lab: Stool should be sent for O&P × 3, culture for bacterial pathogens, *C. diff* antigen, *Giardia* antigen, microsporidia (modified trichrome), Isospora (carbol fuchsin), and tests for *Cryptosporidia* (acid-fast or antigen screen). At least 3 stool samples are recommended, but the optimal number is unknown (GE 1996;111:1724).

Endoscopy: Colonoscopy will demonstrate a cause (usually CMV or *Cryptosporidia*, but also adenovirus or spirochetes) in 30% of pts with negative stool studies and low CD4 counts. Most of these findings were within reach of a sigmoidoscope in 1 series (Gut 1996;39:824), but the yield of colonoscopy vs sigmoidoscopy was 39% vs 22% in another large series (Gastrointest Endosc 1998;48:354). EGD is indicated and may demonstrate the cause (*Cryptosporidia*,

Giardia, Mycobacterium avium, CMV, or microsporidia) in up to 44% of pts with negative stool studies and CD4 counts <200/mL (Gut 1996;39:824). Some authors suggest that colonoscopy with bx of the terminal ileum is just as effective as sigmoidoscopy plus EGD, and suggest that EGD adds nothing. However, these authors had a very low yield of microsporidia on their EGD bx studies (Am J Gastro 1999;94:596). In discussing a strategy with pts, colonoscopy plus EGD has the highest diagnostic yield, and any other approach has a risk of missing treatable diagnoses.

Rx: Specific causes are treated as outlined under the specific pathogens earlier in this chapter. There is no consistently effective rx for *Cryptosporidia* (Postgrad Med J 1997;73:713) or microsporidia, but rx with potent antiretrovirals restores immunity and clears the pathogens (Lancet 1998;351:256). CMV is treated with ganciclovir or foscarnet (p 61).

6.20 Intestinal Helminths

Pts with these infections do not usually present with diarrhea but rather present with nonspecific abdominal pain and eosinophilia. Important cestodes (tapeworms) include *Diphyllobothrium latum*, *Taenia*, *Hymenolepis*, and *Dipylidium caninum* (Gastroenterologist 1993;1:265). Common nematodes include (1) *Ascaris lumbricoides*, (2) *Trichuris trichiura* (whipworm; I saw one that survived a gallon of polyethylene glycol and was swimming around a colon but got away), (3) *Necator americanus* and *Ancylostoma duodenale* (hookworms) (Nejm 2004;351:799), (4) *Enterobius vermicularis* (pinworm), (5) anisakiasis (the sushi parasites) (Am J Gastro 1986;81:1185), and (6) trichinosis (Gastroenterologist 1994;2:39). Ascarids are of special interest to the gastroenterologist because they can migrate into biliary and pancreatic ducts, causing cholangitis and acting as the nidus for stones. Once the dx is made (usually by O&P exams), effective rx is available (GE 2000;118:S48).

6.21 Bacterial Overgrowth

Curr Treat Options Gastroenterol 2004;7:19; Clin Perspect Gastro 2000;3:225

Cause: Colonization of the small intestine with a high concentration of bacteria.

Epidem: The elderly are more prone to bacterial overgrowth in the absence of other identifiable risks (Am J Gastro 1997;92:47).

Pathophys: Normally the small gut contains low concentrations of bacteria ($<10^4$ cfu/mL) that provide several useful functions, including the production of vitamin K and the breakdown of unabsorbed sugars into fatty acids absorbable in the colon. Several conditions can lead to bacterial overgrowth, including loss of gastric acidity (especially iatrogenic due to PPI rx), poor motility (eg, scleroderma, diabetic neuropathy), and anatomic abnormalities (diverticula, blind loops, fistulas, strictures). Pts are usually colonized by multiple genera of oral or colonic bacteria rather than a single species (Am J Gastro 1999;94:1327). Bacteria deconjugate bile acids in the small intestine, preventing the formation of micelles (mixtures of conjugated bile salts and dietary lipids) and thus reducing the absorption of dietary fat. Deconjugated bile salts are also toxic to enterocytes, resulting in malabsorption of carbohydrates and proteins. Bacteria degrade proteins. Vitamin absorption is reduced and

B_{12} levels may fall due to consumption of B_{12} by bacteria and the binding of B_{12} absorption receptors in the ileum by bacterial B_{12} metabolites.

Sx: Chronic diarrhea associated with bloating and crampy abdominal pain is the typical presentation. Pts often note borborygmi and foul flatus. Weight loss is common. In the elderly, the sx may be nonspecific (anorexia, nausea) (Am J Gastro 1997;92:47).

Si: There are no specific findings on exam, though pts may have the findings of the diseases (such as scleroderma) that predispose to bacterial overgrowth.

Crs: Since the predisposing conditions are usually chronic, multiple relapses are common.

Cmplc: Pts may develop complications of malnutrition or specific vitamin deficiency syndromes (night blindness with vitamin A, neuropathy and anemia with B_{12} deficiency).

Diff Dx: The broad differential is that of chronic diarrhea (p 17).

Lab: In pts with a predisposing condition and a good clinical story, empiric rx rather than lab dx is reasonable. The historic gold standard for laboratory dx is a culture of small intestinal aspirate. This is rarely done outside the research setting because of difficulties with anaerobic cultures, the difficulty of obtaining the sample, and the potential of missing distal overgrowth. The ^{13}C-xylose breath test is the preferred method of lab dx. Bacteria metabolize the labeled xylose (which healthy humans usually absorb intact), and the ^{13}C-labeled CO_2 is detected in the breath. The test is >90% sensitive and specific, but expensive. Hydrogen breath tests lack sensitivity and specificity (Am J Gastro 1996;91:1795).

X-ray: SBFT may show evidence of predisposing conditions such as small bowel diverticula, strictures, or Crohn's.

Rx: If possible, the underlying predisposing condition should be treated. Usually, this is not possible. There are very limited data on antibiotic choice or duration of rx. Antibiotics are typically given in 7-10 courses. In pts with frequent relapses, antibiotic courses are given 1 wk per month using a rotating schedule. Norfloxacin (800 mg daily in divided doses) and amoxicillin-clavulanate (500/125 mg 1 tab po tid) have been shown effective in a small crossover randomized trial (GE 1999;117:794). Rifaximin is an expensive, broad spectrum, nonabsorbable antibiotic that is effective with minimal side effects. A dose 1600 mg po daily in 3 divided doses appears more effective than lower doses (Aliment Pharmacol Ther 2007;25:781). On the basis of clinical experience rather than trials, other common choices include tetracycline 250 mg po qid, doxycycline 100 mg po bid, cephalexin 250 mg po qid, or ciprofloxacin 500 mg po bid. Metronidazole is sometimes used as a single agent but is more often combined with an agent active against aerobes.

6.22 Food Poisoning

Postgrad Med 1998;103:125; Feldman M, Scharschmidt B, Sleisenger M, eds. Sleisenger & Fordtran's Gastrointestinal and Liver Disease. 6th ed. Philadelphia: WB Saunders, 1998:1624-1627.

Foodborne illness can be from infection or preformed toxins. Infectious causes have been discussed earlier. The most common causes of foodborne toxic illness are:

***Staphylococcus aureus*:** Preformed enterotoxin from this organism is the most common cause of toxinborne food poisoning. It causes an acute-onset illness of nausea and

vomiting with a short incubation (1-6 hr) and a duration of illness of 24 hr. Fever, cramps, and diarrhea are less prominent. The organism is transmitted from food handler to food (especially foods with high salt or sugar concentrations), where toxin is formed as the organism grows in the warm food.

***Clostridium perfringens*:** This organism produces a toxin as it grows in bulk-cooked meat or poultry that is inadequately cooled. It causes an illness of watery diarrhea and crampy pain with an incubation of 8-24 hr and duration of 24-36 hr.

***Bacillus cereus*:** This produces an illness of cramps, diarrhea, and vomiting. Incubation is 6-14 hr with a duration of 20-36 hr. Fever is not common. It is associated with foods kept warm for prolonged periods. A variant illness of primarily vomiting has been described.

***Miscellaneous*:** Rarer toxic foodborne illnesses include mushroom poisoning, cholera, botulism, tetrodotoxin poisoning from pufferfish, ciguatera from fish, paralytic shellfish poisoning, and scromboid.

6.23 Whipple's Disease

Lancet 2003;361:239; Gastroenterol Clin North Am 1998;27:683

Cause: Rodlike bacilli were described in the first case reported by Whipple in 1907. The causative agent, *Tropheryma whippelii*, a gram-positive actinomycete, was first identified by ribosomal RNA sequencing and recently cultured (Nejm 2000;342:620).

Epidem: The disorder is very rare and typically found in white, middle-aged men.

Pathophys: Whipple's is a chronic, multisystem, relapsing illness. Person-to-person transmission has never been documented, and host factors are probably important. Decreased monocyte interleukin production may be important (Gastroenterol Clin North Am 1998;27:683). Almost any tissue can be infiltrated by the macrophages loaded with periodic acid-Schiff-positive (PAS-positive) material (degenerating bacilli) that characterize the disorder.

Sx: The presentations of the illness can be quite variable. Weight loss (often 20-30 pounds) and diarrhea due to malabsorption are the most common sx. A nondestructive arthritis is common and may precede other sx by years (Mayo Clin Proc 1988;63:539). Abdominal pain is often vague and has no specific features. Cough may be seen. CNS manifestations occur in 10-50% and may include headache, ataxia, weakness, seizures, and personality changes. Some pts present only with CNS disease (Scand J Infect Dis 1999;31:411). Up to 15% of pts never have GI sx (Medicine 1997;76:170). Ocular involvement may occur and present as iritis or visual loss. Heart failure or sudden death due to myocarditis can be a presenting sx.

Si: Peripheral lymphadenopathy, abdominal tenderness, hyperpigmentation, fever, wasting, and peripheral edema are common. Murmurs occur from endocarditis or pancarditis, and friction rubs may be seen. FOBT-positive stool is common (Dig Dis Sci 1994;39:1642).

Crs: Without rx the illness is slowly progressive, but with antibiotics prognosis is good. A symptomatic response is seen in days to weeks after antibiotics. Relapse is common (40%), months or years after successful rx (Gastroenterol Clin North Am 1998;27:683).

Diff Dx: The most difficult part of the dx is considering such a rare illness when nonspecific sx are present. The combination of malabsorption, fever, adenopathy, and joint sx raise the

suspicion. The dx is established by bx of involved tissue, usually small bowel bx at EGD. PCR of infected tissues may be useful in pts who lack small intestinal involvement (Nejm 1995;332:390).

Lab: Anemia (90%), malabsorption (elevated stool fat on 72-hr collection, abnormal d-xylose test), low serum carotene, hypoalbuminemia. PCR can be used to identify *T. whippelii* sequences in tissues when bx features are nondiagnostic.

X-ray: SBFT is usually abnormal with dilatation and mucosal thickening (Mayo Clin Proc 1988;63:539). CT may show adenopathy.

Endoscopy: EGD shows thickened, spaced-out folds with yellow or whitish plaques but may be grossly normal (Medicine 1997;76:170). The typical bx shows dilated lymphatics, infiltration of the lamina propria with macrophages that stain strongly PAS-positive and contain gram-positive, AFB-negative bacilli. Since involvement can be patchy, multiple specimens should be obtained (Scand J Gastroenterol 1994;29:97).

Rx: A variety of antibiotics have been used successfully. Antibiotics that do not cross the blood–brain barrier (eg, tetracycline) should not be used (Mayo Clin Proc 1988;63:539). Tm/S is considered the first-line agent (Dig Dis Sci 1994;39:1642) and is given for a period of 12 months. Oral rx should be preceded by a 2-wk course of ceftriaxone 2 gm iv qd (Lancet 2003;361:239). Antibiotic failures may occur (GE 1994;106:782). The value of repeat bx or PCR of cerebrospinal fluid to assess eradication has not been established.

Chapter 7

Anorectal Disorders

7.1 Hemorrhoids

GE 2004;126:1463; Prim Care 1999;26:35

Epidem: The prevalence of hemorrhoids is 80-90% in U.S. adults, with equal prevalence in men and women (Dis Colon Rectum 1983;26:435). Symptomatic hemorrhoids are unusual before age 20 yr, peak at age 45-65 yr, and are associated with higher socioeconomic status (GE 1990;98:380). Pregnancy is a risk factor.

Pathophys: Hemorrhoids are classified as internal or external based on the anatomic location from which they originate. Two areas are important to recognize. The anal verge is the most distal portion of the anal canal. About 2-3 cm above the verge is the dentate or pectinate line, the junction of anal and rectal mucosa. Hemorrhoids are pathologic dilatations of the normal vascular beds. Hemorrhoids are internal if they originate from the vascular bed above the dentate line, and they are external if they originate below the dentate line in the bed close to the anal verge. The point of origination, not the distal extent of the hemorrhoid, defines it as internal or external. Internal hemorrhoids are covered by rectal mucosa and have no somatic sensation, while external hemorrhoids are covered by anoderm and have the somatic sensation of skin. Internal hemorrhoids are graded based on the degree of prolapse (grade I = no prolapse, grade II = spontaneous reduction, grade III = manual reduction, grade IV = cannot be reduced). The pathogenesis of hemorrhoids is not well understood, though straining is thought to be of importance in disrupting the vascular beds. Both constipation and diarrhea are conditions associated with hemorrhoids (Dis Colon Rectum 1998;41:1534).

Sx: Internal hemorrhoids cause painless bleeding or prolapse. Blood is usually bright red and is seen on toilet tissue or around stool, or it may drip into the toilet if there is prolapse. Prolapsed hemorrhoids may result in a discharge on underwear. Painful thrombosis of internal hemorrhoids is uncommon. External hemorrhoids begin as small skin tags, cause problems with hygiene, cause perianal irritation, and can acutely thrombose, causing acute, severe pain.

Si: External hemorrhoids are visible; internal hemorrhoids are not, unless prolapsed. Most internal hemorrhoids are not palpable, and anoscopy is mandatory to establish their presence or absence.

Crs: Sx are usually mild and intermittent. Only a minority of pts require interventions beyond topical measures or develop complications such as thrombosis or permanent prolapse.

Cmplc: Thrombosis, presenting as acute pain.

Diff Dx: The presence of hemorrhoids is easily established and the diagnostic pitfall is usually in determining if hemorrhoids are the cause of a given sx. The differential includes other causes of rectal bleeding such as fissure, polyp, cancer, and IBD, and other causes of perianal discomfort such as abscess or fistula. A fissure should be suspected if there is pain and spasm on exam. Hemorrhoids should not be accepted as a cause of rectal bleeding without further evaluation (detailed on p 24).

Lab: Usually not indicated except in substantial, chronic bleeding.

Endoscopy: Anoscopy is easy to perform and very informative. Hemorrhoids are better assessed with an anoscope than a colonoscope, though the latter is more fun to use. At anoscopy, the dentate line is identified, the distal rectal mucosa is inspected, and hemorrhoids are identified as reddish-bluish protrusions into the lumen. Anoscopy also allows for the evaluation of fissures.

Rx: A high-fiber diet to keep stools soft is usually all that is needed for sx of painless bleeding from grade I or II hemorrhoids. Some pts experience local problems with itching or burning secondary to difficult hygiene or edema associated with the hemorrhoids. This often improves with local measures such as diaper wipes, witch hazel pads, and sitz baths. Hydrocortisone creams with or without an anesthetic are popular adjunctive rx without proven efficacy.

Rubber band ligation is effective for reducible hemorrhoids. The hemorrhoid is dragged into a hollow chamber and rubber bands deployed off the chamber around the base of the hemorrhoid. Bands are placed at least 5 mm above the dentate line to avoid pain. One hemorrhoid is done at a time, with a 2- to 4-wk wait between treatments. About 5-10% of pts experience achy pain and some bleeding, and rarely, pelvic sepsis is seen. Injection sclerotherapy, infrared coagulation, electrocoagulation, and laser treatment have all been used successfully. Cryotherapy should be avoided because of a high complication rate. Rubber band ligation is cheap and has the highest long-term efficacy, but it has a higher incidence of postoperative pain than infrared coagulation or injection sclerotherapy (Am J Gastro 1992;87:1600). Surgical hemorrhoidectomy is done for pts with prolapse (grades III and IV), pts with concomitant external hemorrhoids, and pts in which other methods fail. Thrombosed external hemorrhoids present with a visibly swollen, often painful mass that is filled with a firm clot. Pts presenting with acute sx should be treated with prompt evacuation of the clot for pain relief.

7.2 Anal Fissure

Brit J Surg 1996;83:1335

Epidem: A common complaint in young adults, affecting men and women equally.

Pathophys: (Scand J Gastroenterol Suppl 1996;218:78) An anal fissure is a crack in the skin of the anal canal. Acute fissures are quite superficial and are usually the result of traumatic laceration from hard, dry stool. A minority of acute fissures fail to heal and become deep, with indurated edges. Chronic fissures occur in the posterior midline in 90% of affected males and

75% of affected females. Most of the remainder occur in the anterior midline. One hypothesis is that elevated resting tone of the internal anal sphincter results in poor perfusion of the skin in the posterior midline and the failure of the fissure to heal.

Sx: The typical sx are pain with or after BMs, blood on tissue or around BMs, and itch.

Si: Acute fissures are superficial lacerations and often can be seen by parting the buttocks. Chronic fissures have heaped-up edges, a fibrotic-looking base, and frequently have a midline skin tag at the end of the fissure. A rectal or anoscopic exam can be difficult because of associated spasm.

Crs: Most fissures are acute and heal spontaneously. A minority become chronic (sx greater than 6-8 wk) and may have cycles of healing and recurrence.

Diff Dx: Fissures can be secondary to Crohn's, syphilis, TB, HIV, leukemia, IBD, or anal cancer. Consider these diagnoses, especially if the fissure is not midline.

Endoscopy: Anal fissures are better seen with an anoscope than a colonoscope. Topical lidocaine can be helpful, but sometimes pain and spasm are too great to proceed without general anesthesia or deep sedation.

Rx: Most **acute fissures** are treated by making the stool softer (high-fiber diet and fiber supplements or stool softeners such as sodium ducosate 100 mg po tid) and with topical hydrocortisone preparations with an anesthetic. Witch hazel pads, diaper wipes, or sitz baths may be soothing. **Chronic fissures** are treated by methods that lower anal sphincter pressure and presumably restore blood flow to the skin of the posterior midline. Forceful anal dilatation is effective but associated with high rates of fecal incontinence. Lateral internal sphincterotomy is the most common current surgical approach. In this procedure, the internal anal sphincter is cut in a lateral position (rather than in the posterior midline). The major problem with lateral internal sphincterotomy is incontinence, with rates as high as 35% reported (Am J Surg 1996;171:512). Modifications such as a sphincterotomy tailored to the length of the fissure may reduce that rate (Dis Colon Rectum 1997;40:1439). The trend in therapy is to use drugs to lower sphincter pressure rather than to cut the sphincter. More than 80 trials of rx to reduce sphincter pressure have been reported (Am J Gastro 2007;102:1312). Topical nitrates dilate the anal sphincter and result in healing of fissures in 40-80% of pts (reviewed in GE 2003;124:235). Glyceryl trinitrate 0.2% is applied bid to the anal canal for 6 wk and is usually well tolerated, though headache is a common problem. This is a much lower concentration of nitroglycerin than is used in cardiac disease, and this concentration is not commercially available in the U.S., but can be made by a compounding pharmacy. Topical diltiazem gel (2%) is effective and well tolerated but not available commercially in the U.S. Botulinum toxin injected into the sphincter is more effective than placebo (Nejm 1998;338:217) and topical nitroglycerin (Br J Surg 2007;94:162) but is expensive and invasive compared with nitrates. A reasonable approach would be to offer nitrates or diltiazem topically as first-line treatment. Failures can be offered botulinum injections, followed by lateral sphincterotomy if medical rx fails.

7.3 Anorectal Fistula and Abscess

Anal glands are located at the dentate line in the anal canal. If these glands become obstructed and infected acutely, the pt develops an anorectal abscess. If the infection

establishes a path to the perianal skin, a chronic anal fistula is created. The dx is usually not difficult, and the rx is surgical (except for fistulas related to Crohn's disease). The surgical approach is dictated by the location of the abscess or fistula (Surg Clin N Am 2002;82:1139).

7.4 Fecal Incontinence

Mayo Clin Proc 2002;77:271; Dig Dis Sci 1999;44:2488

Epidem: The prevalence of incontinence of solid stool is between 0.5% and 1.5%. It is 8 times more common in women than men, and is more common in nursing home pts. Prevalence rises markedly to 17% after age 85 yr (Dig Dis Sci 1999;44:2488).

Pathophys: Continence is maintained by the anal sphincter (a combination of the internal and external sphincters and the puborectalis muscle) and by the 90-degree anorectal angle. The 2 major ways in which this can be disrupted are direct damage to the sphincter and pelvic floor denervation. Specific causes of incontinence include obstetrical injury to the sphincter or its innervation (the most common cause), denervation from straining at stool, pudendal nerve injury, prior anorectal surgery, fecal impaction, cancer, rectal prolapse, other sphincter trauma, and neurologic diseases. Inadequate rectal capacity or sensation can also result in incontinence.

Sx: Pts often do not volunteer a clear hx of their incontinence. High degrees of incontinence (loss of solid stool) are usually clear by hx, but more subtle incontinence (to flatus or liquid stool) may cause a complaint of too much gas, urgency, or diarrhea. Pts will know the location of every public toilet in town and be fearful of going out. The severity can be quantified by asking about use of pads and staining of underwear.

Si: The perianal skin may show soiling or irritation. The sphincter may be visibly gaping in severe cases. Voluntary and resting tone are evaluated by the examining finger. Withdrawal of the finger should elicit a closing reflex. Perianal skin sensation should be evaluated for clues to neurologic disease. A distal rectal mass can be excluded by palpation.

Crs: The course is most often one of slowly worsening degrees of incontinence.

Diff Dx: Fistulas, rectal prolapse, proctitis, and mass lesions are the major differential points.

Lab: A variety of specialized tests can be used to evaluate fecal incontinence. These include anal manometry, endosonography, electromyography (EMG), and others. These specialized tests are not readily available to most practitioners, nor are they needed to manage most pts with this common problem. However, these tests may be needed to determine the best approach for pts who do not improve with medical rx.

Endoscopy: Flex sig is indicated to exclude structural lesions and provides the opportunity to screen the distal bowel.

Rx: Most pts respond to the combination of increased fiber to add bulk to stools and the use of antidiarrheal agents. This creates bulky dry stool that is unlikely to leak out. Loperamide is well tolerated and doses of 1-2 mg daily (not prn) are usually needed. Pts are taught that any cause of loose stool (eg, acute diarrheal illnesses, lactose intolerance, excessive sorbitol, caffeine) will aggravate the incontinence. Biofeedback has its proponents and works best in highly motivated pts. Surgical repair works well (80% success) if there is a defined defect in

the external anal sphincter, but most cases lack a defined defect and are due to pelvic denervation. A variety of surgical approaches are available for these refractory pts with limited success (Surg Clin N Am 2002;82:1139).

7.5 Pruritus Ani

Surg Clin N Am 1994;74:1277

Epidem: M:F ratio 4:1 for those without demonstrable cause of perianal itching.

Pathophys: The most common mechanism for perianal itch is failure to cleanse feces from the perianal area. In some pts, dietary factors, skin disease, or psychogenic factors may perpetuate itch. In some pts, chronic use of irritating substances (such as inadequately rinsed soap) may cause a dermatitis. In many self-limited cases, a cause is not identifiable.

Sx: The irresistible urge to scratch.

Si: Perianal skin may show fecal soilage, deformity, erythema, cracking of thickened skin folds, and evidence of excoriation.

Crs: Episodes are usually self-limited unless a chronic predisposing condition exists.

Cmplc: None.

Diff Dx: Many cases of perianal itching have a definable, treatable cause related to perianal hygiene. The inability to keep the perianal skin clear of feces is seen in pts with poor sphincter tone, chronic diarrhea, external hemorrhoids or skin tags, prior anal surgery, prior fistulas, or perianal abscess that heals with deformity, morbid obesity, and poor personal hygiene habits. Other pts may have underlying dermatologic, dietary, drug, gynecologic, or psychogenic causes of itch. Pinworms should be considered in children.

Lab: Scotch tape test for pinworms. Skin bx or scrapings in unusual cases to look for other primary diseases such psoriasis, fungal infection, or malignancy.

Rx: In pts with evidence of fecal soilage, the underlying cause should be treated if possible. Pts should be advised to cleanse the area with diaper wipes, witch hazel pads, or warm water, but should avoid soap. Excessive rubbing while cleansing should be avoided. Topical hydrocortisone preparations may provide relief. In most idiopathic cases, sx resolve in 4-6 wk. Purported dietary causes include caffeine, chocolate, citrus, and tomato products; dietary exclusions may be tried.

7.6 Fecal Impaction

Mayo Clin Proc 1998;73:881

Epidem: The greatest risk is seen in constipated pts and in pts who are institutionalized with mental or physical impairments.

Pathophys: The initiating event is retention of a bolus of stool due to a variety of underlying causes such as painful conditions of the anus, decreased recognition of the need to evacuate (due to drugs or CNS illness), or lack of rectal sensation. The initiating bolus dries out in the

rectum, and the colon delivers more until a bolus that will not pass the diameter of the anal sphincter is created.

Sx: Those with intact mentation will usually recognize the lack of BMs and have rectal pain. However, the presentation can be nonspecific in pts who are mentally or physically impaired, with sx such as change in performance status, nausea, bloating, or fever. Some pts will present with apparent diarrhea as stool oozes out around the bolus.

Si: Usually a hard bolus of stool may be felt, but sometimes it is softer than expected or the impaction is beyond the reach of the finger. The abdomen may be distended or tender, and stool may be palpable.

Crs: May be recurrent without adequate chronic bowel regimen.

Cmplc: Stercoral ulcers (ulcers caused by local pressure necrosis of bowel by hard, dry stool). Colonic perforation is a rare complication due to full-thickness pressure necrosis.

Diff Dx: The important differential consideration is mechanical obstruction due to tumor.

Lab: Leukocytosis or electrolyte abnormalities may be present in severe cases.

X-ray: Plain films demonstrate stool in the colon and rectum and air-fluid levels in more severe cases. An x-ray is not a substitute for a rectal exam.

Endoscopy: A mechanical cause of impaction should be ruled out with colonoscopy if the cause is uncertain and if the pt is in an age group where CRC is a concern.

Rx: Manual disimpaction is the first step. A topical anesthetic such as lidocaine jelly may be helpful, and conscious sedation may be a kindness in some circumstances. The anal canal is gently dilated with 2 fingers, and the bolus is broken up by the fingers. The examiner should be well garbed for the onslaught of stool. If this is not successful or if the bolus cannot be reached, a tap water or a mineral oil enema is used. If these fail, a milk and molasses enema can be tried. A gastrografin enema can be diagnostic and is usually therapeutic when other measures fail. When there is no evidence of obstruction, oral polyethylene solutions may be given orally or per NG tube at a rate of 100 mL/hr until clear (Dig Dis Sci 1997;42:1454).

7.7 Solitary Rectal Ulcer Syndrome

Brit J Surg 1998;85:1617

Epidem: This disorder is uncommon (1 per 100,000/yr), with onset typical in the 3rd or 4th decade. There is equal prevalence in men and women.

Pathophys: The cause is unknown. It is possible that there are different causes in different groups. Rectal prolapse (either overt or occult) and paradoxical contraction of pelvic floor muscles seem important and may cause ulceration by inducing local ischemia.

Sx: Rectal bleeding, passage of mucus, sense of incomplete evacuation, and straining at stool. Rectal prolapse is common. Some pts are asymptomatic.

Si: The ulcer may be palpable and prolapse may be identified on exam.

Crs: In about half of pts, ulcers persist over 5 yr despite rx (GE 1983;84:1533).

Cmplc: Massive bleeding or stricture formation are rare complications.

Diff Dx: The major differential considerations are malignancy, IBD, and repeated trauma. The disorder is misdiagnosed 25% of the time. The incorrect diagnoses are usually IBD or neoplasia (Dis Colon Rectum 1993;36:146).

Lab: Anorectal manometry shows a variety of abnormalities, but none help with the dx or rx.

Endoscopy: Most of these lesions are found 5-10 cm from the anal verge on the anterior rectal wall. They are usually ulcers of several cm in diameter, but the appearance is variable and multiple ulcers or raised, polypoid, or circumferential lesions may be seen. Bxs show mucosal edema, variable fibrosis, and disorientation of the smooth muscle of the muscularis that extends up into the lamina propria. EUS may show lack of puborectalis relaxation.

Rx: Topical rx are usually ineffective since they do not address the underlying defect. Fiber to minimize straining can be tried. Some pts appear to have a major behavioral component with excessive straining, and biofeedback has been used with some success (Gut 1997;41:817). Surgery is an option for the very refractory pt. Rectopexy is the most common surgery, and about 50% of pts will improve. Anterior resection is disappointing (Brit J Surg 1998;85:1246). Colostomy is a drastic alternative.

7.8 Proctalgia Fugax

This is a very common disorder characterized by intermittent, unpredictable attacks of a severe, spasmodic pain in the rectum that last seconds to minutes. Between attacks, pts feel entirely well and have normal BMs. The cause is unknown but is probably related to internal anal sphincter dysfunction. A hereditary form has been described (GE 1991;100:805). The dx is made on the basis of the characteristic story and by the exclusion of rectal pathology by sigmoidoscopy if there is any clinical doubt. Most attacks are so brief that no rx is needed. Manual pressure applied with a flat hand to the anal area may be helpful. Hot baths and passage of flatus in a knee-chest position have been used. The hereditary form responds to nifedipine but may be a different disorder (Gut 1995;36:581). The inhaled β-agoinst albuterol shortens attacks (Am J Gastro 1996;91:686).

7.9 Cancer of the Anal Canal

This disorder represents about 1.5% of all GI tract neoplasms. It is associated with sexual transmission of the HPV. The majority of pts do not need surgery and can be cured by combination chemotherapy and radiation. (See Nejm 2000;342:792 for a comprehensive review.)

7.10 Hirschsprung's Disease

This disorder results from the congenital absence of ganglion cells in the anus and a variable length of distal bowel (Curr Probl Surg 1996;33:389). This results in a functional obstruction that usually presents in the first year of life as severe constipation or sepsis due to enterocolitis. A presentation in adulthood is rare, and sx in adults usually have been present since childhood (J Clin Gastro 1984;6:205). The rx is the surgical removal of the poorly functioning aganglionic segment.

Chapter 8

Vascular Disorders of the Gut

8.1 Acute Mesenteric Ischemia

BMJ 2003;326:1372; GE 2000;118:954

Cause: This catastrophic illness most commonly results from emboli, but it can also result from arterial or venous thrombi, low-flow states, or vasculitis.

Pathophys: Sudden occlusion of a mesenteric vessel causes ischemia that progresses to infarction, usually within 24 hr. About 50% of pts have arterial occlusion, 15% have venous occlusion, and the remainder have nonocclusive disease. This latter group often develops illness after systemic hypotension, CHF, or septic shock.

Sx: Pts develop severe abdominal pain that is often out of proportion to physical exam findings. There may be associated risk factors such as recent MI, CHF, hypercoagulable states, or evidence of preexisting chronic ischemia (postprandial pain). However, many pts have no associated risk factors.

Si: Early in the course of illness the abdominal exam may be relatively benign, but as ischemia worsens, tenderness increases, bowel sounds are lost, and peritoneal findings develop.

Diff Dx: Acute abdominal pain (p 4).

Crs: Mortality rate is high and varies with etiology. Operative mortality is greatest for arterial thrombosis (77%) and nonocclusive ischemia (73%). It is lower for arterial embolism (54%) and venous thrombosis (32%) (Brit J Surg 2004;91:17).

Lab: No single serum test is helpful in making the dx. CBC with differential, CMP (to look for other causes and evaluate the anion gap as a clue to metabolic acidosis), and amylase should be obtained to help in diff dx.

X-ray: Plain films are used to exclude free air requiring immediate laparotomy. Doppler ultrasonography can evaluate the proximal portions of the celiac, superior mesenteric artery (SMA), and inferior mesenteric artery (IMA), but occlusions can be asymptomatic, making the test less valuable in the acute setting. CT can show abnormalities late in the course of illness caused by SMA emboli (such as gas in bowel wall, thickened bowel, or portal venous gas), but it is insensitive prior to infarction. CT is more helpful in identifying mesenteric vein occlusions. Mesenteric angiography is the diagnostic gold standard, but experts disagree on its routine use in suspected mesenteric ischemia. Proponents of angiography in suspected

AMI cite the many negative results that save a laparotomy and the positives that allow for early dx. Opponents cite delays in dx from lack of ready availability and the time it takes to perform the test. Local expertise will play a big role. Angiography can show embolus (either partially or completely occluding) either in the major vessels or in distal branches. It may also show evidence of nonocclusive mesenteric ischemia (NOMI), in which no occlusion is seen but there is intense microvascular vasoconstriction (Am J Surg 1996;171:405).

Endoscopy: Not indicated.

Rx: Those with suspected mesenteric ischemia and no availability of angiography go to laparotomy as do those with peritoneal signs. Rx of pts with positive angiograms depends on the finding. Major emboli are treated with embolectomy, and thrombus is treated with bypass (Arch Surg 1999;134:328), though surgery may be obviated by thrombolysis in some cases (J Vasc Interv Radiol 2005;16:317). Infarcted segments are resected and a second-look operation may be needed to reassess viability of the remaining bowel (Arch IM 2004;164:1054). Minor emboli (in smaller distal vessels) can be treated with thrombolytics, papaverine, or anticoagulation. Superior mesenteric vein thrombus without peritoneal signs can be treated with anticoagulation. Such pts should be evaluated for a hypercoagulable state. Nonocclusive mesenteric ischemia can be treated with intra-arterial papaverine.

8.2 Chronic Mesenteric Ischemia

BMJ 2003;326:1372; GE 2000;118:954

Cause: Vascular thrombosis from atherosclerotic disease.

Pathophys: Most pts (90%) have severe stenosis or occlusion of 2 or 3 of their mesenteric vessels. They are unable to increase gut blood flow in response to food. A small minority have occlusions of SMA (7%) or celiac (2%) alone.

Sx: Pts develop pain 1-3 hr after meals that persists 1-3 hr, and sx occur with increasing frequency over weeks to months. The pain, aka abdominal angina, creates a fear of eating and subsequent weight loss.

Si: Cachexia and abdominal bruits may be present.

Diff Dx: The differential is that listed for dyspepsia (p 2). The key to making the dx is to consider it on the list of possibilities.

Crs: The 5-yr survival of those who survive revascularization is 70%.

Cmplc: Progression to infarction, malnutrition.

X-ray: Angiography is the gold standard for dx though the use of multidetector CT angiography is growing rapidly as a less invasive alternative (Radiol Clin N Am 2007;45:275). MRI angiography rivals conventional angiography in centers with special expertise. Other tests are available (eg, mesenteric Doppler after meal stimulation [Am J Surg 1995;169:476] or intestinal oxygen consumption), but they lack sensitivity and specificity (GE 2000;118:954). Tonometry (in which luminal pCO_2 is measured and compared to blood values) may be helpful when combined with Doppler but is not widely available (Am J Gastro 2007;102:2005). Asymptomatic pts over 65 yr will frequently (18%) have abnormal Doppler studies (AJR Am J Roentgenol 1993;161:985).

Some clinicians use Doppler in pts with lower pretest probability as a means of avoiding a very low-yield angiography.

Rx: Surgical revascularization (by endarterectomy or bypass [Ann Vasc Surg 1998;12:299]) provides about 70-90% initial success, 10% recurrence rates, and low mortality. Mesenteric angioplasty has similar initial success rates but higher recurrence rates, leading an expert panel to recommend it only in higher risk surgical pts (GE 2000;118:954). However, as endovascular techniques have improved over the last decade, there has been a shift to using angioplasty and stenting as primary rx and reserving surgery for failures of endovascular rx (Can J Gastro 2009;23:365).

8.3 Ischemic Colitis

BMJ 2003;326:1372; GE 2000;118:954

Cause: This illness is caused by inadequate colonic perfusion despite grossly normal mesenteric vessels. It has been associated with prior aortic or cardiac surgery; vasculitis; hypercoagulable states (GE 2001;121:561), drugs (cocaine [Am J Gastro 1994;89:1558], NSAIDs [J Clin Gastro 1993;16:31], pseudoephedrine [Am J Gastro 1999;94:2430], birth control pills [J Clin Gastro 1994;19:108]), prolonged exercise (distance running), obstructing colonic lesions, and cardiopulmonary events that cause hypotension.

Epidem: More common in the elderly.

Pathophys: The most common form of the illness is transient submucosal and mucosal hemorrhage with inflammation. More rarely there can be features of chronic colitis, stricture, or progression to full-thickness gangrene. No vascular occlusion of major vessels is evident, but pts are more likely to have underlying atherosclerosis.

Sx: Pts typically experience the sudden onset of fairly severe crampy abdominal pain and bloody diarrhea. A chronic presentation with pain, bloody diarrhea, or colonic stricture is quite unusual.

Si: Tenderness and localized peritonitis may be found.

Diff Dx: The major considerations are causes of acute bloody diarrhea: infections (*E. coli* O157:H7, *Campylobacter, Shigella*, and *Salmonella*) and IBD. In some cases, diverticulitis, acute mesenteric ischemia, or obstruction are considerations.

Crs: Most pts recover completely without surgery. Academic surgical series seem to overestimate the severity of the illness (eg, Dis Colon Rectum 1992;35:726).

Cmplc: Colonic stricture, gangrene.

Lab: CBC with diff, CMP, and amylase are usually obtained to rule out other disorders. Stool culture, stool testing for *C. diff*, or other stool studies might be warranted.

X-ray: Plain films are useful to rule out free air and to detect thumbprinting of the colon from mucosal edema or obstruction. A CT scan often shows evidence of colitis (Radiology 1999;211:381) and is more sensitive for perforation than KUB. CT is helpful in ruling out other causes of abdominal pain. Angiography is not indicated unless the concern is acute mesenteric ischemia (in which case pts tend to have much more steady midabdominal pain rather than crampy pain with bloody diarrhea).

Endoscopy: Colonoscopy is done to establish the dx and exclude cancer and IBD. The findings are those of a segmental colitis with friability, hemorrhage, and exudate. There can be evidence of fibrosis depending on the duration of the illness. Colonoscopy is usually done after the pt has clinically improved because of the fear of perforation. Bxs are usually nonspecific but may show suggestive coagulation necrosis. The rectum is usually spared, but the splenic flexure is often involved (because it is in the watershed between peripheral branches of the SMA and IMA).

Rx: Pts are kept npo, given iv fluids, and are evaluated and treated for associated cardiopulmonary conditions. Broad-spectrum antibiotics (eg, cefotetan, ampicillin-sulbactam) are given routinely on the basis of experimental studies showing benefit, but data in humans are lacking. If pts improve, diet is advanced and antibiotics are stopped. A small number of pts will deteriorate because of the development of full-thickness gangrene or will have a refractory colitis, and they are treated surgically. Stricture may require segmental resection but may improve over time without rx.

8.4 Angioectasias of the GI Tract

Gastrointest Endosc Clin N Am 1997;7:509; Am J Gastro 1993;88:807

Cause: The underlying cause of angioectasias is unknown. They are commonly called angiodysplasias, though they are not dysplastic lesions. Arteriovenous malformations is another acceptable term for these lesions.

Epidem: More common in the elderly.

Pathophys: These lesions represent ectasia of submucosal veins and overlying capillaries and may occur throughout the GI tract. They are most common in the colon. They generally do not present with massive bleeding because they are low-pressure (venous) lesions. Similar lesions can be seen in hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber) disease (Dig Dis 1998;16:169), Turner's syndrome, or with the CREST syndrome. Pts with von Willebrand's disease may be very difficult to treat because of a predisposition to bleeding with minor lesions (Br J Haematol 2000;108:524). In these conditions, multiple lesions are a clinical challenge. There is an association with aortic stenosis, and valve replacement may stop bleeding. In pts without these associated disorders, lesions are most often found in the cecum and ascending colon. Left-sided lesions of clinical importance are less common. Angioectasias may also be seen in the small intestine or stomach. Multiple lesions in the small intestine are more difficult to treat because it is difficult to reach them endoscopically.

Sx: Most pts are asymptomatic. Some may present with sx secondary to chronic anemia or with acute hematochezia.

Si: Heme-positive stool. Mucocutaneous angioectasias are seen in hereditary hemorrhagic telangiectasia.

Diff Dx: These lesions are considered in the differential of acute or chronic GI bleeding (p 21).

Crs: A small subgroup of pts present with recurrent gross bleeding.

Cmplc: Anemia, massive hemorrhage. Perforation from endoscopic rx.

Lab: CBC is routine. Studies of coagulation may be warranted in problematic pts to look for coagulopathies.

X-ray: Substantial lesions can be seen as a late-draining vein on angiography. Angiography is rarely used for dx. Angiography has a sensitivity of only 17% compared to endoscopy (Mayo Clin Proc 1988;63:993).

Endoscopy: Lesions are red, flat, or minimally raised; may have round or stellate borders; and small vessels can often be discerned. Endoscopy is the diagnostic method of choice. Capsule endoscopy is useful for detecting small bowel angioectasias.

Rx: A variety of endoscopic methods have been described. BICAP, argon plasma coagulation, and heater probe are most widely used. Pts with recurrent bleeding may be treated with estrogens, but the benefit is uncertain, with RCTs showing conflicting results (Can J Gastro 2006;20:171). Recent literature suggests that pts with refractory bleeding may benefit from depot octreotide administered monthly (Aliment Pharmacol Ther 2007;26:935).

8.5 Abdominal Aortic Aneurysm

The gastroenterologist encounters this disorder when it presents with acute abdominal pain due to dissection or as an incidental finding on physical exam or imaging studies. Elective repair is usually appropriate for healthy pts with abdominal aortic aneurysms (AAAs) in the 5- to 6-cm range. Pts with smaller aneurysms can be followed with periodic US, and 60% will eventually end up with elective repair (Mayo Clin Proc 2000;75:395).

Chapter 9

Pancreas

9.1 Acute Pancreatitis

GE 2007;132:2022; Am J Gastro 2006;101:2379; Lancet 2003;361:1447

Cause: Many causes of acute pancreatitis (AP) have been identified (Nejm 1994;330:1198; Gastroenterol Clin North Am 1999;28:571). In most regions of the world, **gallstones** are the leading cause of AP, and **alcohol** is a close second. **Idiopathic pancreatitis** (10-25% of the total) places third on the list, though some of these cases represent a failure to diagnose gallstone disease and microlithiasis (Nejm 1992;326:589). **Hypertriglyceridemia** is a relatively common cause of AP and is seen when TG levels are >1000 mg/dL. Pancreatitis occurs more often in type V hyperlipidemia and less often in types I and IV (Gastroenterol Clin North Am 1990;19:783). A bewildering number of **drugs** have been implicated in AP (Clin Gastroenterol Hepatol 2007;5:648). These include AZA/6-MP, L-asparaginase, 5-aminosalicylic acid compounds (mesalamine, olsalazine, sulfasalazine), didanosine (an antiretroviral), valproic acid, furosemide, cimetidine, famotidine, thiazides, lisinopril, codeine (Am J Gastro 2000;95:3295), antibiotics (tetracycline, metronidazole, nitrofurantoin, erythromycin, sulfonamides, pentamadine), and NSAIDs (ibuprofen, sulindac, celecoxib) (Arch IM 2000;160:553).

Diagnostic **ERCP** is associated with a 3-9% risk of AP, and rates may be higher with sphincterotomy or sphincter of Oddi manometry. **Blunt trauma** to the abdomen can cause AP by disrupting the duct. **Infections** are always listed as a cause of AP, but in adult practice they are uncommon. Mumps, coxsackievirus, CMV, *Campylobacter*, hep A, and hep B have all been implicated. HIV-infected pts have a high incidence of pancreatitis associated with a variety of infections and drugs. The association of **hyperparathyroidism** with AP has received more attention than it deserves and is very infrequent (0.23% of 800 consecutive pts with hyperparathyroidism in 1 series) (Brit J Surg 1986;73:282). Occurrence of AP following **cardiac surgery** is thought to be related to ischemia. **Emboli** and **vasculitis** are rare causes. Scorpion venom (BMJ 1970;1:666), bites of certain spiders and the Gila monster lizard, organophosphorous insecticides, and methanol are rare **toxic** causes of AP. A rare familial form **(hereditary pancreatitis)** is associated with recurrent bouts of AP leading to chronic pancreatitis and caused by mutations in the cationic trypsinogen gene (Gut 1999;45:317). Autoimmune pancreatitis (a cause of chronic pancreatitis, see p 192) can have an acute presentation. Other **obstructive disorders**, such as pancreatic cancer or ampullary cancer, may obstruct the duct and cause AP. In **pancreas divisum**, the dorsal and ventral ducts of

the pancreas do not fuse, and the larger dorsal duct (Santorini duct) drains through the minor papilla. If the minor duct is relatively stenotic, AP may result. Sphincter of Oddi stenosis or dysfunction (p 210) may also result in AP. Choledochal cysts (p 212) and mucinous duct ectasia (p 198), and anomalous union of the pancreaticobiliary duct (Gastro Endosc 1999;50:189) are infrequent causes.

Penetrating peptic ulcer rarely presents as AP. Crohn's disease, cystic fibrosis, and hypothermia usually present with other sx. Postpartum pancreatitis appears to be largely biliary in nature (Mayo Clin Proc 2000;75:361).

Epidem: The disorder is common with an incidence of 24/100,000 per yr in the U.K. (Brit J Surg 1987;74:398). The incidence has risen over the last 40 yr for unclear reasons. The disorder is more common in men than in women.

Pathophys: (Surg Clin N Am 1999;79:699) The means by which the numerous causes of pancreatitis result in a similar clinical illness has not been determined. Biliopancreatic reflux appears to be the important initiating event in gallstone pancreatitis (Gut 1995;36:803). There appear to be genetic predispositions to pancreatitis caused by mutations in genes that normally function to limit the destruction of the pancreas caused by activation of trypsin from trypsinogen. The shared characteristic of the many causes of AP is premature activation of proteolytic enzymes (such as trypsin from trypsinogen) and their inappropriate retention in the acinar cell. Subsequent injury to the acinar cell causes release of cytokines and activation of the complement system. Inflammatory cells are recruited into the pancreas and result in further release of inflammatory mediators (such as platelet activating factor [PAF], TNF, IL-1, and IL-6). These cause local tissue edema, cell necrosis, and the distant, systemic effects of hypotension, fever, hypoxia, leaky capillaries, and ARDS. Improved understanding of the cascade may allow for therapeutic interventions.

Pancreatitis is classified as interstitial, edematous pancreatitis if the pancreatic tissue remains viable. It is classified as necrotizing pancreatitis (which is more severe) if pancreatic tissue becomes nonviable.

Sx: The most common sx is upper abdominal pain, which is usually epigastric and radiates to the back. Pain is generally constant and can be severe. Nausea and vomiting are common.

Si: Fever is common and does not necessarily imply infection. Hypotension and tachycardia may be associated with volume depletion. Abdominal tenderness is greatest in the epigastrium but can be present in any area of the abdomen where the inflammatory process tracks. In more severe cases, there is distention, rigidity, percussion tenderness, or loss of bowel sounds. An upper abdominal mass may be felt if the pt develops a phlegmon or pseudocyst. Bluish discoloration of the flanks (Grey Turner sign) and of the periumbilical area (Cullen sign) is rarely seen and is due to hemorrhage in severe, necrotizing disease. The lung fields can show evidence of effusions or atelectasis. The skin may show eruptive xanthomata (reddish-yellow papules of a few mm, especially on extensor surfaces) if the cause is hyperlipidemia. Tender red skin nodules from fat necrosis are rarely seen.

Crs:

- *Causes of mortality:* The course of the illness is determined by the extent of pancreatic glandular necrosis, by the degree of surrounding tissue destruction by pancreatic juice, by the systemic effects of mediators released in the inflammatory response, and by the development of infection in areas of necrosis. Early death results from multisystem failure (the first week), and late deaths are generally due to infection. About 80% of deaths are due to septic

complications. In necrotizing pancreatitis (cases with sections of nonviable pancreatic tissue), 30-40% of pts develop infection in the necrosis (World J Surg 1997;21:130).

- *Clinical prediction of severity:* A severe course is more likely in the elderly, the obese, and those with evidence of organ failure. Several methods have been described for assessing disease severity (Surg Clin N Am 1999;79:733). Three methods of assessing severity using simple clinical and laboratory tests have been described for pancreatitis. The first method is the **Ranson** criteria. In this system, poor prognostic factors are identified by assessment on admission and at 48 hr. For **alcoholic pancreatitis** these factors are:
  On admission: (1) age >55 yr, (2) wbc >16000/mm^3, (3) glucose >200 mg/dL, (4) LDH >350 U/L, and (5) AST >250 U/L.
  Within 48 hr of admission: (1) drop in hct >10%, (2) increase in BUN >5 mg/dL, (3) Ca^{++} <8 mg/dL, (4) base deficit >4 mmol/L, (5) fluid deficit >6 L, and (6) pO_2 <60 mm Hg.
  If fewer than 3 risk factors are present, mortality is <1%. If 3-4 factors are present, mortality is 15% and climbs with each additional risk factor.
  The less cumbersome **Glasgow** criteria for **gallstone pancreatitis** are applied within the first 48 hr after hospitalization. In this system, poor prognostic factors are (1) age >55 yr, (2) wbc >15000/mm^3, (3) glucose >180 mg/dL, (4) BUN >45 mg/dL, (5) LDH >600 U/L, (6) albumin <3.3, (7) Ca^{++} <8, and (8) pO_2 <60 mm Hg. The presence of 3 or more factors indicates increased risk. The major problem with these systems is the lack of predictive value. With the Glasgow system, 30% of pts with severe pancreatitis are missed, and 40% with 3 or more criteria have a benign course (Surg Clin N Am 1999;79:733).
  The third system, the **APACHE-II** score, is more complex but is superior to other grading systems for predicting severe illness. It is a score generated each day based on several physiologic and laboratory values. A score of ≥8 predicts severe disease. A hct >44 and failure of the hct to drop at 24 hr are markers of severity (Pancreas 2000;20:367). A CRP >150 mg/L in the first 72 hr correlates with pancreatic necrosis. The combination of a normal hct, normal Cr, and the absence of abdominal rebound/guarding predicts a benign course with 98% accuracy (Clin Gastroenterol Hepatol 2009;7:702).
- *CT prediction of severity:* CT scan can assess severity. The prognosis is excellent when CT is normal or shows pancreatic enlargement due to edema or mild peripancreatic inflammatory changes. When fluid collections are seen, the risk of infection rises to 30-50%, and mortality is 15%. CT is also used to determine if the pancreas has become necrotic. Necrotic areas do not enhance with iv contrast. In necrotizing pancreatitis, prognosis is worse, especially if the necrosis becomes infected. CT scan performed less than 72 hr after the onset of the illness may underestimate necrosis.

Cmplc:

- *Systemic complications:* Pulmonary complications include hypoxia, atelectasis, and pleural effusion. In more severe cases, pneumonia or ARDS develops. Renal failure and cardiovascular collapse can result from volume depletion due to bleeding or loss of fluid into the retroperitoneum. Hypocalcemia is common and is due to precipitation of calcium with fats in the process of peripancreatic fat necrosis. Hyperglycemia results from decreased insulin levels. Coagulopathy, sc nodules from metastatic fat necrosis, retinopathy, and psychosis are uncommon.
- *Pseudocyst:* A pseudocyst is a fluid-filled cavity lined by a rind of inflammatory tissue rather than the epithelium of a true cyst. Mature pseudocysts have well-developed, thick

walls and form 4-6 wk after acute illness. These are to be distinguished from the thin-walled peripancreatic fluid collections seen early in the illness.

- *Infected pancreatic necrosis:* When inflamed pancreatic cells become necrotic, they are initially sterile. However, they have the potential to become infected with enteric pathogens. Infected pancreatic necrosis can be identified by CT-guided needle bx and is usually seen after the first wk (GE 1987;93:1315).
- *Pancreatic abscess:* A pancreatic abscess is a pancreatic fluid collection that becomes infected. It is seen in about 1-4% of cases. It requires drainage but is much less dangerous than infected necrosis.
- *Unusual complications:* Pancreatic fistulas into colon, adjacent bowel necrosis, gastric varices from splenic vein thrombosis, splenic hematoma, and acute hemorrhage into pseudocysts or retroperitoneum may be seen.

Diff Dx: See Approach to Acute Abdominal Pain (p 4). The dx of AP is made on the basis of the hx, physical exam, and laboratory studies and is selectively confirmed by imaging studies such as CT. In mild cases presenting late in the illness, the laboratory studies may be less helpful and the imaging is more important.

The cause of pancreatitis is usually evident from the initial H&P, labs, and the abdominal US. However, in 10-25% of cases the cause is not immediately evident. About 50% of these idiopathic cases never recur, but many do and require a more extensive evaluation. There is a range of expert opinions regarding the evaluation of so-called **recurrent AP** (compare GE 2001;120:708 to J Clin Gastro 2003;37:238). The evaluation usually begins with CT scan to look for tumor or chronic pancreatitis. If this is negative, many experts proceed to EUS and/or ERCP to look for chronic pancreatitis, tumors, pancreas divisum (which is then treated by dorsal duct sphincterotomy), annular pancreas, choledochocele, and anomalous union of the pancreaticobiliary duct. EUS is the preferred initial test because it is less risky. Some experts evaluate the sphincter of Oddi by manometry, but others do not because of risk. At the ERCP, bile is aspirated and examined by microscopy for cholesterol monohydrate crystals or bilirubinate granules. If these studies are negative, tests for gene defects (see Pathophys) or testing for autoimmune pancreatitis are undertaken (with IgG4 levels). Many experts skip biliary microscopy and recommend biliary sphincterotomy and/or cholecystectomy if ERCP/MRCP and/or EUS is negative. The approach will vary with the local expertise in the various available modalities.

Lab: **Amylase** is a sensitive predictor of AP, but false-positive elevations may be seen due to pancreatic cancer, mesenteric infarction, bowel obstruction, perforated ulcer, and renal failure. Salivary amylase causes false positives that can be easily identified by amylase fractionation. Macroamylasemia causes a high serum amylase in the absence of pancreatitis and can be detected by fractionation. **Lipase** is more specific than amylase but can be elevated in perforated ulcer, ischemia, or obstruction (though typically such elevations are less than 3 times normal). Lipase is cleared more slowly and can be helpful if pts present days after the event. All pts should have at least a daily **CBC** and **CMP** early in the course of the illness to assess renal function, electrolytes, calcium, glucose, and liver function. Elevations of AST/ALT ($<3 \times$ normal) and bilirubin may suggest gallstones as the etiology. **Triglycerides** should be obtained to exclude hypertriglyceridemia as the etiology.

X-ray: US is a more sensitive test for gallstones than CT scanning and is indicated routinely in pts with AP and no prior hx of cholecystectomy. CT scanning with fine cuts of the pancreas and

large doses of iv contrast are used to stage the disease on the basis of the degree of inflammation and the degree of necrosis. CT scanning should be done in pts who have clinically severe disease or who do not appear to be improving within a few days of admission. A CT done within the first 72 hr may underestimate the extent of pancreatic necrosis. Plain films can be useful if perforation or obstruction is suspected. CT and MRCP may be indicated in the evaluation of recurrent AP (see Diff Dx).

Endoscopy: ERCP is indicated as a therapeutic measure in severe biliary pancreatitis or cholangitis (see Rx). ERCP or EUS may also be indicated in recurrent AP (see Diff Dx).

Rx:

- *Supportive measures:* Pts are kept npo and are given analgesia and vigorous hydration with correction and monitoring of volume status and electrolytes. Ill pts are treated in the ICU. A large fluid deficit may be seen in the first few days, and a large diuresis follows when the pt recovers. A Foley catheter is important to monitor urine output in the severely ill. An NGT does not change outcome but may provide symptomatic relief if the pt is vomiting or has an ileus. IV H2RAs minimize gastric volumes and may improve sx but not outcome. Offending drugs and alcohol are stopped. Incentive spirometry is reasonable to minimize atelectasis.
- *Antibiotics:* The rationale for early antibiotic use in severe pancreatitis is that early use of antibiotics might prevent necrotic pancreatic tissue from becoming infected. Recent meta-analysis suggests that antibiotics are not effective for this purpose (Am J Gastro 2008;103:104). Antibiotics are indicated in (1) pts with cholangitis, (2) pts with clinical evidence suggesting infected necrosis while awaiting definitive testing, and (3) pts with established infected necrosis.
- *ERCP:* The rationale for urgent ERCP in suspected gallstone pancreatitis is to remove the impacted stone to prevent further pancreatitis and cholangitis. Initial studies demonstrated an improvement in outcome for those with severe disease who underwent sphincterotomy (Lancet 1988;2:979). Subsequent RCTs have produced conflicting results. The benefit in 1 large study seems to have arisen mainly from treating cholangitis (Nejm 1993;328:228). A study that excluded pts with bilirubin ≥5 mg/dL or clinical cholangitis showed no benefit from early ERCP and showed an increased frequency of respiratory complications (Nejm 1997;336:237). Most clinicians use ERCP selectively when clinical or laboratory studies suggest biliary obstruction or cholangitis. Recurrent bouts of AP associated with pancreas divisum can be treated with endoscopic stenting or sphincterotomy of the minor duct (Gastrointest Endosc 2000;52:9).
- *Nutrition:* Pts are kept npo in the early phases of the disease. Those with severe disease may have a prolonged illness and be unable to tolerate an oral diet. In the past, such pts were typically begun on TPN to prevent nutritional complications. However, meta-analysis of recent RCTs suggest that feeding with a nasoenteric tube is both safer and cheaper and shortens hospital stay (BMJ 2004;328:1407). Pancreatic stimulation by feeding is avoided by passing the feeding tube distal to the ligament of Treitz.
- *Evaluation of necrosis for infection:* In pts with necrosis on CT who improve clinically, no interventions are needed to prove that necrosis has remained sterile. However, for those who develop worsening systemic illness (fever, tachycardia, respiratory failure) or who fail to improve by the second wk, CT-guided needle aspiration should be performed to determine if necrosis is infected (GE 1987;93:1315). Pts with infection on CT bx usually need complex surgical debridement.

- *Surgical debridement:* Infected pancreatic necrosis is generally an indication for open surgical debridement. Radiologic drainage, minimally invasive surgical procedures, or endoscopic drainage may be appropriate depending on the consistency of the necrotic material, the available expertise, and the overall condition of the pt. A variety of surgical techniques have been described (Nejm 1999;340:1412). There is no indication for surgery in sterile necrosis except in late stages where organized necrosis may cause obstruction or pain.
- *Pseudocysts:* (Am J Gastro 1997;92:377) Asymptomatic pseudocysts do not require intervention. The previously common practice of operating on asymptomatic pseudocysts >5 cm and present for >6 wk is not supported by current data. Symptomatic pseudocysts can be decompressed by surgical, endoscopic, or radiographic means. There are no useful comparative trials that determine the optimal approach, and local expertise is usually the determining factor. Surgical methods include cyst gastrostomy (if the cyst is adjacent to the stomach), Roux-en-Y cyst jejunostomy, and distal pancreatectomy. An endoscopic cyst gastrostomy can be made if the cyst abuts the posterior stomach (Gastrointest Endosc 1989;35:1). The cyst can be drained with a pigtail catheter as long as the main duct is not obstructed (since the cyst will not resolve if the duct is not patent).
- *Cholecystectomy:* Pts with gallstones as the cause of their pancreatitis should undergo cholecystectomy as soon as the pancreatitis subsides. They should not be subjected to long delays because of the risk of recurrence (Am J Surg 1990;159:361). Common duct stones may need to be ruled out with intraoperative cholangiography or MRCP (p 204). If stones are found intraoperatively, they can be removed laparoscopically (in selected expert hands), or postoperative ERCP and stone extraction can be done if the expertise is available.
- *Rx of sludge:* Sludge appears to be a cause of AP, and rx of sludge by sphincterotomy or cholecystectomy lowers recurrence rates (Nejm 1992;326:589). However, in many pts sludge may turn out to be an incidental finding. Pancreatitis recurs in up to 20% despite rx of sludge (Gastroenterol Clin North Am 1999;28:571).
- *Therapy to reduce the systemic inflammatory response:* Since inflammatory mediators cause the systemic illness seen in pancreatitis, attempts have been made to interrupt that process. Antiproteolytic rx, glucagon, atropine, and somatostatin are ineffective (Gut 1998;42:886). A large trial of lexipafant, a PAF inhibitor, showed no efficacy (BMJ 2000;320:244).

9.2 Chronic Pancreatitis

Lancet 2003;361:1447; GE 2001;120:682; J Clin Gastro 1999;29:225

Cause: (GE 2001;120:682) A new classification system has been proposed for chronic pancreatitis (CP) based on etiologic risk factors. It is called the **TIGAR-O** system, with each letter representing the first letter of a risk factor shown in ***bold italics*** in this section. The most common causes are ***toxic metabolic***, and the most frequent toxic cause is alcohol. About 60-70% of CP pts in developed countries have a hx of more than 6 yr of >150 gm ethanol consumption daily. Other toxic causes include cigarette smoking (Pancreas 1996;12:131), hypercalcemia, hyperlipidemia (controversial), and chronic renal failure. Most of the remainder have ***idiopathic*** pancreatitis, which includes a late onset and early onset group as well as the poorly understood entity of tropical pancreatitis (J Clin Gastro 2002;35:61). There appear to be **genetic** predispositions to recurrent pancreatitis caused by mutations in genes that normally

function to limit the destruction of the pancreas caused by activation of trypsin from trypsinogen (Lancet 2003;361:1447). These mutations include (1) mutations in serine protease inhibitors (SPINK1 mutation), (2) mutations in the cystic fibrosis transmembrane conductance receptor (CFTR) gene that are common in pts with apparently idiopathic CP (and no clinical evidence of cystic fibrosis) (Nejm 1998;339:653), and (3) mutations in the cationic trypsinogen gene, which are the cause of familial pancreatitis. **Autoimmune** pancreatitis is being increasingly recognized and is characterized by lymphoplasmacytic infiltration and fibrosis, enlarged pancreas with narrowing of the main duct, elevated IgG levels (especially IgG4) and steroid responsiveness (Am J Gastro 2004;99:1605). Autoimmune pancreatitis can be associated with extrahepatic biliary strictures and compression or thrombosis of peripancreatic blood vessels (Am J Gastro 2009;104:2295). **Recurrent** and severe AP may lead to chronic disease in select cases. A much smaller group will have **obstruction** of the duct such as can be seen with trauma, pseudocysts, ampullary tumors, and pancreas divisum (p 187). Pancreatic insufficiency may be seen in a variety of disorders without pancreatitis, most notably in cystic fibrosis (Surg Clin N Am 1999;79:829).

Epidem: Since the disease is frequently undiagnosed, prevalence rates of CP are unknown and estimates vary from 0.04% to 5.0%. The median age of onset is 45 yr in alcoholic CP. A bimodal incidence is seen in idiopathic CP, with onset in late teens and 50s (GE 1994;107:1481).

Pathophys: (Am J Gastro 2004;99:2256) With many different etiologies, it could be surmised that several different mechanisms might lead to CP. In the case of alcohol there are probably several factors that are important for disease progression since only the minority of alcoholics develop CP. Oxidative stress, direct toxic effects, genetic defects, cycles of necrosis and fibrosis, and chronic obstruction are likely important factors in many cases. Pain may be caused by tissue necrosis, pseudocysts, elevated pancreatic duct and pancreatic interstitium pressures, ischemia, or nerve damage.

Sx: Most pts with CP have a hx of alcoholism and report recurrent attacks of upper abdominal pain radiating to the back. Attacks are partially relieved by being upright. Pain can be intermittent or chronic and unrelenting. About 10-20% of pts present without pain but with diabetes, malabsorption, weight loss, or jaundice.

Si: Epigastric tenderness or mass if a pseudocyst is present.

Crs: In CP, there is generally progressive destruction of pancreatic tissue, resulting in endocrine and exocrine dysfunction. The pain of CP tends to burn out over time and is often accompanied by the development of pancreatic insufficiency. Mortality is 50% at 25 yr, but much of that is due to diseases associated with alcoholism.

Cmplc: Pancreatic cancer occurs in 4% of pts after 20 yr of disease (Nejm 1993;328:1433). Diabetes and exocrine insufficiency are late features caused by destruction of more than 80-90% of the gland. Exocrine insufficiency can result in malnutrition and fat-soluble vitamin deficiency (A, D, E, and K). Pseudocysts may develop and may cause pain, rupture, become infected, bleed, or compress adjacent organs (see p 192). Portal or splenic vein thrombosis rarely occurs, but the latter may result in isolated gastric varices (Dig Dis Sci 1992;37:340).

Diff Dx: The broad differential is that of dyspepsia (p 2). In those presenting with malabsorption, the differential includes the many causes of malabsorption/maldigestion (p 19). Most pts with chronic pain from pancreatitis and normal imaging studies will go without a dx unless

tests of pancreatic function are used (see Lab). Some pts with apparent CP have pancreatic cancer that may be impossible to diagnose without surgery, unless ERCP or EUS can be used to obtain a tissue dx.

Lab: Amylase and lipase may be modestly elevated but are frequently normal because of the glandular destruction. LFTs can be elevated due to associated alcoholism or due to bile duct obstruction (from fibrotic or edematous changes in the pancreas). A variety of impractical and insensitive tests for pancreatic function have been described. The most sensitive is collection of duodenal juice with measurement of its protein and bicarbonate content after secretin administration (the secretin-pancreozymin test). Tests that depend on pancreatic digestion of orally administered substrates or depend on the detection of chymotrypsin or trypsin in stool can also be used to detect more subtle pancreatic dysfunction. The major problem with these tests (eg, pancreolauryl test, bentiromide test) is poor predictive value in the pts for whom the test is needed (those with chronic pain and negative imaging studies). A 72-hr stool collection for fat on a 100-gm daily fat diet is the best test for determining if diarrhea is from fat malabsorption due to exocrine insufficiency. A spot Sudan stain for stool fat is a good positive but not a reliable negative test for steatorrhea.

X-ray: Pancreatic calcifications are seen on KUB in 30% of pts. CT is more sensitive for calcifications and ductal abnormalities (75-90% depending on the study and the degree of disease [GE 1994;107:1481]) but is not as good as ERCP. MRCP is evolving as an alternative to ERCP (Am J Gastro 2002;97:347).

Endoscopy: ERCP is the imaging gold standard for dx and may be indicated for dx if the CT scan is nondiagnostic. Early disease shows mild changes in the main duct and ectasia of the side branches. In more advanced disease, there is beading and dilatation of the main duct and its side branches. ERCP is not perfectly sensitive. A normal ERCP can be seen in pts whose pancreatic function test is abnormal and who subsequently develop sx of CP. EUS has become a sensitive tool for the detection of CP in expert hands. It may be a good alternative to ERCP when CT and MRCP are nondiagnostic because EUS is less risky (Gastro Endosc 2002;56:S76). However, a nonhomogeneous echo texture of the pancreas can be a normal finding, especially in the elderly, leading to some false-positive diagnoses if EUS is used (GE 2007;132:1557).

Rx: (GE 1998;115:765)

- *Medical rx of pain:* Smoking cessation and abstinence from alcohol are important. Episodic pain can be treated with narcotic analgesics prescribed by 1 physician to minimize the abuse potential. Antidepressants such as amitriptyline can be used to minimize pain perception. **Pancreatic enzymes** can be beneficial by causing a negative feedback inhibition of pancreatic secretion by denaturing CCK-releasing peptide. A total of 6 RCTs have been reported, and a meta-analysis failed to show benefit (Am J Gastro 1997;92:2032). However, the 2 positive studies used tablet preparations rather than enzyme capsules. Pancrelipase 6 tab po ac and qhs reduces pain by 75% in pts with mild to moderate disease (GE 1984;87:44). Suppressing pancreatic function by decreasing gastric acidity or by using octreotide does not appear to help. **Nerve blocks** with corticosteroids or alcohol are widely tried in chronic pain and are variably successful.
- *Endoscopic rx of pain:* Pancreatic stenting, which presumably relieves pancreatic ductal obstruction, has been reported in an unblinded fashion to relieve pain in up to 60% of pts with CP (Gastrointest Endosc 1999;49:S77). There are no sham controlled trials

of stenting, but the strength of the data supports its use (Curr Gastroenterol Rep 2006;8:104). Pancreatic stones can be removed from the main duct with improvement in pain in >50% of pts, but the relevance of pancreatic stones in causing pain is far from clear (Int J Pancreatol 1996;19:93).

- *Surgical rx of pain:* (GE 1998;115:765) The procedure of choice for pts with pain unrelieved by medical measures and associated with a dilated pancreatic duct (≥6 mm) is a lateral pancreaticojejunostomy (a so-called Puestow-type operation). It is relatively low morbidity, and pain relief in 60% of pts at 2 yr might be expected. For pts with nondilated ducts, a pancreatic resection is necessary. Thoracoscopic sympathectomy may be a less morbid alternative in expert hands (J Gastrointest Surg 2002;6:845). Distal pancreatic resections frequently fail to relieve pain unless disease is confined to the tail (eg, posttraumatic ductal strictures). Pancreaticoduodenectomy (the Whipple procedure) appears to be an effective though drastic solution. Pain relief is good (85%) even though diseased tail of pancreas is left behind.
- *Malabsorption:* Clinical malabsorption occurs in advanced disease when more than 80-90% of the gland is destroyed. Malabsorption of fat (steatorrhea) and protein (azotorrhea) occurs. Sx are treated by providing about 30,000 IU of lipase and 10,000 IU of trypsin during the postprandial period. This replacement represents only about 5% of the normal digestive output. Either tablets or enteric-coated capsules can be used. Tablets are less expensive, though subject to acid degradation in the stomach (eg, pancrelipase with 8000 U lipase per tablet). Enteric-coated preparations resist acid degradation, have higher lipase concentration per tablet, and may work when uncoated preparations fail. Addition of acid suppression may improve the effectiveness of tablets. Fat-soluble vitamin replacement may be needed.
- *Rx of other complications:* Diabetes tends to be brittle, with a high risk of hypoglycemia because of the loss of glucagon due to islet cell destruction. Pseudocysts are discussed on p 192. For pancreatic ascites, the offending leak from a disrupted duct or pseudocyst is usually treated surgically or endoscopically. Bile duct or duodenal obstruction generally require surgery.
- *Rx of autoimmune pancreatitis:* Most pts respond to steroids, but relapse is common and steroid-sparing drugs such as azathioprine can be used (Am J Gastro 2009;104:2295). Stenting may be needed for biliary strictures.

9.3 Pancreatic Cancer

Lancet 2004;363:1049; GE 1999;117:1464; Lancet 1997;349:485

Epidem: (Surg Oncol Clin N Am 1998;7:67) Pancreatic cancer is the 11th-leading type of cancer in the U.S. (rate 9/10,000) but the 5th-leading cause of cancer death because of a grim death-to-incidence ratio of 0.99. It is slightly more common in men and blacks. The RR for smokers is at least 1.5. A diet high in fat or meat increases risk. High intake of fiber, fruits, and vegetables lowers risk. Coffee was *erroneously* described as a risk in a widely publicized study (Nejm 1981;304:630). Alcohol has no effect. Partial gastrectomy increases risk, and tonsillectomy decreases risk. The risk is 4% after 20 yr of CP (Nejm 1993;328:1433). There is an association with diabetes, but it is not an independent risk factor (Nejm 1994;331:81).

Occupational exposure to aromatic amines (chemical workers) may be a risk. Family hx is a risk, and the disease has been associated with familial pancreatitis, HNPCC (p 144), Peutz-Jeghers (p 149), familial breast cancer, and other genetic disorders.

Pathophys: The underlying defects in pancreatic cancer are acquired and inherited mutations of cancer-causing genes. The genes that become defective are tumor suppressor genes (whose normal function restrains cell proliferation), oncogenes (genes that when amplified or mutated cause cell transformation), and DNA mismatch repair genes (whose normal function is to repair replication errors). Many gene defects have been described (J Am Coll Surg 1998;187:429; Am J Surg 2003;186:279).

Sx: Abdominal pain is present in 90% of pts. The pain can be vague and nondescript and may be felt in the back. Weight loss and early satiety are common. Jaundice occurs as a relatively early finding if the tumor is in the head of the pancreas and obstructs the bile duct. It can be a late finding if the tumor causes jaundice by mets rather than obstruction. Occasionally, pts present with AP (3%). New-onset diabetes may precede pancreatic cancer (15%). Depression may be associated.

Si: Abdominal mass, cachexia, or jaundice may be observed.

Crs: At dx, the tumor is confined to the pancreas in <10% of pts. About 40% have local spread and 50% have distant spread. Most pts die within 1 yr of dx, and survival for 5 yr is less than 3%.

Cmplc: Obstructive jaundice, duodenal obstruction, effects of metastatic disease.

Diff Dx: A major diagnostic pitfall is the distinction of pancreatic cancer from CP, because the clinical and radiographic pictures are similar. Pancreatic adenocarcinoma must be distinguished from other, less common tumors of the pancreatic ductal epithelium (eg, cystic neoplasms of the pancreas [p 197], tumors of the islet cells [p 198], and tumors of acinar cells or nonepithelial tissues [eg, lymphoma]). These other tumors are uncommon.

Lab: CEA and CA 19-9 may be elevated. However, elevated levels provide little in the way of prognostic information and are of no value in staging.

X-ray: CT is the single most useful test, with the detection of tumors as small as 1-2 cm and detection of local spread or distant mets. When CT predicts unresectability, the accuracy is 90%, but when it predicts a resectable lesion, the accuracy is only 50-90%. Needle bx can be accomplished by CT guidance. It is generally reserved for pts who are felt not to be operative candidates because of radiographically unresectable disease or lack of medical fitness.

Endoscopy: ERCP allows for the detection of ductal tumors down to 1 cm in size and separates those pts with ampullary cancer and cholangiocarcinoma who may have a greater chance of resectability. At the time of ERCP, brushings and bx may be obtained, and obstruction can be relieved by stent placement (see Rx). EUS may be superior to CT for smaller lesions, lymph nodes, and vascular invasion, but is very operator dependent.

Rx:

- *Surgery:* The first step in determining the correct approach is to stage with a combination of CT scan and other modalities. Diagnostic laparoscopy is used in some centers to determine resectability since small local mets are frequently missed on other imaging studies. It may be especially useful in tumors of the body and tail (where tiny mets are frequent) and if ascites is present. Surgery is performed if there is no radiographic evidence of vascular invasion, no local or distant spread, and if the pt is

medically fit. Almost all the potentially resectable lesions are in the head since pts develop a sx (jaundice) when the tumor is still a small size. About 80-90% of lesions are found to be unresectable. A **pancreaticoduodenectomy** (Whipple operation) with or without the pylorus-sparing modification is performed. If there is no local or vascular invasion pathologically, the 5-yr survival is 50%, but these pts are few and far between. More radical surgical approaches increase morbidity but do not improve outcome. Tumors <2 cm have better survival. A **bypass** to relieve biliary or duodenal obstruction may be indicated if the pt has unresectable disease at surgery. Intraoperative chemical **splanchnicectomy** (by injection of absolute alcohol) is effective for pain control.

- *Chemotherapy and radiation:* The role of adjuvant chemoradiation in resectable pts is uncertain (Surg Oncol Clin N Am 2004;13:567). Radiation in conjunction with chemotherapy is offered to pts with locally advanced disease. Gemcitabine is more effective than bolus 5-FU (Ann Oncol 2007;18 Suppl 2:ii19). Radiation may reduce local pain. External radiation doses are limited by the radiosensitivity of the surrounding normal structures. Intraoperative implants have been tried with minimal success (J Clin Gastro 2000; 30:230).
- *Palliation of jaundice:* Obstructive jaundice can cause pruritus, malaise, cholangitis, and abdominal discomfort that is disconcerting to pts. Pts can be palliated effectively either by stenting or surgical bypass. Those with advanced disease, the elderly, and those with poor functional status are probably best palliated with stenting. Metal stents result in fewer complications due to clogging than plastic stents changed every 3 months (Gastrointest Endosc 1998;47:1). Plastic stents are cheaper and may be appropriate if life expectancy is short. Young, fit pts may benefit from a surgical approach. In surgery, a tissue dx can be made, and the duodenum and the biliary obstruction are bypassed; pain can be palliated with alcohol injection of the celiac plexus (CA Cancer J Clin 2000;50:241). The advantages of this approach are a lower incidence of cholangitis due to stent obstruction and the prevention of duodenal obstruction in prolonged survivors. This comes at the cost of surgical morbidity.
- *Palliation of duodenal obstruction:* Gastrojejunostomy effectively relieves duodenal obstruction. Endoscopic duodenal stenting can be performed (Gastrointest Endosc 1998;47:267).

9.4 Cystic Neoplasms of Pancreas

Nejm 2004;351:1218

Mucinous Cystadenomas and Carcinomas: (40%) These lesions have large cysts with septa and peripheral calcification, and they may have a solid component. The fluid is usually rich in tumor markers and low in amylase. The benign can be separated from the malignant only under the microscope after resection. The transformation from benign to malignant is a substantial risk, so these lesions must be resected. They can be difficult to distinguish from pseudocysts.

Serous Cystadenomas: (30-40%) These lesions have multiple small cysts with larger cysts in the periphery. There is often a central stellate calcification that allows for their identification on CT scan. They have little if any malignant potential. Serous cystadenomas that have diagnostic CT features can be followed without resection

(unless they are symptomatic), though malignant transformation has been reported (Am J Surg Pathol 1989;13:61).

Mucinous Duct Ectatic Neoplasms: (20-30%) These lesions are neoplastic changes of the main pancreatic duct or side branches (Am J Gastro 1992;87:300). They produce a mucus-filled cavity that communicates with the main pancreatic duct. At ERCP, globs of mucus can often be seen being spit out of a dilated ampullary orifice. These lesions can be benign or malignant. Management depends on surgical risk and potential benefits to the pt.

Papillary Cystic Neoplasms: These are the rarest of the group and are mostly solid tumors with cystic areas of hemorrhage and necrosis and often a capsule. They are most often seen in young women. They may be benign or malignant (GE 1996;110:1909).

9.5 Islet Cell Tumors

GE 2008;135:1469

Epidem: These rare tumors have a combined incidence of 1/100,000/yr.

Pathophys/Sx/Si/Diff Dx: These tumors are derived from neuroendocrine stem cells and as tumors may secrete a variety of polypeptide hormones. Many of these are part of the multiple endocrine neoplasia (MEN) type I syndrome (tumors of pancreas, parathyroid, pituitary, adrenal cortex, and thyroid) (Ann IM 1998;129:484). Several islet cell tumors are recognized:

- *Insulinoma:* (50% of islet cell tumors) This lesion is located in the pancreas and causes fasting hypoglycemia with associated trembling, irritability, weakness, diaphoresis, and hunger (from epinephrine release) or neurologic sx such as confusion, bizarre behavior, and seizures (from the hypoglycemia directly). They are usually single benign adenomas but can be multiple, malignant, or associated with hyperplasia rather than a discrete tumor. The differential includes other causes of fasting hypoglycemia, most notably self-administration of insulin.
- *Gastrinoma:* (10-15%) See p 86.
- *Vasoactive intestinal peptide (VIPoma):* (10-15%) These lesions are located in the pancreas or sympathetic chain and cause watery diarrhea, hypokalemia, hypochlorhydria, and acidosis. The diarrhea is large volume and persists with fasting. They may occur as part of the MEN type I syndrome but are usually isolated lesions. Surreptitious laxative use mimics the syndrome and the broad differential of chronic diarrhea needs to be considered (p 17).
- *Glucagonoma:* (1%) These lesions cause the 4D syndrome: diabetes, dermatitis, depression, and DVT. The pathognomonic rash is necrotic migratory erythema in which red blotches on extremities, thighs, or perineum progress to vesicopustules that desquamate and are pruritic.
- *Somatostatinoma:* These lesions cause diabetes, diarrhea, steatorrhea, and gallbladder disease (type A). A type B lesion is associated with neurofibromatosis and can cause GI bleeding or mass effect. They tend to be large and malignant.
- *Pancreatic polypeptide (PPoma):* These cause no sx until they present with vascular mets. They can be associated with the MEN type I syndrome.

- *Nonfunctioning tumors:* These tumors, with no functioning polypeptide products, present with sx similar to adenocarcinoma of the pancreas (weight loss, pain, jaundice, mass effect).

Lab: For **insulinoma**, serial glucose and insulin levels are diagnostic. C-peptide levels are useful to exclude self-administration of insulin (which is probably more common than insulinoma!). Elevated hormone levels define the **VIPoma** and **somatostatinoma**. Elevated glucagon levels or skin bx are used to diagnose **glucagonoma**.

X-ray: CT scan and/or MRI is used to locate the tumor and assess for mets. Radionuclide scanning with octreotide can be helpful in identifying endocrine tumors with somatostatin receptors (sensitivity 50-75%) but is of low sensitivity for insulinomas (25%).

Endoscopy: EUS is the most sensitive test for the detection of intrapancreatic islet cell tumors (GE 2008;135:1469).

Rx: Once an islet cell tumor is suspected by clinical sx and hormone levels, the rx depends on the presence of mets and upon whether a localized tumor can be found. If mets are found, chemotherapy with streptozotocin and doxorubicin or 5-FU can be offered (with variable, largely disappointing response rates). Angiogenesis inhibitors and therapies directed against growth factors are being investigated. Long-acting octreotide and interferon may stabilize tumor growth. Hepatic mets can be treated with embolization, chemoembolization, and radiofrequency ablation. Sx from VIPomas, glucagonomas, and somatostatinoma may be reduced with long-acting depot octreotide. Octreotide may be of some benefit in insulinomas but may worsen hypoglycemia in some pts. Resection is performed if the tumor can be localized and there are no mets. If the tumor cannot be localized, surgery is still an option in pts with functional tumors because of a high chance of intraoperative tumor localization in experienced hands. Features of the MEN-I syndrome should raise the possibility of multiple lesions.

Chapter 10

The Biliary Tree

10.1 Cholecystitis and Biliary Colic

Am Fam Phys 2000;61:1673; Clin Perspect Gastro 2000;March:87

Epidem: The risk of gallstones rises with age. The prevalence of gallstones in young women is 5-8% and rises to 35% in women over age 75 yr. The prevalence in men rises to 20% by age 70 yr. Risk rises later for men, presumably because pregnancy confers earlier risk on women. Obesity is a strong risk for gallstones, especially in women, and 10-25% of pts develop stones with rapid weight loss (Ann IM 1993;119:1029). In younger age groups, the M:F ratio is 2:1. Estrogen replacement rx increases risk (GE 1988;94:91). Increased levels of estrogens promote biliary cholesterol supersaturation and may account for some of the observed difference. The incidence of gallstones in pregnant pts is 2%, though sludge develops in 30% and disappears postpartum in half of these pts (Ann IM 1993;119:116). Recreational physical activity reduces risk (independent of weight). Magnesium may be protective (Am J Gastro 2008;103:375).

Hypertriglyceridemia increases HMG-CoA reductase activity and thereby increases risk by promoting cholesterol secretion into bile (Semin Liver Dis 1990;10:159). Certain ethnic groups (eg, Pima Indian women of the southwestern U.S., native Chileans) have a very high incidence. Blacks have a lower risk than whites. Spinal cord injury causes gallbladder hypomotility and changes in biliary lipids that promote stone formation (GE 1987;92:966).

Pathophys: In the U.S., 85% of stones are composed of cholesterol. Pigment stones (composed largely of calcium bilirubinate) and mixed stones represent the remainder. The pathophysiology of pigment stone formation is not understood, but the physical-chemical basis of cholesterol gallstone formation has been extensively studied. There are 3 lipid species in bile: (1) cholesterol (4%), (2) phospholipids (22%, mainly as phosphatidylcholine, aka lecithin), and (3) bile salts (67%) (Semin Liver Dis 1990;10:159). Small amounts of bilirubin (0.3%) and protein (4.5%) are also present. Cholesterol is not water soluble (it is hydrophobic). Bile salts and lecithins have polar and nonpolar surfaces and are called "amphiphiles." The polar surfaces allow the bile salts to dissolve in water. The biliary cholesterol is carried in stable particles (micelles) made up of lecithin and bile salts.

Bile is supersaturated when the capacity of the bile salts and lecithin to keep cholesterol in solution is exceeded. **Supersaturation** is the first step in stone formation and

generally occurs because of excess cholesterol secretion into bile. **Nucleation** is the initial transition from liquid cholesterol crystals to solid cholesterol crystals in bile. While many people have supersaturated bile, stones precipitate in only a small number. The most important nucleating factor is gallbladder mucin, but other pronucleating and antinucleating proteins have been identified. Gallbladder **stasis** promotes stone formation by allowing stones to grow without being expelled from the gallbladder.

- *Biliary sludge:* Sludge is a mixture of gallbladder mucin and small cholesterol or calcium bilirubinate crystals from which macroscopic stones can develop (GE 1988;95:508). Sludge can be detected by US and can cause biliary sx such as colic, cholecystitis, or pancreatitis. Pts with asymptomatic sludge can be managed expectantly. Pts who have rapid weight loss, take ceftriaxone, take octreotide, are pregnant, or have undergone organ transplantation are at risk for sludge (Ann IM 1999;130:301).
- *Consequences of stone development:* Pts with gallstones may (1) remain asymptomatic; (2) develop biliary colic from intermittent, brief cystic duct obstruction; (3) develop acute cholecystitis from prolonged cystic duct obstruction, with secondary inflammation and bacterial infection; (4) develop chronic cholecystitis from recurrent acute bouts; (5) experience migration of stones into the common bile duct and into the duodenum that may cause pain, pancreatitis, or cholangitis; (6) develop gallbladder cancer; or (7) develop gallstone ileus (bowel obstruction by a gallstone).
- *Acalculous cholecystitis:* This condition is cholecystitis in the absence of stones. It is most often seen in pts as a complication of major surgery, trauma, or burns. The precise mechanisms are unknown (J Am Coll Surg 1995;180:232).
- *Xanthogranulomatous cholecystitis:* This abnormality is found in about 1.7% of excised gallbladders. It is a destructive, fibrosing, inflammatory condition of the gallbladder characterized by the presence of lipid-laden macrophages, which possibly develop in response to extravasated bile (J Clin Pathol 1987;40:412).

Sx:

- *Biliary colic:* Most gallstones do not cause sx. The most common sx associated with gallstones is referred to as biliary colic (Postgrad Med 1991;90:119). The hallmark of biliary colic is discrete, unpredictable attacks of pain, lasting minutes to 5 hr before subsiding. The frequency of attacks is greater at night. The pt feels well between attacks. The pain is generally epigastric or RUQ (and occasionally substernal or LUQ). The pain often radiates outside the abdomen, typically to below the scapula. Nausea and vomiting may occur. Fever is uncommon without cholecystitis. Contrary to common teaching, there is no evidence that fatty food intolerance, belching, or bloating are related to the development of gallstones (Scand J Gastroenterol 2000;35:70). For sx that occur predictably or very frequently (> once weekly), a cause other than gallstones should be considered.
- *Acute cholecystitis:* In this complication, the pt begins with an attack of biliary colic that fails to resolve. The pain tends to localize to the RUQ and may be associated with vomiting. Fever may develop. An important minority of pts may have little if any pain, especially diabetics, the immunocompromised, pts with CNS disease, and pts on steroids.
- *Acute pancreatitis:* Gallstones may first present with sx of AP (p 187).
- *Choledocholithiasis:* These pts may present with sx of biliary colic (frequently with radiation to the scapula), jaundice, dark urine, or pancreatitis, or they may be asymptomatic.

- *Cholangitis:* Classically these pts present with Charcot's triad: fever, RUQ pain, and jaundice. All of these findings might not necessarily be present.

Si: In biliary colic, there are usually no physical findings. In cholecystitis, localized tenderness with peritoneal findings (percussion tenderness, guarding, or rebound) may develop. Many pts will demonstrate Murphy's sign, the abrupt cessation of inspiration because of worsening of the pain when examiner is palpating the RUQ. A RUQ mass may be palpable. Pts with cholangitis typically have jaundice and fever but are not universally tender in the RUQ.

Crs: (Ann IM 1993;119:606) Most gallstones remain asymptomatic. In the group of pts who initially are asymptomatic with their stones, sx will later develop at a rate of 1-2%/yr. The rate may be higher (4%/yr) in the first 5 yr. Once pts develop an attack of biliary colic, the chance of recurrent attacks is high, but 30% of pts will not have a second attack within 10 yr of follow-up. The rate of AP may be higher in pts with small stones (Arch IM 1997;157:1674).

Cmplc: Gallbladder cancer (p 208). A few pts will develop a stone that is impacted in the gallbladder neck and obstructs the common duct. This is referred to as Mirizzi's syndrome (Am Surg 1994;60:889). Cholecystocholedochal fistula and gallstone ileus (obstruction of the small bowel by a stone passed through a fistula) are uncommon (BMJ 2002;325:639).

Diff Dx: Depending on the presentation, the differential is that of dyspepsia (p 2), pancreatitis (p 187), or jaundice (p 29).

Lab: Labs are normal in biliary colic. LFTs, amylase, and lipase should be obtained in the evaluation of attacks of suspected biliary pain in order to look for evidence of pancreatitis or common duct stones. In the acute passage of stones, the transaminases can be very high (200-800 U/L) and may have a pattern more suggestive of hepatitis than obstruction. If the stone passes, the LFTs rapidly normalize. If obstruction persists, the alk phos and bilirubin slowly climb and transaminases stay 2-3 times normal. A leukocytosis may be seen in cholecystitis.

X-ray:

- *Biliary colic:* US is the test of choice for pts with suspected biliary colic. A typically quoted sensitivity is 97%, with specificity at 99%. However, since many pts with negative US never have the gold standard test (cholecystectomy), adjusted sensitivities of 90% for sensitivity and 97% for specificity have been proposed (Arch IM 1994;154:2573). CT is insensitive and not a reliable negative. In oral cholecystogram (OCG), pts swallow giant tablets of a contrast agent. The contrast agent is excreted in bile and taken up in the gallbladder. OCG is not often used because it is less sensitive than US and because it is nonspecific if nonvisualization of the gallbladder is taken as a positive.
- *Acute cholecystitis:* US is usually the test done first to look for gallstones in this setting. US may reveal direct evidence of cholecystitis, such as a thickened gallbladder wall or surrounding fluid collection. US may show evidence of dilated bile ducts from choledocholithiasis. If US is negative and acute cholecystitis is suspected, a radionuclide scan (typically called a HIDA scan no matter what isotope is used) is performed.
  In normal pts, the radiolabel is excreted into bile and flows into the gallbladder. If the cystic duct is obstructed (as in acute cholecystitis), the tracer is not visualized in the gallbladder and the test is positive. The sensitivity is 97% and the specificity is 90%. Since cholecystitis may occur without stones, HIDA scanning has advantages over US in the dx of acalculous cholecystitis.

- *Common duct stones:* CT and US are poor tests for common duct stones. ERCP is the test of choice for pts with a high clinical suspicion of common duct stones (bilirubin >4 mg/dl, cholangitis, or dilated CBD on US with bilirubin 1.8-4 mg/dl) because of the potential for endoscopic rx. If the pt is undergoing surgery, then an intraoperative cholangiogram is a cost-effective alternative when suspicion is intermediate. Preoperative EUS or MRCP are alternatives when suspicion is intermediate (Gastro Endosc 2010;71:1).

Rx:

- *Laparoscopic cholecystectomy (lap chole):* Pts with symptomatic gallstones should undergo cholecystectomy unless there is a major medical contraindication. Asymptomatic pts are better off waiting for the development of sx than having prophylactic surgery. Those with acute cholecystitis should undergo surgery promptly after resuscitation because up to 20% will have gangrene or perforation, and a delayed operation results in higher complication rates (BMJ 2002;325:639). The laparoscopic approach has replaced open cholecystectomy without a randomized trial to support its use. Shortened hospital stays, reduced pain, shorter recovery time, and consumer demand have dictated that an RCT will never be done. Expected mortality of lap chole is 0.1-0.2%, and complications occur in 5%. These rates are similar to the rates for the open operation (Ann Surg 1993;218:129). Contraindications to the laparoscopic approach include scarring or inflammation that prevents access to the RUQ, diffuse peritonitis, and coagulopathy. The laparoscopic approach cannot be used for all pts, and some pts (less than 5%) must be converted to the open operation. Though indications for lap chole are supposedly no different than for open chole, the advent of the laparoscopic approach has increased utilization by about 11% (Surg Endosc 1996;10:746).
- *Lap chole and the common bile duct:* Access to the bile duct is not as easy with lap chole as with open chole. About 8-17% of pts who undergo cholecystectomy are diagnosed with common bile duct stones (CBDS), and 1-2% will have retained stones diagnosed after surgery (J Am Coll Surg 1998;187:584). A great deal of effort has been put into methods of predicting the presence of common duct stones based on noninvasive data such as LFTs and US findings. About 90% of pts are considered low risk for CBDS because they have normal LFTs, no bile duct dilatation, and no hx of jaundice or pancreatitis. Even in this low-risk group, the incidence of stones is up to 5%. An algorithm for management of suspected common duct stones is available (Gastro Endosc 2010;71:1). When there is a high probability of stones (bilirubin >4 mg/dl, CBD stone on US, cholangitis, or dilated CBD on US with bilirubin 1.8-4 mg/dl) ERCP is performed prior to lap chole. When there is an intermediate probability of stones (abnormal LFTs, gallstone pancreatitis, dilated CBD on US, or age 55 and none of the high probability findings just discussed) then intraoperative cholangiogram, MRCP or EUS are considerations. Pts with positive cholangiograms undergo (1) postoperative ERCP with sphincterotomy and stone extraction, (2) laparoscopic removal of common duct stones (in the hands of experts) (World J Surg 1998;22:1125), or rarely (3) conversion to an open operation. Laparoscopic methods to explore the bile duct have fewer complications and cost less if done at expert centers, but those outcomes are not likely in the typical community (Am Surg 1999;65:135). Local expertise usually dictates the approach.
- *Complications of cholecystectomy:* The most feared complication of lap chole is bile duct injury. Bile duct injuries can be (1) major transections or ligations of the ducts, (2) leaks from the cystic duct stump, or (3) leaks from superficial branches of the right hepatic

ducts that are exposed at surgery (Am J Surg 1994;167:27). Biliary injuries occur more often in the hands of inexperienced surgeons (Brit J Surg 1995;82:307) and in acute cholecystitis (Arch Surg 1996;131:382). Pts with bile duct injuries present with pain and, to varying degrees, abdominal distention, ileus, and fever. LFTs may be normal or near normal in pts with leaks, but jaundice develops if the duct has been ligated. When a leak is suspected, HIDA scan usually demonstrates the leak and imaging studies may show a fluid collection. Leaks of the cystic duct stump or branches of the right hepatic system can be treated by placing a stent across the sphincter of Oddi at ERCP (Gastrointest Endosc 1993;39:416). As long as the stent crosses the sphincter and reduces pressure in the bile duct, the leak is sealed in the vast majority of cases (Am J Gastro 1995;90:2128). The stent is removed several weeks later, and closure of the leak is verified. Some experts prefer to do a sphincterotomy and place a nasobiliary tube. The nasobiliary tube usually can be removed in a few days when the edema of the sphincterotomy subsides, and the pt is spared a second procedure. No direct comparative studies are available. Major transections may require operative intervention and are associated with a high incidence of subsequent stricture, high cost, and mortality (Ann Surg 1997;225:268). Other notable complications are bleeding and bowel injury (Nejm 1991;324:1073). Stones may be lost into the abdomen and infrequently result in infectious or mechanical complications (Surg Endosc 1999;13:848).

- *Cholecystostomy:* Pts with acute cholecystitis who are at very high risk for surgery can be treated with the placement of a cholecystostomy drainage tube or with an ultrasound-guided gallbladder puncture without a drainage tube. These interventions can be life saving (Lancet 1993;341:1132).
- *Gallstone dissolution:* In pts who are not surgical candidates, stones may dissolve with ursodeoxycholic acid (UDCA). This drug reduces cholesterol secretion into bile and allows for dissolution of cholesterol on stone surfaces. Stones must be made of cholesterol (these stones float at OCG) and must not be calcified (determined on KUB), and the cystic duct must be patent (verified with OCG or HIDA). Success rates of 30-55% can be expected. There is a high recurrence rate (43% at 4 yr) (Gut 1988;29:655). Recurrence can be reduced by UDCA or aspirin.
- *Lithotripsy:* Extracorporeal shock wave lithotripsy (ESWL) has been used to shatter stones into smaller pieces that can pass or can be more easily dissolved with UDCA. Lap chole has made ESWL obsolete. Success varies with the size and number of stones (22-90%). The procedure may be complicated by biliary colic from fragments of stones (Ann IM 1990;112:126). Organic solvents instilled directly into the gallbladder may rapidly dissolve stones, but this approach is now seldom used (Gastroenterol Clin North Am 1991;20:183).
- *Prevention of stones during weight loss:* UDCA prevents stones induced by rapid weight loss (Am J Gastro 1993;88:1705).
- *Common bile duct stones postcholecystectomy:* (Am J Gastro 1997;92:1411) Pts may present postcholecystectomy with findings suggestive of common duct stones (attacks of upper abdominal pain radiating to the back, abnormal LFTs, dilated bile ducts, pancreatitis, or cholangitis). Pts with a high probability of stones should undergo ERCP. At ERCP, the bile duct is cannulated and injected with contrast, and a sphincterotomy is made if stones are identified. This allows extraction of stones into the duodenum with use of a balloon or wire basket to capture them. Removal of stones carries a risk of short-term complications of pancreatitis, bleeding, or perforation. The bile duct can be cleared

in >90% of cases. Long-term follow-up indicates that sphincterotomy is not a benign cure-all, with stone recurrence and sphincter stenosis occurring in up to 24% of pts at 15 yr (Gastrointest Endosc 1996;44:643). Very large stones are more difficult to remove because the sphincterotomy cannot be made large enough for the easy passage of the stone (Gut 1993;34:1718). In these cases, the stone can be grasped in a reinforced crushing basket and then fragmented into pieces that will pass through the cut sphincter (mechanical lithotripsy). Other approaches include placement of stents, use of shock wave, laser, or electrohydraulic lithotripsy, and organic solvents for dissolution (Am J Gastro 1991;86:1561).

- *Postcholecystectomy syndrome:* These pts have the same sx that brought them to cholecystectomy or they develop new sx postoperatively that are suggestive of biliary tract pain. These pts represent 3 groups. The first is the group of pts with sphincter of Oddi dysfunction (p 210). The second is the group of pts with CBDS (p 204). The third is the group of pts who came to cholecystectomy for sx not due to gallbladder disease. These pts might have GERD, IBS, PUD, or other serious, undiagnosed pathology. A careful review of the hx guides the choice of the next diagnostic or therapeutic step. It serves little purpose to leave the pt with the nonspecific label of postcholecystectomy syndrome.

10.2 Bacterial Cholangitis

Gastroenterol Clin North Am 2003;32:1145; Am J Gastro 1998;93:2016

Cause: In most cases cholangitis is the result of infection in a biliary tree obstructed by gallstones. Ascariasis is a common cause of cholangitis in Asia.

Pathophys: Bacteria infect bile in the common duct, usually behind an obstructing stone. Pressure rises in the biliary tree, and bacteria reflux into the systemic circulation, causing sepsis. Enteric gram-negative organisms are the most common infecting organisms, but anaerobes may be seen in about 5% of pts (often as part of a mixed infection) (Gastro Endosc Clin N Am 2007;17:289).

Sx: RUQ pain or upper abdominal pain sometimes radiating to the back. Some pts have no pain, and the absence of pain does not rule out cholangitis. Fever or rigors are common. Nausea and vomiting may occur.

Si: Fever, at times very high. Most pts with cholangitis have jaundice. They may have relatively little upper abdominal tenderness compared to pts who present with cholecystitis. Some will have hypotension or altered mental status.

Crs: Without relief of obstruction, mortality is very high. With ERCP, mortality is still as high as 10%.

Diff Dx: The dx needs to be considered in any pt with fever or a sepsis picture and abnormal LFTs. Cholecystitis and pancreatitis are the 2 most common considerations, but perforated viscus, ischemic bowel, or other intra-abdominal catastrophe may give a similar picture. Pneumonia can cause pain and abnormal LFTs with sepsis. Sepsis of any cause can cause abnormal LFTs, especially if there is associated shock liver (p 268).

Lab: LFTs most commonly show an obstructive picture, with elevated bilirubin and alk phos and transaminases usually below 200 U/L. Thrombocytopenia and hypoalbuminemia are risks for a poor outcome (Nejm 1992;326:1582).

X-ray: US may show dilated ducts and occasionally stones or gas in the bile ducts. CT is usually not needed. If oral contrast is given for a CT scan, it must be purged with a laxative because the contrast interferes with ERCP. MRCP may be of use in pts with a low probability of cholangitis but in whom the possibility cannot be completely ignored (Endoscopy 1997;29:472).

Rx: Pts with suspected cholangitis are treated with a broad-spectrum antibiotic (eg, ciprofloxacin with metronidazole, ampicillin/sulbactam) and iv fluids. Ciprofloxacin achieves higher concentrations in obstructed bile ducts than many other antibiotics achieve, but this may not translate into better outcomes (Gastrointest Endosc 1994;40:716). ERCP is performed after fluid resuscitation is complete and after antibiotics are begun. In most pts, sphincterotomy and stone extraction are accomplished at the initial procedure (see p 205 for stone extraction techniques). In some critically ill pts, in pts with a coagulopathy, or in pts with multiple, large stones, a nasobiliary tube or indwelling stent should be placed as a safe and effective alternative (Am J Gastro 1998; 93:2065). The stones can be removed electively after the sepsis is medically treated and the pt is stable. If urgent surgery is done for this group of pts, mortality is 30% (vs 10% for ERCP), and the endoscopic approach is strongly preferred (based on an RCT [Nejm 1992;326:1582]). Percutaneous transhepatic approaches can be used if ERCP is not possible.

10.3 Cholangiocarcinoma

Aliment Pharmacol Ther 2006;23:1287; Nejm 1999;341:1368

Epidem: The incidence is low at 1/100,000/yr. Two out of 3 pts are over age 65 yr (Ann Surg Oncol 2000;7:55). Risk factors include PSC (10% lifetime risk, p 233), cigarette smoking, choledochal cysts, Caroli's disease (p 212), exposure to the contrast medium thorium dioxide, and chronic infection with the parasites *Opisthorchis viverrini* and *Clonorchis sinensis*. In most cases, no risk factor is identified.

Pathophys: Cholangiocarcinoma most commonly involves the distal extrahepatic bile ducts or the hilum of the liver at the bifurcation of the bile ducts (Klatskin tumor). Lesions are less commonly intrahepatic or multicentric. Acute or chronic bile duct epithelial injury is probably important in malignant transformation, but the process is not well understood.

Sx: Pts typically present with sx of biliary obstruction. Jaundice is present in >90% of pts, sometimes with associated clay-colored stool, dark urine, and pruritus. Pain is not a prominent feature. Weight loss suggests advanced disease. Cholangitis is unusual.

Si: Depending on the location of the tumor, there may be a palpable mass or a palpable gallbladder.

Crs: The 5-yr survival rate is 10-45%, with a median of 12-30 months. For pts who are not operative candidates, survival is 3-6 months (Gut 1998;42:76).

Diff Dx: The differential is that of jaundice (p 29). The chief differential considerations are usually pancreatic cancer, ampullary cancer, common duct stones, and benign biliary strictures (often associated with CP or prior biliary surgery).

Lab: LFTs show elevations of bilirubin and alk phos out of proportion to transaminases. The PT may be elevated due to poor vitamin K absorption, because there is no bile in gut lumen for absorption. CA 19-9 is the most useful serum tumor marker and is elevated in more than 80% of pts (Oncology 1996;53:488).

X-ray: US shows evidence of dilated bile ducts but often misses the lesion, especially if the lesion is in the distal bile duct. CT scan is more sensitive and may detect nodes and local invasion. MRI can be used to detect vascular encasement. Cholangiography is the gold standard. ERCP is usually the initial study done (because it is diagnostic and therapeutic), but MRCP can provide useful information if ERCP is inadequate (Nejm 1999;341:258). PTHC can be used if drainage cannot be achieved by ERCP alone.

Endoscopy: ERCP with brushings/bx and stent placement relieves the sx associated with jaundice. In expert centers, brush or fine-needle aspiration cytology may have a diagnostic yield as high as 75% (Gut 1997;40:671), but cytology may be negative because the tumor is desmoplastic. EUS can be used in staging and selecting pts for surgery.

Rx: Surgery is the only modality that prolongs survival. The selection of pts for resection is based on characteristics of the tumor and host (Ann Oncol 1999;10:239). PSC pts usually do not do well with resection since the disease is often multifocal. Many pts are unfit due to performance status, cardiopulmonary disease, or cirrhosis. Resection is performed for intrahepatic lesions. Hilar tumors require resection with hepaticojejunostomy. Distal tumors are treated like cancers of the head of the pancreas with a pancreaticoduodenectomy (Whipple procedure). Distal lesions are more likely to be resectable (Ann Surg 1996;224:463). Liver transplant has been used for cholangiocarcinoma associated with PSC, though initial results were poor. There has been some resurgence in interest in using transplant with neoadjuvant rx (Aliment Pharmacol Ther 2006;23:1287). Radiation (external beam or intraluminal) may be of very limited benefit (Gut 1996;39:852; Brit J Surg 1995;82:1522). Chemotherapy is unhelpful. Stenting palliates jaundice. Metal stents are less likely to clog and cause cholangitis, but plastic stents are cheaper. Pts with tumors >30 mm survive a mean of 3 months, and plastic is adequate. Those with smaller tumors may be better served by metal stents (Gut 1998;42:76). Photodynamic rx prolongs survival in those who fail to clear their jaundice with stenting alone (GE 2003;125:1355).

10.4 Gallbladder Cancer

Am J Surg 2008;196:252; Nejm 1999;341:1368

Epidem: (Am J Gastro 2000;95:1402) The mean age of dx is 65 yr. Women are affected more than men. Rates vary widely by country. High rates are seen in Chile (13/100,000/yr), Israel, Poland, Mexico, and Bolivia. The rate in the U.S. is 2.5/100,000/yr, with rates 50% higher in whites than blacks. Important risk factors include (1) chronic cholecystitis and gallstones (especially if >3 cm), (2) gallbladder polyps (especially solitary, sessile, echopenic lesions >10 mm), (3) anomalous junction of the pancreaticobiliary duct

(where the union is outside the duodenum and there is a very long common channel and risk for gallbladder Ca may be 25% [GE 1985;89:1258]), (4) calcified gallbladder wall (porcelain gallbladder [J Clin Gastro 1989;11:471]), (5) typhoid, (6) PSC, and (7) heavy metal exposure through occupation.

Pathophys: It is speculated that inflammation predisposes to Ca, but the mechanism is unknown.

Sx/Si: Chronic RUQ pain, fever, malaise, weight loss, or an acute bout of cholecystitis are common presentations. A few pts will have the dx made incidentally at cholecystectomy. There may be a palpable, hard mass in the RUQ.

Crs: Most pts present with advanced disease, and 5-yr survival is 5-10%. Median survival is 3 months (Am J Gastro 2000;95:1402).

Cmplc: Biliary obstruction.

Diff Dx: The differential is usually between inflammatory and neoplastic disease of the gallbladder once nonspecific sx have led to an imaging test. The preoperative dx is correct prior to surgery in about 50% of pts (Ann Surg 1994;219:275).

Lab: LFTs may be cholestatic if local invasion or mass effect causes obstruction.

X-ray: Mass lesions and substantial wall thickening may be evident with US. It may be impossible to distinguish inflammatory from neoplastic disease. Curable lesions are typically missed by US and CT (World J Surg 1999;23:708). CT or MRI may provide additional staging information.

Rx: Surgery is the only effective rx, but fewer than 10% of pts have resectable disease. A second resective surgery is indicated for cancers found incidentally at laparoscopic cholecystectomy unless they are stage 0 or stage 1 (Cancer 1998;83:423). Radical surgery seems of little benefit in the U.S. (Arch Surg 1990;125:237), but may show benefit in Japan (World J Surg 1991;15:337). Chemotherapy and radiation are of little value. Since the outcome for symptomatic disease is so horrible, **prophylactic cholecystectomy** is strongly recommended for porcelain gallbladder and anomalous junction of the pancreaticobiliary duct. Prophylactic cholecystectomy might be considered for pts with gallbladder polyps >1 cm, pts with gallstones >3 cm, typhoid carriers, and elderly, Native American women with gallstones (Am J Gastro 2000;95:1402).

10.5 Ampullary Cancer

Nejm 1999;341:1368

Cancer at the ampulla of Vater is an uncommon lesion that presents with obstructive jaundice or occasionally with pancreatitis. Ampullary adenomas are precursor lesions (Gut 1991;32:1558). Adenomas should be excised by surgery (Brit J Surg 1997;84:948) or by endoscopic snare (Gastrointest Endosc 1993;39:127). Ampullary adenomas are more common in pts with FAP who are at risk for ampullary cancer even after colectomy. The presentation is similar to that of pancreatic cancer, and the dx is generally made when ERCP is done to assess biliary obstruction and bxs are obtained. Pancreaticoduodenectomy (Whipple procedure) is done if there is no evidence of distant disease. The 5-yr survival is 40% in expert hands (Ann Surg 1998;227:821).

10.6 Gallbladder Polyps

Am J Gastro 2000;95:1402; Brit J Surg 1992;79:227

Gallbladder polyps are found in 3-6% of pts undergoing US. The most common polyp is a cholesterol polyp, a form of cholesterolosis. These lesions are generally <10 mm, do not require intervention, and if large, can be confidently identified by fine-needle aspiration (Am J Gastro 1996;91:1591). A variety of other nonneoplastic polyps have been identified. The chief concern is the possibility that a polyp will be an adenoma and develop into a carcinoma. The risk of cancer is higher if a polyp is >10 mm, solitary, sessile, echopenic on US, or associated with gallstones (Am J Gastro 2000;95:1402). The optimal management has not been determined. Some experts suggest cholecystectomy if a polyp is >10 mm and the pt is fit (Brit J Surg 1992;79:227). The alternative is serial US, though the yield will be low (Gut 1996;39:860). For smaller polyps (<10 mm), serial US (q 6 months × 3 then yearly) has been suggested with cholecystectomy for polyps that enlarge (South Med J 1997;90:481). Some experts suggest that US is not needed after a stable period of 1-2 yr (Am J Surg 2004;188:186). Many clinicians ignore small polyps, especially if they are multiple and present in a pt without substantial risks for gallbladder cancer. Gallbladder polyps in pts with PSC are more likely to be malignant, and early cholecystectomy may be appropriate (Curr Opin Gastroenterol 2008;24:395).

10.7 Sphincter of Oddi Dysfunction (Biliary Dyskinesia)

Gastro Endosc 2004;59:525; Can J Gastroenterol 2000;14:411

Epidem: The F:M ratio is 7:1, and the disorder peaks in the 40s. About 6% of pts will complain of biliary-type pain postcholecystectomy without a definable cause such as stones.

Pathophys: The sphincter of Oddi (SO) is made of muscle fibers that maintain resting tone and are a resistor to bile and pancreatic juice flow. Pts with dysfunction of the biliary portion of the sphincter experience biliary pain, often with abnormal LFTs and ductal dilatation. Those with pancreatic sphincter involvement may have recurrent pancreatitis. Pts with suspected SO dysfunction are classified on the basis of clinical findings into 3 types (Gastro Endosc 2004;59:525). **Biliary type 1** pts have biliary pain, abnormal transaminases, and a dilated bile duct on imaging studies. All these pts are thought to have SO dysfunction. **Biliary type 2** pts have pain and either a dilated bile duct or abnormal transaminases. Many of these pts will have SO dysfunction if manometry is done. **Biliary type 3** pts have pain but no other abnormalities. Less than 10% have SO dysfunction by manometry. A similar classification (based on abnormal pancreatic enzymes and a dilated pancreatic duct) exists for pancreatic SO dysfunction. The gold standard for dx is SO manometry, but many experts do not use the technique because of the high frequency of pancreatitis. At manometry some pts have SO stenosis (elevated resting pressure), which may indicate a structural lesion such as fibrosis. The remaining pts have findings of an uncoordinated sphincter that is called SO dyskinesia. It is not clear if pts with intact gallbladders develop symptomatic SO dysfunction (since the gallbladder acts as a compliance reservoir to reduce pressures and therefore pain), but a response to sphincterotomy has been reported (Gastrointest Endosc 1993;39:492).

Sx: Pts usually present years after cholecystectomy with attacks of epigastric or RUQ pain sometimes associated with radiation to the back, nausea, or vomiting. The pain can be severe and last hours. In pts with involvement of the pancreatic sphincter, sx of pancreatitis may occur.

Si: Some localized tenderness may be seen in the RUQ or epigastrium, but there is no peritonitis.

Diff Dx: Common duct stones are the major consideration in type 1 pts. Intra-ampullary tumors may mimic SO dysfunction (Gastrointest Endosc 1995;42:296). The diff dx of pancreatitis needs to be considered in pts with pancreatitis as a presenting sx (p 187). The differential is broad in type 3 pts, many of whom have high levels of somatization or depression (GE 1999;116:996).

Lab: LFTs, amylase, and lipase should be obtained 3-4 hr into an attack of pain since they may be normal if done at the onset of pain.

X-ray: Biliary scintigraphy may show abnormalities such as delayed transit time from hilum to duodenum (Dig Dis Sci 1994;39:1985). These studies may have some role in the future as a safer alternative to manometry, but they have not yet been adequately validated. An abnormal US secretin test (the pancreatic duct dilates >1 mm for >20 min in response to secretin) may be an alternative to SO manometry in recurrent pancreatitis (Dig Dis Sci 1999;44:336). MRCP is the most useful noninvasive test to exclude other structural abnormalities such as stones.

Endoscopy: MRCP or EUS is performed to look for CBDS, and to assess ductal dilatation. ERCP is generally reserved for therapeutic intent or to perform manometry (Gastro Endosc 2002;56:803). SO manometry is performed in selected pts in some centers (see Rx). A motility catheter is placed in either the pancreatic sphincter or biliary sphincter (depending on the clinical presentation), and manometry is performed before and after injection with CCK. The risk of pancreatitis is high (8%) and even higher (29%) if the indication for the test is recurrent pancreatitis (J Gastroenterol Hepatol 1995;10:334).

Rx:

- *Biliary SO dysfunction:* If pts have SO stenosis at manometry, sphincterotomy provides sx relief (90% vs 25% in sham-treated pts in an RCT [Nejm 1989;320:82]). In contrast, those with SO motility abnormalities in the same RCT did not benefit from sphincterotomy. All pts with type 1 dysfunction should undergo sphincterotomy, because they get good relief and manometry may be misleadingly normal (Gastrointest Endosc 1993;39:778). Pts with type 2 dysfunction should be considered for referral to an expert center for SO manometry (which is very operator dependent) or should undergo sphincterotomy. Sphincterotomy seems more rational given the risk and limited predictive value of manometry. Type 3 pts may have pain as part of altered visceral sensitivity and are best approached with trials of anticholinergics, antidepressants, and/or calcium channel blockers. Endoscopic rx is not warranted.
- *Pancreatic SO dysfunction:* Pts with recurrent pancreatitis and SO dysfunction may benefit from biliary sphincterotomy, which is much less morbid than pancreatic sphincterotomy. However, many such pts do not benefit and go on to endoscopic pancreatic sphincterotomy often with temporary stent placement to reduce the risk of pancreatitis (Gastroenterol Clin North Am 2003;32:601).

10.8 Choledochal Cysts and Choledochocele

Lancet 1996;347:779; Ann Surg 1994;220:644

Cause: Unknown, but there may be both congenital and acquired cysts.

Epidem: In the West, 1/15,000 live births; more common in Japan.

Pathophys: There are 5 recognized types of cysts: type I (dilatation of the common bile duct), type II (bile duct diverticulum), type III (cyst of the intramural common bile duct protruding into the duodenal lumen, also called a choledochocele), type IV (multiple cysts of the intra- and/or extrahepatic bile ducts), and type V (focal dilatations of the intrahepatic bile ducts, also called Caroli's disease).

Sx: In children sx are typically pain, jaundice, and failure to thrive. Adults may have similar sx but are more likely to develop pancreatitis, bile duct stones, and gallbladder or bile duct malignancy.

Si: Usually none, but jaundice and a mass may be present.

Cmplc: Cholangiocarcinoma, pancreatitis, and bile duct stones may occur.

Diff Dx: Since these lesions are rare, they are usually not considered high on the list of causes of abdominal pain, jaundice, or pancreatitis. Once the bile duct is imaged (for whatever reason), the dx becomes evident.

Lab: Abnormal LFTs or amylase/lipase, depending on the presentation.

X-ray: MRCP is the best noninvasive test to diagnose and characterize the cysts.

Endoscopy: ERCP is reserved for pts who are thought to need endoscopic rx. Type III lesions (choledochocele) are being increasingly recognized and treated during ERCP.

Rx: Once identified, all cysts except type III should be excised with biliary bypass (Ann Surg 1994;220:644). If they are drained, there is a risk of later malignancy, stones, or stricture. Type III lesions (choledochocele) can be treated with sphincterotomy (to relieve obstruction or remove stones), but the endoscopist must recognize the possibility of associated cholangiocarcinoma (Endoscopy 1995;27:233).

10.9 HIV-Related Biliary Disease

Clin Liver Dis 2004;8:213; Gastroenterol Clin North Am 1997;26:323

AIDS-related cholangitis presents with cholestatic LFTs, abdominal pain, and fever. There may be evidence of ampullary stenosis and/or radiographic findings that look like sclerosing cholangitis of the biliary tree (Am J Med 1989;86:539). The cause is unknown, though a variety of AIDS-related pathogens have been described in these pts. Rx is directed at any associated pathogen, and sphincterotomy appears effective for the pain of ampullary stenosis. Pts with HIV can develop **acalculous cholecystitis** secondary to opportunistic infections, usually CMV, *Cryptosporidium*, or *Isospora*. The presentation is usually that of chronic RUQ pain, fever, and cholestatic LFTs due to associated biliary tree involvement.

Rx is cholecystectomy, though survival is short because this disorder is a late finding in AIDS (Gastroenterol Clin North Am 1997;26:323). These disorders are becoming less frequently seen with the advent of highly active antiretroviral therapy (HAART).

10.10 Painful Rib Syndrome

Gut 1993;34:1006; Lancet 1980;2:632

Epidem: This condition accounts for 3-5% of GI clinic referrals in 2 series.

Pathophys: The syndrome is defined by (1) pain in the RUQ or lower chest and (2) tenderness at the costal margin that reproduces the pt's complaints. The cause of the pain is uncertain but has been attributed to abnormal mobility of the lower intercostal joints.

Sx: The pain is frequent, and often worsens with bending forward or stooping. Pts may avoid lying on the affected side. Pain is often decreased when the pt lies down or stretches. Pain may be constant or intermittent.

Si: The exam is normal except when the costal margin is palpated. Hooking the fingers under the costal margin and lifting is especially useful for reproducing the pain and convincing pts that the dx is correct.

Crs: About 70% of pts report persistent pain at a mean follow-up of 8 yr after dx. About 30% of pts had a second referral for the same pain even after a firm dx was made. For the vast majority, the pain is a nuisance and is not disabling.

Diff Dx: See Dyspepsia, p 2.

Rx: No specific rx or testing is usually needed. In pts with refractory pain, intercostal nerve block may be helpful (Postgrad Med 1989;86:75). Surgery to excise the offending rib has been reported (Brit J Surg 1984;71:522).

Chapter 11

Infections of the Liver

11.1 Hepatitis A

Lancet 1998;351:1643; Gastroenterologist 1996;4:107

Cause: The hep A virus, a small, nonenveloped RNA virus of the genus *Hepatovirus*. There are 4 stable human genotypes and 1 serotype.

Epidem: (J Infect Dis 1995;171[suppl 1]:S2) Hep A is commonly acquired before age 5 yr in developing nations of Africa, Asia, and Latin America, where seroprevalence is greater than 90% before adulthood. In Western nations, the seroprevalence is falling and is about 43% in the U.S. The spread is fecal–oral with secondary attack rates of about 20-50% in households. The incubation period is 15-50 days. The virus can be found in feces for about 2 weeks prior to and up to several weeks after the onset of clinical illness. Risk factors for hep A in the U.S. include (1) household or sexual contact of a pt, (2) employee or participant in day care, (3) traveler, and (4) food (including bivalve shellfish) or waterborne outbreaks. There is no risk factor present in 45% of cases (Am Fam Phys 1996;54:107). There has been a marked decrease in incidence in the 17 U.S. states where routine vaccination of children has been practiced (Jama 2005;294:194) and a fall in mortality from hep A in the vaccination era (J Infect Dis 2008;197:1282).

Pathophys: After oral ingestion, the virus is transported across the intestinal epithelium and into hepatocytes. The virus replicates within hepatocytes. Hepatocellular damage results from the host's immune response against infected cells (J Clin Lab Immunol 1993;40:47). Once jaundice occurs, viral titers fall as antibodies are produced against the virus.

Sx: A prodrome of fever, malaise, anorexia, nausea, and vomiting is usually seen in adults. The prodromal sx recede and jaundice develops. In children, the illness is usually anicteric and presents with flu-like sx of pharyngitis, cough, runny nose, photophobia, and headache. Diarrhea is seen in 50% of children but is uncommon in adults.

Si: Jaundice and hepatomegaly are usually noted, but splenomegaly is less common. Spider angiomata may develop but recede after the illness. Posterior cervical nodes may be seen. A cutaneous vasculitis is rare. Impending hepatic failure may be heralded by confusion, irritability, and asterixis.

Crs: The case fatality rate is quoted at 0.35%. However, so many cases go unrecognized that this is probably an overestimate. About 70% of the fatalities occur in the 8% of pts infected after age 50 yr. The typical course is a 3- to 6-month clinical illness. Jaundice usually lasts 6-8 weeks. LFTs resolve with the clinical sx. **Fulminant hepatic failure** develops in 0.14-0.35% of pts hospitalized for hep A. These pts develop worsening LFTs, markedly prolonged PT, and change in mental status. About 70-95% of them go on to develop cerebral edema, multiple organ failure, and death. **Relapsing hep A** occurs in 3-20% of all cases. These pts make an apparent clinical recovery, and weeks to months later develop recurrent illness with worsening LFTs and viral shedding. They ultimately recover (J Clin Gastro 1999;28:355). **Prolonged cholestatic hep A** is seen in 3-5% of pts. These pts have bilirubin >10 mg/dL, alk phos 3-5 times normal, and recover after an illness lasting months (Ann IM 1984;101:635).

Cmplc: Pancreatitis (Am J Gastro 1992;87:1648), renal failure (Clin Nephrol 1993;39:156), cholecystitis (Ann IM 1994;120:398), fulminant hepatic failure, Guillain-Barrè syndrome (Intern Med 1994;33:799), thrombocytopenic purpura (J Clin Gastro 1993;17:166), vasculitis, and arthritis may occur.

Diff Dx: See p 26.

Lab: The dx is made by demonstrating the presence of the IgM ab to hep A, which is always present during acute illness and which persists for 3-6 months. The presence of IgG ab without detectable IgM indicates prior infection and current immunity. Transaminases range from 500-5000 U/L. Bilirubin is usually less than 10 mg/dL but may go to 20 mg/dL in uncomplicated disease. A PT should be obtained as a marker of severity. Atypical lymphocytes are common.

X-ray: US or MRCP may be indicated if obstructive jaundice is a clinical question.

Rx: In most pts the rx is on an outpatient basis with abstinence from alcohol, moderate activity, and diet as tolerated. Bed rest is unnecessary (Nejm 1969;281:1421). Enteric precautions to minimize household spread are crucial.

Two **vaccines** are commercially available in the U.S., and others are under development. They are killed, attenuated virus vaccines that induce an antibody response in almost all healthy pts within a month. Havrix or VAQTA are given to adults in a dose of 1.0 mL im, followed by a booster of 1.0 mL 6-12 months later. They are indicated for travelers to endemic areas, those who live in endemic areas (including many American states), pts with chronic liver disease (especially hep C [Nejm 1998;338:286]), pts with clotting disorders (because of concentrated blood product use), in community outbreaks, for men who have sex with men, and for illicit drug users. Other high-risk occupations might be targeted (sewage workers, day-care workers). Universal vaccination has been proposed, but many practical barriers exist. A combination hep A and hep B vaccine (Twinrix) in a dose of 1.0 mL at 0, 1, and 6 months may be useful for adults needing both vaccines. The vaccine can also be used to prevent secondary spread (NNT = 18 to prevent 1 secondary case) (Lancet 1999;353:1136), but a direct comparison to immunoglobulin in this setting has not been done.

Prophylaxis with immunoglobulin is used for postexposure prophylaxis of household contacts and as primary prevention in infants where vaccine experience is limited.

Immunoglobulin is given in a dose of 0.02 mL/kg as a single im injection as soon as the index case is recognized (Am Fam Phys 1996;54:107). It provides protection if given within 2 weeks of exposure and lasts about 4-6 weeks. Doses of 0.06 mL/kg provide protection for travelers for up to 6 months, but vaccine is preferable.

11.2 Hepatitis B

Clin Gastroenterol Hepatol 2008;6:1315; Nejm 2008;359:1486; Clin Gastroenterol Hepatol 2004;2:87

Cause: The hep B virus (HBV), a DNA virus of the hepadnaviridae family. The virus is made up of a circular, partly double-stranded piece of DNA that is surrounded by a core called the nucleocapsid, which is then surrounded by an envelope. The envelope is antigenic (the hep B surface antigen, or HBsAg), and the nucleocapsid is antigenic (the hep B core antigen, or HBcAg). Immunity to HBsAg is protective and is the basis of natural and vaccine-induced immunity. The hep B e antigen (HBeAg) is derived from the core gene, which is modified and exported from liver cells. It is a marker for active replication of virus and is seen in pts with circulating HBV DNA.

Epidem: In endemic areas (Africa, Southeast Asia, China), 50% of the population become infected and 8% become chronic carriers. Infection is spread from mother to neonate (vertical transmission) or from child to child. In low-prevalence areas (North America, Europe), disease is spread sexually between young adults. Other risks in developed nations are iv drug use, occupational exposure, blood exposure, dialysis, or nosocomial transmission (Nejm 1992;326:721). About 20-30% of pts have no identified risk. Transmission from infected surgeons to pts has been reported (Nejm 1997;336:178). The U.S. prevalence is 0.35% for chronic infection and 5% for lifetime risk of infection. HBV is the leading cause of cirrhosis and HCC worldwide.

Pathophys: (Mayo Clin Proc 2007;82:967) In **acute infection**, clinical hepatitis results from the inflammatory response generated by the host in response to viral antigens presented on the surface of hepatocytes. If the immune response is vigorous, infected hepatocytes are rapidly cleared after an incubation period of 6 weeks to 6 months. This is the typical course for more than 95% of immunocompetent adults. However, if the immune response is ineffective, the pt develops chronic hepatitis. There are **4 phases of chronic** HBV infection. Most pts do not go through all 4 phases, and pts may transition back and forth between some of them.

In Phase 1, **immune tolerance**, pts have not yet developed an effective immune response. This is the case in most pts infected as neonates (95%) and many infected as young children (30%). There are high levels of viral replication as evidenced by high levels of circulating HBV DNA and a positive HBeAg. In this phase there is no clinical hepatitis and ALT levels are normal.

In Phase 2, **HBeAg-positive chronic hepatitis**, the maturing immune system starts to clear infected hepatocytes. Levels of HBV DNA fall but are still high. ALT rises and there is inflammation and developing fibrosis in the liver. For some pts, this leads to cirrhosis. Some pts will successfully inhibit viral replication and undergo seroconversion in which they lose HBeAg positivity and usually develop HBeAb.

In Phase 3, **inactive HBsAg carrier state**, after seroconversion the inflammation subsides, ALT levels normalize, and HBV DNA levels become low or undetectable. These pts have an overall good prognosis. However, a minority will revert back to HBeAg positivity and active viral replication with a flare of hepatitis. The rate of clearance of HBsAg in this stage is relatively low at about 0.1-2% per yr. Some inactive carriers redevelop active disease when given immunosuppressive rx for other diseases. Even in pts who clear HBsAg there is a risk of cirrhosis and HCC.

In Phase 4, **HBeAg-negative chronic hepatitis**, about 20-30% of inactive carriers will develop active disease with mutant viruses that do not express HBeAg. These viruses have mutations in the precore and core-promoter portions of the genome. Some pts enter this phase of disease directly from Phase 2. These pts develop a flare of hepatitis with elevated ALT levels and detectable HBV DNA, though typically at lower levels than in Phase 2 pts. These pts are usually older and have more advanced disease.

Sx: About half of pts with acute hep B have a subclinical illness. Those with clinically detectable illness usually present with jaundice, malaise, anorexia, and fever. Those with chronic hep B are usually asymptomatic but may complain of fatigue or malaise.

Si: In acute infection, jaundice, tender hepatomegaly, and fever. There may be stigmata of chronic liver disease (p 26).

Crs: Most adult pts have an acute hepatitis that clears within 6 months. About 3-5% of infected adults develop chronic hepatitis. Up to half of acutely infected adults are symptomatic. Pts are said to have chronic hepatitis if they have HBsAg detectable in the serum for more than 6 months or have HBsAg with no evidence of IgM anti-HBc. About 95% of infected neonates and 30% of children under age 6 yr have an asymptomatic illness that becomes chronic. Those adults with chronic hepatitis have a risk of progression to cirrhosis of 20% at 4 yr (Gut 1991;32:294). Fulminant hepatitis with coagulopathy, encephalopathy, and cerebral edema occurs in <1% of cases of acute hep B (Nejm 1993;329:1862). Any of the complications of end-stage liver disease may occur (p 255). Pts with concurrent hep C infection have aggressive liver disease, but HIV-infected pts do not have more severe liver disease than those not infected (Ann IM 1992;117:837).

Cmplc: Hep D (Delta) infection, a passenger virus that requires hep B for replication and causes severe liver disease (p 225). HCC (p 247) complicates long-standing hep B infection. It usually occurs in those with cirrhosis 25-30 yr after the onset of infection. HCC can occur in inactive carriers. The incidence of HCC is much higher in Asians and Africans than whites because of a much higher incidence of childhood infection. Polyarteritis nodosa (HTN, eosinophilia, abdominal pain, rash, polyarthritis, and necrotizing vasculitis involving gut, kidneys, and CNS) is a rare but serious complication of hep B infection (Lupus 1998;7:238). Glomerulonephritis (Ann IM 1989;111:479) and leukocytoclastic vasculitis (J Clin Gastroenterol 1995;21:42) are uncommon complications.

Diff Dx: See p 26.

Lab: **Acute infection** is diagnosed by the presence of HBsAg and IgM anti-HBc in the serum. In some very early cases, IgM anti-HBc may be absent, and it becomes positive later in the course. In those recovering from acute infection, IgM core disappears while the IgG core ab appears. HBsAg is cleared in about 24 weeks and anti-HBs appears about 8 weeks later, indicating complete recovery and future immunity. During the gap between the disappearance

of HBsAg and the appearance of anti-HBs (the window), the dx is made by the presence of IgM anti-HBc. IgG antibody to the core antigen (anti-HBc) develops and usually lasts a lifetime. If IgM anti-HBc is present, the pt has likely been recently infected, because the IgM fraction usually clears within 8 months of infection. A small number of pts with a flare of chronic hep B will produce IgM anti-HBc. HBeAg is present during acute infection and clears early in the illness. In **chronic infection**, HBsAg is present in the serum for a period of greater than 6 months (by definition). The IgM anti-HBc is usually absent. The HBeAg is present, and DNA levels are high when viral replication is high. The precore and core-promoter mutants may produce active infection but do not make the HBeAg and may escape laboratory detection unless DNA levels are checked. DNA levels are best measured by real-time PCR assays with high sensitivity and a broad range of accurate quantification. Testing for hep A immunity should be done to select pts for vaccination. Prior to consideration of rx in pts with chronic hepatitis, testing should be done for HBeAg, HBeAb, HBV DNA, hep C, hep D, and HIV. A urinalysis should be done to look for renal complications. Genotype testing can be done if interferon rx is being considered since response rates are higher in pts with genotypes A and B. The suggested upper limit of normal for ALT to be used in hep B monitoring is 30 IU/mL for men and 19 IU/mL in women. Many commercial laboratories report higher normal values. In pts with chronic hepatitis who are not being treated because ALT is normal, the ALT is followed every 3-6 months. In the inactive carrier state, ALT is followed every 6-12 months and HBV DNA is checked if ALT rises.

Liver bx in cases of chronic hepatitis shows variable portal zone inflammation, focal hepatocyte necrosis, and ground glass hepatocytes (containing HBsAg). As the degree of injury progresses, there is more severe necroinflammatory change with eventual bridging or multiacinar fibrosis (Am J Clin Pathol 2000;113:40). Older descriptive terms such as "chronic persistent hepatitis" or "chronic active hepatitis" are no longer used. Instead, pathologists describe the degree of both inflammation and fibrosis (categorized as mild, moderate, marked, and very marked). The histologic patterns have no correlation with sx. The utility of bx is variable, because the decision to treat is usually based on evidence of viral replication rather than histology. However, bx may be especially helpful in pts with normal ALT levels and age >35-40 yr to identify those with active disease (as they transition from the immune-tolerant phase) despite the normal ALT level.

Rx: (Clin Gastroenterol Hepatol 2008;6:1315, Clin Gastroenterol Hepatol 2004;2:87)

- *Acute hep B:* There is no specific rx of acute infection. Precautions are taken against household, sexual, or other bloodborne spread (no sharing of utensils, razors, toothbrushes, or common bathing). There is no reason to restrict activity. Pts are followed for the development of complications suggesting decompensated liver disease.
- *Vaccinate for hep A:* Pts with chronic hep B should receive **hep A vaccine** (p 216).
- *Inactive carriers:* Monitoring with ALT q 6-12 months is recommended. If ALT rises, DNA levels are obtained and the pt is further evaluated. Screening for HCC should be considered (p 247).
- *HBeAg-positive chronic hepatitis:* Rx is indicated for these pts when there are high DNA levels, elevated ALT, and/or active disease of liver bx. When ALT is normal and HBV DNA levels are low (<20,000 IU/mL), pts are monitored but not treated unless there is known active disease on liver bx. If HBV DNA levels are high (>200,000 IU/mL) and ALT is normal, the pt is often in the immune-tolerant phase and rx will not be successful.

If the pt is >35 yr of age (and thus less likely to still be in the immune-tolerant phase), biopsy may be helpful to identify those who need rx because they have transitioned to active disease with normal ALT levels.

- The current rxs of choice are the nucleoside **entecavir**, the nucleotide **tenofovir**, and **peginterferon alfa-2a**. There are other approved nucleoside/nucleotide agents, but they are less potent and/or prone to problems with development of resistance. Interferon has more side effects and is less effective at very high DNA levels but has the advantage of a 1-yr duration of rx. Response is assessed at 12 weeks by measurement of HBV DNA. If the DNA level has not fallen by >10 IU/mL, compliance is assessed and a more potent drug may need to be added. Response is reassessed at week 24. If the pt becomes DNA negative, monitoring is continued every 6 months and the drug is continued. If DNA is >2000 IU/mL at 24 weeks, a more potent drug is added. If the DNA level is persistent but <2000 IU/mL ("partial virologic response"), a second drug is added if the first drug chosen is prone to the development of resistance. If the HBV DNA is still detectable at 48 weeks, another drug is added that is not cross resistant with the first agent chosen. Tests for viral resistance are available. The **duration of rx** with a nucleotide/nucleoside varies with the response. In pts who seroconvert and achieve undetectable HBV DNA, rx is continued for an additional 12 months. Some pts seroconvert but still have detectable, stable DNA levels. In these pts seroconversion is reconfirmed 6 months later, and if DNA levels are stable a trial of stopping rx is considered. Pts may flare after stopping rx, thus frequent early monitoring for a flare and long-term monitoring is needed. Entecavir and tenofovir have minimal side effects. Interferon has many side effects (p 224).
- *HBeAg-negative hepatitis:* These pts have active hepatitis with mutant viruses that do not produce HBeAg. If DNA levels are elevated (>2000 IU/mL) and ALT is elevated, rx with entecavir, tenofovir, or interferon is indicated. If ALT is normal and HBV DNA levels are >2000 IU/mL, consider liver bx to look for active disease. If DNA levels are low (<2000 IU/mL) and ALT is normal, the pt is probably an inactive carrier and should be monitored instead of treated.
- *Rx of cirrhotics:* Compensated cirrhotics with low levels of DNA can be observed, but most experts elect to treat all cirrhotics with entecavir or tenofovir. Interferon should not be used because of the risk of decompensation due to disease flare.
- *Coinfection with HIV:* Therapy of coinfection requires expertise in both illnesses (AIDS 2008;22:1399).
- *Screening and surveillance for hepatocellular carcinoma:* See p 247.
- *Passive immunization:* Serum containing high titers of anti-HBs can be used to create an enriched IgG preparation called HBIG. It is used for postexposure prophylaxis (usually with vaccine) for newborns of infected mothers, those with exposure to HBsAg-positive blood or body fluids, and those infected pts receiving a transplant.
- *Vaccination:* (Nejm 2004;351:2832) Vaccines are prepared with yeast by recombinant techniques. A series of 3 im injections produces immunity in >90% of young adults. It is less effective in the elderly, in pts on hemodialysis, and in the immunocompromised. Combination of vaccine with HBIG is 79-98% effective in preventing chronic infection in newborns of HBeAg-positive women (Clin Microbiol Rev 1999;12:351). Though levels of anti-HBs become very low in most pts over years, protection against clinically apparent acute infection or chronic infection persists. Booster doses are not recommended (except in dialysis pts [Am J Kidney Dis 1998;32:1041]). Vaccine in the U.S. is currently suggested for

(1) all high-risk adults, (2) infants (to prevent childhood acquisition), and (3) adolescents who were not vaccinated as children so that they can be immune before they reach the age of high-risk sexual and drug-using behavior. Two recombinant vaccines are available. The recommended adult doses are Engerix-B 20 mg or Recombivax 10 mg in 3 im doses at months 0, months 1-2, and months 6-12. A combination hep A and hep B vaccine (Twinrix) in a dose of 1.0 mL at 0, 1, and 6 months may be useful for adults needing both vaccines. Postvaccine testing for anti-HBs is needed only for high-risk groups (such as healthcare workers, dialysis pts, men who have sex with men).

- *Transplantation:* With advances in antiviral rx, survival is now better in hep B pts undergoing transplant than in pts undergoing transplant for many other indications (Aliment Pharmacol Ther 2006;23:1031). Pts with fulminant hep B are also good candidates for transplant.

11.3 Hepatitis C

Hepatology 2009;49:1335; Jama 2003;289:2413; Lancet 2003;362:2095

Cause: The hep C virus (HCV) is an RNA virus of the flavivirus family. The nucleotide sequence shows substantial variations and 6 genotypes (numbered 1 to 6), and more than 50 subtypes (designated by a letter—eg, a or b) have been identified. Genotypes 1a and 1b are the most common in the U.S., and, along with genotype 4, they are the most difficult to treat. A single individual may show variations in the sequences of the genotype that infects them (referred to as quasispecies). These may arise from mutations in response to immune surveillance.

Epidem: In developed nations, the seroprevalence is 1-2%, with rates higher in Africa, Eastern Europe, and Egypt. Transfused blood was formerly a major risk (prior to 1992), but that risk has dropped to about 1/100,000 units completely tested (Nejm 1996;334:1685). IV drug abuse is the major risk factor. Intranasal cocaine and ear piercing among males are also associated with infection (Nejm 1996;334:1691). Multiple sexual partners are also a risk factor, but the disease is not readily transmitted sexually (Hepatology 1997;26:66S). The rate of vertical transmission is less than 5% (Nejm 1994;330:744; Obstet Gynecol 1999;94:1044). Iatrogenic spread from surgeons (Nejm 1996;334:555), needles, and organ transplantation does occur, as does spread from human bites (Lancet 1990;336:503). The risk to a health worker following needlestick injury from an infected pt is up to 7% (MMWR Morb Mortal Wkly Rep 1998;47:1). In some studies as many as 25% have no identified risk, but 5-10% is probably closer to the truth.

Pathophys: The virus enters by deliberate injection or inadvertent breakdown of a normal barrier such as skin or mucous membranes. The virus is then taken up by hepatocytes and replication begins. There is both a humoral and cell-mediated response to infection, but the immune response is usually ineffective. The development of mutant quasispecies or the effects of other HCV proteins may be important in the escape from immune clearance. The inadequate immune response not only fails to clear the virus but also causes the destruction of liver parenchyma and ultimately causes cirrhosis.

Sx: Most pts are asymptomatic or have nonspecific sx such as fatigue or joint aches (Am J Gastro 1999;94:1355). Jaundice is rare and may be seen with acute infection. In advanced disease there may be jaundice, ascites, or encephalopathy.

Si: Usually none except in advanced disease, in which signs of cirrhosis or liver failure may be present (p 26).

Crs: (Hepatology 2000;31:1014) Studies of the natural hx of hep C are hampered by short duration follow-up, retrospective design, and referral bias. About 70-85% of infected pts appear to develop a chronic hepatitis. Cirrhosis develops in perhaps 5-15% of pts per 20 yr of infection (Clin Gastroenterol Hepatol 2004;2:183). About 6% of pts develop decompensated liver disease, 4% develop HCC, and 3.6% die as consequence a of infection. Alcohol consumption of >35-50 gm/day, infection after the age of 50 yr, male gender, obesity, and HIV coinfection increase the risk of fibrosis (Lancet 2003;362:2095). Most pts die of causes other than liver disease.

Some groups have a different course. A cohort of young Irish women infected from anti-D immune globulin had only a 2% rate of cirrhosis at 17 yr (Nejm 1999;340:1228). About 50% of children infected during cardiac surgery clear the virus over 20 yr (Nejm 1999;341:866). Pts with normal transaminases have a slower rate of progression of fibrosis (Hepatology 1998;27:868). Any of the complications of end-stage liver disease may occur (p 255).

Cmplc: Cirrhosis with hepatic failure, ascites, and encephalopathy. HCC (p 247) develops in roughly 4% of infected pts, usually after the development of cirrhosis. The incidence of HCC in hep C cirrhotics is 1-4% per yr (GE 2006;130:231). Porphyria cutanea tarda (Hepatology 1992;16:1322), mixed cryoglobulinemia (Ann IM 1992;117:573), and glomerulonephritis are well-established extrahepatic complications (Ann IM 1995;123:615).

Diff Dx: See p 26.

Lab: The dx is usually established by the detection of anti-HCV antibodies using an enzyme immunoassay that is highly sensitive and specific to multiple HCV antigens. With the improvement in sensitivity and specificity of the immunoassays, RIBA testing for antibodies to specific HCV proteins is rarely needed. In pts being considered for rx, it is important to confirm the presence of virus itself in blood by PCR or branched DNA testing. The viral load and genotype are determined prior to beginning rx. Genotype determines the duration of rx. The fall in viral load at 12 weeks is used in the early identification of pts destined to fail rx. A highly sensitive PCR assay should be used after rx and 6 months later to determine if the pt has had a sustained virologic response with therapy. Those with a positive HCV ab test but negative PCR probably have cleared their infections.

Liver bx in hep C shows variable degrees of portal inflammation, largely with lymphocytes, periportal interface hepatitis (formerly called "piecemeal necrosis"), inflammation, bile duct degeneration without bile duct loss, and steatosis. As with hep B, bx are classified on a 4-point (or 6-point in some classifications) severity scale for the degree of inflammation and the degree of fibrosis. This system has replaced the old terminology that used terms such as "chronic active hepatitis" and "chronic persistent hepatitis." Bx provides information about the stage of disease and prognosis but does not always affect initial decisions regarding rx. It may be helpful in deciding whether to treat pts with relative contraindications to rx such as depression, in those who wish to base rx decisions on fibrosis score, and in those with a persistently normal ALT who are at lower risk for fibrosis. In pts who have difficulty with drug side effects, this information may help in deciding whether to continue with rx (for those with nasty-looking bx) or stop rx (for milder-looking bx). Liver bx has risks (p 277), and rx without bx may be more cost effective (Jama 1998;280:2088).

Rx: (Am J Med 2004;117:344; Hepatology 2009;49:1335; Clin Gastroenterol Hepatol 2009;7:397)

- *Prevention and screening:* (MMWR Morb Mortal Wkly Rep 1998;47:1; Hepatology 1997;26:2S) Universal precautions are used in the healthcare setting. An NIH consensus conference suggested that changes in sexual practices are unnecessary for couples in a monogamous relationship. Razors and toothbrushes should not be shared. Pregnancy is not contraindicated, and breastfeeding appears safe. The CDC recommends hep C testing in those who have used illegal injectable drugs, who have used clotting factor concentrates prior to 1987, who have received transfusions or organ transplants prior to July 1992, who are children born to hep C–positive women, who are dialysis pts, who have elevated ALT, and who are workers with exposure incidents (MMWR Morb Mortal Wkly Rep 1998;47:1). However, citing the lack of data on health outcomes of pts likely to be detected by screening, the U.S. Preventive Services Task Force found the data insufficient to recommend for or against screening of high-risk groups (Ann IM 2004;140:465).
- *General measures:* Infected pts should avoid alcohol because no safe level of alcohol consumption has been established. Vaccines should be given for prevention of hep A, which is very morbid in pts with hep C (Nejm 1998;338:286), and for hep B.
- *Selecting candidates for antiviral rx:* The underlying but unproven assumption is that clearing viremia will result in improved outcomes. Rx is considered appropriate for adults who have persistently abnormal ALT, detectable viral RNA in serum, and those with detectable RNA and bridging fibrosis or cirrhosis on bx. Bx is not universally used in selecting rx because pts with mild-looking bx may progress to cirrhosis and pts with mild disease respond best to rx. Pts with well-compensated cirrhosis respond reasonably well to rx, but the rx of decompensated cirrhosis is difficult. Pts with persistently normal transaminases represent a group who fare better (Hepatology 1998;27:868) and may not require rx. Most experts bx these pts and offer them rx if there is significant fibrosis on bx. The elderly are more likely to die of causes other than liver disease and are treated very selectively. Pts being considered for rx should have lab studies to look for other causes of abnormal LFTs (p 28), can be offered bx for staging of disease, and should be assessed for contraindications to rx. Combination rx with interferon/ribavirin is contraindicated in severe psychiatric illness, decompensated liver disease, renal failure, pregnancy, active autoimmune illnesses, hemolytic anemia, seizures, CAD, CHF, and COPD, and for pts in unstable social situations (Jama 2003;289:2413).
- *Interferon/ribavirin for initial rx:* Ribavirin is a nucleoside analog that has antiviral effects but is ineffective as monotherapy. Interferons (which are glycoproteins normally produced by leukocytes in response to infection) have antiviral properties but are a disappointing monotherapy. Standard rx has become the combination of ribavirin with pegylated interferon. Both pegylated interferon α-2b and α-2a are effective, and there are no convincing data that demonstrate that one is better than the other.

  For pts infected with **genotypes 1 and 4**, 48 weeks of rx with weight-based dosing of ribavirin (800 mg for pts <65 kg, 1000 mg for those 65-85 kg, 1200 mg for those 85-105 kg, and 1400 mg for those >105 kg) and either 180 mcg of pegylated interferon α-2a or 1.5 mcg/kg of pegylated interferon α-2b are used. If viral load has not dropped by 2 logs or greater after 12 weeks, then rx is stopped because chance of a sustained response is <2% (Hepatology 2002;36:S145). Viral load is rechecked at 24 weeks, and rx is continued only if the virus is undetectable. Viral load is rechecked at the conclusion of rx and

24 weeks later. A sustained virologic response (those without detectable virus 24 weeks after stopping rx) will be seen in about 50% of pts.

For **genotype 2 or 3** pts, only 800 mg of ribavirin and 24 weeks of therapy are needed to achieve sustained response rates of about 80%.

Pts who clear virus by 4 weeks (called a **rapid virologic response**) may be able to have a shorter course of rx, but the data are still inconclusive. A growing body of evidence suggests that pts who clear virus between weeks 12 and 24 (called **slow responders**) may have greater chance of cure with a 72-week course of rx.

- *Side effects:* Ribavirin causes predictable hemolytic anemia, with mean decrease in Hgb of 2-3 gm, that stabilizes in the first 4 weeks. In 5% of pts, the level may drop below 9.6 gm/dL. Ribavirin is teratogenic and contraception must be assured. Ribavirin may cause cough, dyspnea, rash, nausea, anorexia, and weight loss. Erythropoietin has been used to treat the ribavirin-associated anemia in selected pts, but recent heightened concerns about dangerous adverse events from erythropoietin have made this practice questionable. Adverse reactions to interferon are frequent. Flu-like sx after injection are common and are treated with acetaminophen and hydration. Depression, anxiety, and insomnia may require medical therapy. Depression is the most common reason for stopping rx, and it may occur in up to 50% of treated pts (Hepatology 2000;31:1207). Nausea, anorexia, and weight loss are common. Alopecia usually reverses on stopping rx. Neutropenia and thrombocytopenia are detected by routine lab monitoring. Hyperthyroidism or hypothyroidism occurs in about 3% (GE 1992;102:2155), and diabetes is a rare complication.
- *Treatment failures:* About half of pts who relapse after a response to interferon monotherapy will have sustained virologic response to combination rx. Those who do not respond at all to interferon have a very poor response to combination rx (about 8% sustained response) (GE 2000;118:S104). Pts who failed ribavirin and nonpegylated interferon can be offered weight-based ribavirin and pegylated interferon with a 10-20% chance of success. Pts who relapse or don't respond to combination weight-based pegylated rx can be offered rx within a clinical trial, but there are no highly effective regimens currently available (reviewed in (Clin Gastroenterol Hepatol 2009;7:921).
- *Acute hep* C: No precise definition exists for this disorder, which represents a mix of pts detected because of acute sx of liver disease or exposure to pts with hep C. Spontaneous clearance appears common in symptomatic pts (50% at 12 weeks), and the response rate to therapy is high (GE 2003;125:80). Pts without sx are more likely to develop chronic infection. Most experts initiate rx with interferon no later than 2-3 months after infection and treat for at least 24 weeks (GE 2006;130:225).
- *HIV-coinfected pts:* Response rates to combination rx using pegylated interferon α-2a and ribavirin are 40%, which is lower than that seen in pts without HIV infection (Nejm 2004;351:438).
- *Pts with advanced fibrosis or cirrhosis:* A large trial of low-dose maintenance interferon in pts with advanced fibrosis or cirrhosis who did not clear virus with peginterferon and ribavirin did not show benefit (Nejm 2008;359:2429). However, only a small number of pts in the trial had effective viral suppression with the low-dose therapy. It is still unknown if higher dose maintenance therapy to suppress virus would be of benefit. Pts with decompensated cirrhosis are referred for transplant and can be treated by experts with reduced dose rx with careful monitoring.

- *Pts with advanced renal disease:* Dose modification is needed for standard rx. Most pts who have undergone renal transplant are not treated.
- *Transplant:* (Semin Gastrointest Dis 2000;11:96) Hep C is now the leading reason for liver transplantation in the U.S. Infection of the graft is almost universal. Peginterferon with or without ribavirin is used to treat infected pts. Despite the high reinfection rate, survival after transplant is similar to that seen in other chronic liver diseases (Nejm 1996;334:815).
- *Hepatocellular carcinoma:* A sustained virologic response to interferon lowers the risk of HCC (Ann IM 1998;129:94). An RCT showed that rx with interferon reduced the risk of HCC from 38% to 4% in treated cirrhotic pts despite the fact that only 16% of pts cleared virus with rx (Lancet 1995;346:1051). Screening and surveillance for HCC is further discussed on p 247.

11.4 Other Causes of Viral Hepatitis

Hepatitis D (Delta Hepatitis): (Jama 1989;261:1321) The hep D virus is a defective RNA virus that requires HBV to replicate. Hep D infection occurs only in pts who are coinfected with hep B. In the West, the infection is seen largely in pts with risk factors such as iv drug use or hemophilia with multiple transfusions (Hepatology 1985;5:188). With effective prevention of hep B, the incidence of new delta infections in Western countries is dropping (GE 1999;117:161). Pts simultaneously infected with hep B and hep D usually recover without sequelae. More serious illness occurs when pts with chronic hep B become superinfected with hep D, and severe progressive liver disease may result (Jama 1989;261:1321). Hep D infection should be considered in any pt with chronic hep B who develops unexplained jaundice, in pts with prolonged or severe apparent acute infection, and in those being considered for rx for chronic hep B. In cases of superinfection, the majority progress to clinically overt cirrhosis, but a minority have long survival with mild disease (GE 1999;117:161). The dx is made by the detection of anti-hep D ab in pts with evidence of chronic hep B infection. In cases where the infection is rapidly cleared, the antibody response may be late and weak, but in the case of chronic infection, the antibody response is strong (Lancet 1987;1:478). Doses of interferon typically used in hep B are ineffective in hep D (Hepatology 1991;13:1052). Higher doses (9 million U tiw) improve histology and long-term outcome (GE 2004;126:1740). More recently pegylated interferon has been used (Hepatology 2006;44:728). Lamivudine is ineffective (Hepatology 1999;30:546).

Hepatitis E: (Epidemiol Rev 1999;21:162; Gastroenterol Clin North Am 1994;23:537) The hep E virus is an RNA virus of the calicivirus family. The disease occurs in epidemic forms and endemically in developing nations with poor sanitation. The spread is usually through water contaminated with feces. It most commonly affects pts 15 to 40 yr old. There are animal reservoirs, and zoonotic transmission has been documented (Lancet 2003;362:371). The clinical features are similar to those of hep A, and subclinical infection may occur. The dx should be considered in pts returning from endemic areas who develop jaundice without other etiology within the typical 2- to 9-week incubation period. Mortality rate is low (0.5-4.0%), except in pregnant women, who have fatality rates of 10-42% (mean 20%). Hep E can lead to chronic hepatitis in transplant recipients (Nejm 2008;358:811). Immunoassays for anti-hep E ab and PCR techniques are available. Travel to endemic areas during pregnancy seems ill advised. A vaccine is under development (Nejm 2007;356:895).

Hepatitis F: This virus has been described in a handful of cases in France, and its significance is unknown (J Virol 1994;68:7810).

Hepatitis G: (J Clin Gastroenterol 1997;24:62) The hep G virus was originally derived from a pt with community-acquired chronic hepatitis and was later shown to be 95% homologous with another virus called the "G.B." virus. The latter virus was derived from the plasma of a surgeon with initials G.B. and was transmitted to tamarin monkeys. In later years, 3 viruses were isolated from the tamarins, 2 of which were tamarin-derived (called the A and B viruses). The third virus isolated was named hep GB virus-C (HGBV-C). This results in confusing terminology, but the HGV and HGBV-C are the same RNA virus. The virus is found in 1-2% of U.S. blood donors and in much higher frequencies in hemophiliacs, iv drug users, and hemodialysis pts (Nejm 1996;334:1485). It can be transmitted by transfusion or vertically. It is not clear if this virus causes clinical illness. The vast majority of infected pts have no liver disease. The virus may be a causative agent in some cases of viral hepatitis or may simply be an innocent bystander to some other unknown cause of hepatitis (Nejm 1997;336:741; Nejm 1996;334:1536). The virus can only be detected by PCR. No practical serologic test exists.

Epstein-Barr Virus (EBV): Adolescents and young adults infected with EBV may present with sx and si suggestive of acute viral hepatitis, but other clues that lead to the dx of infectious mononucleosis are usually present. Older adults are less likely to have the pharyngitis and lymphadenopathy that suggest the dx. Pts over age 40 yr develop jaundice >25% of the time (Nejm 1999;340:1228). Transaminases and bilirubin are elevated in 90% of pts, but levels are usually only 2-3 times normal. A heterophile ab test is usually positive, but IgM antibodies to EBV capsid antigens are more specific. A severe hepatitis (Am J Gastroenterol 1999;94:236) or FHF (Liver Transpl Surg 1998;4:469) may occur.

Cytomegalovirus (CMV): This agent can cause a hepatitis similar to that of EBV though jaundice is much less common (Medicine 1986;65:124). The dx is made by the CMV-IgM test or by culture of urine and blood.

11.5 Hepatic Schistosomiasis

Lancet 2006;368:1106; Am J Gastro 1991;86:1658

Five species of schistosomes cause human disease, and 200 million people are infected worldwide. Infection occurs by exposure to cercaria released by the freshwater snail host. The cercaria penetrate the skin, develop into worms, and migrate to the mesenteric vessels where eggs are laid and carried to the liver. Liver injury occurs from the inflammatory response to the eggs, and the severity depends on the worm burden and host factors. Pts may have pain, fever, diarrhea, hepatosplenomegaly, or evidence of portal HTN or variceal hemorrhage. The dx should be suspected in any pt from an endemic area (the Middle East, Saudi Arabia, Egypt, Africa, South America [especially Brazil or Venezuela], the Caribbean, the Philippines, and the Far East) who presents with these findings. The dx is made by finding eggs in feces or tissue (especially rectal bx) specimens. Liver involvement may be too patchy to make bx reliable for dx. Low attenuation branching structures (due to periportal fibrosis) may be seen on CT. Praziquantel is the usual rx. Vaccines are not yet available.

11.6 Pyogenic Liver Abscess

Curr Opin Gastroenterol 2000;16:251

Pathophys: For discussion of amebic liver abscess, see p 164. In the preantibiotic era, most liver abscess was caused by pylephlebitis (inflammation or infection of the portal vein or its tributaries) due to intra-abdominal infection. Now biliary tract infection and idiopathic cases are more frequent (Surg Gynecol Obstet 1992;174:97). Endocarditis and trauma can be associated conditions. Common causative organisms include enteric gram-negative organisms (eg, *E. coli, Klebsiella*), group D *Streptococcus*, and *Staphylococcus*. More than half of isolates are polymicrobial and contain anaerobes (J Med Microbiol 1998;47:1075).

Sx/Si: The presentation is usually insidious, with malaise, anorexia, RUQ pain, and fever.

Crs: Mortality is about 10-20% and is usually seen in pts with significant comorbidities such as malignancy (Ann Surg 1990;212:655).

Cmplc: Uncontrolled sepsis, death.

Diff Dx: The disease is usually discovered when the liver is imaged in the investigation of nonspecific abdominal sx.

Lab: Elevations in alk phos occur in >70%, but jaundice is rare in the absence of biliary obstruction. Leukocytosis is common.

X-ray: CT scanning is very sensitive (95-100%), and US is somewhat less so (South Med J 1993;86:1233).

Endoscopy: ERCP/MRCP should be considered in any pt with stones, biliary dilatation, or persistent cholestatic LFTs because of the high frequency of biliary tract disease in this group (Gastrointest Endosc 1999;50:340).

Rx: Broad-spectrum antibiotics covering the range of possible organisms in Pathophys are given pending culture results. Antibiotics are changed based on culture results and continued until CT suggests resolution or a stable appearance (in some cases CT never normalizes and a cyst remains). The mainstay of rx is percutaneous drainage (though some pts may be cured with antibiotics alone [GE 1979;77:618]). Catheter drainage is more effective than simple aspiration (by RCT [Am J Roentgenol 1998;170:1035]). Surgical rx is indicated when percutaneous methods fail or are not possible due to multiple or multiloculated abscesses.

Chapter 12

Metabolic and Inflammatory Liver Disease

12.1 Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Hepatology 2009;49:306; Nejm 2002;346:1221

Epidem: The prevalence of nonalcoholic fatty liver disease (NAFLD) is estimated between 10% and 24%. NAFLD is a spectrum of disease ranging from simple steatosis, to steatohepatitis, to advanced fibrosis and cirrhosis in the absence of substantial alcohol intake. Nonalcoholic steatohepatitis (NASH) is part of the spectrum of NAFLD that is found in 3% of lean pts and up to 20% of obese pts in Western countries. Obesity (especially central obesity), diabetes, and hyperlipidemia are commonly associated. However, the disease is not limited to pts with these risk factors. A picture of steatosis with or without inflammation and fibrosis can be seen with starvation, TPN use, rapid weight loss, bariatric surgery, inherited metabolic defects, and a variety of drugs. These secondary causes of fatty liver disease all have unique clinical characteristics that are not further discussed here.

Pathophys: NASH is diagnosed when 3 criteria are met: (1) a liver bx shows macrovesicular fatty change and lobular or portal inflammation, with or without fibrosis; (2) there is convincing evidence of <40 gm per week of alcohol use (about 4 drinks per week, see p 250); and (3) there is no evidence of active infection with hep B or C or a secondary cause of steatosis (Hepatology 1990;11:74). Fatty liver (simple steatosis) is diagnosed when there is fatty change without inflammation or fibrosis. The pathogenesis of NAFLD is unknown. The accumulation of lipids in hepatocytes in association with insulin resistance appears to be an important first step. The progression from simple steatosis to steatosis with inflammation and fibrosis may be the result of oxidative stress on hepatocytes. Hepatic stellate cell activation, the inflammatory response, genetics, and other environmental factors have been identified as important factors in disease development (Curr Opin Gastroenterol 2009;25:230).

Sx: Most pts have no sx, but some may have fatigue or RUQ discomfort.

Si: Hepatomegaly is common. A minority present with signs of advanced liver disease (p 26).

Cmplc: Any of the complications of end-stage liver disease may occur (p 255).

Crs: The course of pts with NAFLD is not well understood. Simple steatosis without fibrosis or inflammation typically has a benign course. Pts with NASH have an increased risk of death due to heart disease and liver disease. In a large series, 5% of pts with NASH at initial bx had progression to end-stage liver disease, including HCC at a median of 13.7 yr of follow-up (Hepatology 2006;44:865). In this series about 40% of pts had progression of their degree of fibrosis in follow-up. Since there is a higher than expected proportion of obese, diabetic pts with apparent cryptogenic cirrhosis, it has been postulated that NASH is an unrecognized cause of cryptogenic cirrhosis (Hepatology 1999;29:664).

Diff Dx: NASH is a consideration in pts with abnormal LFTs. The abnormal LFTs are usually found in the process of evaluating other medical problems. Other causes of abnormal LFTs and cirrhosis must be excluded (p 28). The most difficult differential point is that of alcoholic liver disease. A dx of NAFLD can only be made with liver bx. However, given the indolent nature of NAFLD and its lack of proven rx, many physicians forgo bx. It is assumed that pts with an unrevealing evaluation for other causes of abnormal LFTs have either simple steatosis (without inflammation) or NASH. Effective rx for NASH would make the distinction between simple steatosis and NASH more important.

Lab: ALT is usually greater than AST, and both are up to 2-3 × the normal values. NASH can be seen with normal transaminases. Alk phos is often mildly elevated. Bilirubin and PT are usually normal unless there is cirrhosis. Ferritin is elevated in more than half of pts but is generally <1000 ng/mL (GE 1994;107:1103). A variety of histopathologic changes have been described. Steatosis is seen mostly in zone 3 of the liver. Inflammation is usually mild and in the lobules without severe portal changes. Degenerating hepatocytes are present, and Mallory hyalin may be seen (as in alcoholic hepatitis). Fibrosis begins in sinusoids and may progress to cirrhosis. Predictors of fibrosis include age ≥50 yr, body mass index ≥28 kg/m^2, triglycerides ≥151 mg/dL, and ALT ≥2 × normal (GE 2000;118:1117). A variety of serum biomarkers to predict fibrosis, oxidative stress, and inflammation have been investigated, but no reliable method can be recommended for widespread use (Hepatology 2009;49:306).

X-ray: US may show increased echogenicity consistent with fat. CT or MRI may show evidence of fatty change. No study is adequately sensitive or specific for NASH.

Rx: (Hepatology 2009;49:306) Since NASH is associated with an increased risk of heart disease, it makes sense to emphasize the need to modify cardiac risk factors. Statins appear safe for treating hyperlipidemia in compensated liver disease (GE 2008;135:702). No safe, well-proven, and effective drug rx for NAFLD/NASH has been identified. Gradual weight loss and exercise have been advocated and appear to result in histologic and biochemical improvement (Hepatology 2004;39:1647). However, large well-conducted studies are lacking (Am J Med 2003;115:554), and weight loss is difficult to achieve. A reasonable recommendation would be to advise weight loss of 7-10% of body weight over 6-12 months using a balanced diet low in high-glycemic foods, low in saturated fat, and rich in fruits and vegetables. Moderate aerobic exercise of 30-45 min daily, 5-7 times weekly is appropriate. Bariatric surgery improves steatosis, fibrosis, and inflammation in the majority of pts who undergo this drastic intervention (Clin Gastroenterol Hepatol 2008;6:1396). A pilot study of ursodeoxycholic acid showed biochemical and histologic improvement at 1 yr (Hepatology 1996;23:1464), but a subsequent RCT showed no benefit (Hepatology 2004;39:770). Vitamin E has been used because of its antioxidant properties without

convincing evidence of benefit (Am J Gastro 2003;98:2348). Since the disease is associated with insulin resistance, attention has recently been on the use of insulin sensitizing drugs. Metformin may be helpful but the data are not convincing (Cochrane Database Syst Rev 2007;CD005166). The thiazolidinediones (eg, pioglitazone, rosiglitazone) may be somewhat beneficial (GE 2008;135:100; Nejm 2006;355:2297), but concerns about safety and efficacy will need to be settled by large trials. Transplant has been used effectively to treat end-stage disease, though recurrence in the transplant is a risk (Transplantation 1996;62:1802). Screening and surveillance for HCC in cirrhotic pts is discussed on p 247.

12.2 Primary Biliary Cirrhosis

Hepatology 2009;50:291; Am J Gastro 2001;96:3152

Epidem: There is a striking predominance in women (90%). Prevalence ranges from 5-392/1,000,000 (Semin Liver Dis 1997;17:13). Familial PBC is uncommon (1%) and seems to be related to maternally inherited factors (Gut 1995;36:615).

Pathophys: PBC is a destructive disease of small, interlobular bile ducts. It is an autoimmune disease. Almost all pts have antimitochondrial antibodies (AMAs). AMAs are directed against antigens on bile duct epithelial cells with similar antigenicity to the E2 subunit of pyruvate dehydrogenase (J Clin Invest 1993;91:2653). Immune destruction of bile ducts may be mediated in this way. A variety of infectious agents, including retroviruses, have been implicated as inciting antigenic stimuli in susceptible individuals (Am J Gastro 2004;99:2348). As bile ducts are destroyed, concentrations of hydrophobic bile acids and other hepatocellular toxins rise and cause further destruction. This causes recruitment of inflammatory cells, which produce cytokines that may promote fibrosis (Can J Gastroenterol 2000;14:43).

Sx: (Semin Liver Dis 1997;17:23) More than 60% of pts are asymptomatic at dx. Fatigue occurs in more than 60% of symptomatic pts and is a frustrating problem of unknown cause. Pruritus is the second most common sx and can be severe. Some pts will have RUQ pain that usually disappears in time. A minority will present with a complication of end-stage liver disease such as varices or ascites. Many pts have at least 1 other autoimmune disease such as thyroiditis, scleroderma, rheumatoid arthritis, the CREST syndrome, or Sjögren's syndrome.

Si: (Can J Gastroenterol 2000;14:43) Findings vary with the stage of disease. In early disease, excoriations may be seen. Hepatomegaly is common (70%) and splenomegaly develops in about 35%. Jaundice, spider angiomata, and ascites are late manifestations. Xanthomas commonly occur around the eyes (xanthelasma) and less commonly occur on extremities. They disappear as disease progresses.

Crs: The rate of progression varies markedly among pts. UDCA rx has changed the natural history. In the pre-UDCA era, the 10-yr survival for asymptomatic pts was 50-70% and the median survival of symptomatic pts was 5-8 yr. Using a Markov model for 262 pts treated with UDCA, the 10-yr survival was 85% and the 20-yr survival was 66%. When the subgroups with stage 1 and 2 disease were examined, the 10-yr and 20-yr transplant-free survivals were 94% and 78%, respectively (similar to the control population) (GE 2005;128:297). Pts with AMA-negative PBC appear to have a course similar to AMA-positive pts (Hepatology 1997;25:1090).

Cmplc: Osteoporosis is the most common bone disorder. Steatorrhea and fat-soluble vitamin deficiency can be seen in advanced disease. Hypothyroidism is seen in 20% of pts. Rheumatoid arthritis (10%), scleroderma (4%), CREST syndrome, and SLE have been reported (Q J Med 1996;89:5). Up to 68% of pts have xerostomia or xerophthalmia and may have dysphagia (Dysphagia 1997;12:167). Any of the complications of end-stage liver disease may occur (p 255). Hepatobiliary malignancy is more common in PBC (RR = 46 in one referral series [Hepatology 1999;29:1396]), but malignancy is not as frequent as in other causes of cirrhosis (Am J Gastroenterol 1997;92:676). Varices are seen earlier in the course of PBC than with other liver diseases, because the portal HTN is partially presinusoidal and synthetic function may be relatively well preserved.

Diff Dx: PBC is usually considered in the evaluation of an asymptomatic pt with elevated alk phos or when a pt presents with evidence of chronic liver disease such as ascites or bleeding from varices. Some cases of PBC are detected because of autoantibody testing done for other reasons in pts with normal LFTs. This group often evolves into typical PBC (Lancet 1996;348:1399). The diff dx generally includes the other causes of abnormal LFTs or cirrhosis (p 28). The chief points of confusion are sclerosing cholangitis (p 233), which produces similar LFT abnormalities, drug-induced cholestasis, sarcoidosis, and autoimmune hepatitis. When the liver bx shows bile duct lesions suggestive of PBC, but the AMA is negative and the ANA and ASMA are positive, it is difficult to confidently make a dx. These pts are said by some experts to have an overlap syndrome called autoimmune cholangitis that may respond to steroids like autoimmune hepatitis (Gut 1997;40:440). Autoimmune hepatitis can follow an initial dx of PBC. To make a dx of PBC, biliary obstruction must be excluded with imaging studies, especially if the AMA is negative.

Lab: AMA is 95% sensitive and 98% specific for PBC. AMAs are directed against a family of dehydrogenase enzymes, chiefly pyruvate dehydrogenase (Semin Liver Dis 1997;17:61). The major autoantigen, located on the inner mitochondrial membrane, is the E2 component of pyruvate dehydrogenase (J Hepatol 1986;2:123). Levels do not correlate with disease severity. Elevation of alk phos is the most notable laboratory abnormality in early-stage disease. The GGTP and 5'NT are elevated in a parallel fashion. ALT/AST are usually $<5 \times$ normal. Bilirubin and PT become elevated as disease progresses. Most pts have elevated cholesterol. Since the elevation is in the HDL fraction of cholesterol, the risk for heart disease is low (Hepatology 1992;15:858). ANA and antithyroid antibodies are common. Many other autoantibodies have been reported. Elevations of IgM and polyclonal IgG are seen.

Four pathologic stages are recognized on **liver bx**. In stage I, inflammatory cells surround a bile duct with evidence of duct epithelial degeneration. In some cases a frankly necrotic duct can be seen in a granuloma (the florid duct lesion). In stage II, fibrosis develops in the portal zones, and inflammation extends into the lobules. In stage III, fibrosis joins portal triads. Stage IV shows established cirrhosis.

X-ray: Obstruction of the bile ducts should be excluded with US or CT scan. ERCP/MRCP would be reserved for cases in which PSC (p 233) was a serious consideration.

Endoscopy: Endoscopy should be performed in pts with advanced disease to identify and treat varices (p 255).

Rx:

- *Ursodeoxycholic acid*: UDCA has been evaluated in 4 RCTs (Hepatology 1995;22:759; Nejm 1994;330:1342; GE 1994;106:1284; Hepatology 1994;19:1149). A dose of 13-15 mg/kg per day is used and is usually well tolerated. There is improvement in LFTs and in pruritus for some pts. In the trial with 4-yr follow-up, the RR for death or transplant was 0.32 in the treated group (Nejm 1994;330:1342). Increasing the dose to 28-32 mg/kg/day in those with an incomplete response to standard-dose rx does not appear beneficial (Am J Gastro 2001;96:3152). The drug does not improve the course of advanced disease. Pts taking colestipol or cholestyramine for itch should take their UDCA 2-4 hr before or after the bile acid sequestrant.
- *Other medical rx*: Cyclosporine showed no convincing survival advantage compared to placebo and caused worsening of renal function in an RCT (GE 1993;104:519). Colchicine is of no benefit (by meta-analysis) (Am J Gastro 2005;100:1876). Methotrexate (MTX) improves LFTs, pruritus, and histology (GE 1991;101:1332), but the only randomized placebo-controlled trial using a low dose (7.5 mg/wk) showed no benefit (GE 1999;117:400).
- *Liver transplant*: Transplant is highly effective rx (Semin Liver Dis 1997;17:137). One-yr survival is 85-90% and long-term survival is similar to that of age-matched controls. Histologic recurrence has been well documented, but recurrent disease is not rapidly progressive (Hepatology 1993;18:1392).
- *Pruritus*: Most pts have a response to cholestyramine (typically 4 gm po tid) or colestipol. Rifampin 150-300 mg po bid is an effective second-line agent (Am J Gastro 2007;102:1528), but hepatitis, hemolysis, renal failure, drug interactions, and other side effects require cautious use. Naltrexone 50 mg daily is effective but can be associated with an opoid-withdrawal reaction. Sertraline 75-100 mg po daily or antihistamines can be tried.
- *Osteoporosis*: Pts should be screened for osteoporosis and treated with calcium (1500 mg/day) and vitamin D (1000 U/day). Alendronate 70 mg weekly is indicated in osteopenic and osteoporotic pts (Hepatology 2005;42:762; Am J Gastro 2003;98:2268). Estrogen replacement in postmenopausal pts improves bone density (Am J Gastro 1994;89:47), but it is seldom used because of safety concerns. Transplant appears to reverse bone loss after the first few months of steroids and bed rest, which may worsen it (Hepatology 1991;14:296).
- *Other measures*: Pts should be advised not to smoke or drink alcohol. LFTs are followed at 3- to 6-month intervals. Thyroid status is monitored annually. Bone density is measured q 2-4 yr. Fat-soluble vitamin levels should be measured annually in pts with jaundice. Cirrhotics should be screened for varices (p 255) and HCC (p 247).

12.3 Primary Sclerosing Cholangitis

Curr Opin Gastroenterol 2008;24:377; Am J Gastro 2002;97:528

Epidem: About 70% of pts with primary sclerosing cholangitis (PSC) are men. About 75% of pts have IBD. The majority of the IBD pts have UC (85%), but some have Crohn's. The estimated prevalence is 1-15/100,000 with wide geographic variation (Scand J Gastroenterol 1998;33:99).

Pathophys: PSC is characterized by inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts. PSC is defined by the presence of bile duct strictures on cholangiography, by cholestatic LFT abnormalities, and by the absence of diseases that could give a similar picture (see Diff Dx). Immune mechanisms are thought to be important in the pathogenesis, especially since the disease is associated with IBD, autoantibodies and immunoglobulin elevations are present, and inflammation is T-cell mediated. Infectious and toxic etiologies have been considered and rejected. Though PSC causes obliteration of larger bile ducts than PBC, the end result is the same: cholestasis that causes progressive parenchymal destruction.

Sx: Most pts come to dx because of abnormal LFTs, sometimes detected in evaluation of their associated IBD. These pts are usually asymptomatic. Fatigue, pruritus, jaundice, night sweats, and weight loss may occur as disease progresses. An important minority of pts experience attacks of fever, RUQ pain, and worsened LFTs in a picture that mimics bacterial cholangitis.

Si: In early disease, the exam is normal. As disease progresses, jaundice, excoriation from intractable pruritus, and other findings of end-stage liver disease may be evident (p 26).

Crs: The course of PSC is independent of the course of the associated IBD. A 10-yr survival of 70% was seen in a population-based study, and median transplant-free survival appears to be about 9-12 yr (Scand J Gastroenterol 1997;32:1042). Some pts have a rapid downhill course and others go for years without any morbidity. Prognostic models have been developed to help predict the timing of liver transplant (Mayo Clin Proc 2000;75:688; GE 1992;103:1893).

Cmplc: Cholangiocarcinoma (p 207) is seen in 10-20% of pts with PSC (Hepatology 1998;27:311). Seven percent of pts undergoing transplant have cholangiocarcinoma found in the explanted liver. It can be difficult to differentiate benign from malignant strictures. The CA 19-9 may be elevated (Mayo Clin Proc 1993;68:874), but there is no evidence that this marker allows detection at a resectable stage. Early transplant is probably the best option (Hepatology 1996;23:1105). Preliminary data suggest that PET scanning may be superior to other imaging tests for cholangiocarcinoma detection (Hepatology 2006;44:1572). Even small gallbladder polyps may be malignant in PSC pts (p 210). Some data suggest that pts with PSC and UC have a greater chance of colonic dysplasia and CRC than pts with UC alone. However, the data are not adequate to justify more intense colonic surveillance for those with PSC and UC (Hepatology 1999;30:325). Osteoporosis occurs in 8% of pts with PSC compared to 30% with PBC. Osteoporosis is more likely in severe disease or with long-standing IBD (J Hepatol 1998;29:729). Any of the complications of end-stage liver disease may occur (p 255).

Diff Dx: The disease is suspected when a cholestatic pattern of LFTs is seen, especially in a pt with IBD. Cholangiography is the key to dx. Several rare disorders cause a similar cholangiogram. These include HIV cholangiopathy (p 212 bile duct stricture from stones, surgery, ischemic cholangitis (Mayo Clin Proc 1998;73:380), malignancy, intraarterial chemotherapy, the biliary strictures of autoimmune pancreatitis (p 193), or congenital abnormalities. The more limited the cholangiographic abnormality, the more likely an alternative dx is present. Rarely, a pt will have LFT abnormalities suggestive of PSC, a liver bx with changes of PSC, and normal cholangiography. These pts are said to have small duct PSC (Semin Liver Dis 1991;11:11).

Lab: The alk phos is usually disproportionately elevated and rises as disease progresses. GGTP and 5'NT are similarly elevated. Bilirubin rises as disease advances. ALT/AST are usually less than 7 × normal. With advanced disease, albumin falls and PT rises. IgM levels are modestly elevated in half of pts. Perinuclear-ANCA, ANA, and ASMA may be present. AMA is absent. **Liver bx** can be nonspecific; the dx relies on cholangiography. Bx can provide information about staging, but sampling error is substantial (Am J Gastro 1999;94:3310). The staging is similar to that of PBC. In stage I there is degeneration of bile duct epithelium with an infiltrate of lymphocytes and scarring in the portal triads. Bile ducts may proliferate, and rarely the pathognomonic "onion skin" lesion of concentric rings of fibrous tissue around a bile duct can be seen. In stage II, loss of bile ducts is more prominent and inflammation and scarring expand into the parenchyma. In stage III, fibrosis from portal zone to portal zone is seen. In stage IV, there is frank cirrhosis.

Endoscopy: ERCP can be necessary to obtain the quality of cholangiogram needed for the dx, though the use of MRCP as the initial diagnostic test is growing because it is safer. At cholangiography there are multiple strictures and dilatations of varying lengths. Outpouchings and ectatic ducts are seen. Often this results in a beaded appearance of the bile duct. In early disease, there may be subtle changes in large ducts. In severe disease, the intrahepatic ducts may be impossible to visualize because of strictures. Usually the intrahepatic and extrahepatic trees are involved. When only the extrahepatic ducts are abnormal, other diagnoses (other causes of stricture) should be strongly considered.

Rx:

- *Medical rx of underlying disease*: There is no known effective medical rx for PSC. UDCA in a dose of 13-15 mg/kg improves biochemistries but has no convincing effect on transplant-free survival. A 5-yr study of high-dose UDCA (17-23 mg/kg) showed no measurable benefit, though the study was somewhat underpowered to detect a small survival advantage (GE 2005;129:1464). Despite these data, UDCA is still commonly used. UDCA appears to lower colorectal neoplasia risk in pts with PSC and UC (GE 2003;124:889). Methotrexate, azathioprine, colchicine, antibiotics, cyclosporine, nicotine, pentoxifylline, and prednisone are all ineffective for treating PSC. The possible use of tacrolimus and silymarin is being investigated (Curr Opin Gastroenterol 2008;24:377).
- *Rx of strictures*: Some pts develop worsening LFTs or cholangitis because of a dominant stricture in the extrahepatic bile ducts. This can be treated with dilatation and short-duration stenting, with improvement in LFTs and sx. There is no need for further intervention in more than 80% of pts at 1 yr and 60% at 3 yr (Am J Gastro 1999;94:2403). Bile duct perforation can occur with dilatation. For some pts, this may buy time prior to transplant, but the true effect on natural hx is unknown. A variety of other endoscopic approaches to strictures can be used (Am J Gastro 1999;94:2235). Surgical rx of strictures is rarely used. Surgery makes later transplant more difficult, and most cirrhotics are better served with transplant (Surgery 1995;117:146).
- *Rx of pruritus and osteoporosis*: Pruritis is treated as it is in PBC (p 233). Steatorrhea is a late finding. It may be associated with fat-soluble vitamin deficiency and replacement rx may be needed. Osteoporosis is treated as in PBC though data are lacking (p 233).
- *Attacks of cholangitis*: There is very little published on the use of antibiotics in attacks of RUQ pain and fever. However, antibiotics are widely used at the first sign of an attack

and appear to be helpful. Common choices are ciprofloxacin, amoxicillin-clavulanate, and Tm/S, which pts keep on hand and take at the outset of an attack. If attacks are frequent, some pts stay on prophylactic antibiotics in 3- to 4-week rotations (eg, rotating ciprofloxacin, Tm/S, cephalexin, amoxicillin-clavulanate) (Hepatology 1999;30:325). IV rx is used in severe illness and occasionally in prolonged courses.

- *Liver transplant:* This is the only effective rx for pts with end-stage disease who may develop refractory episodes of cholangitis or complications of portal HTN, including variceal hemorrhage and ascites. Survivals are as high at 94% at 1 yr and 86% at 5 yr (Hepatology 1999;30:1121). The optimal timing of transplant (given the scarcity of organs and the resources needed) has not been determined. Quality of life, the presence of complications such as variceal hemorrhage, and the risk of cholangiocarcinoma if transplant is excessively delayed (Hepatology 1996;23:1105) are important factors. Transplant rejection is more common in PSC than in other diseases posttransplant, and CRC is a major cause of death (Hepatology 1995;22:451). Recurrence may occur in up to 20% of pts but does not appear to affect survival (Hepatology 1999;29:1050). CRC is an important postoperative problem, but prophylactic colectomy does not appear to be warranted (Hepatology 1998;27:685).

12.4 Autoimmune Hepatitis

Nejm 2006;354:54; Hepatology 2002;36:479; Scand J Gastroenterol Suppl 1998;225:66

Cause: Autoimmunity.

Epidem: Typically autoimmune hepatitis (AIH) is a disease of women aged 15-40 yr, but type I disease may occur in pts of either sex at any age. Type II is almost exclusively a disease of young women.

Pathophys: There is a defect in T-cell suppression of antibody-producing B cells in autoimmune hepatitis. A genetic predisposition is suggested by the association with HLA loci B8, DR3, and DR4. It is thought that an environmental event, such as viral hepatitis, triggers B-cell responses to hepatic surface antigens in a genetically predisposed pt. Antibody-coated cells are then cleared by natural killer cells, exposing more autoantigens. The defective T-suppressor cells fail to turn down the antibody response and the process continues. This results in hepatocyte destruction, and ultimately cirrhosis. The circulating autoantibodies are markers of disease and do not affect the pathogenesis.

The disease has been classified according to the autoantibodies produced (Am J Gastro 1995;90:1206). In type I (classic) autoimmune hepatitis, there are found antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), perinuclear antineutrophil cytoplasmic antibodies (pANCA), and asialoglycoprotein antibodies (ASGPR). Tests for ASGPR are not readily available. The ASMA represent a group of antibodies of which the f-actin antibody is more specific to autoimmune hepatitis. A commercial ELISA is available for f-actin and appears to have superior sensitivity with no loss of specificity for the dx of autoimmune hepatitis (Am J Gastro 2006;101:2731). ASGPR may be of special interest since it is liver specific and may not be an epiphenomenon. In type II (representing less than 5% of the total), there are antibodies to liver-kidney microsome 1 (anti-LKM-1) and antiliver cytosol antibodies.

Sx: Many pts are asymptomatic and come to attention because of abnormal LFTs. Others have nonspecific sx of fatigue, anorexia, abdominal pain, nausea, and arthralgias. Other present with jaundice or complications of end-stage liver disease (p 255).

Si: The exam findings range from normal to the findings of cirrhosis and portal HTN (p 26).

Crs: Most pts respond to rx and do well. Even pts with established cirrhosis have a 10-yr survival of 90% (GE 1996;110:848). Fibrosis and cirrhosis may be reversible in some pts who respond to rx (Ann IM 1997;127:981). Most pts require long-term or intermittent medical rx.

Cmplc: A variety of concurrent autoimmune diseases have been described, including thyroid disease, ITP, celiac disease, Sjögren's, mixed connective tissue disease, and others (Postgrad Med 1998;104:145). There is an increased risk of HCC (p 247). Any of the complications of end-stage liver disease may occur (p 255).

Diff Dx: The dx of AIH is established by the combination of abnormal transaminases, elevated globulins (>1.5 × normal), positive titers of one of the autoantibodies listed in Pathophys (usually at >1:80), a compatible bx, and the absence of another cause of abnormal LFTs (p 26) or cirrhosis (p 30). Formal diagnostic criteria have been developed (Hepatology 2008;48:1540). Variants of typical AIH have been noted (Ann IM 1996;125:588). In the overlap syndrome, the serology is that of PBC, but the bx looks more like autoimmune hepatitis and the pts respond to steroids. In autoimmune cholangitis, the bx looks more like PBC, but the AMA is negative and the ANA and f-actin are positive, and the response to steroids is more variable. Another troublesome group are those pts with cryptogenic chronic active hepatitis who are clinically similar to those with AIH, lack any autoantibodies, but respond to steroids (GE 1993;104:1755).

Lab: Titers of autoantibodies are usually >1:80. ANA and f-actin ab are usually obtained, and pANCA is another commercially available marker. Tests are not readily available for all of the remaining markers but can be found in specialized labs. LFTs are notable for elevated transaminases with generally mild elevations in alk phos, but a cholestatic picture may emerge in jaundiced pts. In advanced disease, PT may be abnormal. Elevations in gamma globulins are characteristic and may be a clue to AIH in pts with negative tests for available markers.

Liver Bx: Bx is used to stage the disease and to support the dx but is often nonspecific. A portal infiltrate of mononuclear cells spills from the portal zones across the limiting plate of hepatocytes and into the lobule, where it causes hepatocyte necrosis. This process had been called "piecemeal necrosis," but has been recently renamed "interface hepatitis." Fibrosis of varying degrees is present.

Endoscopy: EGD should be considered to look for varices in cirrhotic pts (p 255).

Rx: Rx with prednisone is highly effective, even in severe disease. The response rate is >80%. Depending on the severity of illness (and the preference of the treating physician), pts are treated with an initial dose of 20-60 mg po qd. Biochemical remission, marked by improvement in bilirubin, ALT, AST, and immunoglobulins, occurs within 1-3 months, and steroids are then tapered. Maintenance rx is required in most pts. To minimize the prednisone requirement, azathioprine in a dose of 50-150 mg is used either at the outset or as prednisone is tapered (see p 109 about azathioprine use). Azathioprine as a single maintenance agent is effective in 80% of pts when used at a dose of 2 mg/kg (Nejm

1995;333:958). Low-dose prednisone, keeping the transaminases under 5 × normal, has been advocated to minimize steroid side effects, but the approach has not been adequately studied (Hepatology 1990;11:1044). About 10-20% of pts are either not steroid responsive or intolerant of therapy. Budesonide, as an alternative to prednisone, has been used in small series (Can J Gastro 2008;22:388). There is growing experience with mycophenolate mofetil in these pts (Clin Gastroenterol Hepatol 2007;5:799; Clin Gastroenterol Hepatol 2008;6:1036). Tacrolimus has some efficacy (J Clin Gastro 2004;38:805; Am J Gastro 1995;90:771), but controlled studies are lacking. Cyclosporine (Am J Gastro 1999; 94:241) has been used in small numbers of pts. UDCA is not helpful (Hepatology 1999;30:1381). Transplant is effective, but rejection (75%) and disease recurrence (25%) are frequent. The optimal immune suppression regimen for transplant recipients has not been determined (Hepatology 2000;32:693).

12.5 Hemochromatosis

Nejm 2004;350:2383; Semin Hematol 1998;35:55

Cause: This section reviews hereditary hemochromatosis (HH), which is also called genetic or Type 1 hemochromatosis. This disorder is secondary to phenotypic expression of a mutation in the HFE gene. Juvenile hemochromatosis (a severe early onset form now called Type 2 hemochromatosis) and other rare genetic iron overload syndromes (Types 3-5) are not further discussed (reviewed in Nejm 2004;350:2383). Secondary iron overload (eg, from transfusions) is not further discussed.

Epidem: The HFE gene (see Pathophys) is found in 3-8/1000 subjects of European descent. Heterozygotes are found in 10-16% of the population. This disease does not occur in subjects without Caucasian ancestry. The Cys282Tyr mutation (see Pathophys) is most frequent in populations of Celtic or Viking origin, and the His63Asp mutation has a more global distribution. Because clinical disease does not occur in all homozygotes, the rate of clinically evident HH is roughly estimated to be 0.5-2.5/1000 in males. Phenotypic disease is 4 × more frequent in men.

Pathophys: (Lancet 2002;360:1673) The gene responsible for more than 85% of the cases of HH has been identified and is called HFE (Nat Genet 1996;13:399). It encodes an HLA-like molecule. Two important mutations have been described. Cys282Tyr is the substitution of tyrosine for cysteine at amino acid 282. His63Asp is the substitution of aspartic acid for histidine at amino acid 63. In northern Europe more than 80% of affected pedigrees have 1 of these mutations. Most pts with HH are homozygous for Cys282Tyr, and a few (4%) are compound heterozygotes with 1 Cys282Tyr mutation and 1 His63Asp mutation. Compound heterozygotes are much less likely to develop phenotypic disease. Homozygous mutation of His63Asp rarely results in iron overload.

Dietary iron overload is not the primary defect, though clinical expression is rare in areas where there is a grain-based (not meat-based) diet. Pts with HH appear to have enhanced iron absorption. The exact mechanism of enhanced iron absorption is not well understood but may be related to defects in the regulation of hepcidin, a protein that appears to regulate the release of iron from enterocytes and macrophages into the bloodstream. Pregnancy and menses increase iron loss in women and are partially protective.

Sx: In a large cohort collected over decades, weakness/lethargy (85%), abdominal pain (60%), arthralgias (50%), and loss of libido (40%) were the most common sx (GE 1996;110:1107). As more and more pts are diagnosed at early stages, a greater proportion will be asymptomatic. A large pt survey indicated an average of 10-yr delay between sx and dx (Am J Med 1999;106:619). Currently, the most common presenting sx is arthritis.

Clinical sx are the result of iron overload in different organ systems. Jaundice, ascites, and encephalopathy are late findings. A sudden worsening of hepatic sx should raise the question of HCC. Arthropathy is a frequent problem (40-75%) and may be a presenting complaint. It resembles DJD and progresses despite phlebotomy. A metallic or bronze hue of the skin may be present in advanced disease. Diabetes due to iron overload occurs in 30-60% of pts with advanced disease. Exocrine insufficiency is rare. Loss of libido, impotence, amenorrhea, and sparse body hair are due to iron overload effects on the pituitary. A dilated cardiomyopathy is present in 20-30% of pts with symptomatic disease, and arrhythmias may occur.

Si: Hepatomegaly is common in pts with clinical sx. Ascites is not common and may indicate heart failure. Any of the findings of advanced liver disease may be seen (p 26). Testicular atrophy and sparse body hair represent hypogonadism. Joints may show bony deformity and loss of motion, especially in the metacarpal phalangeal and proximal interphalangeal joints.

Crs: Life expectancy is normal in treated pts who do not present with cirrhosis (GE 1996;110:1107). In pts who are cirrhotic but undergo rx, survival is 80% at 10 yr. Portal HTN in HH does not result in as many complications as it does in other liver diseases (Hepatology 1995;22:1127). Pts treated with phlebotomy are said to feel better, have decreased hepatomegaly, normalize LFTs, and require less insulin. The arthropathy and hypogonadism do not improve dramatically with phlebotomy. Analysis of death certificates suggests a vast underreporting of hemochromatosis. There is excessive occurrence of liver neoplasms (23-fold) and cardiomyopathy (5-fold) as causes of death in HH pts (Ann IM 1998;129:946).

Cmplc: Hepatocellular carcinoma (HCC) occurs with a RR of 200 in cirrhotic pts and ultimately occurs in 30% of these pts. *Vibrio vulnificus* infection (from warm water shellfish) is more likely to cause severe illness in hemochromatosis because of iron needed for microbial metabolism (Arch IM 1991;151:1606). Any of the complications of end-stage liver disease may occur (p 255).

Diff Dx: HH is often considered in the differential of asymptomatic abnormal LFTs and cirrhosis (p 30). Alcoholic hepatitis can mimic hemochromatosis because transferrin saturation can be very high with the release of iron from dying hepatocytes. In addition, elevations of ferritin are common in alcoholic liver disease because ferritin is an acute phase reactant. Repeat iron studies should be done after 2-3 months of sobriety. Alcoholic cirrhosis is distinguishable from HH by bx with iron index determination (see Lab). A negative gene test does not rule out HH. Heterozygotes for HFE cause confusion because they tend to have higher than average transferrin saturations. Hepatic iron index and gene testing will clarify the dx. There are numerous other causes of iron overload, including those associated with multiple transfusions, other generic abnormalities (see Cause), iron-loading anemias, and African iron overload, but these are generally not diagnostic pitfalls (Ann IM 1998;129:925).

Lab: (Ann IM 1998;129:925) Transferrin saturation (the ratio of Fe/TIBC multiplied by 100) is usually elevated but can be normal in young homozygous pts. Levels of >45% are investigated in a screening situation and screening detects 98% of affected individuals. If a pt has a transferrin

saturation >45%, the test should be repeated after fasting, and a ferritin test should be done. If ferritin is normal, the tests should be repeated 2-3 yr later so that early HH is not missed. Ferritin reflects total body iron stores and is usually >>1000 mg/mL in symptomatic disease. In a screening situation, HH is likely if ferritin is >300 mg/mL in a man, >200 mg/mL in a woman, or if transferrin saturation is >55% on repeat testing. False-positive elevations of ferritin (which is an acute phase reactant) occur with inflammation, infection, or malignancy. LFTs can be normal even in cirrhosis normal. Therefore normal LFTs do not rule out the dx of HH.

- *Liver bx*: Early findings include hemosiderin granules in periportal hepatocytes, which involves other hepatocytes as disease progresses. Fibrosis results in a micronodular (or mixed micronodular and macronodular) cirrhosis. Iron stores can be estimated from iron stains, but iron content is better measured directly on bx specimens by atomic absorption techniques. The iron content is best expressed as the hepatic iron index and is equal to micromole iron/gm dry weight/age in yr. This is useful in distinguishing alcoholic iron overload from that of HH (GE 1997;113:1270; Hepatology 1986;6:24). Most clinicians advise liver bx to confirm the dx and to stage the disease, since a bx without cirrhosis means a normal life expectancy and no increased risk of HCC. Pts who are homozygous, have no hepatomegaly, have normal LFTs, and have ferritin <1000 mg/mL can be treated without bx. In this group, the chance of fibrosis is very low (GE 1999;116:193; GE 1998;115:929).
- *Gene testing*: Gene testing is a simple means of confirming the dx and allows for family screening. Most pts will be homozygous for Cys282Tyr. A few pts will be compound heterozygous, and up to 17% will be normal (GE 1999;116:193). False-negative rates in gene testing may be higher in some populations, such as Hispanics and Italians (GE 1998;114:996).
- *Family testing*: If probands are positive on gene tests, family members can obtain accurate information about their status (normal, heterozygous, or homozygous) through gene testing. Family members found to be homozygous are followed by periodic determinations of transferrin saturation and ferritin for evidence of phenotypic disease. Siblings have the highest yield in testing. Children should be screened since homozygote/heterozygote matings are common. One sensible strategy for probands with more than 1 child is to gene test the other parent (assuming parentage is well known) and to test the children only if the other parent is heterozygous (Ann IM 2000;132:261).
- *Population screening*: Early studies had suggested that population screening with transferrin saturation is cost effective (GE 1994;107:453; Arch IM 1994;154:769). However, later synthesis of the data in the ACP guideline of 2005 led to the conclusion that there was insufficient evidence for or against population screening (Ann IM 2005;143:517). For clinicians choosing to screen non-Hispanic white males, transferrin saturation and ferritin was recommended. The USPSTF made a recommendation **against** genetic testing for HH in the asymptomatic population, citing (1) that a low proportion of C282 homozygotes develop symptomatic disease, (2) poor evidence that early phlebotomy improved the outcome any better than phlebotomy given for clinically evident disease, and (3) the harm in labeling and treating pts destined never to have disease (Ann IM 2006;145:204).

X-ray: Chondrocalcinosis can be detected on joint x-ray in 50% of symptomatic pts.

Endoscopy: Consider EGD to look for varices in cirrhotic pts (p 255).

Rx: (Ann IM 1998;129:932)

- *Phlebotomy*: The cornerstone of rx is phlebotomy. Each unit of blood is a volume of 500 cc and contains 250 mg of iron. A typical adult male normally has 1-2 gm of iron stores, and in HH, the total burden is usually >15 gm. Pts who refuse bx and require >4 gm of phlebotomy have definite iron overload. Phlebotomy is usually well tolerated on a weekly basis. In some young, large pts, phlebotomy can be done biweekly. Some elderly pts do not tolerate phlebotomy at that rate. Phlebotomy is continued until a mild anemia occurs (Hgb just below normal). Phlebotomy is then carried out 2-6 times/yr (depending on sex and diet) for the pt's lifetime. The goal is to keep the ferritin on the low side of normal (usually <50 mg/L), but the pt should not be kept anemic.
- *Other rx*: Major dietary changes are of little benefit. Red meat can be eaten in moderation. Iron supplements should be avoided, and vitamin C (which enhances iron absorption) should be limited to 500 mg daily. Alcohol consumption should be limited (or stopped if there is cirrhosis). Shellfish from warm water should be cooked because of enhanced susceptibility to *Vibrio* infections. Testosterone is used for hypogonadism. Desferoxamine (an iron chelator) is occasionally needed in pts who do not tolerate phlebotomy because of cardiac disease.
- *Screening for hepatocellular carcinoma*: See p 247.

12.6 Wilson's Disease

Lancet 2007;369:397; Mayo Clin Proc 2003;78:1126; Gastroenterol Clin North Am 1998;27:655

Cause: Autosomal recessive inheritance of mutations in the Wilson's disease gene, ATP7B, a copper-transporting protein.

Epidem: Wilson's disease (WD) is an autosomal recessive disease with a prevalence of 1/30,000 (Hepatology 1990;12:1234). It is generally diagnosed in the early teens. It can present in young children. Late-onset WD (>40 yr at time of dx) is being increasingly recognized (GE 2007;132:1294).

Pathophys: WD is a multisystem disease of copper (Cu) overload. Copper is absorbed in the proximal intestine from dietary sources (shellfish, nuts, chocolate, mushrooms, and liver) and transported to hepatocytes. In hepatocytes it is incorporated into enzymes, including ceruloplasmin. Excess copper is bound in metallothionein complexes and excreted into bile. In WD, incorporation of copper into ceruloplasmin and excretion into bile are defective. The WD gene (ATP7B) appears to code for a copper-transporting ATPase. This ATPase normally serves to transport Cu intracellularly for export into serum (attached to ceruloplasmin) or into bile. More than 300 mutations of the gene have been reported, and this may account for some of the clinical heterogeneity of the disease. After years of defective excretion, excess Cu appears as stainable granules in hepatocytes, and eventually hepatitis and fibrosis develop. Dying hepatocytes release Cu into the circulation where it accumulates in red cells, the brain, and other organs.

Sx/Si: Several clinical presentations are possible. A hepatic presentation is seen in 40% of pts with acute hepatic failure or chronic hepatitis. Most pts have frank cirrhosis on presentation. Occasionally the liver disease is abrupt in onset. This fulminant presentation is usually

accompanied by hemolytic anemia (causing very high bilirubin levels) and is more common in women. Neuropsychiatric manifestations are common and usually present at an older age. Findings include sx or si resembling Parkinson's disease, multiple sclerosis, dystonia, and choreoathetoid movements. Kayser-Fleischer rings result from copper deposition in the eye and are best detected by slit lamp exam. They are 1-3 mm in diameter, green, yellow, or brown, and they are in the periphery of the cornea. They can rarely be seen in other liver diseases (Am J Med 1992;92:643). Sunflower cataracts may be present. Almost all pts have either neuropsychiatric or liver disease. Additional manifestations include renal disease (Fanconi's syndrome, stones), cardiac disease (abnormal EKG, arrhythmias), joint sx (arthritis, chondrocalcinosis on x-ray), and hematologic abnormalities.

Crs: Prior to chelating agents, WD was uniformly fatal (Arch Neurol 2000;57:276). With penicillamine, the prognosis for pts with chronic hepatitis is excellent (GE 1991;100:762). Neurologic sx improve in more than two-thirds of pts. Survival for those who do not present with FHF is similar to that of age- and sex-matched controls (Ann IM 1991;115:720).

Cmplc: HCC is rare in WD (J Clin Gastro 1989;11:220). Any of the complications of end-stage liver disease may occur (p 255).

Diff Dx: The key to dx is first to entertain the possibility of this rare disease. WD is most often considered in the evaluation of chronic hepatitis or abnormal LFTs (p 28) in a young pt. The dx can usually be established by means of testing for ceruloplasmin and urine copper, and/or by liver bx. It is more difficult to make a dx of WD in FHF because (1) ceruloplasmin may be low or urinary copper may be high in other causes of FHF, (2) bx may not be obtainable because of coagulopathy, and (3) Kayser-Fleischer rings may be absent. In these cases, the hemolytic anemia or the relatively minor elevations in transaminases may be a clue.

Lab: Ceruloplasmin levels are decreased in WD because copper fails to be incorporated into ceruloplasmin and it is rapidly degraded. The ceruloplasmin level is <20 in 90% of pts (lower in some series [GE 1997;113:212]). False negatives occur with estrogens or hepatic inflammation. Normal levels are 20-40 ng/mL, and decreases are seen in WD heterozygous pts, in pts with Menkes disease (an X-linked disease of poor copper absorption), in pts with protein-losing states like nephrotic syndrome, in pts suffering malnutrition, and in pts with severe liver disease. Twenty-four-hr urinary copper excretion is almost always elevated, and measurement of levels is the best noninvasive test. Initial diagnostic testing with a gene test is not practical because there are too many possible mutations. Liver bx usually shows evidence of cirrhosis, chronic hepatitis, and excess stainable copper. The best test on bx is quantitative determination of copper levels. The results of this test may be falsely low if the sample has lots of fibrous tissue or if the specimen is mishandled. Levels may be high in other cholestatic liver diseases. Molecular genetic analysis and/or haplotype analysis of markers around the ATP7B gene can be useful for testing family members of a proband.

Endoscopy: Consider EGD to look for varices in cirrhotic pts (p 255).

Rx: Copper-chelating drugs are highly effective. Penicillamine is the most frequently used agent, and rx is lifelong. It can be used in pregnancy (Hepatology 2000;31:531). Neurologic sx largely resolve in more than two-thirds of pts, though deterioration (sometimes irreversible) may first occur (Q J Med 1993;86:197). Side effects, including hypersensitivity reactions, are problematic in 20% of pts. Trientene is a useful alternative with fewer side effects (Lancet 1982;1:643). Tetrathiomolybdate followed by zinc as maintenance rx may be an

alternative that does not cause the initial deterioration seen with penicillamine (Arch Neurol 1991;48:42). Chelators are used together with a low-copper diet. Zinc has been used as an alternative to chelators and works by increasing metallothionein synthesis. This binds copper safely in cells, but this rx has not been adequately compared to penicillamine. Urinary copper excretion and free copper levels are used to monitor rx. Liver transplant is required in FHF and cures the underlying disease by providing hepatocytes without the gene defect (Hepatology 1994;19:583).

12.7 Alpha-1 Antitrypsin Deficiency

Semin Liver Dis 1998;18:217; J Inherit Metab Dis 1991;14:512

Cause: Mutation in the α_1-antitrypsin gene

Epidem: The frequency of the α_1-AT PI*ZZ phenotype (described in Pathophys) is about 0.3-0.6/1000 for whites of European descent. The PI*ZZ phenotype is almost never seen in blacks or Japanese (Respir Med 2000;94[suppl C]:S12).

Pathophys: (Nejm 2002;346:45) The α_1-AT is a protease inhibitor. Its chief function is to protect tissue against destruction by elastases produced by neutrophils. Deficiency is most often a clinical problem because of the destruction of lung tissue resulting in emphysema. The lung disease is clinically the more important adult problem (Am Rev Respir Dis 1989;140:1494) and is not reviewed here. An α_1-AT deficiency causes liver disease by a mechanism related to accumulation of high levels of the molecule in the endoplasmic reticulum of hepatocytes (Thorax 1998;53:501). Pts with complete absence of α_1-AT develop lung disease but not liver disease since there is no α_1-AT to accumulate in hepatocytes. Deficiency is classified according to the protease inhibitor (PI) system. The normal alleles are referred to as M, and a normal phenotype is called PI*MM. More than 90 allelic variants have been described, most of which are single point mutations (Am J Hum Genet 1994;55:1113). The most common variant is the Z variant. Most liver disease is associated with the PI*ZZ state. Heterozygous individuals (PI*MZ) may also have higher incidence of other liver diseases and are overrepresented in the population that ends up coming to liver transplant for any reason (Hepatology 1998;28:1058).

Sx: Only about 15% of PI*ZZ pts develop clinical liver disease. It most often occurs in infancy with presentations of neonatal hepatitis. It can present late in childhood or adolescence with portal HTN or liver failure. Asymptomatic abnormal LFTs may persist in a subgroup without clinical illness. Autopsy studies suggest that PI*ZZ is associated with cirrhosis and HCC in adults and that these pts may have no prior hx of childhood liver disease (Nejm 1986;314:736).

Si: In adults, signs of end-stage liver disease are rarely seen.

Crs: The majority of pts never develop liver disease. The natural hx of PI*ZZ liver disease in adulthood is not well known. The population-based studies of liver disease are all studies of children.

Cmplc: HCC (Nejm 1986;314:736). Any of the complications of end-stage liver disease may occur (p 255).

Diff Dx: The diff dx in adulthood is usually that of abnormal LFTs (p 28) or cirrhosis (p 30).

Lab: Serum levels of α_1-AT are low. If levels are low or borderline, phenotyping should be done. Liver bx, if done, shows intracytoplasmic inclusions in hepatocytes that stain strongly with PAS and resist diastase treatment. The degree of fibrosis and inflammation is quite variable.

Rx: There is no specific rx for the underlying liver disease other than to treat the complications. Transplantation cures the disorder by providing a normal phenotype (Clin Exp Immunol 1986;66:669). Screening cirrhotics for HCC is a consideration p 247.

12.8 Acute Intermittent Porphyria

Semin Liver Dis 1998;18:17; Lancet 1997;349:1613

Epidem: The prevalence has been estimated at 1/10,000, but the prevalence of gene mutation may be as high as 1/1700 in some regions of the world (Semin Liver Dis 1998;18:17). Attacks are rare before puberty and peak in the 30s. Most pts (80%) are women.

Pathophys: (BMJ 2000;320:1647) The porphyrias are a heterogeneous group of inherited disorders of heme synthesis. Acute intermittent porphyria (AIP) is the most clinically relevant to the gastroenterologist since it is the most common of those that present with unexplained attacks of abdominal pain. Depending on which enzyme in the heme synthetic pathway is deficient, different groups of heme precursors accumulate. These result in a variety of clinical syndromes, including the cutaneous porphyrias (reviewed in [BMJ 2000;320:1647]). In AIP deficiency of porphobilinogen (PBG) deaminase results in accumulation of the heme precursors 5-aminolevulinate (ALA) and PBG. The liver increases synthesis of these precursors in response to inadequate heme production, and massive amounts are excreted in urine. This is the presumed cause of the neurologic and psychiatric sx of the disease. Since pts have enzyme levels that are reduced but not absent, they often do well until some inciting event occurs. Only 10-15% of gene carriers develop overt disease, and many have no known family hx. Attacks are often precipitated by (1) drugs (especially barbiturates and estrogens, but the list is long), (2) fasting, (3) smoking, (4) alcohol, (5) infection, (6) emotional and physical stress, and (7) estrogen peaks such as pregnancy or premenstrual phase of cycle.

Sx: (Neurology 1997;48:1678) Pts present with attacks characterized by abdominal pain (80%), nausea and vomiting (50%), constipation (50%), tachycardia (40%), dark urine (25%), and fever (16%). Neuropsychiatric manifestations include limb weakness (40%) and delirium (22%). Less frequently, cranial nerve abnormalities, seizures, depression, and psychosis may occur. Muscle weakness may progress to frank paresis of the extremities. Cranial nerve involvement may cause bulbar paralysis, respiratory failure, and death.

Si: (Neurology 1997;48:1678) There may be physical exam evidence of proximal muscle weakness, a mild sensory neuropathy, hyporeflexia, or HTN during acute attacks.

Crs: Attacks may be fatal in a small percentage of pts, especially when the dx is delayed or management is inappropriate. The risk of future attacks correlates with remission levels of PBG in the urine (Medicine 1992;71:1). However, the course is not readily predictable and some unfortunate pts have continued attacks without inciting factors.

Diff Dx: Clinically identical attacks may be seen with AIP, variegate porphyria, hereditary coproporphyria, and plumboporphyria, which can be distinguished by their patterns of urine and fecal porphyrins (BMJ 2000;320:1647). Acute attacks may mistakenly be thought of primarily as psychiatric illness, and misdiagnosis is common. Muscle weakness with respiratory involvement can mimic Guillain-Barré syndrome.

Lab: The dx is made by detecting elevated urinary levels of ALA and PBG during an attack. This can be done on spot urine but is best performed by an experienced reference lab on a 24-hr sample. Levels may normalize between attacks. Additional tests of urine and feces can be used to distinguish AIP from other, rarer porphyrias with similar sx (coproporphyria and variegate porphyria). Urine may turn dark on exposure to light because of precipitation of PBG. Hyponatremia, leukocytosis, or abnormal LFTs are seen in about 20% of pts (Neurology 1997; 48:1678).

Rx: The precipitating cause should be identified and treated. A comprehensive list of forbidden medicines should be consulted (Medicine 1992;71:1). Morphine may be used for pain. Fluids with 10% glucose are given. Heme arginate (hematin) (3 mg/kg/day qd × 4 days) is the drug of choice and should be given early in an attack (Arch IM 1993;153:2004). It reduces synthesis of ALA and is highly effective in aborting attacks. It does not reverse established neuropathy. The duration of remission induced by heme arginate can be prolonged by tin protoporphyrin (GE 1993;105:500). Seizures should be treated with an agent that does not induce porphyrins, such as gabapentin (Neurology 1995;45:1216). Family members should be screened for asymptomatic disease so that preventative measures can be undertaken. Prevention is accomplished by avoiding known precipitants.

Chapter 13

Neoplastic Liver Disease

13.1 Hepatocellular Carcinoma

Lancet 2003;362:1907; Postgrad Med J 2000;76:4

Cause: (Nejm 1999;340:798) The vast majority of cases of hepatocellular carcinoma (HCC) are due to chronic hep B or chronic hep C infection (RR = 100-200). In the U.S., where infection rates are lower, viral hepatitis still accounts for 71% of HCC (Hepatology 1993;18:1326). Cirrhosis of any cause is a risk. The cirrhosis of hep B, hep C, or hemochromatosis is associated with a RR of >100. Other causes of cirrhosis (eg, alcohol, PBC, Wilson's, α_1-AT deficiency, autoimmune disorders) are associated with a much lower RR of 2-5. Glycogen storage disease, tyrosinemia, and porphyria cutanea tarda are causative. Aflatoxin (a toxin from *Aspergillus* found in a variety of stored foods like peanuts, corn, and rice), anabolic steroids, and thorium dioxide (an obsolete radiographic contrast medium) are apparent toxic causes. The fibrolamellar variant occurs in younger pts lacking chronic liver disease (Am J Gastro 2009;104:2617).

Epidem: The incidence of HCC varies widely by region and correlates with chronic hep B infection. The highest rates are in Asia and sub-Saharan Africa, where 10-25% of the population is infected by hep B and the HCC incidence is 30-120/100,000 per yr in men. In Japan, HCC is the third-leading cause of cancer death, largely due to hep C (Nejm 1993;328:1797). Incidence in southern Europe is 5-10/100,000 per yr (Brit J Surg 1998;85:1319). The incidence in the U.S. has risen over the past 3 decades from 1.4/100,000 to 2.4/100,000 per yr, and the disease is occurring at a younger age. This is probably a result of the increasing incidence of hep C infection. Blacks are affected twice as often as whites, and men 3 times as often as women (Nejm 1999;340:745).

Pathophys: The mechanisms by which viral hepatitis causes HCC are unknown. Chronic inflammation and increased hepatocyte turnover are probably important. There may be direct oncogenic effects of the viruses as well. Aflatoxin induces p 53 mutations, allowing unrestrained cell proliferation (Lancet 1991;338:1356).

Sx: Weight loss, RUQ pain, malaise, and jaundice are the typical sx of advanced disease. Sudden clinical decompensation in a pt with established cirrhosis is a second common presentation. With the advent of detection by screening, many pts are asymptomatic.

Si: RUQ mass, hepatomegaly, irregular liver edge, bruit over the liver, stigmata of chronic liver disease (p 26), tumor-induced fever.

Crs: The tumor grows locally, compromises hepatic function, invades blood vessels, and spreads to lungs and then to distant sites. Median survival without rx is 3-6 months after the onset of sx. Five-yr survival of pts treated with transplant for small lesions is similar to the survival of pts undergoing transplant for any reason. Five-yr survival for those undergoing successful resection may be as high as 50% (see Rx). Five-yr survival in the fibrolamellar variant is better, as these pts do not generally have chronic liver disease and can have wide resections (66%).

Cmplc: Paraneoplastic syndromes are frequent. These include hypercholesterolemia (11%), hypoglycemia (2.8%), hypercalcemia (1.8%), and erythrocytosis (2.5%) (Cancer 1999;86:799).

Diff Dx: The differential is that of a hepatic mass (p 250). The suggested approach to dx varies with the size of the lesion, and guidelines have been developed based on this (Hepatology 2005;42:1208). Nodules found on US <1 cm should be followed at 3- to 6-month intervals for 2 yr, and if stable routine surveillance is done. Nodules of 1-2 cm found on US are investigated with 2 dynamic contrast studies such as MRI and CT scan. If both scans show a typical appearance for HCC (hypervascular with washout in the portal venous phase), then the pt can be treated as HCC. If both scans do not show this appearance, then the lesion is biopsied. If the nodule is greater than 2 cm at the initial dx and has typical HCC features on 1 dynamic imaging test or an AFP >200 ng/mL, then bx is not needed. If the imaging is nondiagnostic or the liver is not cirrhotic, bx is done. A cavernous hemangioma should be ruled out prior to bx by MRI or by tagged rbc scan if the initial imaging study suggests that possibility. The dx should always be considered when a pt with cirrhosis has a clinical deterioration.

Lab: Serum AFP is elevated in 80% of pts with HCC. Elevations occur in hep B, hep C, germ cell tumors, pregnancy, and other causes of cirrhosis. Pathologically, the gross appearance of HCC ranges from a discrete nodule to a diffuse lesion. The fibrolamellar variant of HCC is a large, hard tumor with bands of fibrous tissue that arises in a noncirrhotic liver.

X-ray: US is the most commonly used initial test for detection and surveillance. In this setting it has a sensitivity of 65-80% and a specificity of 90%. However, the test is less sensitive and specific in cirrhotic pts, is operator dependent, and is limited in obese pts. Dynamic, contrast-enhanced CT or MRI can be used to assess the lesions found on US. MRI is slightly better than CT for HCC dx (sensitivity 75% vs 61% and specificity 76% vs 66%) (Clin Liver Dis 2009;13:233). When there is characteristic arterial enhancement and washout in the venous phase (where density becomes lower than the surrounding liver parenchyma) in a cirrhotic liver, specificity climbs to 95-100%.

Rx:

- *Surgical resection:* Resection is the treatment of choice in pts without cirrhosis. Only a small proportion (10% in Western countries) of pts with HCC are candidates for cure by resection or transplantation. Resection is also used in selected Child-Pugh grade A (p 31) cirrhotic pts with single lesions, a wedged hepatic vein pressure gradient of <10 mm Hg (a measure of the degree of portal HTN), and a normal bilirubin. Adjuvant rx is not indicated, and 5-yr survival can be >50%. Many of the recurrences in cirrhotic pts are probably new primary lesions.

- *Transplantation:* Transplantation has the advantage that it can be performed in pts with advanced cirrhosis who do not tolerate wide resections. Transplant rids the pt of a diseased liver that is very likely to generate new lesions even if the first lesion is cured in the resection. Initial transplant experience in unselected pts who received no adjuvant rx was poor, with only 9% of pts free of disease at 2 yr, perhaps because HCC implanted in the donor liver (Surgery 1991;110:726). However, if transplantation is reserved for pts with a single lesion <5 cm in diameter or no more than 3 lesions each <3 cm, then recurrence-free survival climbs to 83% at 4 yr (Nejm 1996;334:693). Therefore, transplant is indicated for lesions meeting these size criteria. Pts with HCC receive additional points in the UNOS system used to allocate available organs. If the wait is expected to make the tumor not amenable to transplant, a living related donor could be used. If the wait is going to be more than 6 months, an ablative rx should be considered as a bridge.
- *Percutaneous ablation:* Percutaneous ablation is the appropriate choice for pts with early stage disease who cannot undergo transplant or resection. Radiofrequency ablation has emerged as the preferred technique though alcohol injection can be used for lesions under 2 cm. Five-yr survival may be >50% in Child's A pts with 3 or fewer lesions under 3 cm. Transarterial chemoembolization (TACE) is a technique in which intra-arterial chemotherapy suspended in lipiodol is administered into the tumor after which the artery is embolized with gelatin foam or other materials. It is the first-line rx for nonsurgical pts with large or multifocal tumors who do not have vascular invasion or metastatic disease. It is not curative.
- *Chemotherapy:* Chemotherapy after transplantation for small tumors is unlikely to be of benefit since those pts do well with surgery alone. For more advanced lesions, most chemotherapy is disappointing and its use is not recommended. Sorafenib shows a small survival benefit with moderate toxicity in advanced disease (Expert Rev Anticancer Ther 2009;9:739).
- *Screening and surveillance:* Screening (initial testing) and surveillance (repeated application of a screening test) for HCC has been endorsed in recent guidelines for at-risk pts (Hepatology 2005;42:1208). The best evidence supporting its use is a large randomized trial of Chinese pts with hep B that showed a 37% reduction in mortality with screening with AFP and US every 6 months (J Cancer Res Clin Oncol 2004;130:417). The at-risk pts include the following hep B surface ag carriers: (1) Asian males ≥40 yr, (2) Asian females ≥50 yr, (3) cirrhotics, (4) those with an HCC family hx, (4) Africans >20 yr, and (5) other at-risk pts such as those with high HBV DNA and ongoing inflammation. Other at-risk pts without hep B were defined as cirrhotics with (1) hep C, (2) alcoholic cirrhosis, (3) hemochromatosis, and (4) PBC. The guideline did not recommend for or against surveillance in cirrhotics with NASH, autoimmune hepatitis, or alpha-1 antitrypsin deficiency, but it is widely practiced.

  Pts on the transplant list should be screened since the development of HCC improves their position on the transplant list and they could develop HCC without sx that might preclude transplant. US is the recommended screening test at an interval of q 6-12 months. AFP was not recommended as a primary screening test because of the lack of sensitivity and specificity. Citing concerns about cost, false positives, and radiation exposure, the use of CT for screening was not recommended. However, some data suggest that pts listed for transplant might get the greatest benefit from CT as a screening tool (Liver Transpl 2003;9:672).

Strategies using MRI and/or CT may be worth considering but have not yet been validated (Clin Gastroenterol Hepatol 2009;7:397).

- *Prevention:* Universal vaccination of Taiwanese children against hep B has resulted in a dramatic drop in chronic infection and in the incidence of HCC (Nejm 1997;336:1855). A reduction in incidence of HCC was seen in 1 trial of interferon for hep C (Lancet 1995;346:1051) but not in a prospective cohort study (Hepatology 1998;28:1687). Elimination of aflatoxin from stored food may be of benefit.

13.2 Hepatic Masses

Semin Liver Dis 1993;13:423

There are many lesions that can present as hepatic masses (see Semin Liver Dis 1993;13:423). Common considerations include:

- *Hepatic adenoma:* These lesions are most often associated with oral contraceptive use. They typically present as palpable or radiographic masses in women. Because of the risk of rupture or malignant transformation, surgical resection is indicated, and preoperative bx is avoided because the lesions are vascular.
- *Focal nodular hyperplasia:* These lesions are masses with a thick central stellate scar. They can cause pain, but rupture is rare and malignant transformation is not seen. CT, MRI, or US may detect the characteristic scar that distinguishes these lesions from more serious tumors. Bx should be avoided because of the risk of bleeding.
- *Cavernous hemangioma:* These lesions are very common (found at up to 20% of autopsies) and are usually asymptomatic. They can grow and cause pain, but rupture is rare. They may be detected by several imaging studies, but MRI is the most sensitive for distinguishing them from malignant tumors. Only symptomatic lesions should be treated with surgery, and bx should be avoided.
- *Cysts:* (J Am Coll Surg 2000;191:311) Simple cysts are commonly seen on imaging studies. They are generally asymptomatic but can enlarge and cause sx. Neoplastic cysts are usually detected because of papillary projections and multiloculations on imaging studies. They are treated surgically. Cysts may be seen after trauma. Hydatid cysts (from *Echinococcus*) need to be considered in endemic areas (Gastroenterol Clin North Am 1996;25:655).
- *Other lesions:* Hepatobiliary cystadenomas are detected by their septations and should be resected. Focal fatty infiltration, HCC (see p 247), metastatic disease, and abscess can present as masses.

Chapter 14

Drug- and Toxin-Induced Liver Disease

14.1 Alcoholic Liver Disease

Mayo Clin Proc 2001;76:1021; Postgrad Med J 2000;76:280

Cause: Excessive intake of ethanol. For practical purposes, alcohol has been defined in units. A unit is 1 oz of spirits, 12 oz of beer, or 4 oz of wine, and it contains about 10-12 gm of alcohol. Most individuals developing alcoholic liver disease (ALD) consume more than 35 units/week. A safe level of 21 units/week for men and 14 units/week for women has been proposed.

Epidem: Alcohol is the major cause of cirrhosis in Western countries. The risk of alcoholic liver disease is higher in those who consume >30 gm daily (Gut 1997;41:845), though only 5% of pts with this level of consumption have overt disease. Risk climbs markedly with increasing consumption. Female sex, drinking without food, binge drinking, and drinking concentrated beverages or multiple types of beverages increase risk. Coffee may be protective against cirrhosis (Arch IM 2006;166:1190).

Pathophys: Three forms of ALD are recognized. Steatosis (**alcoholic fatty liver**) occurs in 90-100% of heavy drinkers and is reversible with abstinence. In **acute alcoholic hepatitis**, there is hepatocyte ballooning and necrosis with cholestasis, but no evidence of cirrhosis. This occurs in about 10-35% of heavy drinkers. **Alcoholic cirrhosis** is the most severe form of injury and is seen in 8-20% of heavy drinkers. Histologically, there are bridges of fibrosis that develop between central veins and portal tracts. This creates a micronodular pattern of regenerating nodules.

Multiple factors are thought to mediate alcoholic liver injury (Postgrad Med 1998;103:261). Ethanol is oxidized to acetaldehyde by alcohol dehydrogenase, and then to acetate. Changes that occur in the redox potential of the cell from this oxidation have harmful effects on lipids and carbohydrate metabolism. Acetaldehyde binds to proteins, creating antigenic targets and starting an inflammatory cascade. Iron deposition may play a role.

Sx: Many pts are asymptomatic and come to evaluation because of abnormal LFTs detected at a checkup or as part of an alcohol detoxification evaluation. Pts may have nonspecific complaints of anorexia, malaise, or abdominal pain, which are often related to their

alcoholism. The most crucial point is eliciting the alcohol hx. A variety of screening questionnaires have been developed. The CAGE questionnaire is widely used. It consists of 4 questions:
C: Have you ever felt the need to **cut** down your drinking?
A: Have you ever felt **annoyed** by criticism of your drinking?
G: Have you ever felt **guilty** about your drinking?
E: Have you ever taken a drink first thing in the morning (**eye opener**)?
Two or more positive responses suggest problem drinking. Pts often lie about their alcohol use, and hx from family members may be critical.

Si: In steatosis there is often hepatomegaly. In alcoholic hepatitis, the pt looks ill, and there may be fever, jaundice, spiders, tender hepatomegaly, ascites, or encephalopathy. Alcoholic cirrhosis causes signs of end-stage liver disease (p 26) that cannot be distinguished from signs caused by other liver diseases.

Crs: Five-yr survival in cirrhosis is 35-50%. Survival is much better in abstinent pts than in those who continue to drink. The prognosis in acute alcoholic hepatitis can be determined from laboratory parameters (see Lab).

Cmplc: HCC is a risk in cirrhotic pts (p 247). Any of the complications of end-stage liver disease may occur (p 255).

Diff Dx: The diff dx may be that of abnormal LFTs, cirrhosis, or jaundice (p 26).

Lab: LFTs, CBC with diff, and PT should be obtained. Transaminases are elevated in alcoholic hepatitis, usually in a pattern of AST > ALT with neither more than 7 × the upper limit of normal. GGTP is frequently elevated. In advanced disease, albumin drops and the PT is elevated. An elevated MCV can be a clue to alcoholism, and a random alcohol level can be informative. In alcoholic hepatitis, a severity score, called the discriminant function, is calculated as 4.6 × (pt's PT – control PT) + bilirubin (mg/dL) (GE 1978;75:193). A score of >32 or spontaneous encephalopathy is associated with high mortality (>30%). Leukocytosis is common in alcoholic hepatitis. Thrombocytopenia can be seen with portal HTN or as a result of toxic effects of alcohol on bone marrow. Tests to exclude other causes of abnormal LFTs should be considered (p 28), and all pts should be tested for hep C. Liver bx is prognostic and can confirm the dx. It is usually not necessary to perform bx.

X-ray: US should be performed to rule out obstruction or tumor. Pts with alcoholic cirrhosis may not dilate their bile ducts in response to obstruction (because of severe fibrosis), so caution in interpretation is warranted.

Endoscopy: Consider EGD to look for varices in cirrhotic pts (p 255).

Rx: ACG guidelines for management (Am J Gastro 1998;93:2022) include:

- *Abstinence:* This is the most important factor in successful rx but the most difficult to achieve. Individual counseling, support groups such as Alcoholics Anonymous, and other structured rx programs have variable efficacy. Drug rx such as naltrexone or acamprosate may have a role in reducing consumption (Jama 1999;281:1318).
- *Nutritional support and supplements:* In hospitalized pts with severe disease, enteral feedings improve outcome (GE 1992;102:200). Pts with cirrhosis rapidly recruit alternative fuels such as skeletal muscle, and prolonged starvation should be avoided. A nighttime snack and early morning feeding are important. Expensive formulations of branched chain amino

acids (which may reduce encephalopathy) are usually not needed. Thiamine, folate, and multivitamins should be routinely given.

- *Corticosteroids for alcoholic hepatitis:* A course of prednisolone 40 mg po qd (for 4 weeks with or without a 2-week taper) reduces mortality in pts with severe alcoholic hepatitis. The data for benefit are most clear in pts with encephalopathy or a high discriminant function (described above) (Aliment Pharmacol Ther 2009;30:3). Pts with active bleeding, active infection, renal failure, pancreatitis, or poorly controlled diabetes were excluded. A recent report suggests that infection is not necessarily a contraindication to steroids (GE 2009;137:541). The long-term benefits are unknown.
- *Pentoxifylline:* Pentoxifylline 400 mg po tid improved short-term survival in a single RCT of severe alcoholic hepatitis (GE 2000;119:1637). Given the excellent safety profile, its use has become widespread.
- *Other drug rx:* Propylthiouracil 300 mg po qd for up to 2 yr reduced mortality from 25% to 13% in an RCT of pts with ALD, but the data have not been replicated and the drug is not widely used (Nejm 1987;317:1421). Colchicine was effective in prolonging median survival in an RCT, but methodologic flaws and the lack of a confirmatory study have stopped its widespread use (Nejm 1988;318:1709). A more recent study showed no benefit (GE 2005;128:882). The TNF-α inhibitors etanercept and infliximab appear to increase mortality due to infection (GE 2008;135:1953).
- *Liver transplant:* Liver transplant is effective in ALD and has survival comparable to transplant for other liver diseases (Surgery 1992;112:694). Abusive levels of drinking diminish posttransplant survival (Liver Transpl 2007;13:197).
- *Screening and surveillance of HCC in cirrhotics:* See p 247.

14.2 Drug-Induced Liver Injury

There are more than 600 described drug, chemical, and herbal causes of liver injury. Several patterns of liver injury may be seen, including acute hepatocellular injury, cholestasis, granulomatous hepatitis, chronic hepatitis, vascular injury, FHF, and neoplasia. Drugs should be suspected in all cases of asymptomatic LFTs or clinically overt liver injury. A methodical listing of all the pt's current and recent medicines is the cornerstone of dx. Herbal remedies should not be overlooked (Jama 1995;273:502). A current reference (such as the American Hospital Formulary) should be used to research each drug, and a list of suspected agents should be made. A literature search for case reports can be helpful when the reference source provides scant information. Antimicrobials and CNS agents appear to be the most frequent causes of drug-induced liver injury (GE 2008;135:1924). Given the long list of offending agents, it is not possible to provide a meaningful review of the individual agents in a text of this size. Excellent reviews are available (Nejm 2003;349:474).

14.3 Acetaminophen Overdose

Postgrad Med 1999;105:81; Lancet 1995;346:547

Cause: Intentional overdose with suicidal intent, excessive doses without suicidal intent, and therapeutic doses in a pt predisposed to toxicity (usually because of alcohol) (Hepatology 1995;22:767).

Epidem: Fifty percent of exposures to toxic doses are seen in children, and 63% of poisonings are accidental (Am Fam Phys 1996;53:185). Accidental misuse has higher morbidity and mortality and is common in alcoholics (Nejm 1997;337:1112).

Pathophys: About 5-10% of ingested acetaminophen is converted via the P450 enzyme system to a toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). Normally the sulfhydryl groups of glutathione rapidly bind this metabolite and inactivate it. However, when high levels of NAPQI overwhelm the available glutathione, binding occurs with sulfhydryl groups of hepatic proteins, causing hepatocyte necrosis (Postgrad Med 1999;105:81). Oxidative stress, and effects on mitochondrial permeability are among other important factors in the development of toxicity (GE 2008;135:1047). Intentional overdose is the most common presentation. However, those with enhanced activation of P450 systems (due to alcohol and a variety of drugs) or those with reduced glutathione stores (cirrhosis, starvation, alcoholism, or eating disorders) can develop toxicity without intentional overdose.

Sx/Si: Following intentional overdose, there is anorexia, nausea, and vomiting for the first 24 hr. From 24 hr to 48 hr the pt improves. Thereafter some pts develop sx and si of liver failure with RUQ pain, hepatomegaly, jaundice, somnolence, confusion, coma, and oliguria. By day 6-7 those destined to recover will begin to improve.

Crs: Of untreated pts with levels in the toxic range, 1-2% die of liver failure.

Cmplc: FHF, renal failure, acidosis.

Diff Dx: The diff dx may be that of FHF (p 30) or abnormal LFTs (p 28).

Lab: In a single-dose ingestion, acetaminophen levels are obtained serially and are plotted on a nomogram to determine if they cross the toxic threshold that requires rx (Ann EM 1991;20:1058). PT/INR and LFTs are followed serially to look for evidence of hepatic damage. Cr is obtained daily to look for evidence of renal failure. Acid-base status is assessed at 24 hr because acidosis is common in severe toxicity. A toxic screen to look for other ingestions is indicated (Dig Dis Sci 2000;45:1553).

Rx: Charcoal is given if less than 1 hr has elapsed since substantial overdose. Depending on the acetaminophen level, the time since ingestion, host factors, and stage of illness, rx with N-acetylcysteine is given. The drug is uniformly effective in preventing fatality if given within 16 hr of single-dose ingestion (Nejm 1988;319:1557). The iv formulation may be more consistently effective (because of nausea and vomiting) and is now FDA approved in the U.S. The duration varies depending on the clinical course. The drug is indicated in pts with chronic overdose and evidence of hepatotoxicity. Prolonged courses are indicated in FHF. Those caring for such pts must consult a comprehensive source (eg, Lancet 1995;346:547) for details. In the U.S., consultation with poison control centers may be valuable for current protocols. A transplant center should be contacted for advice if there is evidence of developing severe liver damage (ALT/AST >1000 U/L). The rx of FHF is complex and belongs in specialty centers (Lancet 1997;349:1081).

Chapter 15

Complications of End-Stage Liver Disease

15.1 Portal Hypertension and Variceal Hemorrhage

Am J Gastro 2007;102:2086; Gastroenterol Clin North Am 2003;32:1079; Nejm 2001;345:669

Cause: Rupture of varices secondary to portal HTN, defined as portal venous pressure >5 mm Hg.

Epidem: Most varices are associated with cirrhosis, and the epidemiology of varices is that of the underlying cause of cirrhosis.

Pathophys:

- *Portal HTN:* The portal vein forms from the confluence of the superior mesenteric and splenic veins. Portal pressure can rise because of increased outflow resistance or increased portal inflow. Increased resistance can be due to (1) prehepatic causes (portal vein thrombosis); (2) hepatic causes (cirrhosis, inflammation with hepatocyte swelling, mass, regenerating nodules); or (3) posthepatic causes (hepatic vein obstruction; see Budd-Chiari syndrome p 267). Increased portal inflow results from peripheral vasodilatation and the hyperdynamic circulation of cirrhosis due to an imbalance of vasodilators and vasoconstrictors.
- *Varices and bleeding risk:* In portal HTN, the increase in pressure causes the opening of collateral vessels. Most of these vessels are in the retroperitoneum. The most troublesome collaterals are veins intrinsic to the distal esophagus and proximal stomach that become dilated and tortuous (Lancet 1997;350:1235). As variceal pressure rises, wall tension and the risk of bleeding also rise (Hepatology 2000;32:842). Direct pressure measurements are not readily available to most clinicians, and risk must be estimated by other criteria. Three clinical criteria are used to predict risk: (1) variceal size, (2) Child-Pugh grade (p 31), and (3) the presence of red wales (endoscopically identified longitudinal, dilated venules on varices that look like whip marks) (Nejm 1988;319:983). Varices are called size **F1** if they are small and straight, **F2** if enlarged, tortuous, and occupying less than one-third of the lumen circumference, and **F3** if coiled and occupying more than one-third of the circumference of the lumen (Nejm 1988;319:983). Small varices are those ≤5 mm (Am J Gastro 2007;102:2086).

- *Unusual varices:* Isolated gastric varices can occur with splenic vein thrombosis (Am J Gastro 1984;79:304). Ectopic varices can form in the duodenum, in adhesions to the abdominal wall, in surgical anastomoses, and at ostomies (Hepatology 1998;28:1154).
- *Portal hypertensive gastropathy (PHG):* (Am J Gastro 2002;97:2973) PHG is a lesion seen in the stomach of pts with portal HTN. Microscopically, it represents an area of microvascular ectasia and perivascular fibrosis. Endoscopically, it is recognized as multiple small erythematous areas outlined by subtle lines giving a cracked sand or snakeskin appearance to the mucosa. In more severe disease, there is oozing and more prominent red spots, and lesions may be seen in body, fundus, and antrum. In the largest series followed endoscopically over 3 yr, acute bleeding was rare (2.5% over 3 yr), and chronic bleeding was seen in 11% (GE 2000;119:181). Disease parallels the severity of portal HTN and may worsen or improve spontaneously.

Sx: Pts present with sx of UGI bleeding (p 21). Hematemesis and melena are common.

Si: Melena or hematochezia are typical. Pts may become encephalopathic. Other stigmata of portal HTN may be present (ascites, splenomegaly), and other findings of chronic liver disease may be present (p 31).

Crs: About 50% of cirrhotics have varices. Cirrhotics without varices develop them at 5-15%/yr. Varices become large (and therefore at risk to bleed) at a rate of 4-10%/yr. Only about one-third of pts with varices bleed, but each bleeding episode carries a 20-30% risk of death. Rebleeding often occurs within 48 hr of the initial bleed, but risk remains high for 6 weeks. Rebleeding is most frequent in pts with severe liver failure, massive initial bleed, ongoing alcoholism, HCC, large varices, or renal failure (Gastroenterol Clin North Am 2000;29:337). Untreated pts rebleed or die within a yr about 70% of the time. Isolated gastric varices are at very high risk for bleeding (Hepatology 1992;16:1343). Pts with small varices have a low risk of bleeding (8% at 4 yr), but a worsening Child-Pugh grade (p 31) may suggest variceal enlargement and a higher risk of bleeding (Am J Gastro 2000;95:503).

Cmplc: Variceal hemorrhage can lead to death, SBP (p 261), renal failure, and aspiration pneumonia.

Diff Dx: The differential of variceal hemorrhage is that of UGI bleeding. The differential for portal HTN is that of causes of cirrhosis (p 30), causes of thrombosis of the portal vein or its tributaries (p 269), and Budd-Chiari (p 267).

Lab: See Approach to Acute Bleeding, p 21. An elevated PT in a pt with evidence of UGI bleeding may be a clue to varices as the cause.

X-ray: Radiographs are not indicated in the evaluation of bleeding. Imaging may be needed to evaluate the underlying cause of portal HTN, especially to rule out malignancy and to evaluate portal vein patency.

Endoscopy: (Semin Liver Dis 1999;19:439) Varices are easily diagnosed at endoscopy as bluish veins, and size is best estimated after air insufflation. **Endoscopic sclerotherapy** (EST) is performed by the injection of a sclerosant (eg, sodium tetradecyl sulfate, polidocanol, or ethanolamine) into or around variceal channels. Sessions are continued every week or 2 until varices in the distal 5 cm are eliminated. Follow-up EGD is done q 3 months × 6 months, then q 6-12 months to look for recurrence. Complications include fever, retrosternal pain, pleural effusions, esophageal ulcers (which may bleed in up to 20%), esophageal stricture, perforation from full-thickness necrosis, and mediastinitis (Endoscopy 1992;24:284). **Endoscopic variceal ligation** (EVL) has largely replaced sclerotherapy. In this

technique, a 1-cm barrel wrapped with rubber bands on its outside is attached to the end of the endoscope. The varix is sucked into the hollow portion of the barrel. A band is deployed off the barrel and wraps itself around the base of the varix. The band and the clotted varix fall off a few days later, leaving a small ulceration. This technique has fewer associated complications than sclerotherapy (see Rx). Pts are treated biweekly until eradication of varices, but bimonthly sessions may be more effective than biweekly sessions in a recent trial (Am J Gastro 2005;100:2005). A 6-band maximum per session is most efficient (Am J Gastro 2007;102:1372).

Rx: Because of the frequency and high mortality associated with variceal bleeding, a bewildering number of clinical studies and meta-analyses have been published. Recent guidelines have proposed the following (Am J Gastro 2007;102:2086):

- *Prevention of a first variceal bleed:* Pts with cirrhosis should have EGD when first diagnosed. If there are no varices in a well-compensated cirrhotic (Child's A), the EGD is repeated in 3 yr or sooner if there is a decompensation of the cirrhosis. In decompensated cirrhotics (Child's B/C), EGD should be done annually if the initial exam is negative for varices. Beta-blockers are not recommended to prevent varices from developing. **For small varices that have not bled:** (1) Beta-blockers are used if the pt is Child's B/C or if there are red wales on the varices; (2) if the pt is Child's A and there are no red wales, beta-blockers can be used to prevent worsening of the varices, but the benefit is uncertain; and (3) pts not treated should have repeat EGD in 2 yr, earlier if hepatic decompensation occurs. The nonselective beta-blockers (propranolol and nadolol) reduce the incidence of a first bleed by about 45% (for a meta-analysis, see Ann IM 1992;117:59). Ideally, pts would have the dosage adjusted on the basis of portal pressure gradients, but in practice, the dosage is adjusted until resting heart rate is reduced to 55-60. The starting dose of propranolol is 20 mg po bid, and that of nadolol is 20 mg po daily. **For medium/large varices that have not bled:** (1) Either beta-blockers or variceal ligation should be used if the pt is Child's B/C or red wales are seen; (2) beta-blockers are preferred in Child's A pts with no red wales, and ligation is reserved for those who cannot take or do not tolerate beta-blockers.
- *Rx of acute bleeding:* Fluids are given to bring the blood pressure in the 90- to 100-mm Hg systolic range and the pulse under 100. Pts are transfused to a Hgb of about 8 gm/dL, avoiding excessive transfusion. Higher levels of transfusion increase portal pressure and the risk of rebleeding and death (Am J Gastro 2009;104:1802). Endoscopic control of bleeding is the rx of choice for acute hemorrhage. EVL is preferred over sclerotherapy because eradication occurs more quickly, with lower mortality and fewer complications (major RCT, Nejm 1992;326:1527; meta-analysis, Ann IM 1995;123:280). Octreotide, a somatostatin analogue with a longer half-life, has become the drug of choice for acute bleeding episodes and is given for 3-5 days. The addition of octreotide (50 mcg iv bolus and 50 mcg/hr as a continuous infusion for 5 days) to EVL lowers early rebleeding compared to ligation alone (Lancet 1995;346:1666) or sclerotherapy alone (Nejm 1995;333:555). Prophylaxis against infection (p 263) should be given using ceftriaxone 1 gm iv q 24 in the sickest pts. Gastric varices are difficult to treat, and injection with cyanoacrylate glue has become a widely used initial rx where available (Gastroenterol Clin North Am 2003;32:1079). TIPS is used where bleeding cannot be controlled.
- *Prevention of recurrent bleeding:* Sclerotherapy has been well shown (in 8 trials) to be superior to placebo in the prevention of further bleeding. Ligation has been shown to be

superior to sclerotherapy regarding rebleeding rate, mortality, and complications (meta-analysis, Ann IM 1995;123:280). Beta-blockers are effective in preventing recurrent bleeding compared to placebo (meta-analysis, Lancet 1990;336:153), but in practice most pts have endoscopic obliteration with EVL. The current guideline suggests EVL in combination with beta-blockers as the best choice (Am J Gastro 2007;102:2086).

- *TIPS:* (Gastroenterol Clin North Am 2000;29:387) A transjugular intrahepatic portosystemic shunt (TIPS) is a stent placed between a hepatic vein and an intrahepatic portion of the portal vein. It can be placed in 90% of pts, with a 10% complication rate and a 2% procedure-related death rate (Radiographics 1993;13:1185). Complications include mechanical events during placement (such as bleeding, rupture of the capsule), complications of shunting (encephalopathy in 15% [Gut 1996;39:479] and worsened liver function), and stent-related complications (hemolysis, infection, stenosis). The established indications for TIPS are active variceal bleeding despite endoscopic rx (including a second attempt) and prevention of recurrent variceal hemorrhage in pts awaiting liver transplantation (Jama 1995;273:1824). TIPS may also be useful in refractory ascites and Budd-Chiari (GE 1996;111:1700). A TIPS behaves like a surgical shunt with decompression of the portal system. A TIPS is much more prone to occlusion than a surgical shunt. Occlusion due to clot or stent kinking can occur within weeks in about 3-10% of cases. Recurrent portal HTN from stenosis due to pseudointimal hyperplasia occurs frequently (about 60%). This problem can be treated with repeated dilatations (GE 1997;112:889). Right-sided heart failure is a catastrophe if it develops in a TIPS pt, because the elevated right atrial pressure is transmitted directly to the portal system, causing recurrent varices. As long as the stent is patent, esophageal varices resolve, but fundic varices often do not because of splenorenal collaterals or massive splenomegaly excessively feeding the short gastric vessels (GE 1997;112:889). Monitoring with Doppler is commonly done but can miss significant stenoses. Some centers do periodic angiography and/or endoscopy.
- *Surgical shunts and decompression:* (Gastroenterol Clin North Am 2000;29:387) A variety of surgical shunts to decompress the portal system have been described. All shunts reduce bleeding but are accompanied to varying degrees by encephalopathy and worsened liver failure. A side-to-side anastomosis of IVC to portal vein reduces bleeding and ascites, but is prone to clot and makes transplant surgery more difficult. Distal splenorenal shunt (joining a transected splenic vein to the left renal vein) lowers pressure in varices but does not reduce portal inflow, and so ascites is a problem with this technically demanding operation. Esophageal transection with an automated suturing device and other devascularization procedures are not widely used. These procedures may be alternative salvage strategies (Hepatology 1992;15:403) for those who fail endoscopic rx and TIPS.
- *Balloon tamponade:* Balloon tamponade is effective in controlling hemorrhage in 80-90% of pts, but complications and early rebleeding are common (Scand J Gastroenterol Suppl 1994;207:11). Aspiration pneumonia occurs in 10% of pts and orotracheal intubation is routinely used. The 4-lumen Sengstaken-Blakemore tube has esophageal and gastric balloons and an aspiration port and is most often used. The Linton-Nachlas tube has a bigger gastric balloon and is used for gastric varices. It is important to make sure that the position of the gastric balloon within the stomach is confirmed radiographically to prevent accidental inflation in the esophagus. The tube must be deflated for 30 min q 4-6 hr, and duration of use must be minimized. Generally, tubes are a temporizing

measure used in desperate circumstances when endoscopic and pharmacologic methods fail while awaiting TIPS.

- *Portal hypertensive gastropathy (PHG):* Rx is that of the underlying portal HTN with medical rx, TIPS, or shunt (Dig Dis 1996;14:258). In a small trial, propranolol was effective in reducing bleeding (Lancet 1991;337:1431).

15.2 Ascites

Nejm 2004;350:1646; Hepatology 1998;27:264

Cause: (Nejm 1994;330:337) Ascites can be secondary to portal HTN or due to a variety of conditions in which portal pressures are normal. Causes of ascites associated with portal HTN are cirrhosis (the vast majority), alcoholic hepatitis, heart failure, hepatic mets, fulminant hepatic failure, Budd-Chiari, venoocclusive disease, myxedema, and fatty liver of pregnancy. Causes of ascites without portal HTN include peritoneal carcinomatosis, TB, pancreatic ascites (from a disrupted pancreatic duct), biliary ascites (bile in the belly, usually from a biliary surgery mishap), chylous ascites (milky ascites from disrupted lymphatics often associated with malignancy [Am J Gastro 2002;97:1896]), nephrotic syndrome, bowel obstruction/infarction, and serositis from connective tissue disease. The serum-ascites albumin gradient is used to separate these 2 groups (see Lab).

Epidem: Varies with underlying cause.

Pathophys: (Lancet 1997;350:1309) The pathogenesis of ascites due to cirrhosis is complex and incompletely understood. Cirrhotics develop increased cardiac output, decreased peripheral vascular resistance, and splanchnic vasodilatation. This is probably a result of an imbalance between vasodilating and vasoconstricting substances. This leads the neurohumoral system to detect a decreased effective circulating volume. This causes (1) increased activity of the renin-angiotensin-aldosterone system, (2) increased levels of ADH, (3) increased sympathetic nervous system activity, and (4) alterations in intrarenal factors such as kallikrein and endothelin. These 4 factors result in reduced renal blood flow and retention of sodium and water.

Sx: Pts may present with bloating or pain if ascites develops rapidly.

Si: Ascites can be detected by bulging flanks, shifting dullness, or a fluid wave (p 27). The physical exam can be misleading. Findings of associated malignancy or other underlying diseases (such as end-stage liver disease) may be present.

Crs: About 50% of cirrhotics will develop ascites over 10 yr. Cirrhotic ascites is a poor prognostic sign with a 2-yr survival of 50%. A striking 40% of pts with ascites will develop hepatorenal syndrome (HRS) within 4 yr (GE 1993;105:229). The course of noncirrhotic ascites is dependent on the underlying disease.

Cmplc: SBP (p 261) and HRS (p 265).

Diff Dx: Analysis of ascitic fluid and imaging the abdomen are usually sufficient to determine the cause of ascites.

Lab: Ascitic fluid is obtained by paracentesis to determine the underlying cause and to look for evidence of SBP in pts with a clinical deterioration. Paracentesis is safe even with mild to

moderate defects in coagulation (PT <2 × the normal value, platelet counts 50,000-100,000). Fresh frozen plasma or platelets are not needed prior to the procedure with these moderate hemostatic defects (Transfusion 1991;31:164). Risks are hematoma, infection, or, rarely, massive bleeding and death. Cell counts, albumin, total protein, culture (in blood culture bottles to improve sensitivity [Arch IM 1987;147:73]), and Gram stain are useful in most instances. The **serum-ascites albumin gradient** is calculated by subtracting the ascites albumin (in mg/dL) on an initial paracentesis from the serum albumin obtained the same day. A gradient of ≥1.1 gm/dL is indicative of portal HTN as the cause of ascites (Ann IM 1992;117:215). Total protein of <1.0 gm/dL predicts a high future risk of SBP. Cytology is obtained if the pt is not a known cirrhotic, has other findings to suggest malignancy, or has an ascites cell count of >500 lymphocytes. TB culture and AFB smear is considered if the cell counts show a large number of lymphocytes and the albumin gradient is <1.1. Triglycerides are obtained if the specimen looks milky to prove the presence of chylous ascites. Neutrophil counts >250 cell/mm^3 indicate infection (see SBP, p 261). Most pts with infected ascites have SBP, but some have peritonitis secondary to an intra-abdominal infection, such as a perforated viscus. In many of these cases, ascites total protein is >1.0 gm/dL, ascites LDH > serum LDH, and ascites glucose is <50 mg/dL (GE 1990;98:127). Pancreatic ascites (from a disrupted pancreatic duct) is identified by high amylase in ascitic fluid.

X-ray: US is very sensitive for the detection of ascites, and all pts with suspected ascites should undergo an imaging study to confirm the ascites and to look for evidence of malignancy. Cardiac echo may be needed to evaluate a cardiac cause of ascites.

Rx: (Hepatology 1998;27:264)

- *Diet:* Ascites disappears to the extent that sodium excretion exceeds sodium intake. The first step in rx is to limit intake. A 2-gm Na diet (= 88 mEq of Na) is about all that can be realistically expected. Extensive teaching is needed for the pt and his or her personal chef. Fluid restriction is needed only if there is significant hyponatremia. Restricting fluids to 1500 mL if Na falls below 130 seems prudent. Bed rest is not needed.
- *Diuretics:* (Nejm 1994;330:337) The combination of furosemide 40 mg po qd and spironolactone 100 mg po qd is a starting point for rx that often results in speedy diuresis without hypokalemia. Spironolactone can be given in 1 dose in the morning since the drug half-life is very long in cirrhosis (GE 1992;102:1680). If weight or urine Na excretion has not responded, then the dose should be doubled. The unusual pt who fails to respond can be treated with up to 160 mg furosemide and 400 mg spironolactone. Amiloride can be used in place of spironolactone (starting at 10 mg and increasing to 40 mg). This avoids gynecomastia, which can be seen with spironolactone, and amiloride has a faster onset of action (Adv Intern Med 1990;35:365).
- *Monitoring rx:* The pt monitors weight, aiming to lose 1 lb per day (or more if peripheral edema is present). If there is inadequate weight loss, urine volume and urine Na are measured to estimate Na balance. If a pt has a good response to diuretics, a high urinary excretion of Na is expected. The net Na balance can be calculated if urine Na and volume are measured. For example, if a pt on diuretics makes 2 L of urine with a urine Na concentration of 80 mEq Na/L, the pt's urinary Na excretion is 160 mEq/day. If the pt is compliant with a 2-gm Na diet, the intake is 88 mEq (there is 44 mEq Na in 1 gram NaCl). Therefore, the pt's net loss of Na is calculated as follows: **88 mEq** (what was eaten in a 2-gm Na diet) – **160 mEq** (sodium excreted in 2 L of urine at 80 mEq/L) = **72 mEq**

(net loss of Na per day). Since the average L of ascites has 128 mEq of Na in it (Adv Intern Med 1990;35:365), the pt would lose 72/128 = 0.56 L of ascites per day. If the pt has urine with a high volume and sodium content but fails to lose ascites, then diet noncompliance is likely. If urine Na and volume are low, then the response to diuretics has not been adequate and doses should be increased if possible. Diuretics can be stopped if the urinary sodium is very low on maximum doses. Rx is monitored with periodic lytes, BUN, and Cr to assess for excessive azotemia or electrolyte disturbances. Diuretic doses often need to be reduced in pts who respond well.

- *Tense ascites:* A total paracentesis should be performed at the outset in tense ascites for more rapid sx relief.
- *Refractory ascites:* About 10% of pts are resistant to diuretics. Repeated therapeutic paracentesis is effective for this group. The use of volume expanders to protect against azotemia is controversial. An RCT compared the use of 40 gm of albumin after each paracentesis vs placebo and showed that albumin prevented azotemia and hyponatremia (GE 1988;94:1493). However, mortality was not affected. Several small series indicate that clinically important azotemia is uncommon, and many experts question the importance of albumin given its great expense (GE 1991;101:1455). The plasma expander Dextran 70 is a cheap alternative to albumin (Dig Dis Sci 1992;37:79), but its use does not have the support of an RCT as does the use of albumin. Given the safety of albumin, the use of 8 gm of albumin for every L of ascites removed has been recommended (Lancet 1997;350:1309). TIPS (p 258) is an alternative in refractory ascites. It is effective in preventing recurrent ascites and may improve survival compared to large-volume paracentesis (GE 2007;133:825). The chief disadvantages of TIPS are shunt stenosis, hepatic encephalopathy, and cost. It may be best for pts without severe liver failure in whom frequent repeated paracentesis is needed but are not practical or desired by the pt. Liver transplantation is the ideal rx for pts with refractory ascites since it is the only intervention that will improve the otherwise dismal prognosis.
- *Shunts:* Peritonovenous shunts (eg, the LeVeen or Denver shunts) were developed in the 1970s as physiologic rx of ascites. Their value is severely limited by poor long-term patency and complications, including adhesion formation, that can make transplant difficult. Their use should be restricted to pts who have refractory ascites, are not transplant candidates, and are unable to have repeated paracentesis (Hepatology 1998;27:264).
- *Malignant ascites:* Repeated paracentesis is the usual rx. Some pts with ascites from massive intrahepatic mets may respond to diuretics (GE 1992;103:1302).
- *Hepatic hydrothorax:* This is defined as a pleural effusion in a pt with cirrhosis and no evidence of cardiopulmonary disease. It is due to movement of ascites across defects in the diaphragm and is seen in 4-10% of pts with ascites. It can be debilitating and is managed with thoracentesis, diuretics, TIPS, or transplant (Am J Med 1999;107:262).

15.3 Spontaneous Bacterial Peritonitis

Nejm 2004;350:1646; J Hepatol 2000;32:142; Semin Liver Dis 1997;17:203

Cause: Bacterial infection. Gram-negative aerobic bacteria and nonenterococcal *Streptococcus* are the most common organisms.

Epidem: The prevalence of spontaneous bacterial peritonitis (SBP) in cirrhotics on hospital admission is 10-30%.

Pathophys: Most episodes of SBP are thought to occur by translocation of bacteria from gut to mesenteric lymph nodes (J Hepatol 1994;21:792). Translocation implies movement of bacteria across an intact gut. Some cases may occur from seeding from another source (eg, lung, urinary tract).

Sx/Si: Some pts present with obvious peritonitis with severe pain, fever, abdominal tenderness, hypotension, and leukocytosis. Others present with milder sx of pain or with nonspecific sx such as worsened encephalopathy and azotemia. About one-third of pts may be initially asymptomatic.

Crs: Survival after SBP is only 30-50% at 1 yr.

Cmplc: Encephalopathy, renal failure, and death. Pts admitted to the ICU with SBP and shock have a very high incidence of adrenal insufficiency (68%) and testing/treatment should be considered in this setting (Hepatology 2006;44:1288).

Diff Dx: SBP is considered in pts with ascites who develop sx of pain, infection, or clinical deterioration. The major differential point is that of peritonitis secondary to an intra-abdominal process. Pts with secondary peritonitis often are infected with more than 1 organism and do not respond to antibiotics. They may have ascites with glucose <50 mg/dL, ascites LDH > serum LDH, or protein >1.0 gm/dL (GE 1990;98:127).

Lab: A diagnostic paracentesis should be done on admission to hospital or if during hospitalization pts develop abdominal pain, fever, leukocytosis, renal failure, or unexplained encephalopathy. SBP is diagnosed when PMN count is >250/mm^3, though counts are usually greater than 500/mm^3. If the tap is bloody, subtract 1 PMN for each 250 rbc present. Culture is obtained directly into blood culture bottles at the bedside. Culture will be negative in half of pts with suggestive sx and elevated PMN counts. Pts with PMN count >250/mm^3 and negative cultures are labeled "neutrocytic ascites" and have a clinical course and prognosis indistinguishable from culture-positive SBP (Dig Dis Sci 1992;37:1499). Those with counts <250/mm^3 and positive ascites cultures have bacterascites (Dig Dis Sci 1995;40:561). A repeat tap is done to determine which pts had early SBP and which had transient seeding of ascites, perhaps from another source such as pneumonia or UTI.

Rx:

- *Acute infection:* Antibiotics are begun when paracentesis shows PMN counts >250/mm^3. Cefotaxime 2 gm iv q 8 is the most studied choice. Aminoglycosides must be avoided. A variety of other agents including ceftriaxone, ceftazidime, amoxicillin-clavulanic acid, ciprofloxacin, norfloxacin, and ofloxacin are effective. If the pt develops SBP while on quinolone prophylaxis, cefotaxime should be used, though quinolone resistance is uncommon (J Hepatol 1997;26:88). A follow-up tap may be done 2 days later, and a 25% decrease in PMN count is expected. If the pt is responding clinically, the repeat tap may not be worth the risk. If rx appears to be failing, antibiotics are changed and the possibility of secondary peritonitis is reconsidered. The addition of iv albumin (1.5 gm/kg on dx and 1 gm/kg on day 3) to cefotaxime improves renal function and survival (mortality 10% in albumin/antibiotic group and 29% in antibiotic-alone group by RCT) (Nejm 1999;341:403). Albumin is indicated, especially in pts with impaired renal function,

but is very expensive (U.S. $5-25/gm). Pts with SBP should be evaluated for transplant and treated with SBP prophylaxis because of the poor prognosis.

- *Prophylaxis against a second episode of SBP:* (GE 2006;131:1049) In pts who have had a previous episode of SBP, norfloxacin 400 mg/day is suggested because of a 40-70% risk of recurrence (GE 1992;103:1267).
- *Primary prophylaxis:* Antibiotics appear to lower the risk of SBP and death in pts with advanced liver disease. In a study of pts with **low protein ascites** (<1.5 gm/dL) and either **advanced liver disease** (Child's score [p 31] ≥9 or bilirubin ≥3.0 mg/dL) or **renal insufficiency** (Cr ≥1.2 gm/dL or BUN 25 mg/dL or serum Na ≤130 mEq/L), norfloxacin 400 mg daily reduced the incidence of SBP, HRS (p 265), and death (GE 2007;133:818).
- *Prophylaxis in UGI bleeding:* Antibiotic prophylaxis should be given to cirrhotics with UGI bleeding (meta-analysis [Hepatology 1999;29:1655]). Oral norfloxacin 400 mg q 12 hr for 7 days is an effective regimen (GE 1992;103:1267), but combinations of other agents (amoxicillin-clavulanic acid with quinolones) have been used. Ceftriaxone 1 gm iv q 24 is more effective than oral norfloxacin in pts with advanced cirrhosis (defined as at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/d) (GE 2006;131:1049).

15.4 Hepatic Encephalopathy

Nejm 1997;337:473; Am J Gastro 1997;92:1429; Aliment Pharmacol Ther 1996;10:681

Pathophys: The pathogenesis of hepatic encephalopathy (HE) is not well understood. Elevations in blood ammonia are important, and most effective therapies are directed at lowering levels. Ammonia worsens brain function by inhibiting neurotransmission and synaptic regulation. Increased levels of serotonin (synthesized from high levels of tryptophan found in HE) and its metabolites may contribute to the sleep disturbance and depression seen in HE (The Neurologist 1995;1:95). It has been hypothesized that endogenous benzodiazepines, acting at GABA-benzodiazepine binding sites, contribute to HE. Alterations in the blood–brain barrier, zinc deficiency, manganese deposition, and disturbed ATPase function may play roles (Mayo Clin Proc 2000;75:501).

Precipitants: There are several common clinical events that may precipitate HE by a variety of mechanisms. Increased ammonia production may result from excessive dietary protein, digested blood in UGI bleeding, constipation, or infection. Ammonia may more easily cross the blood–brain barrier in hypokalemia, azotemia, and alkalosis. Decreased clearance of hepatic toxins may result from worsening liver function, HCC, TIPS, surgical shunting, or hypotension. Benzodiazepines or other psychoactive drugs may potentiate the abnormalities of HE. Fulminant hepatic failure (p 30) causes an encephalopathy associated with severe cerebral edema and is not discussed here.

Sx: Early-stage HE (called subclinical HE) is subtle. It causes impairment of complex activities such as driving a car or balancing a checkbook. As disease worsens there may be increasing levels of confusion, disorientation, and personality change, progressing to somnolence, stupor, and finally coma.

Si: Early-stage HE may only be evident on psychometric tests (such as connecting dots). Pts initially may have a mild tremor that may progress to asterixis. Asterixis is a momentary loss of tone that results in a flapping motion. It is best demonstrated by having the pt extend the wrists while holding arms outstretched. Asterixis can be seen in the tongue. As disease progresses, reflexes become hyperactive, and rigidity may develop. When coma develops, asterixis may not be detectable.

Crs: Generally the course is that of the underlying liver disease. Some pts have acute encephalopathy due to a reversible precipitant, and others have chronic sx in the absence of precipitants.

Diff Dx: The differential is broad. Important considerations are subdural hematoma (especially in alcoholics with coagulopathy), intracranial trauma, meningitis, stroke, tumor, abscess, and Wernicke's encephalopathy. Metabolic abnormalities such as hypoglycemia, hypoxia, uremia, electrolyte abnormalities, and encephalopathy induced by drugs should be considered.

Lab: In the evaluation of other causes of mental status change and possible precipitants of HE, a CMP, CBC, oxygen saturation, toxicology screen, urinalysis, and a paracentesis are usually indicated. EEG abnormalities are well described but are not pathognomonic. EEG is not usually helpful or necessary. A lumbar puncture may be selectively indicated.

X-ray: MRI or CT of the brain may be needed to exclude structural diseases.

Rx: Any precipitants should be identified and treated. In the early stages of rx, dietary protein can be restricted if necessary (to as low as 20 gm/day, increasing as the pt improves). In the long term, protein intake must be increased to the needed 1.0-1.5 gm/kg/day (BMJ 1999;318:1364). **Lactulose** is the cornerstone of rx, though high-quality trials supporting its use are lacking (BMJ 2004;328:1046). It works by reducing ammonia levels (and potentially levels of other toxins), by its cathartic effect, and by lowering colonic pH. The reduction in colonic pH decreases urease production by bacteria and traps ammonia in the lumen by converting it into hydronium ion. Lactulose is given in divided doses totaling 30-100 gm (or 45-150 mL) daily. The dose is adjusted to produce 3-4 soft stools daily. If sx are severe, 30 gm are given every 2 hr until the pt stools vigorously. Lactulose enemas can be given if oral rx is not possible. Pts with subclinical encephalopathy benefit from lactulose, and there should be a low threshold to empirically treat any pts with any suggestive sx in the setting of cirrhosis (Hepatology 1997;26:1410). Lactitol is a more palatable alternative not available in the U.S.

Rifaximin (a poorly absorbed oral antibiotic) 400 mg po tid is an effective but expensive treatment for HE (J Hepatol 2003;38:51). It appears to be at least as effective as lactulose but better tolerated (Pharmacotherapy 2008;28:1019). Because of its excellent side effect profile, it is now used instead of **neomycin** which causes ototoxicity and nephrotoxicity. **Metronidazole** (Gut 1982;23:1) is an alternative. Metabolism of ammonia to urea is zinc dependent, and zinc repletion may be important in deficient pts. **Sodium benzoate** reduces ammonia production and is another inexpensive alternative rx (Hepatology 1992;16:138).

Aromatic amino acids may produce false neurotransmitters that worsen encephalopathy. A diet rich in **branched chain amino acids** may be useful in malnourished cirrhotics who do not tolerate oral protein (Hepatology 1984;4:279). The use of branched chain preparations in parenteral formulations is usually unnecessary (Hepatology 1994;19:518).

15.5 Hepatorenal Syndrome

Lancet 2003;362:1819

Pathophys: The dx of hepatorenal syndrome (HRS) requires (1) chronic or acute liver disease with liver portal HTN; (2) Cr >1.5 or Cr clearance <40 cc/min; (3) no evidence of shock, bacterial infection, excessive fluid loss, or recent use of nephrotoxic drugs; (4) no sustained response to 1.5 L of saline as a challenge; (5) proteinuria <500 mg/day; and (6) no evidence of obstruction on US. Variable features include a urine volume <500 mL/day, urine Na <10 mEq/L, urine osmolality < plasma osmolality, serum Na <130, and no hematuria (Liver Transpl 2000;6:287). When renal failure progresses rapidly (50% worsening in under 2 weeks), the disorder is called type 1 HRS. In type 2 HRS, there is steady deterioration over weeks to months.

HRS is functional in that kidneys from pts who die of HRS can be successfully transplanted with normalization of renal function. The imbalance of vasoconstrictors and vasodilators as a result of the cirrhosis seems crucial. It has been hypothesized that some other direct message is sent from liver to kidney resulting in the intense vasoconstriction, but the nature of that message has not been determined. Precipitating events are volume depletion, paracentesis, overdiuresis, bleeding, infection, x-ray dye, NSAID use, and worsening liver function.

Sx: Those with type 1 HRS usually have Child-Pugh grade C cirrhosis (p 31) and have the clinical findings of advanced liver disease with jaundice. Those with type 2 HRS are likely to have less severe liver disease and usually have diuretic-resistant ascites.

Si: Those of end-stage liver disease (p 26).

Crs: Most pts with type 1 HRS die within 2 weeks. Those with type 2 survive a few months.

Diff Dx: HRS is a dx of exclusion made when renal failure occurs in the setting of advanced liver disease. Almost all pts have ascites. Other causes of renal failure need to be excluded, including volume depletion, nephrotoxic drugs, intrinsic renal disease, sepsis, and obstruction.

Lab: See definition of HRS in Pathophys.

X-ray: US is indicated to rule out obstruction.

Rx: Type I pts require urgent intervention. Inadequate central volume is excluded by monitoring central volume, sometimes with a Swan-Ganz catheter. Diuretics are stopped, nephrotoxic agents are held, and infection is treated. If the pt gets better with these measures, he or she does not have HRS. A variety of medical therapies have been tried with limited success. Current evidence supports the use of midodrine (a vasoconstrictor) with octreotide (to inhibit endogenous vasodilator release), which has been effective in uncontrolled studies (Dig Dis Sci 2007;52:742; Hepatology 1999;29:1690). The combination of terlipressin (an ADH analogue that is a splanchnic vasoconstrictor) and albumin was effective in a small RCT (GE 2008;134:1352). Terlipressin is not available in the U.S. N-acetylcysteine has been of benefit in a small, uncontrolled trial (Lancet 1999;353:294). Noradrenaline and albumin were effective in a pilot study (Hepatology 2002;36:374). TIPS has been effective in improving renal function in a small number of pts (Hepatology 1998;28:416). Dialysis and peritoneovenous shunting do not improve outcome, unless as a

bridge to transplant. Liver transplant is effective, but survival is diminished compared to transplantation in pts without HRS (Transplantation 1995;59:361). HRS might be prevented by prophylaxis against SBP and by treating SBP pts with iv albumin (p 261).

15.6 Hepatopulmonary Syndrome

Nejm 2008;358:2378; Lancet 2004;363:1461

This syndrome is the combination of pulmonary vascular abnormalities with hypoxemia in the setting of advanced liver disease. Pts have intrapulmonary vascular dilatations and direct arteriovenous shunts. Hypoxia often worsens in the upright position. Dx is confirmed by contrast-enhanced echocardiography and lung scanning. Liver transplant is especially beneficial in pts whose hypoxemia responds to 100% oxygen (and presumably have fewer shunts) (Mayo Clin Proc 1997;72:44).

15.7 Portopulmonary Hypertension

Lancet 2004;363:1461; Clin Chest Med 1996;17:17

A small number of pts with advanced liver disease develop pulmonary HTN due to a vasoconstrictive/obliterative process of pulmonary vessels. Pts present with dyspnea and near syncope. The dx is confirmed by right heart catheterization. Epoprostenol (a pulmonary vasodilator) improves hemodynamics and may be a bridge to liver transplant (Hepatology 1999;30:641). Transplant mortality is high if pulmonary HTN is moderate to severe.

Chapter 16

Vascular Liver Disease

16.1 Budd-Chiari Syndrome

Nejm 2004;350:578; J Clin Gastro 2000;30:155; Brit J Surg 1995;82:1023

Cause: Budd-Chiari syndrome is caused by obstruction of the normal hepatic venous outflow. This can occur at the level of the hepatic veins or in the vena cava. Many diseases can result in venous obstruction. **Mechanical** causes include congenital membranous obstruction of the IVC (common in Asia) or posttraumatic, postsurgical, or invading malignancy such as HCC. **Hypercoagulable** causes include paroxysmal nocturnal hemoglobinuria; polycythemia vera; other myeloproliferative disorders; deficiencies of protein C, S, or antithrombin III; estrogens; or other hypercoagulable states. About 30% of cases are idiopathic.

Epidem: In a large U.S. series, 83% of pts were women, and the mean age was 37 yr (range 14-68) (Ann Surg 1990;212:144).

Pathophys: There are 3 hepatic veins that drain the liver. The course of the Budd-Chiari syndrome is determined by the degree of obstruction of these veins and the acuity of onset. When obstruction occurs, there can be increase in the direct flow from the caudate lobe to the IVC. This results in caudate hypertrophy that may be seen on imaging studies. Venous obstruction causes hypoxia and increased sinusoidal pressure, with resultant hepatomegaly and varying degrees of liver failure. When onset is sudden and massive, FHF may occur (p 30). When the obstruction is gradual or limited, portal HTN (ascites and varices) is a greater problem than hepatocellular failure.

Sx: The sx can vary widely, as indicated. There may be evidence of RUQ pain from Glisson's capsule distention, distention from ascites, and a complaint of generalized weakness (Lancet 1993;342:718).

Si: Ascites is almost universal. Tender hepatomegaly is common with acute presentations. Prominent veins may be seen over the abdominal wall or back. Those with acute presentations may also have evidence of hepatic encephalopathy or hepatorenal syndrome. Those with chronic presentations predominantly have findings of portal HTN and cirrhosis. Leg edema is common with IVC obstruction.

Crs: Mortality is almost universal if the disease is not treated. The course varies widely depending on the extent and acuity of obstruction and the underlying predisposing condition. If hepatic venous drainage can be restored, the majority of pts survive long term (Gut 1999;44:568).

Cmplc: Liver failure, variceal hemorrhage, encephalopathy.

Diff Dx: The disease needs to be considered in any pt presenting with ascites and a tender liver. Some pts present with evidence of portal HTN or cirrhosis. The usual pitfall in dx is to fail to consider this unusual disease. Once this disease is considered, the dx can usually be made by imaging studies. The broad diff dx is that of jaundice or cirrhosis (p 30).

Lab: Liver bx, which is characteristic, shows centrilobular congestion and necrosis with dilated sinusoids. LFTs vary widely depending on the severity of illness. Transaminases are typically 8 × normal and alk phos 3 × normal. Hypoalbuminemia and elevated PT are common.

X-ray: Doppler US of the hepatic veins is the initial study. Positive exams are confirmed by angiography. CT or MRI may show evidence of clot. Hypertrophy of the caudate lobe may be seen on any imaging study.

Rx: Pts whose obstruction is due to malignancy should receive palliative care. Thrombolysis can be used in acute thrombosis. Those with a reversible degree of liver failure and focal obstruction (eg, IVC web, short lengths of hepatic vein occlusion) can be treated with angioplasty (Lancet 1993;342:718) with or without stent placement. Anticoagulation is used after angioplasty (Gut 1999;44:568). If the clot is extensive and liver dysfunction is not too severe, surgical shunts have been used but are falling out of favor due to lack of survival benefit (Clin Liver Dis 2009;13:127). With severe liver dysfunction, liver transplantation is the best option, with a TIPS as a temporizing measure (Am J Gastro 1999;94:603). An underlying hematologic disorder should be sought and treated if found.

16.2 Venoocclusive Disease

Venoocclusive disease (VOD) is a nonthrombotic obliteration of the intrahepatic veins by loose connective tissue (Am J Med 1986;81:297). It causes jaundice, RUQ pain, ascites, weight gain, and hepatomegaly. It is almost exclusively seen in stem cell transplant pts. No single rx is highly effective, and morbidity and mortality are substantial (Br J Haematol 1999;107:485; Mayo Clin Proc 2003;78:589).

16.3 Ischemic Hepatitis (Shock Liver)

Am J Med 2000;109:109; J Clin Gastro 1996;22:126

Epidem: The epidemiology is that of the underlying cardiac disease that predisposes to the illness.

Pathophys: The precise mechanism of hepatic injury in ischemic hepatitis is unknown. Hypotension is the typical inciting insult. However, hypotension alone does not explain the syndrome. Trauma pts are hypotensive but rarely develop ischemic hepatitis. The major difference between pts with trauma and ischemic hepatitis is that the latter pts almost always have heart failure (Am J Med 2000;109:109). CHF causes passive congestion of the liver with

resultant necrosis, and in severe cases can cause cardiac cirrhosis (Sherlock S, Dooley J. Diseases of the liver and biliary system. 10th ed. Boston: Blackwell Science, 1997:196-199). A sudden ischemic insult presumably causes abrupt hepatocellular damage in a pt predisposed to injury by underlying passive congestion from CHF.

Sx/Si: Usually pts are critically ill, and they may have many sx and signs associated with CHF.

Crs: The course is determined by the underlying illness.

Cmplc: There are no convincing data to suggest liver sequelae.

Diff Dx: The major differential points are viral hepatitis and toxic hepatitis from drugs. However, those illnesses are usually not associated with such a sudden and massive rise and rapid fall of transaminases.

Lab: Pts with underlying CHF commonly have elevated bilirubin (>2 mg/dL in one-third of pts, and at times much higher) with normal alk phos and mild transaminase abnormalities. With an acute bout of ischemic hepatitis, the laboratory picture is so distinctive that the dx is easy to make. Following a clinical insult, typically hypotension in a CHF pt, there is a rapid rise of transaminases to >20-200 × normal (Am J Gastro 1992;87:831). The values then fall steadily over the next week to normal or near normal. The PT/INR is often elevated (J Clin Gastro 1998;26:183). Hypoglycemia occurred in one-third of pts in one adult series (J Clin Gastro 1998;26:183). Bx is not needed, but if done (at autopsy), shows midzonal (GE 1984;86:627) or centrilobular necrosis (Dig Dis Sci 1979;24:129).

Rx: The rx is that of the underlying hypotension and cardiac illness.

16.4 Portal Vein Thrombosis

Am J Gastro 2002;97:535; Am J Med 1992;92:173

Portal vein thrombosis is a rare cause of portal HTN. It occurs in young children (usually due to intra-abdominal infection) and in middle-aged adults. Causes include cirrhosis, neoplasia (pancreatic cancer and HCC), infection, pancreatitis, myeloproliferative disorders, and hypercoagulable states. Many other uncommon causes have been described. The dx is made by Doppler US of the portal vein. If that is a limited quality study, MRI or CT is done. In acute cases, there may be a role for thrombolysis or anticoagulation. In chronic cases, rx is usually directed at associated variceal hemorrhage.

Chapter 17

Liver Disease in Pregnancy

Am J Gastro 2004;99:2479; Nejm 1996;335:569

Liver disease in pregnancy may represent a disease present at conception, a disease acquired unique to pregnancy, or a disease acquired coincident with but not unique to pregnancy. Pregnancy results in several changes in LFTs that might be interpreted as pathologic. Albumin falls 10-60% in the second trimester, and alk phos rises to 2-4 × normal in the third trimester. Transaminases remain normal. There are several hepatic disorders unique to pregnancy, including:

Hyperemesis gravidarum, intractable vomiting seen in the first trimester, can be associated with mild transaminase abnormalities (usually <2 × normal).

Intrahepatic cholestasis of pregnancy presents as pruritus, generally in the third trimester of pregnancy. Jaundice follows pruritus in 20-60% of women. Bilirubin is usually <6 mg/dL, alk phos is 4 × normal, and transaminases are 2-10 × normal. Serum bile acids are markedly elevated. There is an increased risk of premature delivery or stillbirth. Vitamin K is given prophylactically to prevent deficiency due to malabsorption. Ursodeoxycholic acid improves itch and LFTs, and reduces preterm deliveries more effectively than cholestyramine (GE 2005;129:894).

Preeclampsia/eclampsia is a disorder in which the liver is 1 of several target organs. Abnormal transaminases are frequent in moderate to severe disease but are usually less than 500 U/L. **Hepatic rupture** is a rare, catastrophic event typically associated with preeclampsia/eclampsia.

HELLP syndrome and **acute fatty liver of pregnancy** are discussed in the following sections.

17.1 HELLP Syndrome

Obstet Gynecol 2004;103:981; J Perinatol 1999;19:138; Am Fam Phys 1999;60:829

Cause: Unknown.

Epidem: HELLP is a catchy acronym for **h**emolysis, **e**levated **l**iver enzymes, and **l**ow **p**latelets. Pts with HELLP are a subset of the pts with hypertensive disorders of pregnancy who are at risk for a more severe course. HELLP has an incidence of about 2-6/1000 pregnancies and is seen

in about 4-12% of pts with preeclampsia or eclampsia (Am Fam Phys 1999;60:829). The onset is usually in the third trimester.

Pathophys: (Jama 1998;280:559) The pathophysiology of this disorder, like that of preeclampsia, is not understood. Endothelial injury from a placental toxin and an enhanced thrombotic tendency may be important. Platelets become activated, resulting in vasospasm, platelet aggregation, and further damage. In the liver, damage to endothelium results in fibrin deposition in hepatic sinusoids with hemorrhage and hepatocyte necrosis. The disorder usually occurs with preeclampsia but may occur on its own.

Sx: RUQ pain is an important clue. Malaise, nausea, vomiting, and headache are typical. Seizures may occur.

Si: HTN (> 30/15 over baseline or > 140/90) is present in 85%. RUQ tenderness and edema are common. Hyperreflexia may be detected.

Crs: Maternal mortality is 1-4% from a variety of causes, including hepatic rupture, pulmonary embolus, and hypoxic encephalopathy. Perinatal mortality is 5-20% and is largely dependent on gestational age and birth weight.

Cmplc: Hepatic rupture is a dreaded complication that occurs in 1% of pts. Ascites, pleural effusions, pulmonary edema, or multisystem organ failure may occur.

Diff Dx: The findings may suggest viral illness, musculoskeletal pain, cholecystitis, hepatitis, PUD, pyelonephritis, nephrolithiasis, ITP, other microangiopathic anemias, and acute fatty liver of pregnancy (Jama 1998;280:559).

Lab: Hemolysis is proven by a low haptoglobin level and sometimes occurs with evidence of a microangiopathic process (schistocytes, burr cells). ALT and AST are elevated and platelets are <100,000/mL. Proteinuria is typical.

Rx: Delivery is indicated as soon as there is a reasonable chance of fetal survival. Management in stable pts far from term (when fetal lungs are immature) is controversial (Hepatology 2008;47:1067). Bed rest, magnesium sulfate to prevent seizures, and blood pressure control are adjunctive therapies

17.2 Acute Fatty Liver of Pregnancy

Semin Perinatol 1998;22:134; Nejm 1996;335:569

Cause: Defects in mitochondrial fatty acid oxidation.

Epidem: This is a rare disorder occurring in 1/13,000 deliveries. It is more common in a first pregnancy or when the mother is carrying multiple fetuses.

Pathophys: Understanding of the pathogenesis is evolving. It has been recently noted that mothers who carry a fetus homozygous for a defect in the long chain 3-hydroxyacyl-CoA (LCHAD) gene are at very high risk for the disease (Curr Gastroenterol Rep 2008;10:15). This is an enzyme important in fatty acid oxidation. Other defects in short- and medium-chain fatty acid metabolism may be important. The histologic hallmark of the disorder is microvesicular fatty infiltration of hepatocytes.

Sx/Si: Pts present in the third trimester. The most common initial sx are nausea and vomiting (76%), abdominal pain (43%), anorexia (21%), and jaundice (16%). Pruritus is uncommon. Late findings can include asterixis or coma, and deterioration can occur rapidly. Half of pts have preeclampsia. The liver is usually normal or small.

Diff Dx: Considerations include HELLP, viral or drug hepatitis, and biliary tract disease. In HELLP, the bilirubin is usually <5 mg/dL, and hypoglycemia is rare. In practice, it is not essential to distinguish the HELLP syndrome from acute fatty liver of pregnancy by liver bx since the rx is the same for both.

Crs: Maternal mortality is less than 10% with disease recognition and rx (Semin Perinatol 1998;22:134). Fetal mortality is <20% (Nejm 1996;335:569). Recurrence is uncommon with a subsequent pregnancy, but it does occur. The illness resolves rapidly with delivery.

Lab: ALT is elevated but is typically <1000 U/L. Bilirubin is usually elevated, except in mild cases. Hypoglycemia and elevated PT are common in severe disease. Thrombocytopenia is common, but DIC is seen only in more severe cases.

X-ray: US may show fat and excludes biliary obstruction as the cause of jaundice.

Rx: Rx is prompt delivery and supportive care for hypoglycemia, coagulopathy, and encephalopathy. Liver transplant has been used in rare instances (Hepatology 1990;11:59).

Chapter 18

Procedures

Comment: Because the endoscopist may not meet the pt until minutes before the procedure, particularly in open-access systems, it is important that a clinician be able to describe to the pt the experience and the more common complications of endoscopy prior to referral for the procedure. The list of complications listed here is not comprehensive but is a reasonable list to use in discussions with pts.

18.1 Upper Endoscopy (EGD)

Description: The pt is kept npo, brought to the unit, and an iv is placed. The pt lies left lateral decubitus and is sedated. Moderate sedation with midazolam and a narcotic is commonly used, but deep sedation with propofol is becoming more popular. A mouthpiece is placed to protect the teeth and the endoscope. The endoscope is passed and the upper tract examined. Gagging and belching may occur but are usually minor. Breathing is not significantly affected by the instrument. The procedure is not generally painful and takes 10-15 min after sedation. Amnesia is common but not universal with moderate sedation. If abnormalities are seen, bxs (which are painless) may be taken and strictures may be dilated (p 44). Endoscopic rx is possible for bleeding ulcers (p 75) or varices (p 255). Pts cannot drive or work for 24 hr after the exam because of the sedation.

Complications: (Gastrointest Endosc Clin N Am 1996;6:287) Perforation (< 1/5000 if no dilatation, < 1/500 if esophageal dilatation is needed), bleeding, infection, adverse reaction to sedation, failure to detect important abnormalities. Minor problems include sore throat (not commonly) and iv site phlebitis.

18.2 Colonoscopy

Description: The pt undergoes a bowel prep, generally with polyethylene glycol solution. Na phosphate is out of favor as a prep due to concerns about renal injury. The pt is kept npo, brought to the unit, and an iv is placed. The pt lies left lateral decubitus and is sedated. Moderate sedation with midazolam and a narcotic is commonly used, but deep sedation with propofol is becoming more popular. The colonoscope is advanced to the cecum in >95% cases in competent hands. Cramps are common during the advance, but the sedation makes

it very tolerable for most pts. Sometimes the pt changes positions or the assistant palpates the abdomen to aid the advance of the scope. Polyps are removed and bxs are taken, both of which are generally painless. The exam lasts 15-30 min depending on the quality of the prep, the ease of the exam, and the need for rx. The pt may feel gassy, bloated, or crampy because of insufflated air for up to several hr after the procedure. Pts cannot drive or work for 24 hr after the exam because of the sedation.

Complications: (Gastrointest Endosc Clin N Am 1996;6:343) Risks include perforation (< 1/1000 if no polypectomy; higher with polypectomy) that may require urgent surgery, possibly with a temporary colostomy. Bleeding is uncommon and occurs in 0.07% of diagnostic studies and in 1.2% of procedures with polypectomy. Bleeding is more common after the removal of large polyps. Bleeding might require transfusion, a second procedure (for endoscopic control of bleeding), or surgery. Infection, adverse reaction to sedation, and failure to detect important abnormalities may occur. Minor problems include iv site phlebitis and perianal irritation from the prep and scope.

18.3 Sigmoidoscopy

Description: Same as colonoscopy, though the exam is often done without sedation and usually takes less than 10 min.

Complications: (Gastrointest Endosc Clin N Am 1996;6:343) Same as with colonoscopy, though the perforation rate is much lower (1-2/10,000).

18.4 Endoscopic Retrograde Cholangiopancreatography

Description: The pt experience for endoscopic retrograde cholangiopancreatography (ERCP) is the same as for EGD, but the position on the table is semiprone. The exam takes 10-60 min depending on complexity. Stones may be removed or stents placed, depending on the findings. The exam is generally done in situations where therapy is likely to be needed, and deep sedation is typically used.

Complications: (Gastrointest Endosc Clin N Am 1996;6:379) Pancreatitis is the most frequent complication of ERCP and occurs in 3-7% of pts. It can be severe but usually is not. Perforation or bleeding may occur in 1-2% after sphincterotomy and is usually managed without surgery. Cholangitis may occur if the biliary tree is obstructed, and antibiotics are usually given prophylactically. The other complications are those of EGD.

18.5 Percutaneous Endoscopic Gastrostomy

Description: A diagnostic EGD is done, and the pt is placed supine with the scope in the stomach. An area about two-thirds the distance from umbilicus to left costal margin is prepped, draped, and injected with lidocaine. A catheter with a stylet is passed into the stomach, and through the catheter a long suture is passed and brought out through the mouth when the endoscope is withdrawn. The feeding tube is attached to the suture

(several techniques exist), and the tube is pulled into place in the stomach. Mild discomfort at the site is common for 2-3 days. When the tube is no longer needed, it is usually pulled out by traction through the abdomen, and the hole rapidly seals over. Oral intake is possible with the tube in place.

Complications: (Gastrointest Endosc Clin N Am 1996;6:409) Because most pts undergoing PEG are ill, complications are frequent. Major complications occur in 2.7% of pts and include aspiration, peritonitis, perforation, gastrocolic fistula, necrotizing fasciitis, tumor implant at stoma, tube migration, or accidental removal. Minor complications include wound infection and leakage and occur in 6-7% of pts. Procedure-related death occurs in 0.7% of pts.

18.6 Liver Biopsy

Description: The pt lies supine, and an area in the midaxillary line overlying the liver is identified for bx, usually using US. The area is prepped and draped, and lidocaine is injected. The pt is asked to inhale, exhale, and stop breathing, at which time the bx is obtained. The bx is an odd sensation that many people liken to being punched, but the immediate pain is usually minimal. Over the minutes following the bx, pain often increases and is sometimes felt in the shoulder. Pain is managed in some pts with analgesics. In only a tiny percentage of pts is the pain severe. The pt is observed for 1-6 hr and discharged. About 3% of pts having bx require admission.

Complications: (Ann IM 1993;118:96) Complications occur in up to 3% of pts and include severe pain, bleeding, bile peritonitis, hemothorax (rare), and perforation of a viscus (rare). Most complications resolve without intervention. Transfusion can be required. Death occurs in 0.01% of pts.

18.7 Liver Transplantation

Postgrad Med 2004;115:73; Dis Mo 1999;45:150; Int Surg 1999;84:297

Description: Liver transplantation is the most useful rx for end-stage liver disease. Practice guidelines have been developed (Liver Transpl 2000;6:122). The most common indications are end-stage chronic viral hepatitis, alcoholic liver disease, cryptogenic cirrhosis, PBC, PSC, and FHF. Pts should be evaluated for transplant when their survival without a transplant becomes less than it would be with a transplant. This includes pts with Child-Pugh grade B or C cirrhosis (p 31), diuretic resistant ascites, HRS, SBP, severe encephalopathy, and variceal hemorrhage. Quality of life, rather than life expectancy, may be the issue for pts with pruritus, recurrent bouts of cholangitis, or sx of the portopulmonary syndrome. The major contraindications are HIV positivity, active alcohol or illicit drug use, extrahepatic malignancy, cholangiocarcinoma, systemic infection, lack of portal venous inflow, and advanced cardiopulmonary disease. Pts need adequate social and family supports to deal effectively with the complexities of posttransplant rx. Pts undergo a comprehensive evaluation of cardiopulmonary status, renal function, portal vein patency, and psychosocial, psychiatric, and financial circumstances.

The major limitation is the scarcity of organs. In the U.S., the United Network for Organ Sharing (UNOS), has developed a system for organ allocation based on disease severity.

Since 2002, allocation is based on the Model for End-Stage Liver Disease **(MELD)** score (Hepatology 2001;33:464). This score is based on objective criteria including bilirubin, Cr, and INR; time on the transplant list is no longer a factor. Because of the scarcity of organs, the wait is long and varies by geographic location. Split liver transplantation allows living donor transplantation and doubles the organs available for cadaveric transplantation. Living donor transplantation is associated with improved survival compared with waiting for a cadaveric transplant (GE 2007;133:1806).

The liver is harvested from the donor and can last up to 12 hr in preservative solution. Through a large bilateral subcostal incision with xiphoid extension, the native liver is removed after the pt is put on venous bypass. The anastomoses are made beginning with the vena cava followed by the portal vein to allow reperfusion. The bile duct is done with an end-to-end anastomosis, except in PSC when a Roux-en-Y choledochojejunostomy is done.

Complications: Within the first 3 days, hemorrhage, graft nonfunction, and hepatic artery thrombosis may occur. Acute cellular rejection, neurologic complications, and biliary complications occur in the first few weeks. Late complications include opportunistic infections and ductopenic rejection. Lymphoproliferative disorders are the major malignancy seen in transplant pts. Many diseases can recur in transplant pts, especially hep B and hep C.

Long-Term Rx: Immunosuppression is usually achieved with cyclosporine or tacrolimus along with azathioprine and prednisone. This multidrug rx results in a number of problems, including HTN, azotemia, obesity, diabetes, infection, and bone disease.

18.8 Enteral Nutrition

Dis Mo 1997;43:349; GE 1995;108:1280

Description: Enteral nutrition via feeding tubes is widely used in hospitalized pts. Tube feeding is considered for all pts who go 1-2 weeks without nutrition, who cannot take adequate oral calories, and in whom a feeding tube can be placed. Nasoenteric tubes are used for short-term feeding. If a tube can be placed beyond the third portion of the duodenum, there is a reduced risk of aspiration, so this should be attempted. Most pts can be fed with bolus infusions, but continuous infusions are used for jejunal feeding or in pts with reflux. PEGs are indicated when prolonged tube feeding is expected. Isotonic polymeric formulations are almost always sufficient to meet nutritional needs. Additional free water is usually required. Elemental formulas are reserved for pts with short bowel syndrome.

Complications: Aspiration can occur after gastric feeding. The risk can be minimized by elevation of the head of the bed with feeding, continuous rather than bolus feeding for those at risk, checking for gastric residuals, and monitoring sx. Diarrhea is common and may have many causes that should be evaluated and treated. Many uncommon nasoenteric tube complications may occur, and care must be taken to avoid feeding the lungs!

18.9 Parenteral Nutrition

Dis Mo 1997;43:349

Description: Parenteral nutrition (PN) can be lifesaving in severely malnourished pts who cannot be fed enterally. Its efficacy has been established in a limited number of conditions. However, there is no clear benefit of PN in many of the conditions in which it is used (Jama 1998;280:2013). It should only be used where the enteral route is not available. Specific indications are beyond the scope of this summary. PN can be given through a peripheral vein in large-volume solutions or through a central vein in more concentrated solutions. The formulation of PN is based on an assessment of nutritional status and the underlying disease. Elements of the PN formula include (1) protein given as amino acids (0.8-1.5 gm/kg per day depending on clinical state); (2) glucose to provide about 50-60% of calorie requirements; (3) lipid emulsion to provide 25-30% of calorie requirements; (4) electrolytes (including Na, K, phosphate, Cl, and acetate if a source of bicarbonate is needed); (5) vitamins; and (6) trace elements (Zn, Cu, chromium, and manganese). H2RAs and heparin may be added. Some other trace elements (iodine, selenium, molybdenum) may be needed in prolonged PN. Vitamin K is not included in multivitamin preparations and is given separately.

Complications: Numerous complications occur from the central venous catheter. These include pneumothorax, air embolus, hemothorax, catheter sepsis, and venous thrombosis. Metabolic abnormalities that result from parenteral feeding include hyperglycemia and electrolyte abnormalities. Parenteral nutrition can especially increase the risk of complications if given to well-nourished, obese, or hyperglycemic pts (Nat Clin Pract Gastroenterol Hepatol 2007;4:260). Elevated transaminases are common at the beginning of rx and usually resolve. Cholestasis, steatosis, and steatohepatitis may develop (GE 1993;104:286), and hepatic failure has been seen with long-term feeding. Refeeding syndrome may occur in severely malnourished pts.

Chapter 19

Pearls in Gastroenterology

- Today's pearls are tomorrow's fecaliths.
- The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is a valuable resource for pt education materials. Information is distributed through the National Digestive Diseases Information Clearinghouse (NDDIC). Publications are available online, and copies suitable for distribution to pts can be ordered at their Web site: http://catalog.niddk.nih.gov/materials.cfm?CH=NDDIC.
- GERD is a frequently mismanaged illness. Physicians often underestimate the impact GERD has on quality of life and dismiss it as a minor problem not worthy of aggressive therapy (p 33).
- Hp infection limited to the antrum might worsen reflux by increasing acidity. However, more commonly (especially in the developing world), Hp gastritis infects the antrum and body of the stomach, and the resultant gastritis reduces acid production and reduces the incidence of GERD (p 34).
- Most PPIs must be given 30 min to 1 hr prior to breakfast for optimal effect because they require meal-stimulated parietal cell pH drop for effective binding. H2RAs should not be given prior to PPI doses, as they block PPI binding (see p 37).
- Many pts with dysphagia and recurrent episodes of food impaction will not volunteer this important hx unless asked. Since most dysphagia is readily treatable, this sx must not be overlooked (p 6).
- Pts with reflux-related strictures should be maintained on PPIs (not H2RAs) to reduce the risk of recurrence (p 45).
- Though surveillance for Barrett's esophagus is widely performed in the U.S., its benefits are far from proven, its costs are high, the yield is modest, and the optimum surveillance strategy has not yet been determined (p 41).
- Gastritis is best considered a histologic term. There are no consistent sx or endoscopic findings that correlate with the microscopic appearance of gastritis (see p 63).
- There is little point to obtaining a UGI series in the evaluation of dyspepsia. The sensitivity of UGI series for ulcers and esophagitis is limited. If the UGI series shows a gastric ulcer, EGD is done to rule out malignancy, and if the UGI is negative, EGD is still needed for dx (p 2).
- In pts with refractory peptic ulcers, ongoing NSAID use must be excluded by random salicylate levels, NSAID levels, and questioning of relatives. Pts who continue to use

NSAIDs in the face of ulcer disease have a high incidence of stenosis and multiple operations (p 71).

- Consider the possibility of past or present physical or sexual abuse in pts with complaints that sound functional and do not respond readily to routine measures and in pts who have seen multiple providers for the same complaint (p 96).
- Colorectal cancer is the second-leading cause of cancer death in the U.S., with a lifetime incidence of 5% (p 131).
- Most cases of colon cancer associated with the hereditary nonpolyposis colon cancer syndrome (HNPCC) go unrecognized because clinicians are unaware of its existence (p 144).
- Diverticular bleeding is arterial. Thus, it tends to be fairly large volume and abrupt in onset (p 99).
- Nuts and popcorn lower, rather than raise, the incidence of symptomatic diverticular disease (p 100).
- Fecal incontinence is frequent, but pts are reluctant to discuss it. They will often complain of excessive flatus, diarrhea, and urgency rather than recognize incontinence as the cause of sx (p 176).
- Acute mesenteric ischemia (p 181), chronic mesenteric ischemia (p 182), and ischemic colitis (p 183) are 3 distinct syndromes with differing sx and signs. They are frequently misdiagnosed.
- All too often, pts suffer with undiagnosed fecal impactions or are not aggressively and promptly treated after the dx is made (p 177).
- Contrary to traditional teaching, there is no evidence that fatty food intolerance, belching, or bloating are sx of gallbladder disease (p 201).
- HIDA scan with ejection fraction is widely used to select pts for cholecystectomy with suspected acalculous gallbladder disease, but there is no high-quality evidence to support the value of this approach (p 4).
- The painful rib syndrome is a commonly overlooked cause of RUQ pain, for which there is a characteristic hx and exam (p 213).
- Genetic hemochromatosis pts will be found in almost all primary care practices, but the onset of sx is typically 10 yr prior to the time of dx (p 238).
- The incidence of hepatocellular carcinoma is rising in the West and will continue to do so because of hep C (p 247).
- Pts with cirrhosis should undergo endoscopy to look for varices because prophylactic medical therapy reduces the bleeding rate (p 255).
- Ischemic hepatitis (shock liver) has a spiking pattern of transaminases that is diagnostic in the appropriate clinical setting (p 268).
- An elevated PT in a pt with evidence of UGI bleeding may be a clue to varices as the cause (p 255).
- Pts admitted to the ICU with spontaneous bacterial peritonitis and shock have a very high incidence of adrenal insufficiency, and testing/treatment should be considered in this setting (p 261).
- Concise summaries of available guidelines for GI and liver diseases can be accessed at http://www.guideline.gov.
- The best names for authors of GI literature include: **Butt** (Medicine 1987;66:472), **Terdiman** (Clin Gastroenterol Hepatol 2008;6:616), and **Neugut** (Jama 2009;302:688).

Index

5-aminosalicylates, 109–118
6-mercaptopurine, 109, 116

A

Abdominal aortic aneurysm, 4, 185
Abdominal pain, 1–6
    dyspepsia, 2–4
    history in, 1
    physical exam in, 2
Abetalipoproteinemia, 20
Abscess, anorectal, 175
Absorption, 20
Abuse
    physical, 96–97
    sexual, 96–97
Acetaminophen overdose, 253–254
Achalasia, 53–54
Acute fatty liver of pregnancy, 272–273
Acute intermittent porphyria, 244–245
Acute mesenteric ischemia, 181–182, 282
Adalimumab, 110, 111
Adenoma
    colonic, 141
    hepatic, 250
Adenomatous colonic polyps, 141–144
Aeromonas, 163
Aerophagia, 9
Albumin, 28, 260–262
Alcoholic liver disease, 251–253
Aloestron, 96
Alpha-1 antitrypsin deficiency, 243–244
Amebiasis, 164–165
Aminosalicylates, 115
Amitriptyline, 95, 194
Ammonia, 263, 264
Amoxicillin, 67
Amoxicillin-clavulanate, 100, 170, 236
Ampullary cancer, 209
Amsterdam criteria, 145
Anal cancer, 179
Anal fissure, 174–175
Anemia, iron deficiency, 25
Angiodysplasias. *See* Angioectasias
Angioectasias, 184–185
Anomalous union of the
        pancreaticobiliary duct, 188, 190
Anorectal fistula, 175–176
Anorectal manometry, 13, 179
Antibiotic-associated diarrhea, 155–158
Antiemetic drugs, 9
Antiendomysial anibody, 120
Aortoduodenal fistula, 21
Apoptosis, 133, 147
Appendicitis, 4, 103–104
Arteriovenous malformations. *See* Angioectasias
Ascites, 27, 259–261, 267
Asterixis, 27, 264
Attenuated APC, 147
Autoimmune hepatitis, 28, 236–238
Azathioprine, 109, 237, 278
Azithromycin, 16, 159

B

Bacterascites, 262
Bacterial overgrowth, 169–170
Balloon expulsion tests, 13
Balsalazide, 116
Barium defecography, 13
Barrett's esophagus, 41–44
    dysplasia in, 43
Beano, 11
Belching, 9–10, 34
Bezoars, 88
Bifidobacterium infantis, 95
Bile salt malabsorption, 17, 19, 93, 95
Biliary colic, 201–206
Biliary dyskinesia, 210–211
Biliary sludge, 202

Bilirubin, isolated elevation of, 30
Biopsy
liver, 277
small bowel, 121
Bisacodyl, 14, 19
Bismuth subsalicylate, 16, 21, 67, 118
Blastocystis hominins, 167
Bleeding, gastrointestinal. *See* Gastrointestinal bleeding
Bleeding ulcer, 75–76
Bloating, 10
Boerhaave's syndrome, 57
Borborygmi, 17, 20, 120, 170
Botulinum toxin, 54, 56, 78, 175
Bowel obstruction, 123–124
Budd-Chiari syndrome, 267–268
Budesonide, 109, 118, 238
Button batteries, 48

C

Cameron ulcer, 79
Campylobacter, 158–159
Cancer
ampullary, 209
anal, 179
bile ducts, 207
cholangiocarcinoma, 207–208
colorectal, 131
esophageal, 49–51
gallbladder, 208–209
gastric, 65, 81–83
gastric, early, 81
hepatocellular, 225, 239, 247–250
hereditary nonpolyposis colon, 144–146
pancreatic, 195–197
rectal, 136
Candida esophagitis, 59
Carcinoid tumor, 152–153
Caroli's disease, 207, 212
Caustic ingestion, 51–52
Cavernous hemangioma, 248, 250
Cefotaxime, 262
Celiac disease, 119–121
Celiac sprue, 119
Certolizumab pegol, 110, 111
Chest pain, noncardiac, 54–56
Child-Pugh classification, 31
Chinese herbs, 96
Cholangiocarcinoma, 207–208
Cholangitis, 31
bacterial, 206–207
primary sclerosing, 233–236
Cholecystitis, 201–206
Choledochal cysts, 212
Choledochocele, 212
Cholera, 162
Cholestyramine, 95, 118, 122, 157
for chronic diarrhea, 19
Chronic intestinal pseudo-obstruction, 126–127
Chronic mesenteric ischemia, 182–183, 282
Cimetidine, 37, 41, 70, 187
Ciprofloxacin, 16, 100, 109, 207, 262
Cirrhosis. *See also* listing by etiology
alcoholic, 251
cryptogenic, 30, 230
evaluation of, 30
primary biliary, 231–233
Cisapride, 38, 77, 78
Clarithromycin, 67, 112
Clostridium difficile colitis, 155–158
Colchicine, 233, 235, 253
Colestipol, 95, 157, 233
Colitis
collagenous, 118
Crohn's, 105–113
diversion, 119
indeterminate, 107, 115
ischemic, 4, 15, 115, 183–184
lymphocytic, 119
microscopic, 118
ulcerative, 113–117
Collagenous colitis, 118
Colon Cancer. *See* colorectal cancer
Colonic transit study, 13
Colonic volvulus, 124–125
Colonography, 135
Colonoscopy, 275–276
Colorectal cancer, 107, 114, 131, 137
Congenital esophageal stenosis, 47
Constipation, 11–14
pelvic floor dysfunction, 11
slow transit, 12
Cowden's disease, 151

Crigler-Najjar syndrome, 30
Crohn's disease, 105–113
Cryptosporidiosis, 166
CT angiography, 23
CT colonography, 135, 139–140, 143
Cullen sign, 188
Cyclospora, 16, 18, 166–167
Cyclosporine, 111, 116, 233, 238
Cystic neoplasms of pancreas, 197–198
Cysts
    choledochal, 212
    hepatic, 250
    hydatid, 250
Cytomegalovirus hepatitis, 226
Cytomegalovirus esophagitis, 60–61

D

DALM, 114–115
Delta hepatitis, 225
Dermatitis herpetiformis, 120
Desipramine, 95
Devon polyposis syndrome, 151
Dexlansoprazole, 37, 38
Diarrhea
    acute, 14–16
    acute, empiric antibiotics, 16
    chronic, 17–19
    traveler's, 16
Dicyclomine, 95
Dientamoeba fragilis, 168
Dieulafoy's ulcer, 89–90
Diffuse esophageal spasm, 56
Digestion, 19
Diiodohydroxyquin, 168
Dipentum, 116
Diversion colitis, 119
Diverticulitis, colonic, 98–101
Diverticulosis, colonic, 98–101
Diverticulum
    colonic, 98–101
    epiphrenic, esophageal, 58
    hypopharyngeal, 57
    Meckel's, 129
    Zenker's, 6, 7, 57–58
D-lactic acidosis, 122
Domperidone, 77, 78
Drug-induced liver injury, 253
Dubin-Johnson syndrome, 30
Dumping syndrome, 71
Duodenal ulcer, 64, 68–71
Dyspepsia, 2–4
    nonulcer, 65, 76–77
Dysphagia, 6–7
Dysplasia
    associated lesion or mass, 114
    in Barrett's esophagus, 43
    DALM, 114, 115
    in ulcerative colitis, 114

E

E. Coli
    enteroinvasive, 163
    enteropathogenic, 163
    enterotoxigenic, 163
    O157:H7, 161
Early gastric cancer, 81
Ejection fraction, gallbladder, 4, 282
Encephalopathy, hepatic, 263–264
Endometriosis, 129
Endoscopic retrograde cholangiopancreatography, 276
Endoscopic sclerotherapy, 256
Endoscopic variceal ligation, 256
Endoscopy
    colonoscopy, 275
    EGD, 275
    endoscopic retrograde cholangiopancreatography, 276
    sigmoidoscopy, 276
    upper, 275
Entecavir, 220
Enteral nutrition, 278
Eosinophilic esophagitis, 46–47
Eosinophilic gastroenteritis, 129
Epiphrenic diverticulum, 58
Epiploic appendagitis, 129–130
Epstein-Barr virus, hepatitis, 226
Eructation, 9
Erythromycin, 78, 159
Erythropoietin, 224
Esomeprazole, 37, 39, 67
Esophageal cancer, 49–51

Esophageal dilatation, 7, 45, 50
Esophageal intramural pseudodiverticulosis, 62
Esophageal leiomyoma, 62
Esophageal papilloma, 62
Esophageal ring, 44–45
Esophageal spasm, 56
Esophageal stricture, 44–45
Esophagitis
candida, 59
cytomegalovirus, 60–61
herpes simplex, 60
pill, 6
reflux, 33–41

F

Familial adenomatous polyposis, 131, 146–149
Famotidine, 37, 38, 187
Fecal impaction, 177–178
Fecal incontinence, 176–177
Fetor hepaticus, 27
Fiber, 11, 17, 98, 132
supplements, 13, 94
Fish oil, 116, 133
Fissure, anal, 174–175
Fistula, anorectal, 175–176
Flatulence, 10–11
Fluid wave, 27
Focal nodular hyperplasia, 250
Food allergy, 97–98
Food poisoning, 170–171
Foreign bodies, 47–48
Friction rub, 26
Fructose, 10, 17
Fulminant hepatic failure. *See* Hepatic failure
Fundic gland polyps, 84
Fundoplication
Nissen, 40–41
Toupet, 40

G

Gallbladder cancer, 208–209
Gallbladder polyps, 210
Gardner syndrome, 147
Gastric antral vascular ectasias, 88–89
Gastric cancer, 65, 81–83
Gastric lymphomas, 83–84
Gastric polyps, 84–85
Gastric ulcer, 64, 68–71
Gastric volvulus, 80–81
Gastrinoma. *See* Zollinger-Ellison syndrome
Gastritis, 63, 281
Gastroenteritis
eosinophilic, 129
viral, 168
Gastroesophageal reflux disease, 33–41
Gastrointestinal bleeding, 21–26
diverticular, 91
obscure, 24
occult blood in stool, 24
rectal, small volume, 24
transfusion, 25
Gastrointestinal stromal tumor, 85
Gastroparesis, 77–78
Gastropathy, NSAID, 71–73
GAVE, 89
GERD, 33–41
Giardiasis, 163–164
Gilbert's syndrome, 30
GIST, 85
Glucagonoma, 198
Gluten sensitive enteropathy. *See* celiac disease
Glomus tumor, 85
Grey-Turner sign, 188

H

Havrix, 216
Helicobacter pylori, 3, 63–68
HELLP syndrome, 271–272
Helminths, 169
Hemangioma, cavernous, 250
Hematemesis, 21
Hematochezia, 21
Heme arginate, 245
Hemochromatosis, 238–241
Hemolysis, 29
Hemorrhoids, 173–174
Hepatic adenoma, 250
Hepatic encephalopathy, 263–264
Hepatic failure, 30, 216

Hepatic hydrothorax, 261
Hepatic masses, 250
Hepatitis. *See also* listing by etiology
    alcoholic, 251, 253
    autoimmune, 28, 236–238
    cytomegalovirus, 60–61
    drug, 253
    Epstein-Barr, 226
    ischemic, 268–269
Hepatitis A, 215–217
Hepatitis B, 217–221
Hepatitis C, 221–225
Hepatitis D, 225
Hepatitis E, 225
Hepatitis F, 226
Hepatitis G, 226
Hepatocellular carcinoma, 225, 239, 247–250
Hepatopulmonary syndrome, 266
Hepatorenal syndrome, 265–266, 267
Hereditary hemorrhagic telangiectasia, 150, 184
Hereditary nonpolyposis colon cancer syndrome, 144–146
Herpes simplex esophagitis, 60
Hiatal hernia, 33, 79–80
Hirschsprung's disease, 179
Histamine-2 blockers in GERD, 37
Human immunodeficiency virus
    biliary, 212–213
    diarrhea in, 168–169
    esophageal, 61–62
Hydatid cysts, 250
Hyoscyamine, 95
Hyperbilirubinemia, 30
Hyperemesis gravidarum, 271
Hyperplastic polyposis, 151
Hypertension
    portal, 255
    portopulmonary, 266
Hypertensive lower esophageal sphincter, 56
Hypertrophic gastropathy. *See* Ménétrier's disease
Hypopharyngeal diverticulum, 57

I

Ileitis, Crohns, 163
Impaction, fecal, 177
Incontinence, fecal, 176–177, 282
Indeterminate colitis, 107, 115
Infliximab, 110
Insulinoma, 198, 199
Interferon, 223
Interferon α-2b, 223
Intestinal metaplasia, 41
    GE junction, 42
Intestinal pseudo-obstruction
    acute, 125
    chronic, 126–127
Intrahepatic cholestasis of pregnancy, 271
Intussusception, 127
Iron deficiency anemia, 25, 134
Irritable bowel syndrome, 91–96
Ischemia
    acute mesenteric, 181–182, 282
    chronic mesenteric, 182–183, 282
Ischemic colitis, 4, 15, 115, 183–184
Ischemic hepatitis, 268–269
Islet cell tumors, 198–199
Isospora belli, 167

J

Jaundice, 29–30, 197
Juvenile polyposis, 150–151
Juvenile polyps, 150–151

K

Krukenberg tumor, 82

L

Lactoferrin, 15
Lactose intolerance, 102–103
Lactulose, 13, 264
Lansoprazole, 37, 67, 70, 73
Laxatives
    osmotic, 13
    stimulant, 14
Leiomyoma, esophageal, 62
LeVeen shunts, 261
Levofloxacin, 68
Lipoma, gastric, 85

Liver abscess
amebic, 164–165
pyogenic, 227
Liver biopsy, 277
Liver disease, 26–31, 271–273
abnormal alkaline phosphatase, 29
asymptomatic abnormal transaminases, 28
cirrhosis, 30
evaluation of, 26
fulminant hepatic failure, 30–31
history in, 26
isolated abnormal bilirubin, 30
jaundice, 29
physical exam in, 26
prolonged prothrombin time, 31
Liver transplantation, 277–278
Loperamide, 16, 19, 95, 118, 162, 166, 176
Lubiprostone, 14, 96
Lymphangiectasia, 20
Lymphocytic colitis, 119
Lymphoma
gastric, 83–84
MALT, 65, 83–84
Lynch syndrome, 145

M

Malabsorption, 19–20, 195
Maldigestion, 19–20
Malignant ascites, 262
Malignant polyp, 144
Mallory-Weiss tear, 56–57
MALT lymphoma, 65, 83–84
Mass, hepatic, 250
Meckel's diverticulum, 129
Melena, 21
Ménétrier's disease, 81, 90
Mesalamine, 109, 112, 115, 187
Mesenteric ischemia, 181
acute, 181–182
chronic, 182–183, 282
ischemic colitis, 183–184
Mesenteroaxial volvulus, 80
Metachronous colon cancers, 134
Metformin, 231
Methotrexate, 111, 233, 235
Methylcellulose, 13, 94
Methylnaltrexone, 14
Metoclopramide, 9, 38, 77, 78
Metronidazole, 18, 67, 100, 109, 113, 157, 164, 165, 168, 264
Microscopic colitis, 118
Microsporidia, 167
Milk of magnesia, 13
Misoprostol, 14, 73, 128
Muir-Torre syndrome, 145
Murphy's sign, 2, 203
Mycophenolate mofetil, 238

N

Naltrexone, 233
Narcotic bowel syndrome, 130
Nausea, 7–9
drugs for, 8
Necrotic migratory erythema, 198
Necrotizing pancreatitis, 188
Neomycin, 264
Neurofibromatosis, 151
Nissen fundoplication, 40
Nizatidine, 37
Nonalcoholic fatty liver disease, 229–231
Nonalcoholic steatohepatitis, 229–231
Noncardiac chest pain, 54–56
Nonspecific esophageal motility disorder, 56
Nonulcer dyspepsia, 65, 76–77
and *Helicobacter*, 65
Norfloxacin, 16, 160, 170, 262, 263
NSAID gastropathy, 71–73
Nutcracker esophagus, 56
Nutrition
enteral, 278
parenteral, 279

O

Obstruction, intestinal, 123–124
Obturator sign, 2, 103
Octreotide, 153, 166, 185, 194, 199, 257, 265
Odynophagia, 6–7
Ogilvie's syndrome. *See* Pseudo-obstruction: acute colonic

Olsalazine, 116
Omeprazole, 36–39, 67, 70, 73–75
Omeprazole test, 36
Opisthorchis viverrini, 207
Oropharyngeal dysphagia, 6
Overdose, acetaminophen, 253

P

Painful rib syndrome, 213
Palmar erythema, 26
Pancreas, cystic neoplasms, 197–198
Pancreas divisum, 187
Pancreatic cancer, 195–197
Pancreatic neoplasms adenocarcinoma, 196
    cystic, 197
    islet cell, 198
Pancreatic polypeptide, 198
Pancreadicoduodenectomy, 197
Pancreatitis
    acute, 187–192
    chronic, 192–195
Pantoprazole, 37, 39, 67, 75
Papilloma, 62
    esophageal, 62
Paracentesis, 259–262
Paraesophageal hernia, 79
Parenteral nutrition, 279
Parietal cell vagotomy, 71
Pearls in Gastroenterology, 281–282
Peginterferon alfa-2a, 220
    with ribavirin, 223
Peginterferon alfa-2b, 223
Pelvic floor dysfunction, 11
Penicillamine, 242, 243
Pentoxifylline, 235, 253
Peptic ulcer, 68–71
Percutaneous endoscopic gastrostomy, 276–277
Peritonitis, 2
    spontaneous bacterial, 261–263
Peritonovenous shunts, 261
Peutz-Jeghers syndrome, 149–150
pH probe
    indications, 35
    technique, 35
Pheochromocytoma, 19
Phytobezoar, 88
Pill esophagitis, 6
Plesiomonas, 163
Pneumatosis intestinalis, 128
Polyarteritis nodosa in Hepatitis B, 218
Polycarbophil, 13
Polyethylene glycol, 13
Polyposis
    Cowden's disease, 151
    Devon, 151
    familial adenomatous, 131, 146–149
    hyperplastic, 151
    juvenile, 150
    MYH, 147
    neurofibromatis, 151
    Peutz-Jeghers, 149
    Ruvalcaba-Myhre-Smith, 151
    syndromes, miscellaneous, 151
Polyposis syndromes miscellanous, 151
Polyps
    adenomatous colonic, 141–144
    fundic gland, 84
    gallbladder, 210
    gastric, 84–85
    hyperplastic, 84, 142, 151
    juvenile, 150–151
    malignant, 144
Porphyria, acute intermittent, 244
Portal hypertension, 255–259
Portal hypertensive gastropathy, 256, 259
Portal vein thrombosis, 269
Portopulmonary hypertension, 266
Post gastrectomy syndromes, 71
Postpolypectomy syndrome, 143
Postural vital signs, 21, 25
Pouchitis, 117
PPoma, 198
Prednisone, 109, 237, 253
Pregnancy
    acute fatty liver, 272
    HELLP syndrome, 271–272
    liver disease and, 271–273
Primary biliary cirrhosis, 231–233
Primary sclerosing cholangitis, 233–236
Probiotics, 95
Proctalgia fugax, 179
Proctitis
    radiation, 127–128
    ulcerative, 113–117

Promotility agents in GERD, 38
Propylthiouracil, 253
Prothrombin time, elevated, approach to, 31
Proton pump inhibitors
    in GERD, 37
    in ulcer disease, 70
Pruritus ani, 177
Pseudodiverticulosis esophageal, 62
Pseudo-obstruction
    acute colonic, 125–126
    chronic, 126–127
Psyllium, 13
Pyogenic liver abscess, 227

R

Rabeprazole, 37, 67
Radiation
    enteritis, 127–128
    proctitis, 127–128
Ranitidine, 37–39, 41, 67, 70
Red blood cell scan, 23
Red wales, 255, 257
Reflux, gastroesophageal, 33–41
Regional enteritis. *See* Crohn's disease
Reiter's syndrome, 160
Ribavirin, 223, 224
Rifampin, 233
Rifaximin, 16, 95, 170, 264
Ring, esophageal, 44–47
Ringed esophagus, 46
Rotor syndrome, 30
Rumination syndrome, 58–59
Ruvalcaba-Myhre-Smith syndrome, 151

S

Salmonella, 159–160
Schatzki's rings, 6
Schistosomiasis, hepatic, 226
Schwannoma, gastric, 85
Scleroderma, 34
Sclerosing cholangitis, 233–236
Screening
    for colorecal cancer, 137
    for FAP, 148
    for hemachromatosis, 240
Senna, 14
Serum-ascites albumin gradient, 260
Sexual abuse, 96–97
Shigella, 160–161
Shock liver, 268–269
Short bowel syndrome, 121–122
Short segment Barrett's esophagus, 42
Sigmoidoscopy, 276
Simethicone, 77
Sister Mary Joseph's node, 82
Sitzmarks, 13
Sliding hiatal hernia, 79
Sludge, 192
Smooth muscle relaxants, 95
Sodium benzoate, 264
Solitary rectal ulcer syndrome, 178–179
Somatostatinoma, 198
Sorbitol, 11, 13, 17
Spastic disorders of esophagus, 56
Sphincter of oddi dysfunction, 210–211
Splanchnicectomy, 197
Spontaneous bacterial peritonitis, 261–263
Sprue, celiac, 119
Steatorrhea, 20
Sterocoral ulcer, 178
Stool
    72 hour collection, 19
    electrolytes and osmoles, 19
    lactoferrin, 15
    laxative screen, 19
    wbc, 15
Stress ulcer, 73–74
Stricture, esophageal, 44–45
Subepithelial gastric lesions, 85–86
Sucralfate, 74, 77
    in GERD, 38
Sulfasalazine, 116

T

Tacrolimus, 238
Tardive dyskinesia, 78
Tegaserod, 14, 96
Tenofovir, 220

Thiazolidinediones, 231
Thrombosis
hepatic vein, 267
portal venous, 269
Tinidazole, 164, 165
Tissue transglutaminase, 120
Toupet fundoplication, 40
Toxic megacolon, 115
Transfusion, 25–26
Transjugular intrahepatic portosystemic shunt, 258
Transplantation, liver, 277
Trichobezoar, 88
Trimethoprim-sulfamethoxazole, 100
Turcot syndrome, 147
Typhlitis, 128

U

Ulcer
bleeding, 75–76
Cameron, 79
Dieulafoy's, 89–90
duodenal, 64, 68–71
gastric, 64, 68–71
peptic, 68–71
solitary rectal, 178–179
stress, 73–74
Ulcerative colitis, 113–117
Upper endoscopy, 275
Urea breath tests, 66
Urease testing, 65–66
Ursodeoxycholic acid, 205, 230, 233, 235, 238, 271

V

Vaccines, hepatitis A, 216
Vaccines, hepatitis B, 219–220
Vagotomy, 71
Vancomycin, 157
VAQTA, 216
Variceal hemorrhage, 255–259
Vascular spiders, 26
Venoocclusive disease, 268
Vibrio, 162
VIPoma, 198, 199
Viral gastroenteritis, 168
Viral hepatitis. *See* hepatitis or specific agent
Virchow's node, 82
Virtual colonoscopy, 139, 143
Volvulus, 80
colonic, 124–125
gastric, 80–81
Vomiting, 7–9
drugs for, 9

W

Water brash, 34
wbc, stool, 15
Whipple operation, 197
Whipple's disease, 171–172
Wilson's disease, 241–243

Y

Yersinia enterocolitica, 163

Z

Zenker's (hypopharyngeal) diverticulum, 6, 7, 57–58
Zollinger-Ellison syndrome, 86–87