Pierre Poitras *Editor*

The Digestive System: From Basic Sciences to Clinical Practice

Springer

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Preface

This book aims to facilitate your learning experience during your undergraduate studies, as well as to guide you later in your clinical practice as a general practitioner or as a physician nonspecialist in digestive diseases.

We deliberately chose a direct style, unencumbered by references, hoping to stimulate in you the desire to further explore the scientific literature.

As editor, I wanted to offer a personalized version of digestive medicine, as I discovered it with outstanding mentors such as Robert Modigliani, Jean- Claude Rambaud, John H. Walsh, Charles Code, Morton Grossman, and Serge Bonfils during my years of training in gastroenterology, and as I evolved within it during 40 years of professional life with my colleague gastroenterologists, GI surgeons, radiologists, and pathologists at Hôpital Saint- Luc in Montreal, all passionate like me about the digestive system.

Our approach is to introduce the disease as a dysregulation of the healthy state. Anatomy, histology, and physiology illustrate the normal functioning of the organs, and pathophysiology teaches us the dysregulation process involved. Semiology allows us to build a differential diagnosis from the patient symptoms. Finally, we confirm the diagnosis by various measures of investigation, and we use pharmacology to apply the proper treatment.

The amount of bioscientific knowledge is huge and is growing every day. It is impossible to assimilate and control, quantitatively or qualitatively, all available data from genetics, molecular biology, etc. Some of these basic discoveries will have an immediate impact on our medical practice, while others will have to wait. This book seeks to link basic sciences and clinical practice. The authors made special efforts to highlight the fundamental notions that impact on current patient care, but, needless to say, this requires continual reassessment.

We thank you in advance for sending us your comments and suggestions to improve this work. You can reach us at the following address:
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Acknowledgments

This book was made possible thanks to the contribution of many people, who I would like to thank here:

Thank you to my teachers and mentors, who taught me to give the best for the care of my patients.

Thank you to my colleagues at Hôpital Saint-Luc de Montréal, gastroenterologists, hepatologists, surgeons, radiologists, pathologists, biochemists, and experts in digestive diseases who have been able to create, during all these years, a hospital environment conducive to happy and efficient work.

Thank you to the University of Montreal, which has allowed me to have a career that has been as exciting as it has been fruitful.

Thank you to all the students that I have met throughout my career and who were a constant stimulus for this profession as a clinician and a teacher.

Thank you to all the colleagues who participated in the writing of this book.

Thank you to all our readers of previous French editions. Your appreciation and comments have been an inspiration to us.

Thank you to all our past and present sponsors who support us in the dissemination of knowledge.

Thank you to our publishers, Springer Nature for this English version and Les Presses de l'Université de Montréal for the French editions, for their editorial expertise and support.

Finally, special thanks to Monique, an exceptional life companion, psychotherapist, and constant collaborator, who has taught me so much about life and medical humanism, and who has allowed me to become who I am, personally, socially, and professionally. It is to her that I dedicate this book.

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Introduction

This book is organized into two parts. In the first part, the eight main organs of the digestive system are studied, and in the second part, the major clinical symptoms that afflict the digestive system are revised.

In the first part, each organ is presented in the same way: the first five sections of a chapter deal with "basic" knowledge of macroscopic and microscopic anatomy, embryology, absorption-secretion, and motor-sensory functions; the clinical disorders are then listed in three general sections: inflammation, tumor, and function disorders.

In the second part, digestive symptoms are presented in order to facilitate rapid and effective clinical management.

To guide your readings, colored boxes are used to highlight important issues: blue for diagnostic key points, orange for therapeutic considerations, green for pediatric aspects, yellow for tropical specificities, and pink for interactions between basic and clinical sciences.

Our goal is to make you appreciate the digestive system and thus stimulate your interest and curiosity. Do not hesitate to increase your knowledge by consulting specialized books to answer any questions that may arise in you while reading this book.

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Abbreviations

5-ASA	5-amino salicylic acid (mesalamine)
5-HIAA	5-hydroxy indole acetic acid
5-HT	5-hydroxytryptamine (serotonin)
6mp	6-mercaptopurine
AA	Amino acid
AB	Antibody
ac	Ante cibum (before meal)
ACE	Angiotensin converting enzyme
Ach	Acetylcholine
ADP	Adenosine diphosphate
Ag	Antigen
Ag	Silver
AIH	Autoimmune hepatitis
Al	Aluminum
alk phos	Alkaline phosphatase
ALT	Alanine aminotransferase
am	Before noon
AMA	Anti-mitochondria (antibody)
AMP	Adenosine monophosphate
ANS	Autonomic nervous system
APC	Adenomatosis polyposis coli (gene)
APUD	Amine precursor uptake decarboxylase
ASA	Aminosalicylic acid (Aspirin®)
ASBT	Apical sodium bile acid transporter
ASM	Anti-smooth muscle (antibody)
ASO	Atherosclerosis obliterans
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AZA	Azathioprine
BA	Bile acid
BAO	Basal acid output
BBM	Brush border membrane
BCRP	breast cancer resistant protein
BD	Bile duct
bid	(bis in die) 2 times a day
BLM	Basolateral membrane
BMI	Body mass index
BP	Blood pressure
BS	Bile salt
C	Carbon (atom)
C4	7α-Hydroxy-4-cholesten-3-one
Ca	Calcium

cAMP	Cyclic AMP (adenosine monophosphate)
CBD	Common bile duct
CCK	Cholecystokinin (also called CCK-PZ)
CCK-PZ	Cholecystokinin-pancreozymin
CD	Crohn's disease
CFTR	Cystic fibrosis transmembrane conductance regulator
Cl	Chloride (ion)
ClC	Chloride channel
CMV	Cytomegalo virus
CN (or cn)	Cranial nerve
CNS	Central nervous system
CO_2	Carbon dioxide
COX	Cyclo-oxygenase enzyme
CP	Chronic pancreatitis
Cr	Chromium
CRF	Corticotropin releasing factor
CSA	Cyclosporin
CT	Celiac trunk
CTscan	Computerized axial tomography
Cu	Copper
Cx	Surgery
CYP	Cytochrome P450
D2 (D3, D4)	Duodenum second (third, fourth) portion
DMT	Divalent metal ion transporter
DRE	Digital rectal examination
DU	Duodenal ulcer
Dx	Diagnosis
E+	Electrolytes
E coli	Escherichia coli
EC	Enterochromaffin
ECEH	Enterohemorrhagic Escherichia coli
ECL	Enterochromaffin-like
EGF	Epidermal growth factor
EHBD	Extrahepatic bile duct
ENS	Enteric nervous system
ENT	Ear-nose-throat (medical specialist)
EPS	Epigastric pain syndrome
ERCP	Endoscopic retrograde cholangio-pancreatography
ETOH	Ethanol
FA	Fatty acid
FATP	Fatty acid transport protein
FDA	Food and Drug Administration (USA)
Fe	Iron
FGF19	Fibroblast growth factor 19
FGID	Functional gastro-intestinal disorder

FODMAP	Fermentables, oligosaccharides, disaccharides, monosaccharides, and polyols
FXR	Farnesoid X
g (or gm)	Gram
GABA	Gamma-aminobutyric acid
GERD	Gastroesophageal reflux disease
GDA	Gastro-duodenal artery
GRP	Gastrin releasing peptide
GU	Gastric ulcer
H	Hydrogen (atom)
H. pylori	Helicobacter pylori
H_2O	Water
H2RA	Histamine H2 receptor antagonist
HAMP	Hepcidin antimicrobial peptide
Hb	Hemoglobin
HbsAg	Hepatitis B surface antigen (Australian antigen)
HCC	Hepatocellular carcinoma
HCl	Hydrochloric acid
HCO_3	Bicarbonate
HCP	Heme carrier protein
HFE gene	High iron gene (hemochromatosis gene)
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HNPCC	Hereditary non-polyposis colon cancer
Hp	Helicobacter pylori
hr	Hour
HR	Heart rate
HS (or hs)	(hora somni) at bedtime
Ht	Hematocrit
HUS	Hemolytic uremic syndrome
IBABP	Ileal bile acid binding protein
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICU	Intensive-care unit
id	(in die) once a day
IF	Intrinsic factor
Ig	Immunoglobulin
IHBD	Intrahepatic bile duct
IL	Interleukin
IM (or im)	Intra-muscular
INR	International normalized report (prothrombin coagulation test)
IPAN	Intrinsic primary afferent neuron
IPMN	Intraductal papillary mucinous neoplasm (of the pancreas)
IR (or ir)	Intra-rectal
ITP	Inositol triphosphate

IV (or iv)	Intra-venous
K	Potassium
Kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LES	Lower esophageal sphincter
LGIB	Lower Gi bleeding
LH	Left hypochondrium
LIF	Left iliac fossa
LKM	Liver-kidney microsomes
LT	Leukotriene
LUQ	Left upper quadrant (abdomen)
MALT	Mucosa associated lymphoid tissue
MAO	Maximum acid output
max	Maximum
MDR	Multidrug resistance (gene)
MELD	Model end-stage liver disease
MEN	Multiple endocrine neoplasia
min	Minute
min	Minimum
Mg	Magnesium
MgOH	Magnesium hydroxide
$MgSO_4$	Magnesium sulfate
MMC	Migrating motor complex
MMF	Mycophenolate mofetil
Mn	Manganese
MRI	Magnetic resonance imaging
N	Nitrogen
Na	Sodium
NALFD	Non-alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NET	Neuroendocrine tumor
NG tube	Nasogastric tube
NH_3	Ammonia
NH_4	Ammonium
NHE	Na (sodium) – hydrogen exchanger
NK	Neurokinin
NMR	Nuclear magnetic resonance
NO	Nitric oxide
NPO	(nil per os) nothing by mouth, fasting
NPY	Neuropeptide Y
NSAID	Non-steroidal anti-inflammatory drug
OST	Organic solute transporter
PACAP	Pituitary adenylate cyclase-activator peptide
PBC	Primary biliary cholangitis

PC (or pc)	(post cibum) after meal
PCFT	Proton coupled folate transporter
PDS	Postprandial distress syndrome
PEG	Polyethylene glycol
PEPT-1	Peptide transporter-1
PET	Positron emission tomography
PgE	Prostaglandin E
PGP	P-glycoprotein
PLC	Phospholipase C
pm	Afternoon
plt	Platelets
PO (or po)	(per os) oral
PO_4	Phosphate
PPI	Proton pump inhibitor
PRN (or prn)	(pro re nata) as needed
PSC	Primary sclerosing cholangitis
PYY	Peptide YY
Q 3-4 hrs	(quaque) every 3 to 4 hours
QID(or qid)	(*quater in die*) four times a day
RBC	Red blood cells
RH	Right hypochondrium
RIF	Right iliac fossa
ROH	Alcohol
RR	Relative risk
RUQ	Right upper quadrant (abdomen)
RX	Radiology
Rx	Treatment
SB	Small bowel
SC (or sc)	Subcutaneous
SGLT-1	Sodium glucose transporter 1
SIBO	Small intestinal pullulation overgrowth
SMA	Superior mesenteric artery
SO	Sphincter of Oddi
SP	Substance P
SPINK	Serine peptidase inhibitor, Kazal type 5
SSRI	Selective serotonin reuptake inhibitor
T4	Thyroxine
TCA	Tacrolimus
TG	Triglycerides
TID (or tid)	(ter in die) three times a day
TIPS	Transjugular intrahepatic portal shunt
TLESR	Transient lower esophageal sphincter relaxation
TNF	Tumor necrosing factor
TNM	Tumor-node-metastasis (classification)
TPMT	Thiopurine methyl transferase

TPN	Total parenteral nutrition
TRPM	Transient receptor potential melastatin
UC	Ulcerative colitis
UES	Upper esophageal sphincter
UGIB	Upper GI bleeding
VHA	Hepatitis A virus
VHB	Hepatitis B virus
VHC	Hepatitis C virus
VHD	Hepatitis D virus
VIP	Vasointestinal polypeptide
vit	Vitamin
WHO	World Health Organization
X-ray	Radiography, radiology
ZE	Zollinger-Ellison
ZES	Zollinger-Ellison syndrome

Warning

This book is not a “tricks list” for your exams.
It is not a “recipe book” for the treatment of your patients on the ward.
This book is to discover, learn, understand, and appreciate the digestive system.
Enjoy.

Pierre Poitras

The Digestive Organs

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The Esophagus

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1.1 Macroscopic Anatomy

1.1.1 Shape and Structure

The digestive tract begins, we often forget, with the oral cavity. The teeth grind the food before the tongue and the striated muscles of the pharynx push it into the esophagus.

(a) Esophagus. The esophagus is a tube with an approximate diameter of 2.5 cm, which allows the passage of food from the oral cavity through the thoracic cavity into the stomach. The esophagus starts at the cricopharyngeal muscle (or upper esophageal sphincter) located at about 15 cm of the incisors, anterior to the C6 vertebra, and continues until the lower esophageal sphincter (positioned at the cardia, approximately 40 cm from the incisors at the level of T11 vertebra) before its entry in the abdominal cavity and the stomach. The esophagus is classically divided into three relatively identical segments identified as the upper, middle, and lower thirds of the esophagus (Fig. 1.1a).

At the cervical level, the esophagus is located in front of the vertebral column and behind the trachea. On each side, we find the carotid arteries and the recurrent laryngeal nerves, branches of the vagus nerve controlling motility of the pharynx and upper esophagus.

The thoracic esophagus then passes into the posterior mediastinum in front of the spine, behind the trachea, the carina, the heart, the aortic arch, then to the right of the aorta, and bordered by the pulmonary pleura (Fig. 1.1b).

The abdominal esophagus is made up of a short segment (1–2 cm long) between the diaphragm and the stomach. The two branches of the vagus nerve descend from the central nervous system by running on both sides of the esophagus; at the level of the diaphragmatic hiatus, the left and right branches of the vagus nerve are found on the anterior and posterior walls, respectively, of the esophagus (due to the rotation of the stomach during its fetal development; see ▶ Sect. 2.3 in ▶ Chap. 2). The surgical procedure of truncal vagotomy, once used to reduce gastric acid secretion and treat peptic ulcer, consisted of sectioning both of these vagal branches in the lower esophagus.

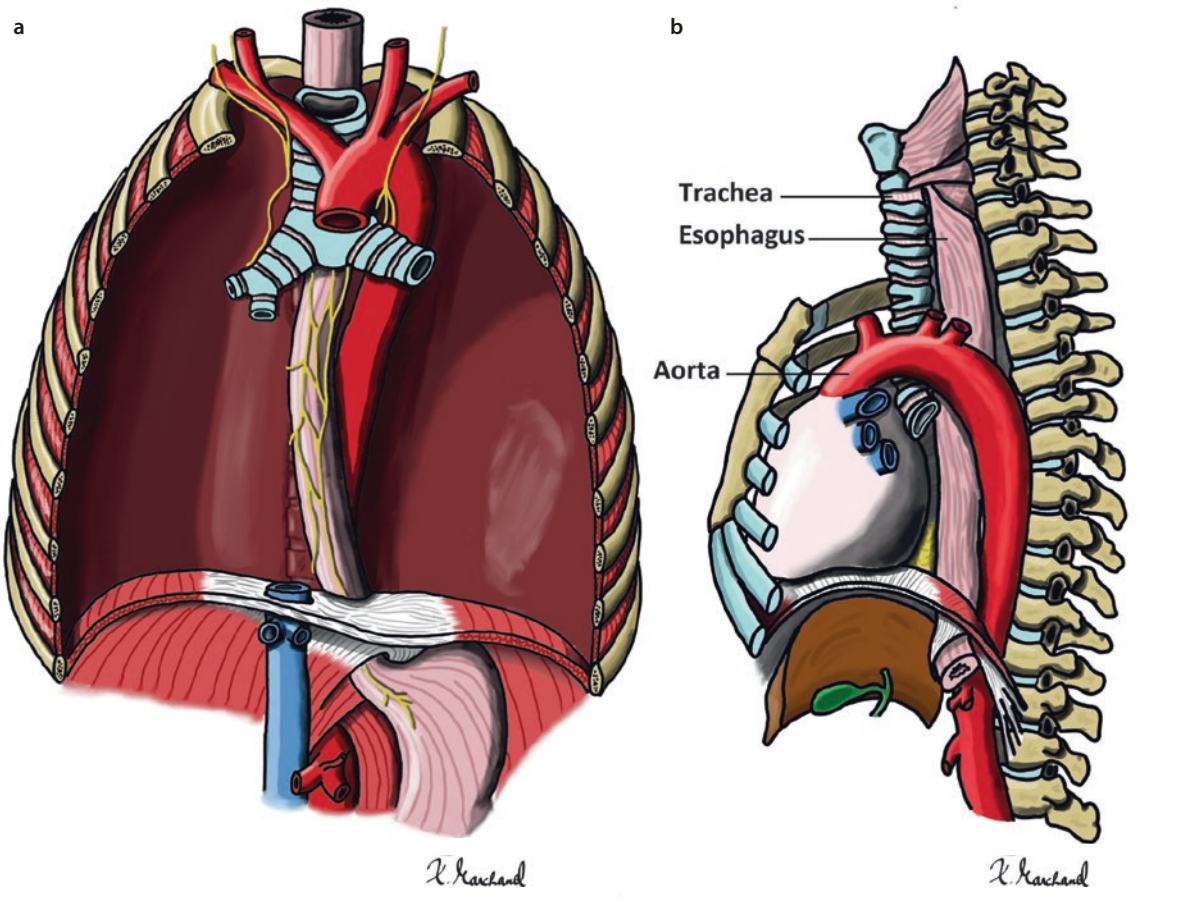

Fig. 1.1 **a** (left figure). Esophagus anatomy: front view. **b** (right figure). Esophagus anatomy: side view

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(b) Sphincters. At both ends of the esophageal tube, we find sphincters, areas of high pressure designed to close the tube entrance and acting as a one-way valve.

The upper esophageal sphincter (UES) or cricopharyngeal muscle is composed of fibers from pharyngeal muscles aligned transversally and of transverse fibers from the esophagus that encircle the esophageal tube and form a high-pressure zone probably intended to protect the tracheal airway from possible gastroesophageal regurgitations. Between the oblique muscle fibers from the pharynx and the transverse fibers from the upper esophageal sphincter, we find an area of potential weakness, Killian's triangle, that may give rise to Zenker's diverticulum (discussed later in this chapter), especially in the presence of a high pressure within the UES that generates an obstacle to food swallowing.

The lower esophageal sphincter (LES) is an area of high pressure, approximately 2 cm long, located at the esophagogastric junction that prevents regurgitation of gastric contents into the esophagus. It is normally located at the thoracoabdominal junction, at the level of the diaphragm, mainly on its abdominal side. This sphincter area is made up of muscle fibers from the lower esophagus ("internal" sphincter), and muscle fibers from the gastric fundus as well as the diaphragm pillars ("external" sphincter). Its role in gastroesophageal reflux disease (GERD) will be discussed subsequently.

1.1.2 Vascular Supply

(a) Arteries. The esophagus is supplied in its upper segment by four to six small arteries derived from the thyroid arteries, by arteries originating directly from the aorta or derived from intercostal or bronchial arteries in the middle segment, and by gastric arteries in the distal segment (Fig. 1.2a). The arteries form a dense irrigation network which protects the esophagus from an ischemic process.

(b) Veins. An extensive network of small veins drains the esophagus via the thyroid veins at its upper part and toward the azygos and intercostal veins in its middle

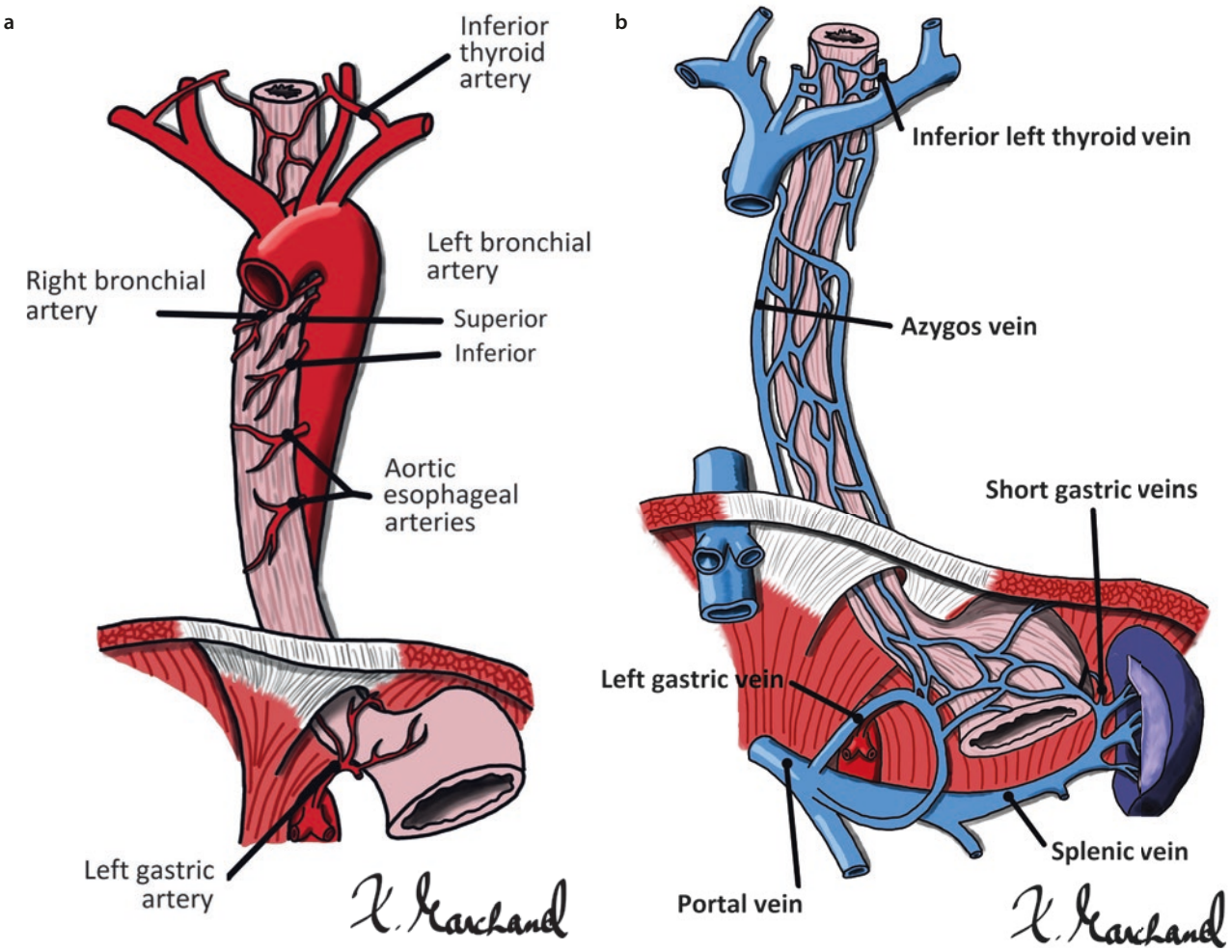


Fig. 1.2 **a** (left figure). Arteries of the esophagus. **b** (right figure). Veins of the esophagus

part. At the lower portion, esophageal veins may drain toward the abdomen to the short gastric veins or to the left gastric vein and thus toward the portal circulation; this explains then the possible formation of venous dilatations in the lower esophagus (called esophageal varices) in the setting of portal hypertension due to liver cirrhosis (◘ Fig. 1.2b).

(c) Lymphatics. Lymphatic channels arise in the mucosa and muscular region of the esophagus and drain to paraesophageal lymph nodes distributed all along the organ. In case of neoplasia, the lymphatic flow from the upper 2/3 of the esophagus moves upward (cervical lymph nodes, paratracheal lymph nodes of the upper mediastinum, paraesophageal lymph nodes of the middle or inferior mediastinum, etc.), while the lower esophagus may drain into the abdomen to celiac and perigastric lymph nodes.

The abdominal lymphatic secretions are channeled, via the thoracic duct running up along the esophagus, to join the left subclavian vein near by the jugular vein. Trauma, surgical or otherwise induced, of the cervical esophagus, may therefore damage this structure and lead to chylothorax and even intestinal lymphangiectasias.

1.1.3 Innervation

Intrinsic innervation of the esophagus is provided by the enteric nervous system (ENS) with a relatively sparse Meissner's submucosal plexus (controlling microcirculation and secretion) and Auerbach's myenteric plexus (regulating muscle contractions for motility), as elsewhere in the gastrointestinal tract (see ▶ Chap. 3).

Extrinsic innervation depends on sympathetic and parasympathetic systems. Cervical and thoracic sympathetic ganglia provide motor and sensitive innervation to the entire esophagus. The vagus nerve exerts a parasympathetic motor innervation to the upper esophagus as well as in the pharynx. Afferent fibers of the vagus nerve are also probably important in esophageal sensory transmission.

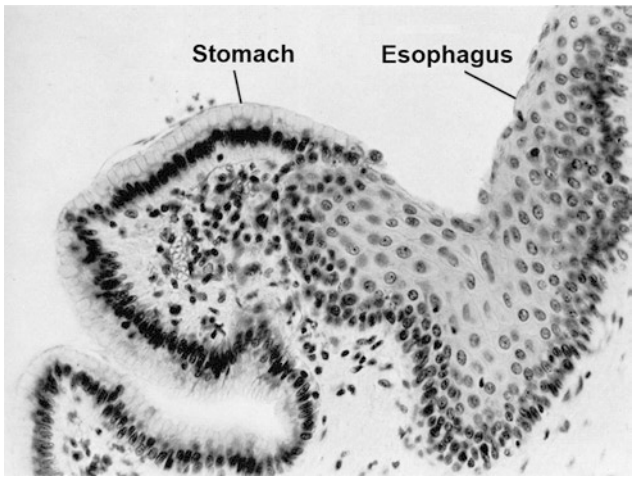
At the buccopharyngeal level, cranial nerves IX and XII are responsible, respectively, for sensitive and motor innervation. A damage of these nerves, after a vascular stroke of the brain stem, for example, will create swallowing dysfunction.

1.2 Microscopic Anatomy

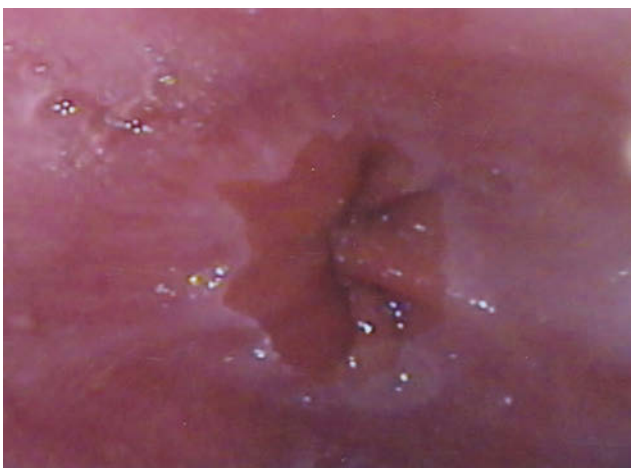
Like the rest of the digestive tract, the esophagus is made up of an internal mucosa layer resting on a muscular structure. The peculiarities of the esophagus are as follows:

1.2.1 Esophageal Mucosa

The esophageal *mucosa* is made of a stratified squamous epithelium (◘ Fig. 1.3). This squamous mucous membrane is also found at the very distal end of the digestive tract, at the anus, while the columnar (glandular) epithelium is the normal histology of the entire gastrointestinal tract from the stomach to the rectum. At approximately 40 cm from the incisor teeth, at the gastric cardia level, we find the Z line that marks the transition, clearly visible macroscopically (e.g., in endoscopy; ◘ Fig. 1.4), between the whitish squamous mucosa of



◘ **Fig. 1.3** Esophagus normal histology: squamous mucosa of the esophagus (on the right part of the figure) and columnar mucosa of the stomach (on the left part) as seen at the gastroesophageal junction. (Photo from W. Bloom and D.W. Fawcett, Textbook of Histology, 1968)



◘ **Fig. 1.4** In endoscopy, the meeting junction between the gastric reddish mucosa (at the center of the image) and of the esophageal whitish mucosa is obvious. (Photo by P.Poitras)

the esophagus and the reddish columnar epithelium of the stomach. The Z line corresponds to the lower portion of the lower esophageal sphincter.

The epithelial structure of the esophagus explains the relative paucity of absorptive or secretory phenomena so common to the rest of the digestive tract. This squamous mucous membrane also explains the presence of squamous cell neoplasia at this site level of the digestive tract. In Barrett's esophagus (secondary to GE reflux as discussed later), the squamous mucosa is replaced by a columnar mucosa allowing then the development of adenocarcinomas.

In the *submucosa*, we find blood vessels, lymphatics, some nerves of Meissner's plexus, as well as glandular cells secreting mucus and bicarbonate involved in the defense of mucosal integrity.

1.2.2 Muscularis

The esophagus, as most of the digestive tract, is made up mainly of smooth muscles organized in a circular inner layer and a longitudinal outer layer. The upper esophagus, however, contains striated muscles that are in fact an extension of the pharyngeal muscles. Diseases of the smooth muscles can thus affect the middle and distal esophagus, while pathologies of the striated muscles can affect the proximal region of the esophagus.

As elsewhere in the gastrointestinal tract, the intrinsic enteric nervous system is made up of the myenteric and submucous plexuses, respectively, located between the longitudinal and circular muscle layers and between the circular muscles and the mucous membrane.

1.2.3 Serosa

The serosa, usually lining the external muscle layer of digestive cavities, is absent in the esophagus. It is replaced by a thin adventitia (thin connective tissue layer).

1.3 Embryology/Development

1.3.1 Normal Development

The oropharynx, trachea, lungs, and esophagus develop from a common tube: the endoderm. In the 4th week of fetal life, a bud forms at the ventral part of the tube to become the respiratory system. The dorsal part of the tube will turn into the esophagus and a foregut from which the stomach will arise. The separation of the two tubes in respiratory and digestive organs is carried out around the 6th week. Esophageal lumen is formed around week 10 and will be epithelialized with squamous cells from the 16th week. From week 18 to 20, the fetus can swallow up to 500 ml amniotic fluid per day; the impossibility to perform this function (e.g., due, to esophageal atresia) may lead to an increase in this fluid and of uterine volume. Mechanisms of suction-deglutition and of esophageal peristalsis are mature enough at 34 weeks to allow bottle-feeding from that point onward.

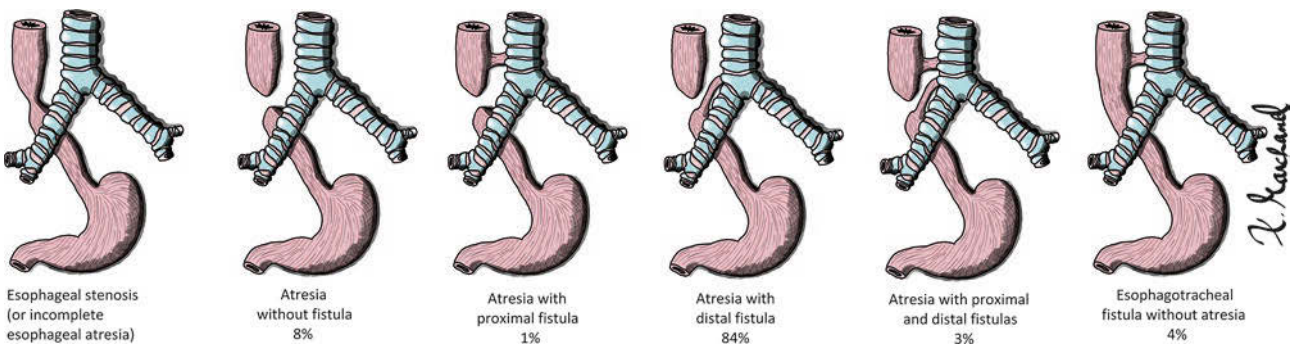
We will now describe different malformations that may arise during development.

1.3.2 Atresias of the Esophagus

Atresias of the esophagus are often accompanied by a tracheoesophageal fistula (◘ Fig. 1.5). They affect 1/3000 to 1/4500 births; 50% of the children carriers of these manifestations also have other abnormalities such as imperforate anus and heart defects.

Atresia of the esophagus results from an impaired canalization of the esophageal lumen, while broncho-esophageal fistulas are more likely the result of a separation failure of the two tubes.

These malformations will be suspected in a newborn baby that regurgitates saliva and liquids after ingestion. Passage through the bronchial tubes will cause coughing



◘ **Fig. 1.5** Congenital atresia of the esophagus: various malformations are possible

and choking. Surgical correction will be required promptly.

1.3.3 Esophageal Stenosis/Strictures

These are rare congenital malformations that occur in 1/50,000 births. Stenoses are most often short and of fibrous or cartilaginous in nature (tracheobronchial remnant). They are often tolerated in the very young age when feeding only liquid food, but they will be revealed subsequently when dysphagia occurs when taking solid food.

1.3.4 Duplications and Cysts

Duplications and cysts are found in 1/8000 births. Double esophageal tubes are rare; most of the time, it consists in "cystic" structures located in the paraoesophageal region and without communication with the real esophagus. Patients are often asymptomatic (the condition being discovered accidentally during a radiological examination) or may suffer from symptoms due to compression by these additional structures. Surgical treatment will be required to control symptoms.

1.3.5 Rings and Webs

The most common ring is Schatzki's ring, an annular fibrous ring located at the esophagogastric junction. However, the congenital nature of Schatzki's ring is being questioned; there is increasing evidence that this band is the consequence of gastroesophageal reflux disease (GERD). See ▶ Sect. 1.9, point 6.

The membrane, or web, is a noncircumferential band, found mostly in the upper esophagus or middle esophagus. It can be solitary, sometimes associated with iron deficiency anemia, then called Plummer-Vinson's syndrome (or Paterson-Kelly's syndrome), or they can be multiple.

Esophageal dilatation per endoscopy is the usual treatment of symptomatic rings and webs.

1.4 Secretion/Absorption

Although some secretion of bicarbonates and mucus by submucosal glands occurs, overall the esophagus has minimal absorptive or secretory function.

Swallowing, however, benefits from saliva secretion. The parotid, submaxillary, and sublingual glands produce 1–2 liters of liquid daily, often in response to chewing, which will help the swallowing by lubricating the food. Saliva also contains enzymes, such as amylase and lipase, which initiate the digestion process. Bicarbonate-rich saliva plays an important role in the esophagus's ability to neutralize the gastric acid that could backflow into it.

1.5 Motility/Sensitivity

The role of the esophagus is to transport food from the mouth to the stomach. The act of swallowing (deglutition) involves a transfer of the food bolus from the oral cavity to the esophageal cavity and then a transport of the bolus through the esophageal body toward the stomach.

1.5.1 Oropharyngeal (Transfer) Motility

The food undergoes a first transformation in our plate (shredding by our utensils) before its form is again altered by dental chewing. This is how the food bolus is formed. The transfer of this bolus into the esophageal cavity initially involves a voluntary action of the striated muscles of the tongue and oropharynx, controlled mainly by the cranial nerve XII (hypoglossal nerve), followed by involuntary movements of the palate, the pharynx, the larynx, as well as the upper esophagus, all regulated by the vagus nerve (CN X) and glossopharyngeal nerve (CN IX). The stages of swallowing are represented in ◘ Fig. 1.6.

Any damage to neural structures (brain stem damage by vascular stroke, amyotrophic lateral sclerosis, Parkinson's, etc.) or striated muscles (oculopharyngeal dystrophy, myasthenia gravis, etc.) of this region may disrupt the physiology of swallowing and lead to a proximal dysphagia with possible false routes to the upper (nasal regurgitations) or lower (cough, choking) airways.

1.5.2 Esophageal (Transport) Motility

Once the voluntary swallowing of the bolus provided by the striated muscles of the oropharynx has pushed the food bolus into the esophageal cavity, the smooth muscles of the esophagus will ensure the progression of the

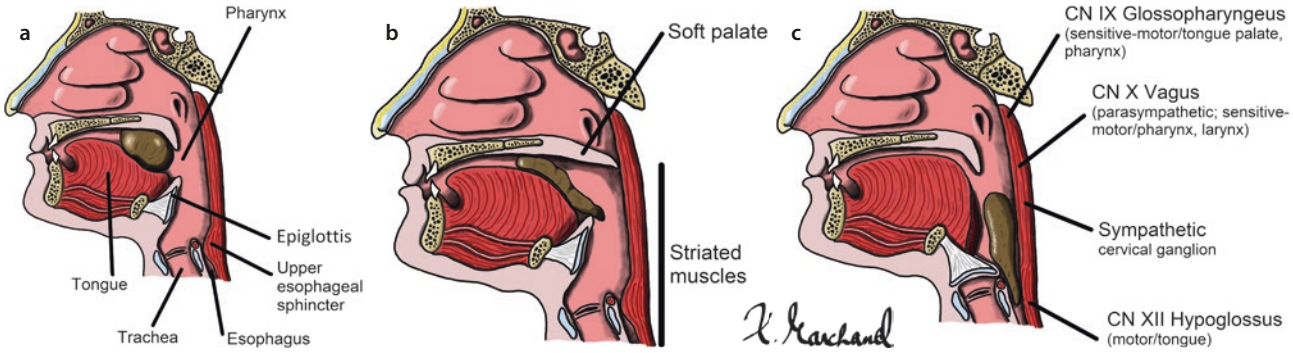


Fig. 1.6 Swallowing: **a** The bolus is pushed by the tongue towards the pharynx. **b** The soft palate rises to block the nasopharynx (and avoid regurgitation of food through the nose). **c** The larynx moves upward and anteriorly, while the epiglottis goes down to block the entrance to the trachea (and avoid intrabronchial aspiration of food resulting in acute airway obstruction, or complicated by aspiration pneumonia); the upper esophageal sphincter, normally closed and under tension, relaxes to let the food bolus get into the esophageal cavity where transport motility will take over. Swallowing is controlled by cranial nerves IX, X, and XII and cervical sympathetic ganglion

bolus along the organ. As explained extensively in ▶ Chap. 3, this peristalsis is mainly involuntary and relies on the enteric nervous system of Auerbach's plexus. The following steps are involved:

- Detection of the intraluminal food bolus with activation of sensitive afferent neural fibers [usually CGRP (calcitonin gene-related peptide)] in mucosa and muscle layers of the intestinal wall.
- The information is transmitted to the efferent motor neurons that will activate, via acetylcholine and neurokinins, the contraction of the circular muscles of the esophagus upstream of the bolus.
- At the same time, the efferent neural fibers will cause the relaxation, via VIP (vasointestinal polypeptide) and NO (nitric oxide), of the circular muscles localized downstream of the bolus to allow a well-synchronized propulsion forward.

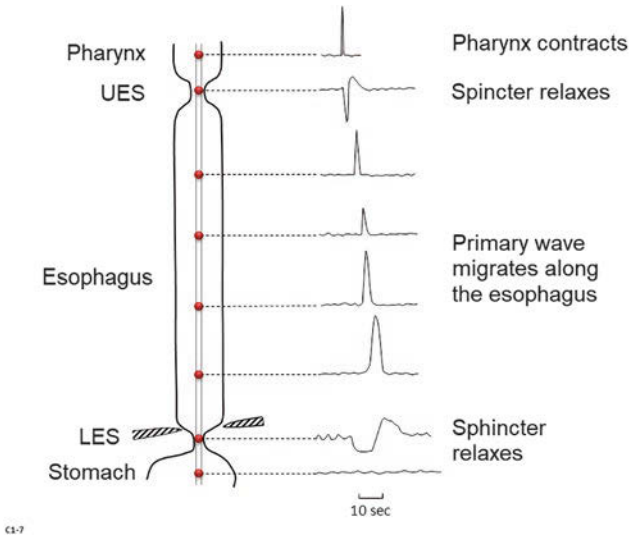


Fig. 1.7 Normal motility (on standard classical manometry) of the esophagus recorded using a probe inserted through the nose into the esophagus and the stomach to measure, at various levels of the organ, the intraluminal pressure variations secondary to contractions of the esophageal wall during swallowing a sip of water

Esophageal motility can be easily analyzed in clinical or research settings using manometry with the help of pressure sensors (installed on a thin tube or a wire introduced, usually nasally, into the esophagus to the stomach) that record the contractions of the esophagus at different points along the organ. Various contractile waves are identified (Fig. 1.7):

- The *primary wave* is a peristaltic contraction normally initiated in response to the ingestion of the food bolus. It migrates, at a rate of 3–4 cm/second, all along the esophagus, from top to bottom, pushing the bolus in front of it. The primary wave thus allows eating in a lying down position ("Roman" style), or even upside down as the opossum. In case of disappearance of this contractile wave, usually by damage to the smooth muscles of the esophagus (e.g., scleroderma), gravity becomes the only factor allowing the descent of food along the esophagus toward the stomach (and thus forcing a vertical position when eating).
- The *secondary wave* is identical to the primary wave above described, but not induced by swallowing. Initiated by local distension, it can start at any level of the esophagus and migrate downward. It can be triggered experimentally by the infusion of a liquid or by local distension (with a balloon) of an esophageal segment. It is generated strictly by the sensory and motor functions of the peristaltic reflex described before. In practice, it will occur during episodes of reflux to "clean" the esophagus of material refluxed by the stomach that could irritate or inflame the esophagus.

- *Tertiary waves* are nonperistaltic simultaneous contractions. They are independent of swallowing and have no obvious motor function. They are encountered during pathological states such as achalasia or diffuse spasm.

1.5.3 Sphincters: Upper and Lower

Sphincters are areas of high intraluminal pressure that act as barriers functioning like unidirectional valves being closed and contracted in the resting state to prevent reflux, but getting relaxed and opened during swallowing to allow the passage of the bolus across.

(a) Upper esophageal sphincter or cricopharyngeal muscle. The upper esophageal sphincter (UES), which is composed of striated muscles, forms a barrier between the esophageal and oropharyngeal cavities, thus serving to protect the trachea of unexpected reflux from the esophagus.

When the bolus arrives from the oropharynx, the sphincter relaxes and opens to let the bolus enter the esophageal cavity. The cranial nerves IX, X, and XII play an important role in this coordination. Impaired relaxation or opening of the UES will result in upper (oropharyngeal/ transfer) dysphagia, and possibly the creation of a diverticular pouch (Zenker's diverticulum; see ► Sect. 1.9.1) in the area of wall weakness (Killian's triangle) between the oblique pharyngeal muscle fibers and the transverse fibers of the cricopharyngeus.

(b) Lower esophageal sphincter. LES is a high-pressure area, created by tonic contraction of specialized circular smooth muscle, that separates the stomach from the esophagus to prevent reflux of gastric material to the esophagus.

Hypotension or defective contraction of this sphincter will result in gastroesophageal reflux and possibly secondary esophagitis.

The LES normally contracted during the "resting state" must relax to open in a coordinated manner at the arrival of the esophageal bolus for its passage into the stomach. This highly coordinated relaxation relies on the NO and VIP inhibitory neurons of the enteric nervous system. Insufficient relaxation of the LES (as encountered in achalasia discussed later) will compromise esophageal transit, and this will result in lower (esophageal/transport) dysphagia.

Transient inappropriate lower sphincter relaxation (TILSR) not triggered by swallowing may occur "spontaneously" (or due to distension of the gastric fundus; 2–3/hr in normal individuals) and allow the retrograde passage of air (belching) or, unfortunately, of gastric fluid (gastroesophageal reflux). Their increased frequency is responsible for most cases of GE reflux disease (GERD) as discussed later.

1.5.4 Sensory Function

Sensory function is essential to detect the presence of the intraluminal food bolus (or refluxed gastric material) which then triggers peristaltic contractions that will harmoniously propel esophageal content toward the stomach.

In normal situations, we are not consciously aware of the passage of food or other sensations within the esophagus. Painful sensations can be perceived in abnormal situations, such as strong spastic contractions, food blockage, or prolonged acid exposure to the esophageal mucosa. Sensory or painful sensation can also be facilitated by visceral hypersensitivity as documented in various functional digestive disorders.

1.6 Inflammation Disorders

Inflammation of the esophagus can appear under different forms in response to different causal factors.

1.6.1 Peptic Esophagitis

Peptic esophagitis is secondary to the reflux of acidic gastric content into the esophagus [GERD (gastroesophageal reflux disease) extensively discussed in this chapter in the Sect. ► 1.8]. Peptic esophagitis is the most common form of esophagitis met in practice.

(a) Symptoms of peptic esophagitis. Esophagitis is clinically revealed by sensations of chest discomfort. Regurgitation of food or acidic-bilious liquid, retrosternal burning, and pyrosis (burning sensation along the esophagus from the bottom to the top) suggest GERD (with or without esophagitis); odynophagia (pain during the passage of food bolus) or dysphagia (feeling of food getting stuck during passage to the stomach) suggests esophagitis (secondary to acid GE reflux).

(b) Diagnosis of esophagitis. Esophageal endoscopy is the best way to diagnose esophagitis. The macroscopic appearance of esophageal mucosa seen at endoscopy (◘ Fig. 1.8) and/or its microscopic aspect on mucosal biopsies obtained during endoscopy will establish the diagnosis.

(c) Pathophysiology of peptic esophagitis. Acid-peptic reflux from the stomach is the dominant cause of peptic esophagitis. However, all individuals with GERD are

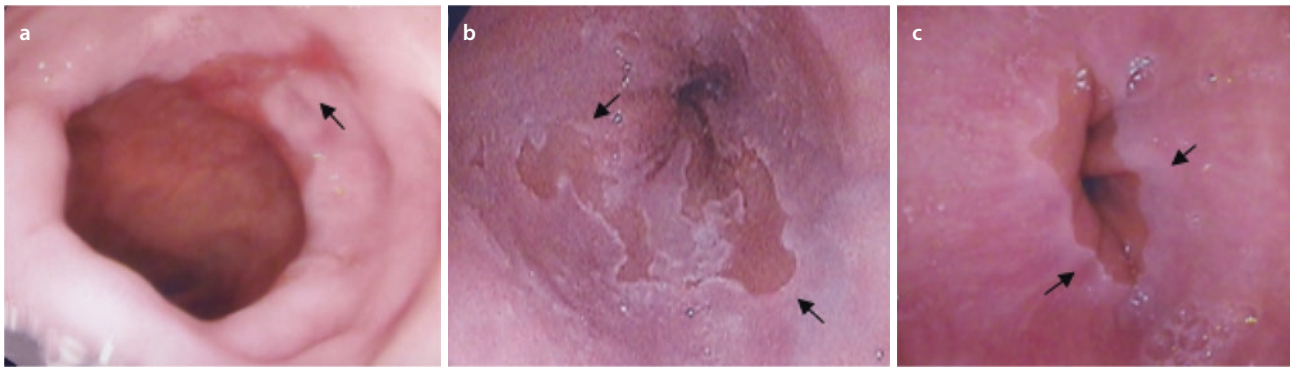


Fig. 1.8 Peptic esophagitis seen in endoscopy: **a** re-epithelialized ulceration (arrow) at the gastroesophageal junction (the gastric columnar and esophageal squamous mucosa are, respectively, of reddish and whitish coloration); **b** Barrett's esophagitis with columnar-type mucosa extending up above the GE junction into the esophagus; **c** normal GE junction. (Photos by P. Poitras)

not victims of esophagitis. A balance between aggression factors and esophageal defense probably explains this situation.

Aggression Factors:

- *Quantity of reflux*: Quantification of gastroesophageal reflux, by continuous recording of esophageal pH, reveals a certain relationship between the magnitude of the refluxed acid material into the esophagus and the severity of the esophagitis.
- *Quality of reflux*: Although the degree of acidity is paramount, bile, under experimental conditions, acts as a potentiating agent to acid in inducing esophageal inflammation, so it may contribute to the severity of esophagitis. Hypersecretion of gastric acid could be, in rare cases (such as a gastrinoma that causes a major hypersecretion of gastric acid; see Zollinger–Ellison syndrome in ▶ Chap. 2), a factor promoting mucosal damage to the esophagus.

Defense of the Esophagus:

- *Mucosal resistance* of the esophagus to aggression, for example, by secreting local mucus or bicarbonates, could be a protective factor. The concept of "mucosal barrier" so important in gastric pathophysiology (see ▶ Chap. 2) is however not as well developed in esophageal pathology.
- *Esophageal peristalsis* contributes to the defense of the esophagus by promoting the flow of refluxed gastric material back into the stomach (esophageal clearance). The loss of peristaltic secondary contractions, normally initiated during a backflow, probably contributes to the severe esophagitis seen in patients with esophageal muscle disease due to scleroderma.
- *Saliva,* rich in bicarbonate and with a neutral or alkaline pH, is a factor favoring the neutralization of gastric acid refluxed into the esophagus. However, no clinical situation (e.g., during hyposalivation by Sjogren's disease or after maxillary gland radiotherapy treatment) can confirm its clinical importance in the genesis of esophagitis.

(d) Complications of esophagitis. *Acute bleeding* from an esophagitis lesion is rare. More severely ulcerated areas or the use of anticoagulants may be contributing factors. Chronic occult bleeding from ulcerated esophagitis may explain some cases of iron deficiency anemia.

Stenosis is a narrowing of esophageal lumen due to local inflammation or scar from healed ulceration. It will be suspected in the presence of dysphagia, typically more with solid than with liquid foods, and it will be confirmed by endoscopy or radiology. The treatment of stenosis requires control of esophagitis and acid reflux, usually by proton pump inhibitors (PPIs). In some cases, mechanical dilatation with bougies or balloons will be required.

Barrett's esophagus: The squamous esophageal mucosa, in this condition, is replaced by an intestinal-type columnar mucosa.

The diagnosis is suspected during endoscopy which reveals a reddish, gastric-looking mucosa above the cardia, in esophageal territory. The esophagus may thus appear short (hence the name endo-brachy-esophagus) since the junction of the esophageal and gastric mucosa is higher than the usual endoscopic Z line classically located at 40 cm from the incisor teeth. The differential diagnosis will be made with a hiatal hernia raising the cardia (and thus the Z line) into the thorax above the usual diaphragmatic location. Endoscopic biopsies will confirm histological presence of intestinal metaplasia, in an anatomical segment otherwise identified as the esophagus.

Barrett's esophagus is important since it is considered preneoplastic, precursor to the development of a local adenocarcinoma. The risk of malignant evolution is estimated at 1/200 patients.

Treatment of Barrett's esophagus is disappointing since the suppression of reflux by medication or surgery does not seem to induce regression of the re-epithelialized glandular mucosa of the esophagus. Follow-up of this condition (with endoscopy and biopsies every 3–5 years) is often recommended hoping for early detection of high-grade dysplasia or early adenocarcinoma lesions allowing treatment of an early-stage cancer disease. The benefit of this monitoring strategy is however unclear.

(e) Treatment of peptic esophagitis. Treatment of peptic esophagitis is based on the reduction of acid exposure in the esophagus. This is usually achieved satisfactorily by inhibiting the activity of the proton pump located on gastric parietal cells secreting HCl in the stomach cavity and abnormally refluxed in the esophagus (see ▶ Chap. 2). Healing of inflammation is seen in 80–90% of cases of peptic esophagitis after 4–8 weeks of treatment with proton pump inhibitors (PPIs).

In case of failure of the usual therapy with a PPI administered at least 30 min before breakfast for optimal bioefficacy, various pharmacological strategies are possible: (a) doubling the PPI dose (in a single morning dose or, preferably, in divided doses, 30 min before breakfast and dinner); (b) addition of an H2 blocker (e.g., ranitidine 150–300 mg at bedtime) to optimize nocturnal acid suppression; and (c) addition of prokinetics (e.g., domperidone 10–20 mg before meals and at bedtime) to facilitate gastric emptying and possibly increase the tone of the lower esophageal sphincter can sometimes be tried, although evidence for efficacy is limited. Medication failure is usually not an indication for surgery since the results are often disappointing, except in cases where the control of incapacitating regurgitation is sought.

Discontinuation of PPIs results in clinical and/or endoscopic recurrence in 2/3 of patients, unless a predisposing condition (e.g., obesity, drugs reducing sphincter tone) was present and can be corrected. Continuation of PPI therapy appears to be the optimal solution (at the present time); PPIs are considered as safe drugs for chronic prolonged use (even for years). However, long-term disadvantages to chronic PPI therapy (based on retrospective case-control and cohort studies) are present, such as an increased risk of enteric infections (*Salmonella* RR 3, *Clostridium difficile* RR 2, etc.) or pneumonia (RR 4), as well as a possible risk of hip fracture; malabsorption of iron, calcium, and vitamin B12; or interaction with certain drugs including the antiplatelet agent clopidogrel (interaction on P450 cytochrome) or drugs requiring gastric acid milieu for optimal absorption (e.g., ketoconazole).

Anti-reflux surgery does not offer medical or economic benefits at the present time (aside for patients with predominant regurgitation). The role of novel endoscopic anti-reflux procedures remains to be defined.

1.6.2 Infectious Esophagitis

Infectious esophagitis is usually of viral or mycotic origin, more rarely bacterial.

(a) **Symptoms of infectious esophagitis**. Odynophagia as well as dysphagia or chest pain is found in infectious esophagitis. Heartburn or pyrosis is rare.

(b) **Viral esophagitis.**

- *Herpes simplex 1* can cause esophagitis in immunosuppressed patients, often by chemotherapeutic agents. It can also be seen during a primary infection to herpes in healthy subjects.

  Endoscopy may reveal along the esophagus vesicular lesions similar to herpes skin lesions, or small ulcers surrounded by healthy mucosa. Biopsies will reveal typical intranuclear inclusions on histological analysis, and culture can confirm the diagnosis of the virus (but is rarely done).

  Esophagitis usually resolves spontaneously in 1 to 2 weeks. Acyclovir (400 mg po 5 times/day or IV 5 mg/kg q 8 h for 7–14 days) will accelerate resolution of the infection, as well as foscarnet or other antiviral agents.
- *Cytomegalovirus:* CMV esophagitis is encountered mainly in patients immunosuppressed by HIV. It is often a source of severe esophageal pain.

  Endoscopy may reveal long, penetrating ulcers of esophageal mucosa, and biopsies will show characteristic intracytoplasmic viral inclusions.

  Treatment requires the use of ganciclovir or foscarnet.
- *Human Immunodeficiency Virus*: The HIV has been implicated in some cases of viral-looking esophagitis in HIV-positive patients when it was not possible to identify CMV or herpes. Transient symptoms of esophagitis may accompany the primary HIV infection.

(c) **Mycotic esophagitis.**

- *Candida albicans* is responsible for esophagitis in patients with AIDS or immunosuppressed by undernutrition, systemic diseases, chemotherapy, etc., but also in subjects whose immunity is only partially or locally compromised, such as asthmatics using corticosteroids administered by bronchial inhalation or people treated with antibiotics.

  The infection is often localized more in the proximal esophagus and may include the oral

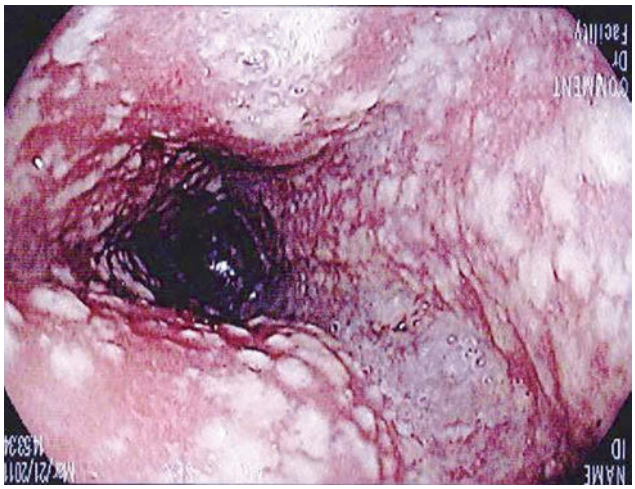


Fig. 1.9 Candida esophagitis: endoscopic view, white and flaky membranes attached to the esophageal mucosa. (Photo by P. Poitras)

cavity. The diagnosis is suspected at endoscopy in front of whitish and flaky membranes comparable to the thrush of oral candidiasis. Biopsies or cytological analyses reveal the presence of *Candida albicans* (Fig. 1.9).

The treatment can be done, in milder cases, with a topical solution of nystatin (500,000 U qid for 7–14 days). In severe cases or in HIV patients, fluconazole (100–200 mg per os id for 2 weeks) will be preferable.

- *Others:* Histoplasmosis, aspergillosis, cryptococcosis, and blastomycosis can occasionally affect the esophagus.

1.6.3 Eosinophilic Esophagitis

(a) **Definition of eosinophilic esophagitis.** Eosinophilic esophagitis refers to an infiltration of the esophagus by eosinophils as detected by microscopic analysis of endoscopic biopsies. It is characterized by massive eosinophilic infiltration (>15 eosinophils/high-powered field) distributed all along the esophagus. Eosinophil infiltration can also be found in gastroesophageal reflux, but it is usually moderate (less than five eosinophils/field) and restricted to the lower esophagus, as well as in eosinophilic gastroenteritis (with or without blood eosinophilia) damaging other digestive organs.

(b) **Clinic.** Eosinophilic esophagitis was first described in the 1970s, but its incidence has been rising steadily since then. Well known in pediatrics where it affects often atopic or allergic children, it is encountered now more and more frequently in the adult (often young men).

Dysphagia for solid foods and/or food impaction are cardinal symptoms of eosinophilic esophagitis.

(c) **Diagnosis of eosinophilic esophagitis.** Endoscopy may reveal, surprisingly considering the symptoms, an almost normal mucosa macroscopically (but microscopically infiltrated by eosinophils) or reveal suggestive changes such as longitudinal furrows, a trachea-like appearance with multiple thin rings distributed along the esophagus, or a diffuse narrowing of the esophagus. Biopsies are necessary and diagnostic.

(d) **Treatment of eosinophilic esophagitis.** The etiopathogenesis of eosinophilic esophagitis is poorly known, as is its treatment. PPIs appear to help in 40% of cases. Corticosteroid therapy is effective, preferably by topical application (fluticasone or budesonide) rather than oral in order to minimize steroid side effects. Exclusion diets (wheat, milk, eggs, peanuts, soy, seafood) have given very encouraging results (75–95% success in children, but diet compliance is difficult), thus supporting an allergic origin of the problem. Hypoallergenic elemental diet is also an option. Dilatation of stenosis by bougie or endoscopic balloon seems hazardous.

(e) **Evolution.** The long-term evolution is poorly known; some patients, unfortunately, seem to deteriorate, while many others seem to have a favorable spontaneous evolution.

1.6.4 Caustic Esophagitis

Ingestion of caustic acid or alkali often results in severe esophageal damage. It is usually accidental in children and linked to suicidal acts in adults. Corrosive household products, such as ammonia, laundry detergents, pipe cleaners, and pool acids, are frequently involved.

(a) **Symptoms.** In the acute initial period, dysphagia, chest pain, and/or sore mouth are often present. Esophagitis is often severe and can lead to perforation with secondary mediastinitis and its lethal complications if not treated. Perforation can also occur in the gastric area or intestine if these organs have been in contact with the corrosive agent.

Long-term symptoms include parietal healing with fibrosis and strictures of the esophageal lumen, which often requires mechanical dilatations, often repeated, or even surgical replacement of the esophagus. In the very long term, there is an increased risk developing squamous cell cancer.

(b) **Investigation.** Alkaline or acidic agents are equally toxic (even if their mechanisms of toxicity are different). Domestic bleach, fortunately, rarely leads to severe complications.

Endoscopy may be used to confirm the extent and severity of the caustic burns in order to assist in prognosis and care planning. Endoscopy (if one decides to do it) should be performed with great delicacy in order to avoid perforating necrotic and fragile organs.

(c) **Treatment of caustic esophagitis.** Careful monitoring of the patient is recommended so that early intervention can be initiated if complications ensue. Preventive maneuvers seem to be ineffective: forcing vomiting may make worse contact of the toxic agent with the esophagus; diluting or neutralizing solutions seem to be ineffective and may also promote harmful vomiting. Reducing the inflammatory reaction with systemic steroids (e.g., methylprednisolone 20–40 mg q 6 h IV) remains a debated therapeutic issue.

Esophageal and/or gastrointestinal perforations will require emergency, and often morbid, surgery. Depending on the condition of the tissue, drainage with suture of the perforation or more or less extensive removal of the affected organs will be required.

1.6.5 Drug-Induced Esophagitis

(a) **Pill esophagitis.** This is due to a medication pill "trapped" or stagnating in an esophageal segment that induces a local corrosive damage. It occurs most often in the upper esophagus, and it is characterized by localized chest pain, often with odynophagia and dysphagia, starting few hours after ingestion of the drug.

Endoscopy usually shows a well-circumscribed ulcer (or two "kissing" ulcers) surrounded by healthy mucosa, reflecting the "burn" by the stagnant pill. Aggravating factors are as follows:

- Some medications seem more irritating or corrosive; this includes potassium supplements, tetracycline and its derivatives, aspirin, and NSAIDs.
- Certain conditions are known to favor poor transport of the pill down the esophagus and "stagnation of the pill" with secondary corrosive damage. Any condition associated with abnormal esophageal transit is a risk factor.
- Most of the time, taking the medication in a lying down position, and with insufficient fluid bolus to promote trans-esophageal passage, is involved in pill-induced ulceration.

The ulcer usually heals spontaneously in a few days. Antacids, possibly with local anesthetics ("Pink Lady": 15–30 mL of antacid and 15–30 mL of viscous Xylocaine), can help relieve pain.

(b) **Bisphosphonates.** Frequently used bisphosphonates for the treatment of osteoporosis are associated with chemical esophagitis often more diffuse than those described above. The esophagitis mechanism remains unclear and implies, among other things, the reflux in the esophagus of the drug once dissolved in the stomach. To counteract this complication occurring mainly with alendronate, it is suggested to take the drug in a standing position (and stay in this position for at least 1 hr) and to ingest a large quantity of fluids to promote passage of the drug through the intestine and avoid its reflux in the esophagus or its stagnation in the stomach.

1.6.6 Radiation Esophagitis

Radiotherapy for the treatment of thoracic neoplasia (lymphoma, cancer of the lung/esophagus, etc.) can affect the esophagus. In the acute phase, during the treatment period, mucositis causing pain, odynophagia, and dysphagia can occur. Treatment with local analgesics and antacids helps relieve these symptoms. In some cases, dysphagia can be severe enough to compromise food ingestion, and temporary artificial tube feeding may be required. Delayed complications such as stenosis may require mechanical dilatations.

1.7 Tumor Disorders

1.7.1 Types of Esophageal Neoplasia

Squamous cell (epidermoid) carcinoma and adenocarcinoma are the two main malignant neoplasms that affect the esophagus (◘ Fig. 1.10).

(a) **Squamous cell neoplasia** develops from the esophageal squamous epithelium. It is most commonly located to the middle and upper thirds of the organ. It preferentially affects males over 50. Its prevalence is high in some parts of the world including China, the northeast of France, or in the black population of North America. Predisposing factors involving chronic mucosal damage are well recognized: heavy alcohol ingestion, smoking, ingestion of hot tea, caustic esophagitis, etc. Previously established as the most important type of esophageal cancers, the frequency of the epidermoid carcinoma seems to have regressed in the recent decades (perhaps in response to a decreased exposition to predisposing factors).

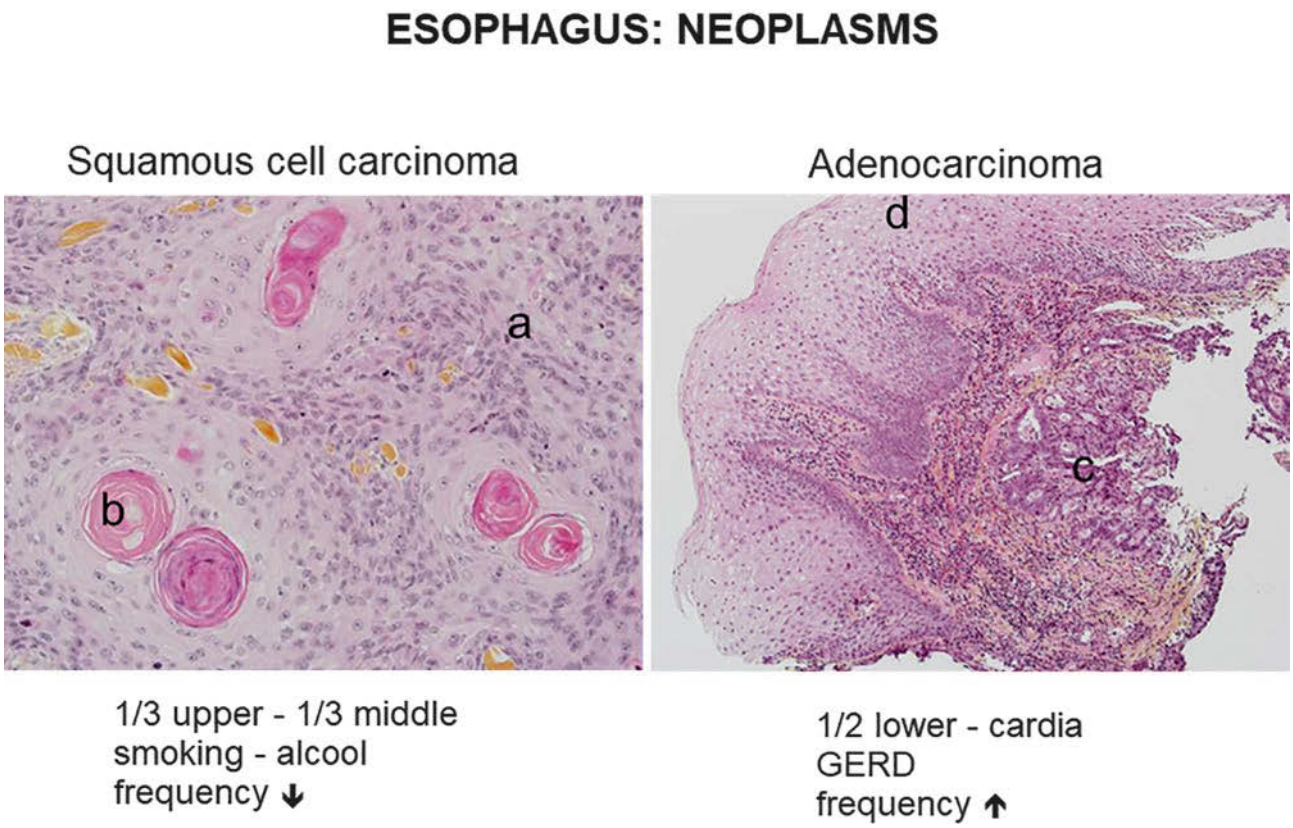


Fig. 1.10 Histology and characteristics of esophageal neoplasms: (1) The picture on the left shows a well-differentiated squamous cell carcinoma {(a); compared with the normal squamous cells (present on d)} with formation of keratin pearls (b); squamous cell cancer is most often located in the upper or middle esophagus. (2) the right picture shows adenocarcinoma cells (c) infiltrating the mucosa under a normal squamous epithelium (d). (Photos by G.Soucy)

(b) **Adenocarcinoma** was classically considered as a rare esophageal tumor, but it is now the most common esophageal cancer in the Western world. Adenocarcinoma develops from glandular tissue; it is therefore more readily seen during the re-epithelialization of the normal squamous esophageal epithelium by the glandular lining seen in Barrett's esophagitis. This type of cancer mainly affects the distal esophagus. It develops more readily in male subjects, of Caucasian origin, aged over 50 years and suffering from chronic gastroesophageal reflux.

1.7.2 Clinical

Esophageal neoplasia grows intra-luminally to obstruct the esophageal channel, thus causing progressive dysphagia, initially presenting with solid food and later on affecting also liquids. Weight loss, due to a deficient caloric intake, is common. Anemia caused by chronic bleeding from the ulcerated tumor may occur.

1.7.3 Diagnosis of Esophageal Cancer

X-rays of the esophagus (Fig. 1.11) can reveal the luminal obstruction by the tumor (although not as sensitive as endoscopy), but will not be able to differentiate the nature of the cancer.

Endoscopy is the best test to diagnose esophageal cancer; biopsies and/or cytology are required to confirm the diagnosis.

The progression of the disease is usually toward the adjacent lymph nodes and thus to the cervical, thoracic, or abdominal regions depending on the location of the primary tumor. Extent of the disease will be evaluated by axial tomography (CT scan), positron emission tomography (PET), or echo-endoscopy.

1.7.4 Treatment of Esophageal Cancer

Unfortunately, no curative treatment can be offered for esophageal cancer in a large proportion of patients. Survival after treatment is 30 to 40% at 5 years.

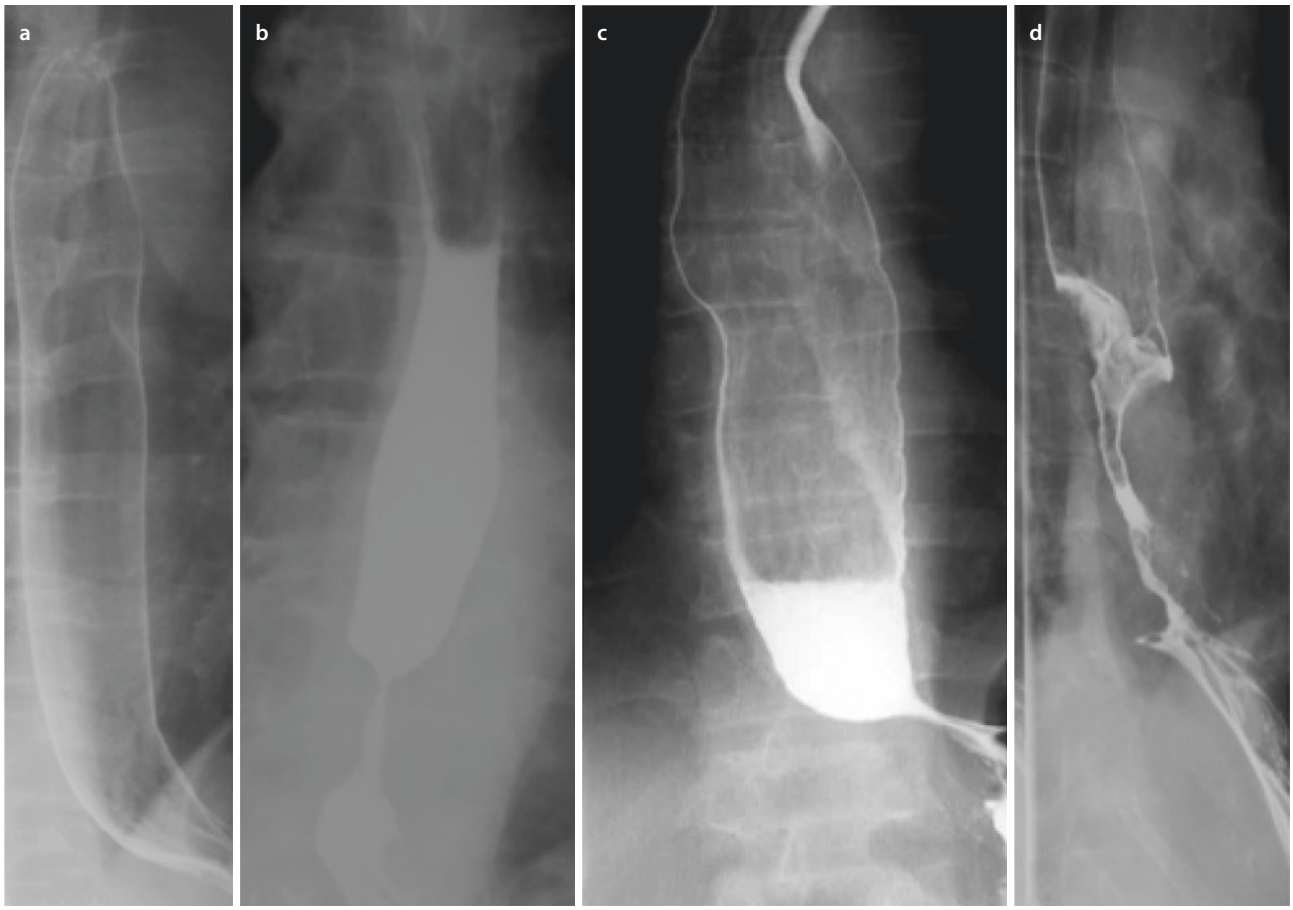


Fig. 1.11 **a** Radiography of a normal esophageal appearing as a cylinder about 25 cm long and 2.5 cm wide. **b** Peptic stricture is seen here in the distal esophagus with a typical smooth and symmetrical narrowing of the lumen. **c** Achalasia (1) the lumen of the esophagus is distended; (2) the cardia is slim and slender, appearing as a bird's beak. **d** Neoplasia (epidermoid here): the esophagus is narrowed by a proliferative mass protruding into the lumen of the organ and mimicking an "apple core." (Photos by R. Déry)

The overall therapeutic strategy is comparable for the epidermoid carcinoma or adenocarcinoma.

Faced with a disease that is believed to be limited and curable, the therapeutic procedures include radiation therapy, usually combined with chemotherapy (with cisplatin) frequently followed by excision surgery. Esophagectomy, with different reconstruction techniques (esophagogastric anastomosis with a pull-up of the stomach, interposition of a colonic or jejunal segment, etc.), is a complex and unfortunately often morbid procedure to be carried out in expert centers.

In the case of an advanced, unresectable disease, the strategies of palliation include chemotherapy ± radiotherapy to decrease the volume of the obstructive mass and secondary dysphagia, or stent placement, using endoscopic or radiological guidance, that re-establishes the esophageal lumen to allow an oral feeding.

1.8 Function Disorders

1.8.1 Gastroesophageal Reflux Disease (GERD)

(a) Definition. GERD is defined as the reflux of gastric material into the esophagus, resulting in troublesome symptoms.

(b) Symptoms of GERD. Regurgitation of food with a feeling of retrosternal discomfort or with bitter taste in the mouth, heartburn (retrosternal burning sensation due to the acidic pH of the refluxed material), and pyrosis (heartburn radiating upward, progressing from the bottom to the top of the esophagus) are indicative of GERD (with or without esophagitis). Odynophagia (retrosternal pain at the passage of food) or dysphagia (blockage sensation

at the passage of food) is suggestive of esophagitis (a complication of GERD).

GERD symptoms are common, being reported in 30 to 50% of the population, and their frequency appears to be increasing with age. GERD is considered as an illness when symptoms occur at least weekly and have an impact on the quality of life.

(c) Pathophysiology of GERD. Gastric content, made of ingested food and secretions produced by the stomach (HCl, pepsin) or refluxed from the intestine (e.g., bile), will be, under normal conditions, pushed to the duodenum by propulsive contractions of the stomach. The lower esophageal sphincter (LES) works as a unidirectional valve that relaxes to allow the swallowed food to enter the stomach cavity and then contracts back to its basal state in order to close the upper end of the stomach and thereby prevent reflux of gastric contents back up into the esophagus. The reflux from the stomach into the esophagus thus occurs when the gate capacity of the valve is insufficient to impede the passage of gastric material.

The LES measures 2 cm in length and is located at the diaphragm, mainly on the abdominal side of the thoracoabdominal junction. The sphincter can be seen as a two-component structure. The "internal" sphincter corresponds to an area made of specialized smooth muscles of the lower esophagus, which, although not identified histologically, generate a short high-pressure zone between the positive intra-abdominal and the negative intrathoracic pressures. The "external" sphincter is made of various anatomical factors of the lower esophagus that bolster this physiological high-pressure zone: the diaphragm (making a constrictive ring around the esophagus), the right crus of the diaphragm as well as the phreno-esophageal membrane (surrounding and fixing the lower esophagus to the thoracoabdominal junction), the size of the angle of His (allowing compression of the distal esophagus by the gastric fundus), and the intra-abdominal localization of the sphincter.

Circumstances favoring reflux are shown in Fig. 1.12 and discussed here:

- *Increased intragastric pressure* exceeding the lower esophageal sphincter retention capacity. The pressure is naturally positive in the abdomen and negative in the thorax. Pregnancy, abdominal obesity, and tight waist clothing are factors that increase intra-abdominal and, consequently, intragastric pressures. Gastric emptying failure by either distal obstruction or gastroparesis will result in stagnation of gastric contents and promote reflux into the esophagus. The recumbent position will shift the gastric content into the upper stomach, facilitating its reflux upward.

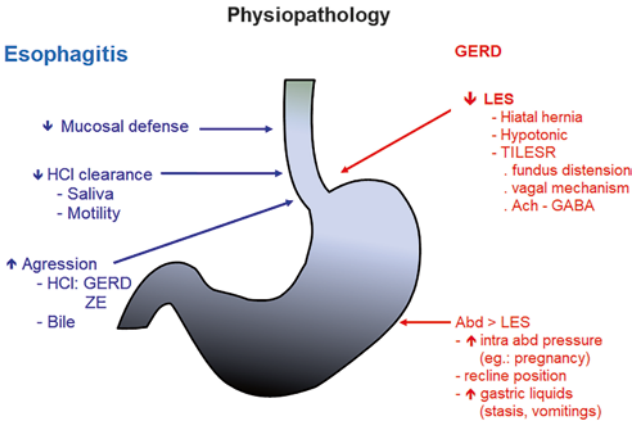


Fig. 1.12 Pathophysiology of gastroesophageal reflux disease (right of the picture in red characters) and of its most frequent complication, esophagitis (left of picture in blue)

- *Decreased barrier pressure*. The LES normally has a basal tone of 20–25 mmHg to impede reflux of gastric contents into the esophagus. Sphincter hypotonia (pressure below 10 mmHg) is a logical and obvious cause for reflux; it is found, however, in only a small percentage of cases. Smooth muscle esophageal diseases, such as scleroderma, can reduce the pressure of the lower esophageal sphincter (even to 0 mmHg) and result in marked gastroesophageal reflux. Some drugs (e.g., theophylline, calcium channel blockers, nicotine) as well as certain foods (e.g., chocolate, mint) can lower the pressure of the sphincter and may promote reflux.

  Hiatal hernia (intrathoracic displacement of the esophageal-gastric junction) seems to be a condition that alters the tension resistance of the LES, probably by compromising the anatomic factors that produce the "external sphincter."
- *Normotensive but incompetent barrier*. The lower esophageal sphincter normally relaxes during swallowing to let the food bolus migrate from the esophagus to the stomach. Transient and inappropriate relaxation, i.e., without being induced by swallowing, may occur. This phenomenon usually occurs in response to fundic distension, via a vagal reflex involving VIP and the GABA (gamma-aminobutyric acid). Studies have confirmed that the gastric content could use these transient and inappropriate relaxations to reflux into the esophagus. TILSR (transient inappropriate lower sphincter relaxation) which occurs 2–3 times/hr in normal subjects are more frequent in GERD (8–12/hr); increased number of TILSRs is now considered the main pathophysiological mechanism for GERD.
- The *acid pocket* is a concept born in 2001. It results from the simple observation that acid reflux occurs often after the meal, a paradoxical situation since the

gastric pH is then high due to the food present in the stomach. Studies have shown that acid secretions accumulate on top of food to form an acidic pocket in the upper part of the stomach. If the acid pouch is located in a hiatus hernia, chances for gastroesophageal reflux are clearly increased. PPIs raise the pH of the pocket secretions (from pH 1 to pH 4). Alginate foam (Gaviscon®, discussed below) works by forming a raft on this pocket (rather than mixing with the food chyme as other antacids) to "locally" neutralize the acid in the pocket.

(d) Complications of GERD. Esophageal as well as extra-esophageal complications are seen:

Esophageal complications:

- Peptic esophagitis is the main complication of gastroesophageal reflux, as previously discussed in the section of inflammatory diseases (► Sect. 1.6.1); stenosis or neoplasia is then possible.
- Nonerosive reflux disease (NERD) refers to GERD without esophagitis as established at endoscopy (endoscopy is positive in only 30% of patients suspected of GERD; among the patients with negative endoscopy, 50% have reflux documented on pH studies and are therefore identified as NERD). Since these patients seldom develop peptic complications (including esophagitis), even in the long run, NERD requires only a symptomatic treatment.

Extra-esophageal complications:

- ENT: Hoarse voice, pharyngeal pain, and cough may be symptoms of posterior laryngitis believed to be due to a reflux of irritating gastric material in some cases.
- Lungs: Asthma may possibly be exacerbated by gastroesophageal reflux. The mechanisms proposed are either intrabronchial aspiration of material refluxed into the hypopharynx or bronchiolar spasms triggered by a vagal reflex possibly induced by distension or irritation of the esophagus secondary to reflux. In rare cases, aspiration of the refluxed material may cause aspiration pneumonia.
- Chest pain: Retrosternal pain, sometimes even mimicking that of angina pectoris (including irradiation to the left arm or jaw), may be due to reflux. It is assumed that the pain is due to an esophageal spasm triggered by reflux. The possibility of coronary spasms in response to a vagal reflex triggered by GERD has also been proposed in some patients.

In presence of a clearcut gastroesophageal reflux, a good response of these extra-esophageal symptoms to treatment with acid suppression can be expected. When a reflux is suspected, a therapeutic test (using a twice daily PPI regimen for 4–8 weeks) could be useful in establishing the contribution of gastroesophageal reflux in the genesis of these extra-esophageal symptoms. The very limited effectiveness of PPIs (success of less than 40% and comparable to placebo in several studies) to relieve coughs, hoarse voice, or asthma raises doubts about the importance of GERD in these symptoms in a majority of patients.

(e) Investigation of GERD. Gastroesophageal reflux disease is a very common condition, but fortunately in most patients the diagnosis can be made based on clinical presentation, and further investigations are not required. Investigations need to be pursued in patients who do not respond appropriately to treatment, or in those with features suggesting complications (e.g., dysphagia, odynophagia, weight loss, anemia). Although of unproven value, many experts suggest screening endoscopy to rule out Barrett's esophagus be performed in certain higher risk patients (e.g., male Caucasians older than 50 years of age with chronic reflux symptoms for more than 5 years).

Modes of Investigation:

- *Endoscopy* is the most useful examination to confirm the diagnosis of GERD (if esophagitis is present in the esophagus), to guide management of esophagitis (in order to avoid long-term complications), to identify subjects at risk for adenocarcinoma (Barrett's esophagus), and to reassure the reflux patient without esophagitis (since these individuals usually continue to live without ever developing inflammation and its complications). In patients with heartburns, endoscopy reveals esophagitis in 30% of cases; others suffer from either NERD (nonerosive reflux disease) or esophageal hypersensitivity or functional heartburn.
- *Recording of esophageal reflux* can be done when the diagnosis is still unclear following endoscopy (e.g., normal endoscopy) or when other conditions justify to confirm the diagnosis (e.g., poor response to antireflux treatment). GERD can be confirmed by various methods that measure reflux of gastric material into the esophagus. Esophageal pHmetry, the most commonly used of these methods, continuously measures the esophageal pH using an electrode either installed on a catheter that is passed transnasally into the lower esophagus and connected to a device worn on a belt or shoulder strap, or clipped to the distal esophageal mucosa endoscopically. Esophageal pH is then monitored over a period of usually 24 hours or more. Detecting episodes of esophageal pH < 4 indicates reflux of gastric acid into the esophagus.

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Other methods, such as using the concentration of bile in the esophagus or esophageal impedance, can also be used in select cases, particularly if non-acidic reflux is suspected.

- *Radiography* of the esophagus (or barium meal) can demonstrate reflux of the barium substance from the stomach into the esophagus. It can occur spontaneously (mainly in the recumbent position) or can be induced by different maneuvers increasing abdominal pressure (raising legs, etc.). However, the barium meal is neither specific nor sensitive for the diagnosis of GERD or esophagitis, and it rarely helps in the management of these diseases. It can be of some interest, however, in the study of dysphagia, as discussed subsequently.

(f) Treatment of GERD.

(a) ***Correction of risk factors and life style habits*** that promote GERD is important. Correcting an excessive intra-abdominal pressure (losing weight if obese, abandoning tight clothing, etc.), avoiding reclining positions favoring reflux (no lying down after meals, elevating the head of the bed, etc.), and minimizing LES hypotension (avoiding fatty foods, chocolate, peppermint, alcohol, tobacco, or drugs such as calcium channel blockers, nitrates, theophylline) can provide significant improvement in certain cases. Weight gain is often the trigger for GERD, and weight loss, although often difficult to achieve, is likely the most useful "lifestyle" intervention.

(b) ***Suppression of refluxed acid*** is currently the most effective pharmacological method to stop symptoms of reflux (and secondary esophagitis). Different approaches are used.

- Antacids: These drugs typically contain buffering agents such as bicarbonate, magnesium, and aluminum, to neutralize gastric HCl. They are available in liquid form (Maalox, Riopan, Amphogel, Gaviscon, 15–30 ml q 1–2 h prn) or tablets (Tums, Rolaids, etc.). Symptom relief is usually obtained rapidly within a few minutes, but it is short-lived. Available over the counter in pharmacies, these agents are useful for self-treatment of mild or occasional symptoms. High doses of antacids may cause side effects (especially diarrhea due to magnesium).
- H2 blockers: These (also called H2 receptor antagonists or H2RA)) suppress gastric H+ secretion by the parietal cells by blocking the histamine stimulation. More powerful than antacids, they revolutionized the treatment of acid-related diseases when introduced in 1977. Their ability to suppress acid is however limited by, among other things, tachyphylaxis due to downregulation of histamine receptors after a few days of pharmacological treatment. H2 blockers may be useful to control mild to moderate reflux symptoms (ranitidine 150–300 mg bid or famotidine 20–40 mg bid). They can also be used "on demand" for the relief of occasional reflux or peptic symptoms (in many countries, H2RA can be conveniently purchased over the counter without a prescription). Occasional use of these drugs will prevent tachyphylaxis, but because they require gut absorption and systemic circulation, it takes 30 to 60 minutes before they begin to inhibit acid production. Accordingly, they are not well suited for the prompt relief of symptoms when taken on a prn basis. In case of nocturnal symptoms uncontrolled by PPI, an H2RA taken at bedtime can help in some people.
- Proton pump inhibitors (PPIs): These are potent inhibitors of gastric acid secretion (see ▶ Chap. 2). Since their introduction in the 1980s, they have revolutionized the treatment of GERD and currently constitute the most effective treatment for reflux esophagitis. The usual doses of dexlansoprazole (30 mg die), esomeprazole (20 mg), lansoprazole (30 mg), omeprazole (20 mg), pantoprazole (30 mg), and rabeprazole (20 mg), taken in the morning at least 30 minutes before breakfast, will control the symptoms of reflux and heal reflux esophagitis in 80–90% of patients. Some individuals will benefit from a double dose (administered once in the morning or preferably in divided doses 30 minutes before breakfast and dinner). Recurrence of symptoms (or of esophagitis) when treatment is discontinued occurs in 2/3 of patients, and often a continuous therapy may be required. Maintenance therapy using PPI has been used for 20 years without significant side effects. It currently appears as the treatment of choice for most patients.

Reflux without esophagitis (NERD), given the absence of complications, can be treated symptomatically and on demand. On the other hand, reflux esophagitis should, even in the absence of symptoms, be managed, most of the time, by a continuous maintenance treatment to minimize the chance of peptic or neoplastic complications.

(c) ***Reducing reflux material*** appears as a logical therapeutic strategy. It could, in theory, be obtained by increasing the tone of the LES, by decreasing the numbers of TILSR (transient inappropriate lower sphincter relaxation), or by promoting gastric emptying of gastric contents to the intestine in order to

decrease the amount of material likely to backflow into the esophagus.

- However, few drugs are available that decrease the GE reflux. Domperidone (10 mg before meals and at bedtime), a gastrokinetic agent that increases gastric emptying and LES tone by acting as an antidopaminergic, may be useful in a small subset of patients, especially to decrease regurgitations poorly controlled by acid reduction agents.
- Reducing TILSRs appears as a logical pharmacological target, given their important role in the pathophysiology of GERD. Agonists of GABA (gamma-aminobutyric acid) are considered as therapeutic candidates; baclofen is sometimes used.
- Surgery can be used to decrease reflux (see below).

(d) ***Anti-reflux surgery*** was, before the demonstrated efficacy of PPIs, the only valid treatment for GERD. The Nissen fundoplication not only corrects the hiatal hernia but also wraps around the cardia a portion of the gastric fundus to restore the "external" sphincter (discussed in the anatomy ▶ Sect. 1.1.1 of this chapter). Fundoplication is usually performed laparoscopically; it may involve different technical variations such as the classical Nissen procedure or the partial Toupet fundoplication. Fundoplication decreases reflux by raising the basal tension of the LES while reducing TILSRs by incompletely understood mechanisms. Aside from the usual morbidity related to abdominal surgery, fundoplication can cause side effects in about 10% of subjects operated, including the following:

- Dysphagia: This may require dilatations to loosen up a too tight fundoplication.
- Gasbloat: in the majority of the subjects operated on, the new fundic valve will create a difficulty with vomiting or belching. In some patients, the inability to belch will cause abdominal discomfort by accumulation of gastric air.
- Dyspepsia: Functional dyspepsia is often due to a poor accommodation of the gastric fundus (see ▶ Chap. 2). This motor dysfunction can obviously be enhanced by a fundoplication procedure compromising fundic anatomy and function. The indication for fundoplication must therefore be considered very carefully in a patient with GERD and coexisting symptoms of functional dyspepsia.

In the case of "medical dependence" (i.e., patients who cannot stop their PPIs without a relapse of symptoms), surgical fundoplication does not seem, in the medium or long term, to provide results superior to those obtained by chronic PPI treatment. In fact, 5–10 years after fundoplication was performed to avoid the need of chronic PPI therapy, many patients will still require anti-reflux pharmacotherapy. In the setting of "medical resistance" (i.e., patients with persistent symptoms despite optimal twice daily PPI therapy), fundoplication often leads to disappointing results. Its place in GERD therapy today seems limited to patients where troublesome regurgitations resistant to medical treatment is the major issue, or for GERD patients who, for various reasons, prefer this intervention over chromic PPI therapy.

New techniques (e.g., magnetic sphincter augmentation device implanted at the cardia) could offer in a near future valid alternatives for GERD patients who desire to discontinue medical therapy, or are not compliant or are resistant to medical therapy.

(e) ***Endoscopic therapy***: A variety of endoscopic techniques aimed at correcting the sphincter barrier defect have been developed. These include intragastric plication of the fundus, longitudinal plication of the cardia, infiltration in the cardia with synthetic material(s), electro-fulguration of lower esophagus by radiofrequency (Stretta procedure), etc. The benefit of these endoscopic maneuvers over the current pharmacological or surgical treatments remains to be demonstrated.

(g) In Pediatrics:

- Gastroesophageal reflux disease (postprandial non-bilious food regurgitation) is physiological in infants up to 18 months of age.
- Only the occurrence of complications (peptic esophagitis, growth retardation, or respiratory problems secondary to the reflux) should trigger additional investigations and drug treatment.
- GE reflux is not the cause of the unexplained crying ("colic") in infants.
- Peptic esophagitis is rare in children.
- Children at risks for peptic esophagitis include those with chronic respiratory pathology (like cystic fibrosis), previous surgery for esophageal atresia, or neurological disability (encephalopathy of neonatal ischemic origin, of metabolic or genetic origin).
- There is no correlation between symptoms and the endoscopic aspect of the esophagus.
- Barium meal is not indicated to establish the diagnosis of GERD in children.
- The barium meal can document anatomical abnormalities that could generate regurgitations/vomiting in infants such as an intestinal malrotation, an obstacle to gastric evacuation (pyloric stenosis also seen in ultrasound), and a congenital stenosis of the esophagus.

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1.8.2 Oropharyngeal (Transfer) Dysmotility

(a) **Symptoms**. Proximal dysphagia perceived in the oropharyngeal or cervical region is the predominant symptom. It may be associated with symptoms of nasal regurgitation, coughing, choking, and aspiration pneumonia, related to misdirection of the swallowed food or fluid into the nasopharynx, larynx, or trachea.

(b) **Pathophysiology.**

Damage to nerves (cranial nerves IX, X, and especially XII) controlling the transfer motor function:

- Brain stem nuclei damage by cerebral vascular stoke, tumors, Parkinson's, etc.
- Peripheral nerve damage by demyelinating disease (multiple sclerosis) or others (sclerosis, amyotrophic lateral sclerosis, etc.).

Damage to the striated muscles involved in transferring the food bolus from the oropharynx to the esophagus by diseases such as myasthenia gravis (dysphagia often worsening with fatigue), oculopharyngeal dystrophy (hereditary dystrophy common in Quebec and affecting pharyngeal and palpebral muscles), etc.

(c) **Investigation.** Radiology and endoscopy are both useful to evaluate oropharyngeal dysmotility.

Radiological assessment of the swallowing process, using fluoroscopy during barium ingestion, will be crucial to identify and characterize the motor disorder. Its diagnostic yield, however, is dependent upon the expertise of the examiner.

The radiological assessment will also be used to identify Zenker's diverticulum or an obstructive lesion of the hypopharynx or proximal esophagus that could give clinical symptoms of high dysphagia.

Endoscopy may be required to rule out a luminal obstructing lesion.

However, it must be remembered that the upper localization of dysphagia reported by the patient can be misleading since a middle or distal lesion may cause a sensation of upper dysphagia (on the other hand, the lower localization of dysphagia is more reliable to identify the obstructing site since a sensation of a blockade in the lower esophagus is never due to a proximal lesion).

(d) **Treatment of oropharyngeal dysmotility.** Various options are available:

- Treatment of the causal pathology if possible (e.g., myasthenia gravis).
- Diet adjustment and safe swallowing education by specialists (occupational therapist, dieticians, speech language pathologists, etc.).
- Surgical (or endoscopic) myotomy (or pharmacological relaxation by infiltration of botulinum toxin) of the UES can be done in some very selected cases to reduce sphincter resistance and then facilitate the passage of the bolus from the oropharynx toward the esophageal lumen.

1.8.3 Esophageal (Transport) Dysmotility

Transport dysmotility along the esophagus, which usually produces dysphagia or thoracic pain, can be due to hypo- or hypercontractility disorders of the smooth muscles of the esophagus or of the lower esophageal sphincter (LES). These disorders are recognized mainly by measuring contractile pressure waves of the esophagus via intraluminal manometry (see ◘ Fig. 1.13).

A. Hypomotility disorders. Absent contractility (as referred to in Chicago Classification) is most often due to *scleroderma,* a disease characterized by a collagenous fibrosing infiltration of skin tissues; it can also affect the digestive tract, with the esophagus being the most common region affected. It is characterized manometrically by esophageal contractile waves markedly decreased in amplitude (even not existing) and a lower esophageal sphincter with a very weak tone (even absent).

Esophageal hypomotility can also be seen with neuromuscular disorders affecting the GI tract (rare conditions often leading to pseudo-obstruction syndrome; see ▶ Chap. 3) or, sometimes, be due to an inflammatory response to esophagitis (peptic, caustic, etc.).

Symptoms Patients with scleroderma typically develop severe GERD symptoms (heartburn, regurgitation) because of their defective LES pressure barrier and poor esophageal clearance secondary to weak or absent peristalsis. Dysphagia is also common, and, although partly related to the absence of propulsive waves, is usually due to the development of reflux esophagitis, often complicated by peptic stricture formation. Overt or occult bleeding from esophageal ulceration may also occur.

Investigation ***Manometry*** of the esophagus is the determinant examination to identify the diagnosis. Hypomotility profile is mostly due to scleroderma, but it can be seen in rare infiltrative disorders such as amyloidosis or in chronic reflux esophagitis.

Endoscopy is essential to assess the severity of esophagitis.

Treatment GERD can have severe consequences in patients with scleroderma esophagus (due to the absence of LES to block reflux and of esophageal contractions for clearance of refluxed acid) and requires an aggressive treatment. Suppression of acid reflux is essential. PPIs can be given at high doses for optimal acid suppression.

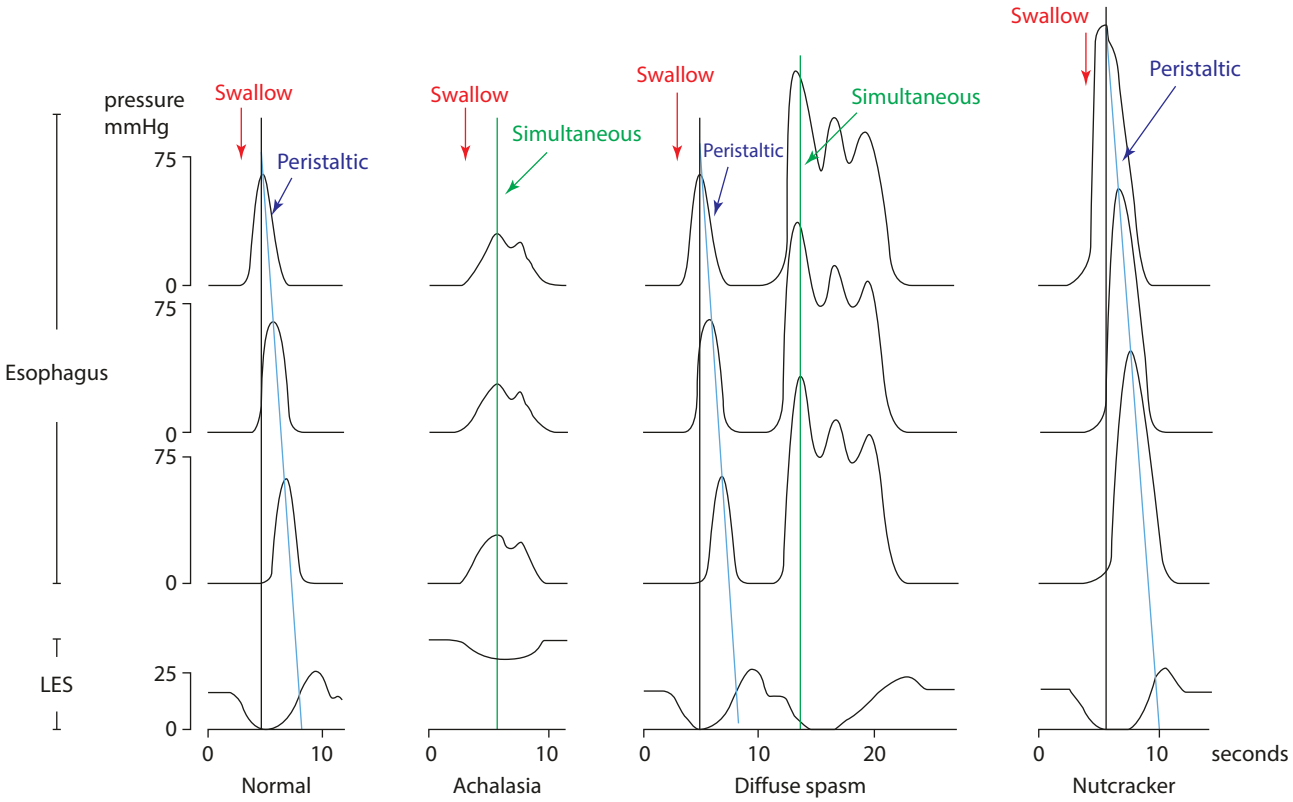


Fig. 1.13 Esophageal manometry contractions recorded in various conditions of hypermotility. (Modified from Smout 1992)

They can be coupled with prokinetics to promote gastric emptying (potentially affected by gastric hypomotility secondary to scleroderma infiltration of gastric smooth muscles).

B. Hypermotility disorders. Hypermotility of the esophagus is described under the following categories:

1. ***Achalasia of the esophagus*** is a disease of the intrinsic innervation of the esophagus (infiltration of lymphocytes into the myenteric plexus leading to destruction of neurons controlling LES relaxation and esophageal peristalsis) and is classically characterized by the following contractile anomalies:
   - Inadequate relaxation of the LES at the passage of the food bolus.
   - Increased basal tone of the LES.
   - Absence of peristaltic waves within the esophageal body.
   - Possibility of tertiary spastic waves of the esophageal body.

Symptoms Lower (transport) dysphagia, often for both liquid and solid foods, and regurgitations of undigested stagnant food from the esophagus are cardinal symptoms of achalasia; chest pain is also reported by some patients. Complications such as weight loss and aspiration pneumonia (if nocturnal regurgitation is present) can occur.

Causes of achalasia Idiopathic primary achalasia is the most common.

Achalasia can also be secondary to the following:

- Chagas disease due to the *Trypanosoma cruzi* parasite, present mainly in South and Central America and capable of attacking esophageal innervation. This parasite also frequently affects the innervation of the heart resulting in fatal heart failure.
- A tumor of the gastric cardia infiltrating the enteric nervous system in the region of the LES.
- A paraneoplastic manifestation (most often from lung cancer) affecting the motor function of the esophagus as well as the stomach (probably by antibodies against the enteric nervous system).

Investigation of achalasia A *barium swallow* (see Fig. 1.11) can reveal a characteristic image of (1) esophageal dilation (mega esophagus), with possibly a fluid level and food retention, and (2) narrowing of the esophagogastric junction mimicking the beak of a bird. Plain films of the lungs and abdomen may suggest the diagnosis of achalasia by showing an enlargement of the mediastinum due to the esophagus filled with fluid, as well as an absence of the gastric air bubble.

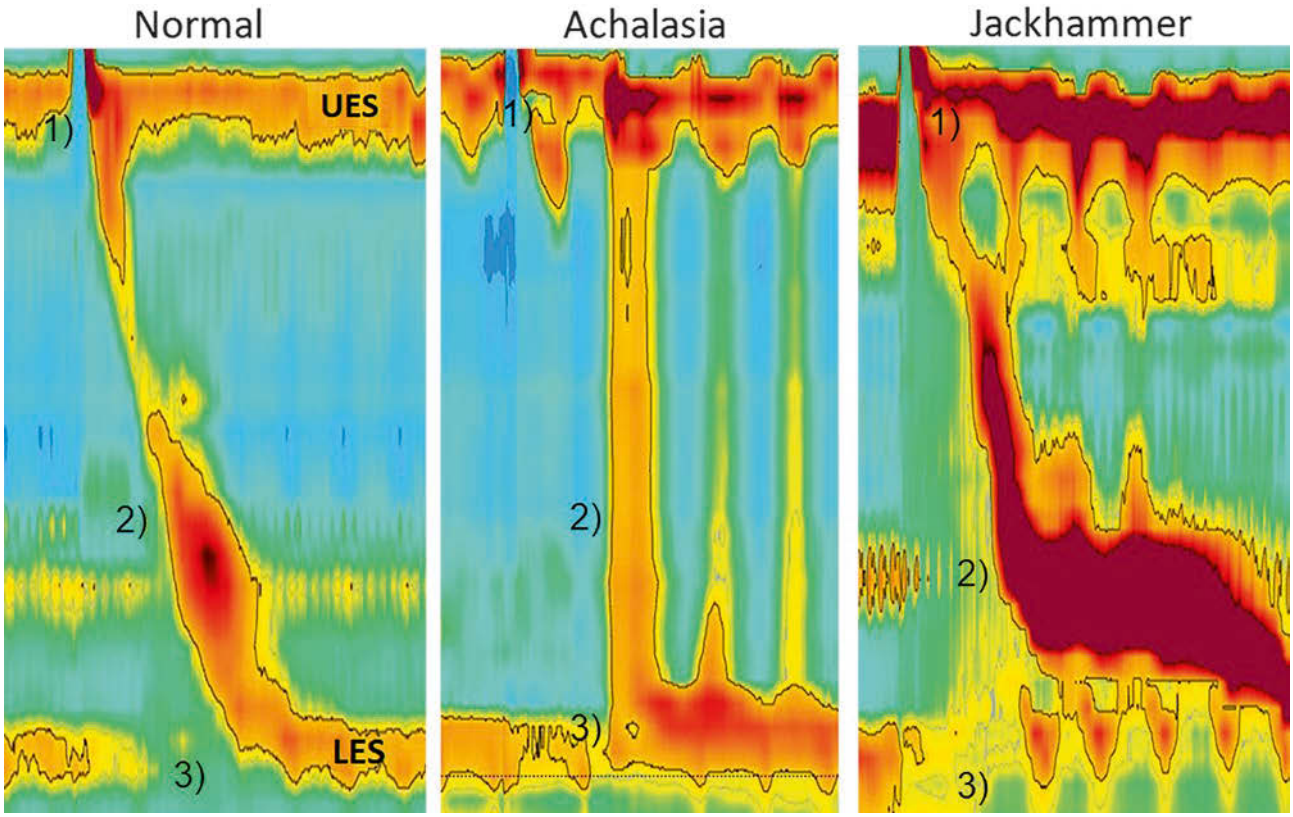
During *endoscopy*, the LES is usually closed, and some difficulty or resistance can be felt in passing the endoscope through the cardia. Endoscopy is essential to eliminate a tumoral infiltration of the cardia.

Manometry is the definitive test to diagnose achalasia of the esophagus.

An example of conventional (or traditional) manometry is presented in ◘ Fig. 1.13 (characteristic motor abnormalities were described above). Since the year 2000, high-resolution manometry (HRM) has been used to more precisely study the motor activity of the esophagus. Done with a nasogastric manometry catheter carrying several electronic pressure sensors distributed every centimeter (at least) along the esophagus and combined with sophisticated computer analysis of the obtained data, HRM allows a graphic representation of the esophageal transit and pressures (◘ Fig. 1.14), as well as an objective quantitative analysis of the motor function (with newly identified computerized parameters such as IRP (integrated relaxation pressure of the LES) or DIC (distal integrated contraction of the peristaltic distal wave). Observations and concepts obtained by HRM are grouped together in the "Chicago Classification," a tool in perpetual development (a bit like the DSM in psychiatry). Achalasia is now divided into three manometric types (I, II, III; ◘ Fig. 1.15), suggesting the presence of differing pathophysiology (and/or stage) of disease and, possibly, the need for targeted adapted therapies.

Treatment of achalasia. In order to alleviate dysphagia, the treatment aims to reduce the obstacle created by the nonrelaxing sphincter. The therapeutic possibilities are as follows:

- Surgical myotomy of the LES, usually done laparoscopically, and often with reconstruction by fundoplication to avoid GE reflux secondary to the sphincter weakness induced by myotomy.
- Myotomy can also be performed endoscopically (POEM: per oral endoscopic myotomy).



◘ **Fig. 1.14** High-resolution esophageal manometry: examples of tracings with colors that identify a pressure gradient (green < yellow < red). Left tracing: normal. (1) During swallowing, the upper esophageal sphincter (UES) relaxes; (2) a peristaltic contraction develops in the esophageal body (3) the lower esophageal sphincter (LES) relaxes allowing the bolus to pass into the stomach. - Central tracing: achalasia (type II). (1) After the relaxation of the UES, (2) no propulsive wave (here we have a diffuse luminal pressurization) occurs in the esophagus; (3) the LES does not relax. - Right tracing: jackhammer esophagus. (1) normal relaxation of the UES; (2) a propulsive esophageal wave is present, but it is of very large amplitude and prolonged duration in the distal region; (3) the LES relaxes normally. (Tracings from M. Bouin)

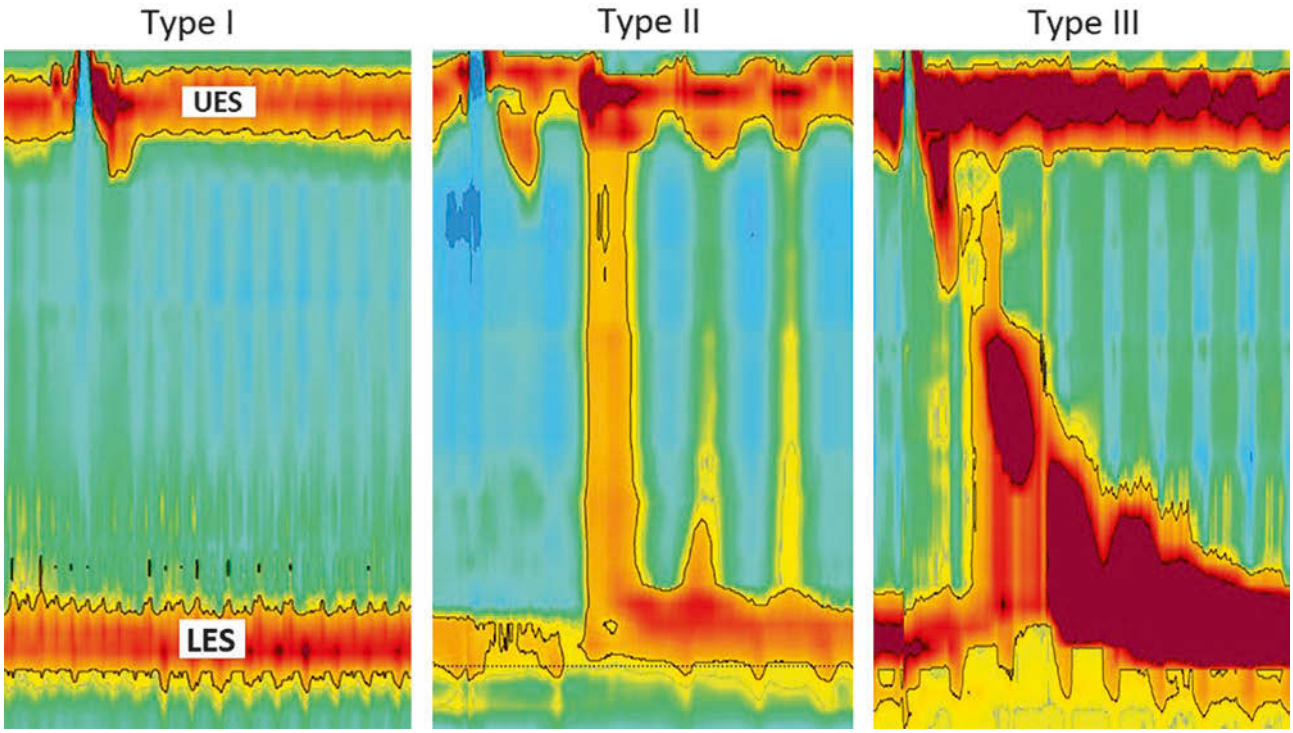


Fig. 1.15 Achalasia of the esophagus according to MOHR (Chicago Classification 3.0, 2015). -Type I: absence of measurable contractions-pressures in the esophageal lumen. -Type II (most common): no migratory contractions, but diffuse increase (pressurization) of intra-esophageal pressure. -Type III (most difficult to treat): achalasia with spasmodic contractions of the esophageal muscle. The lower esophageal sphincter (LES) is incapable of relaxation in all three types. (Tracings from M. Bouin)

- Pneumatic dilatation of the LES by per oral dilatation balloons. It is a simple technique, performed under endoscopic and/or fluoroscopic visualization, but having a significant risk of perforation (5–10% of procedures).
- Botulinum toxin endoscopic infiltration of the LES is a simple technique, however, with short-lasting results (3–12 months, and can be repeated). It can be very helpful for nonsurgical candidates.
- Pharmacological reduction of sphincter tone with calcium channel blocker drugs (nifedipine, etc.) or nitric derivatives (isosorbide, etc.) may help some patients.

These treatments, by alleviating the sphincter obstacle, usually allow an adequate caloric feeding, but the swallowing function may remain suboptimal due to the absence of esophageal contractions for propulsion of the food down within the esophagus (many patients need to eat in upright position relying upon gravity for food transit to the stomach).

2. ***Diffuse esophageal spasm*** (distal esophageal spasm, DES) is an abnormality characterized by nonperistaltic, multiphasic, prolonged contractile waves (tertiary waves), often of excessive amplitude (Fig. 1.13).

(a) Symptoms of DES. The primary symptoms are dysphagia and chest pain. The latter occurs sporadically, is usually of short duration (seconds to minutes), and can be qualitatively similar to the pain of cardiac ischemia.

(b) Causes of DES. Diffuse spasm is rarely seen during manometry tests (mainly due to its intermittent schedule). It may be idiopathic or more often associated with achalasia of the esophagus (and responsible for chest pains that may be experienced by patients suffering of achalasia).

The term "esophageal spasm" is frequently used in clinic to refer to constrictive chest pain of noncardiac origin and that is attributed to presumed esophageal spasm. These spastic phenomena can be caused by the ingestion of very cold or very hot food or occur during episodes of GE reflux. The manometric (or other) documentation of these episodes is difficult precisely because of their brief and intermittent nature.

3. ***Jackhammer esophagus*** is detected by HRM: LES relaxation is normal, but the esophageal waves are markedly hypercontractile (DIC > 8000 mmHg) and

often repetitive (such as the bursts of a jackhammer) (Fig. 1.14). It is seen in about 3% of the manometry tracings in a tertiary center. It is most often associated with dysphagia, but symptoms of reflux or chest pain are not rare (40%).

Treatment by endoscopic injections of botulinum toxin or by surgical (or endoscopic) long myotomy of the esophagus can be proposed.

4. ***Nutcracker esophagus*** [called so because of the spiral spastic contraction of the esophagus mimicking a nutcracker (or corkscrew) seen during barium X-ray in some of these patients] identified in traditional manometry is probably close to the jackhammer esophagus seen in high resolution manometry. It is characterized by peristaltic waves of exaggerated amplitude and duration. Its clinical significance has always been debated.
5. ***Opioid-induced esophageal dysmotility***. Chronic use opiates can affect the esophagus just as it affects the colon (constipation) or stomach (gastroparesis). It is now recognized as a cause of esophageal dysmotility (often with dysphagia and syndrome of obstruction of the GE junction in manometry).

In 2021, Chicago Classification v. 4.0 was proposed to identify contractile abnormalities detected during high resolution manometry testing of the esophagus (see Table 1.1).

Table 1.1 Esophageal manometric abnormalities on HRM: Chicago Classification v. 4.0

Disorders of esophagogastric junction outflow
Achalasia type I (no esophageal contractility)
Achalasia type II (with esophageal lumen hyperpressure)
Achalasia type III (with esophageal spasm)
Esophagogastric junction outflow obstruction (mechanical obstruction)
Disorders of peristalsis
Absent contractility (scleroderma)
Distal esophageal spasm
Hypercontractile esophagus (jackhammer, opiates)
Ineffective esophageal motility

1.8.4 Sensitivity Disorders

Some patients will experience esophageal symptoms (pyrosis, dysphagia, acute retrosternal pain, etc.) unexplained by any lesional or recognized motor abnormality of the esophagus.

- Globus (previously called globus hystericus) refers to a sensation of a lump or tightness in the throat (without laryngeal or upper esophageal lesion to explain it). It is usually clearly related to stress or anxiety and treated by reassurance.
- Esophageal hypersensitivity and functional heartburn refer to patients with heartburns without esophagitis (only 30% of endoscopies for reflux symptoms indicate erosive esophagitis) or reflux [only 50% of symptomatic patients with a negative endoscopy have reflux documented on pH studies and are identified as NERD (nonerosive reflux disease)].

In many of these patients, an exaggerated sensitivity to various provocative stimuli such as intraesophageal infusion of acid (Bernstein test) or balloon dilation can be demonstrated. Hypersensitivity is manifested either by an abnormally low pain threshold that results in patients feeling stimuli at undetectable levels in a normal subject (allodynia)or by a painful sensation of exaggerated intensity (hyperalgesia).

As with other digestive pathologies involving visceral hypersensitivity (irritable bowel syndrome, functional dyspepsia, etc.), the pathophysiology and treatment of these conditions remain poorly defined. Tricyclic agents (amitriptyline), serotoninreuptake inhibitors (SSRI: citalopram, venlafaxine, etc.), or pregabalin are often prescribed to alleviate symptoms. Psychological interventions may also help.

1.9 Miscellaneous

1.9.1 Hiatal Hernia

(a) **Sliding hernia**. In this hernia, the cardia (and upper stomach) abandons its intra-abdominal place to slip up into the chest cavity (see Fig. 1.16). This is the most common hiatal hernia. It is frequently observed in radiological or endoscopic examinations, and it is often wrongly accused as the source of the patient symptoms. Hiatal hernia was long considered as a

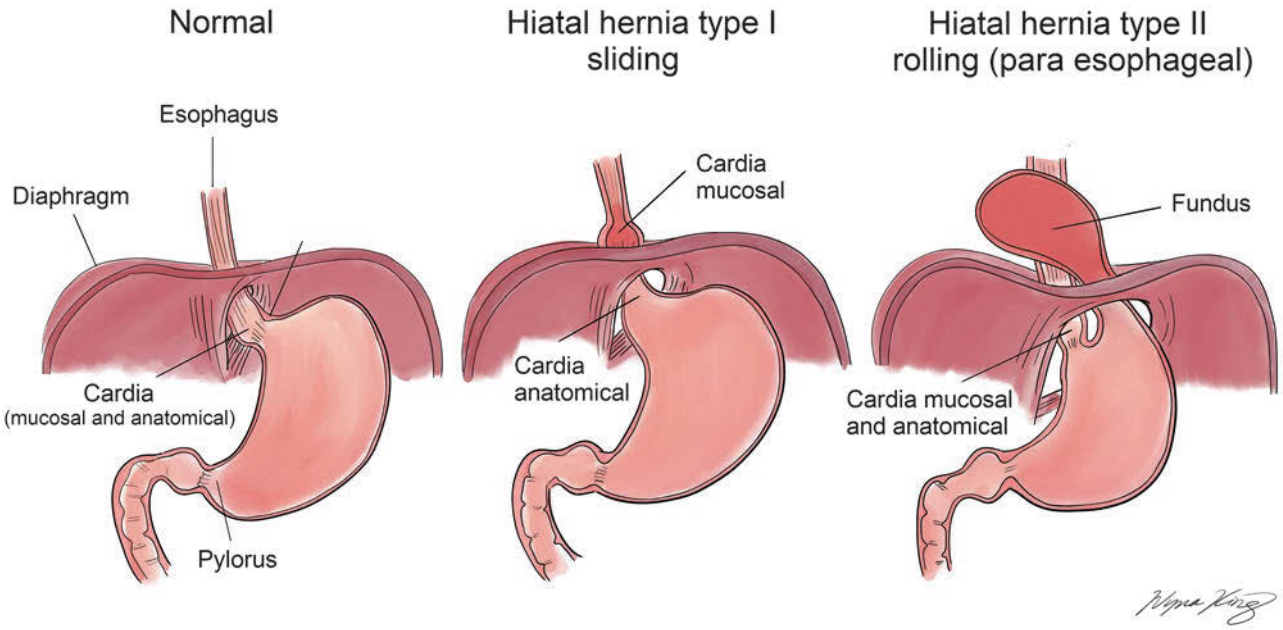


Fig. 1.16 Representation of the most frequent forms of hiatal hernias

synonym for gastroesophageal reflux [since the only treatment for esophagitis or reflux available then involved the surgical correction of the hernia by a fundoplication procedure (Nissen, Belsey, etc.)]. It is now recognized that (1) large hernias are certainly involved in reflux or regurgitation and may require surgical correction, (2) hiatal hernia may be a risk factor for GERD by modifying the anatomy of the cardia and disrupting the barrier function normally carried out by the internal and so-called external sphincters as previously discussed, but (3) hiatal hernia is not a disease in itself, and can be found in many asymptomatic individuals.

(b) **Paraesophageal (or diaphragmatic or rolling) hernia.** This is frequently considered as a serious condition. In this form of hernia, the cardia (usually) remains in its normal anatomical position, but a portion of the fundus (or gastric body) is herniated (rolls) into the chest cavity through a paraesophageal hiatus or diaphragmatic tear (see Fig. 1.16). This hernia does not cause acid reflux, but may lead to dysphagia (compression of the distal esophagus by the dilated herniated fundic pouch) or pain (fundic distension of the pouch after meal). Given the associated risk of gastric volvulus, corrective surgery is usually recommended.

The following hernia classification is also used:

- Type I: sliding hernia (90% of cases).
- Type II: paraesophageal hernia (rolling).
- Type III: mixed hernia where Types I and II coexist.
- Type IV: hernia of the whole stomach [often with other viscera (small bowel, colon, etc.)].

1.9.2 Diverticulum

(a) **Traction diverticulum** is due to attraction of the esophageal wall by its adhesion to a surrounding lesion (e.g., tuberculous granuloma). The entire esophageal wall is then present in these diverticula that remain, in most cases, asymptomatic.

(b) **Pulsion diverticulum** is obtained by the thrust of the mucosa through a weakened area of the muscular layers:

- *Epiphrenic diverticulum* is located above the lower esophageal sphincter. It develops most of the time in conjunction with esophageal achalasia or diffuse esophageal spasm where the exaggerated intraluminal pressure in the distal esophagus forces herniation of the mucosa through the muscle layers of the esophageal wall. The diverticulum itself is rarely symptomatic.
- *Zenker's diverticulum* is found in the posterior pharynx, in front of the vertebral column, just above the upper esophageal sphincter (UES), and, as for the epiphrenic diverticulum described above, is usually related to a sphincter defect. It develops in Killian's triangle (where the oblique fibers of the pharynx meet the transverse fibers of the UES) that constitutes a zone of relative weakness where the mucosa can protrude through the muscle layers in response to pathologically elevated intraluminal pressure caused by a poorly compliant and relaxing UES.

Zenker's diverticulum is manifested by the following phenomena:

- Upper dysphagia (obstruction to food passage by a poorly relaxing UES or due to external compression by a large diverticulum).
- Cervical mass (rare), created by the diverticulum (filled with secretions and food).
- Regurgitation, often nocturnal and spontaneous, of undigested food.
- Halitosis, due to stagnation of food and debris in the diverticulum.

Barium X-ray will demonstrate the diverticulum localized at the posterior part of the pharynx, in front of the vertebral column, and above an often hypertrophic-appearing cricopharyngeal muscle.

Endoscopy must be carried out with great caution since the instrument may inadvertently enter and perforate the diverticulum. Investigation of upper dysphagia is often better served by a preliminary radiological study to guide the endoscopic maneuvers.

Treatment of Zenker's diverticulum is realized by a myotomy of the cricopharyngeal muscle, surgically or endoscopically, to release the sphincter obstruction.

1.9.3 Esophageal Rupture

Rupture of the esophagus is a catastrophic condition, due to the ensuing mediastinitis, and it must be identified and treated promptly. Patients present with severe chest pain, fever ± septic state, and subcutaneous emphysema (feeling of crackling of the subcutaneous tissue of the upper chest or neck due to infiltration of swallowed air through an esophageal perforation).

Radiological examination, preferably by CT scanning of the thorax, will reveal the localization and size of the perforation as well as possible fluid collections or abscesses of the mediastinum.

Most perforations are iatrogenic (e.g., during endoscopy and/or dilatation by balloon or bougie). It can complicate severe caustic esophagitis, but can also occur spontaneously (Boerhaave's syndrome), in which case it is often associated with a chest trauma (car accident, violent vomiting or coughing, etc.) resulting in a strong and acute increase in intraesophageal pressure.

Small esophageal perforations may spontaneously close fairly quickly. These cases may be treated with antibiotics and cessation of oral feeds. Other cases require surgical drainage, ± suture of the perforation or even removal of the esophagus.

1.9.4 Esophageal Bleeding

Bleeding of esophageal origin will present with hematemesis of bright red blood and/or melena (see ▶ Chap. 11 on upper digestive hemorrhage).

Endoscopy may reveal the following:

- An esophagitis with or without esophageal ulcer (a rare cause of massive acute bleeding).
- An ulcerated neoplasia (chronic bleeding is more frequent).
- Esophageal varices secondary to portal hypertension (a common cause of massive upper GI hemorrhage in patients with cirrhosis of the liver).
- A Mallory-Weiss tear (see next point).

1.9.5 Mallory-Weiss

The Mallory-Weiss tear is a common cause of digestive hemorrhage. It is a longitudinal mucosal tear (1–2 cm long) of the cardia. It is a mechanical tear secondary to vomiting efforts with up and down movements of the cardia. In most cases, the bleeding of a Mallory-Weiss will be moderate and will cease spontaneously with rapid tear re-epithelialization in 24–48 hours.

1.9.6 Schatzki's Ring

It was classically identified on radiological barium swallow as a circumferential ring at the gastroesophageal junction that caused intermittent dysphagia to solid foods. It is now recognized mainly by endoscopy (◘ Fig. 1.17) and treated by per-endoscopic dilatation (if dysphagia is present). Initially considered as a birth defect, it is increasingly seen as a subtle form of peptic stricture associated with GE reflux and requiring treatment with PPIs to prevent its recurrence.

PS: For complementary readings on the esophagus, see ▶ Chaps. 9 and ▶ 29.

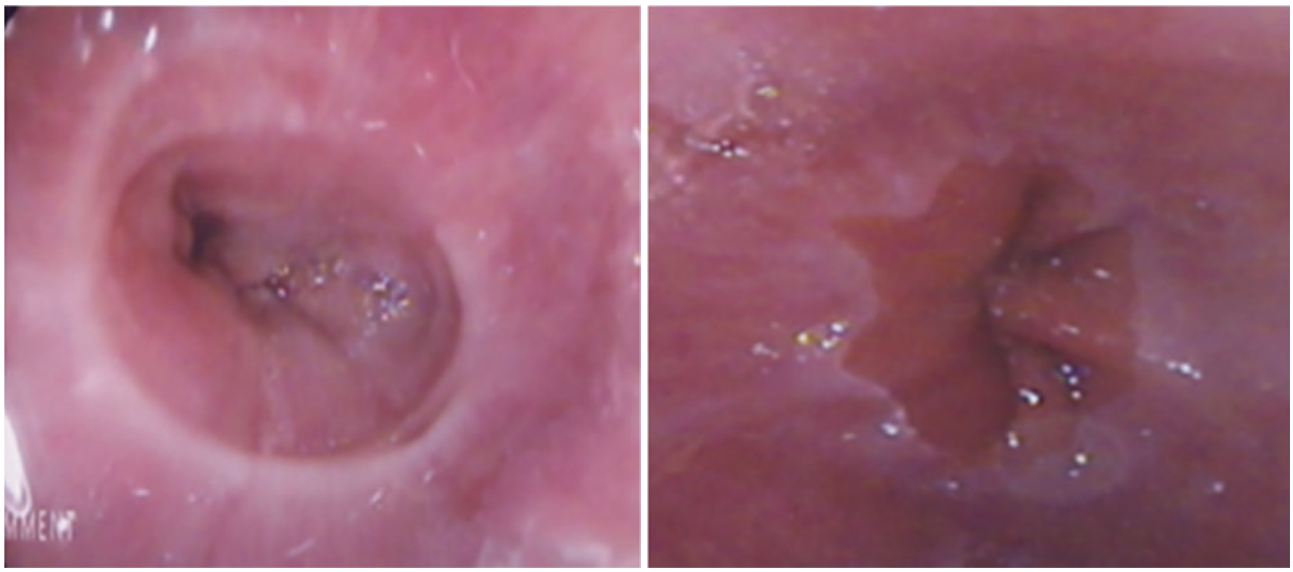


Fig. 1.17 Left: Schatzki's ring seen in endoscopy as a fibrous narrowing of the esophagogastric junction and that may block the transport of solid foods; figure on the right: normal GE junction. (Photos by P. Poitras)

The Stomach

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Contents

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The human stomach has two physiological functions:

1. To prepare ingested food for absorption in the small intestine by converting it into a semiliquid solution and suspension of food particles through the process of chemical digestion [secretion of hydrochloric acid (HCl) and pepsin] and mechanical trituration (gastric contractions)
2. To regulate the passage of chyme into the small intestine at a rate that allows for the optimal digestion and absorption of nutrients by the intestine

Moreover, the stomach can inactivate or kill microorganisms that would otherwise cause infectious injury or complications more distally in the gastrointestinal tract.

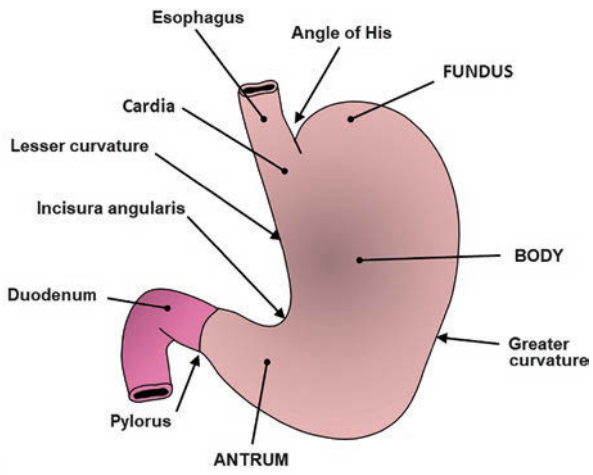
2.1 Macroscopic Anatomy

2.1.1 Shape and Structure

The stomach (◘ Fig. 2.1) is a large J-shaped pouch located in the upper left part of the abdomen that serves as a reservoir for the transit and processing of food swallowed into the esophagus and on its way to the small intestine where it will be absorbed.

The cardia, at the thoracoabdominal junction, incorporates the lower esophageal sphincter, a one-way valve for the entry of food into the stomach.

The fundus forms a pocket lying under the left diaphragm which can expand to accommodate swallowed gas and food through a mechanism of parietal relaxation. The angle of His or esophagogastric angle is an acute angle formed by the cardia, between the fundus and the esophagus; distension of the fundus compresses the angle of His to prevent reflux and, as such, is an important landmark for anti-reflux surgery.



◘ **Fig. 2.1** Macroscopic anatomy of the human stomach

The gastric body, the vertical portion of the stomach between the cardia and the incisura angularis (or angular notch), is the site of HCl and pepsin secretion. This is where food is mixed and ground.

The gastric antrum, distal to the incisura angularis, is oriented horizontally, ending at the pylorus which acts as a sphincter or valve (normally unidirectional) which opens to allow the movement of gastric contents into the duodenum.

The stomach has a shape vaguely reminiscent of a bean, with a left lateral surface called the greater curvature and resting on the spleen. On its inner side, the lesser curvature faces the left lobe of the liver.

The proximal and distal ends of the stomach, the cardia and pylorus, respectively, are fixed anatomically, while the intervening part of the stomach is mobile; this allows for distension of the stomach by ingested food but, also, renders the stomach susceptible to torsion around the longitudinal axis from cardia to pylorus (see Volvulus discussed at the end of this chapter).

2.1.2 Vascular Supply

Arteries Four main vessels feed the stomach by running along the lesser curvature (the left and right gastric arteries) and the greater curvature (the left and right gastroepiploic arteries), forming a network of arterial anastomoses (◘ Fig. 2.2). The celiac trunk, via its three major divisions (left gastric, hepatic, and splenic arteries), is the important vessel for gastric irrigation, giving rise, directly, to the left gastric artery, and, indirectly, to the right gastric artery (via the hepatic artery), the right gastroepiploic artery (via the gastroduodenal artery connecting the hepatic artery and the superior mesenteric artery), and the left gastroepiploic artery (via the splenic artery).

Veins The veins follow the arteries. The left and right gastric veins drain directly from the lesser curvature into the portal vein and will give rise to esophageal varices during portal vein hypertension (often due to liver cirrhosis). The left gastroepiploic vein drains the greater curvature into the splenic vein; gastric fundic varices may thus be encountered in portal hypertension affecting the splenic vein, or in splenic vein thrombosis (e.g., pancreatitis). The right gastroepiploic vein drains rightward toward the head of the pancreas, to join the superior mesenteric vein.

Lymphatics These vessels basically follow the arterial and venous vessels and drain mainly to the celiac lymph nodes, and ultimately to the thoracic duct. Lymphatic drainage of the stomach is an intricate network with the result that gastric neoplasia may metastasize unpredictably, often at a distance from the stomach and its immediate drainage nodes.

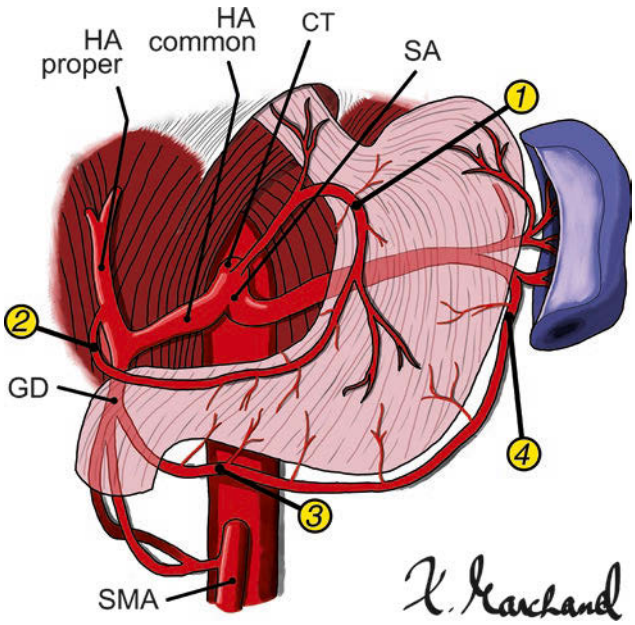


Fig. 2.2 Four arteries of the stomach:
(1) The left gastric artery emanates from the celiac trunk (CT) which also gives rise to the splenic artery (SA) and the hepatic artery (HA)
(2) The right gastric (or pyloric) artery comes from the hepatic artery (HA), which in turn comes from the celiac trunk (CT)
(3) The right gastroepiploic artery comes from the gastroduodenal artery (GD) connecting the hepatic artery (HA) to the superior mesenteric artery (SMA) via the duodenopancreatic arteries
(4) The left gastroepiploic artery comes from the splenic artery (SA) coming from the celiac trunk (CT)

2.1.3 Innervation

Like the other digestive organs, the intrinsic innervation of the stomach relies on the enteric nervous system (ENS), which is linked closely to an extrinsic innervation that mediates parasympathetic control via the vagus nerve and sympathetic control, mainly via the celiac ganglion.

(a) Parasympathetic innervation. The vagus nerve (or cranial nerve X), named from the Latin word meaning "wandering," is a long, widely distributed nerve with diffuse and extensive ramifications that originates in the dorsal motor nucleus (DMN), located on the floor of the fourth ventricle. The vagus nerves descend through the cervical region in the carotid sheaths (between the internal carotid artery and the internal jugular vein) before entering the mediastinum and running to the left and right of the esophagus. At the cardia, the left vagus nerve is anterior to the esophagus, while the right branch is posterior, due to rotation of the stomach during fetal development. The left vagus nerve (Fig. 2.3) gives rise to branches innervating the liver, biliary tree, pylorus, and proximal small intestine; the right vagus nerve, via its celiac branches, supplies the pancreas, spleen, kidneys, adrenals, and small intestine.

It has long been known that the vagus nerve affects gastric motility and secretion and its key role in the control of acid secretion led to the development of surgical vagotomy in which the vagal nerve was cut to reduce gastric acidity and allow healing of peptic ulcers. The posterior location of the right vagus nerve could make the truncal vagotomy procedure difficult and compromise the success of the treatment. Indeed, the persistence of the Grassi nerve, the first branch of the posterior vagus nerve, was frequently involved in so-called incomplete vagotomies (unable to stop gastric acid secretion and control ulcer disease). Moreover, unfortunately, truncal vagotomy, with division of both vagal trunks proximal to the gastroesophageal junction, leads to adverse effects such as gastroparesis, dumping syndrome, and diarrhea (discussed later) by impairing normal vagal regulation of gastric contractility, fundic relaxation and accommodation, pyloric relaxation, gall bladder motility, and small intestinal motility. The side effects of truncal vagotomy were mitigated, initially, by the development of selective vagotomy which divided only the anterior gastric nerve of Latarjet, a branch of the left vagus nerve which runs along the lesser curvature, to innervate the gastric body, and, later on, by highly selective vagotomy which involved meticulous division of the fibers supplying the acid-secreting gastric body mucosa while preserving vagal innervation of other organs.

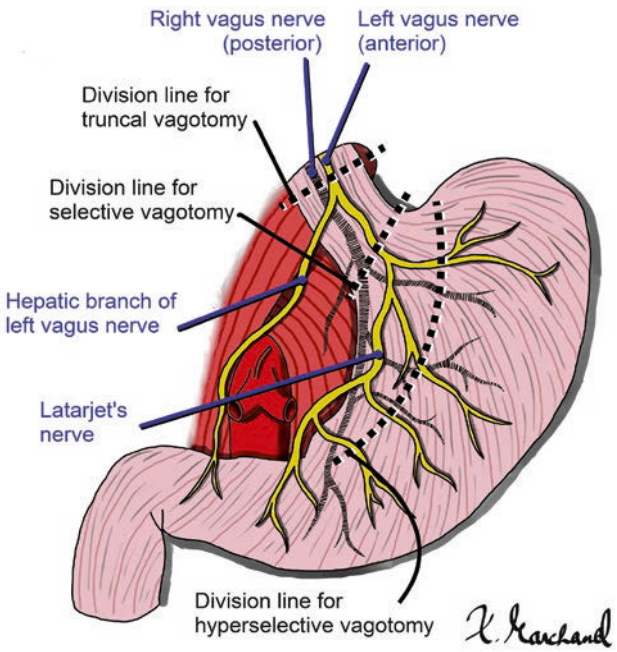


Fig. 2.3 Vagal innervation of the stomach

Much of the research into vagal nerve function was directed at its efferent effects on gastric acid secretion and gastrointestinal motility, mediated by acetylcholine. However, it is now known that 90% of the vagus nerve is comprised of afferent fibers that transmit sensory information from the digestive tract to the brain. The physiological or pathophysiological roles of these afferent fibers have yet to be clarified, but it is thought that the vagus nerve, through its afferent and efferent fibers, participates in numerous entero-enteric reflexes (intestine → vagal afferents → vagal efferents → intestine) that affect gastrointestinal secretion and motility (discussed later).

(b) Sympathetic innervation. Spinal cord nerves from T5 to T10 (preganglionic sympathetic nerves) converge at the celiac ganglion, giving rise to postganglionic fibers that innervate the stomach and the proximal small bowel. The role of the sympathetic nervous system in regulating gastric function is less well understood than that of the parasympathetic system. Adrenergic mediators (adrenalin, noradrenalin, dopamine) generally have an inhibitory effect on gastrointestinal secretomotor functions, counterbalancing the excitatory cholinergic effects of the parasympathetic system. Very few gastrointestinal conditions have been linked to sympathetic dysregulation; celiac sympathectomy has been associated with diarrhea due to increased motility and rapid intestinal transit, consistent with the established inhibitory effects of adrenergic sympathetic *efferents* on digestive motor function.

Sympathetic nerves also have *afferent* fibers that carry information from the digestive tract to the brain. Sympathetic afferences are thus responsible for the perception of pain arising from the vast majority of abdominal viscera (gastric distension, intestinal occlusion, appendicitis, diverticulitis, etc.); celiac sympathectomy can be used to relieve severe pancreatic pain. As for the vagus nerve, sympathetic afferent (and efferent) fibers are involved in entero-enteric reflexes (intestine → sympathetic afferences → sympathetic efferent nerves→ intestine) that can affect digestive functions, although their precise clinical impact is often misunderstood.

Extrinsic nerves, whether sympathetic or parasympathetic, do not communicate directly with their target organs (e.g., parietal cell or smooth muscle cell) but, rather, regulate end organ activity via the intrinsic pathways of the enteric nervous system.

(c) Intrinsic innervation or enteric nervous system. Intrinsic innervation is made up of Auerbach's myenteric plexus located between the muscle layers to regulate the contraction of these muscles and Meissner's submucosal plexus involved mainly in the regulation of secretory mucosal phenomena.

2.2 Microscopic Anatomy

The stomach wall consists of four layers, the outer serosa, the muscularis, the submucosa, and the innermost mucosa.

The *serosa* is formed by the visceral peritoneum which overlies the gastric muscularis propria (or muscularis externa).

The gastric *muscularis* is the main, thick muscle of the stomach and it consists of three layers. The outermost layer of longitudinal muscle is in continuity with the longitudinal muscles of the esophagus; the middle, circular muscle layer plays a major role in gastric peristalsis, and it becomes thicker distally to form the pyloric sphincter. The innermost, oblique muscle layer is adjacent to the submucosa. These three layers constitute the contractile apparatus of the stomach, necessary for the trituration and mixing of ingested food to form chyme. Auerbach's myenteric plexus is situated between the muscle layers to regulate gastric contractile activity.

The *submucosa*, between the muscularis and the mucosa, consists of connective tissue and lymphatic vessels as well as the nerve fibers of Meissner's submucosal plexus which is involved mainly in secretory phenomena.

The *mucosa* consists of a glandular epithelium (see below), the lamina propria, and the muscularis mucosae, a thin outer layer of muscle that separates the lamina propria from the submucosa. The muscularis mucosae supports the gastric epithelium and lamina propria, controls local mucosal motility, and is the demarcation zone that differentiates invasive from non-invasive neoplasia.

The gastric epithelium consists of tubular glandular structures (see ◘ Fig. 2.4) comprised of two parts. The first most superficial part, near the gastric lumen, is composed of a surface epithelium (mucus cells) and crypts called foveolae or gastric pits with an epithelium that also contains mucus cells. The second deeper part of the tubular structure is the glandular portion (oxyntic gland) which, in the body and fundus, contains chief, parietal, endocrine, and stem cells and, in the antrum, mucus, endocrine, and stem cells.

Chief (zymogenic) cells are the most abundant gastric epithelial cells and secrete pepsinogen. Mucous cells (40% of the cells) secrete mucus and bicarbonate. Parietal (oxyntic) cells, while constituting only 13% of the gastric cell population, are the best known; they secrete hydrochloric acid (HCl) and intrinsic factor (essential for vitamin B12 absorption). The remaining population consists of endocrine cells producing gastrin (G cells), somatostatin (D cells), histamine (ECL cells: enterochromaffin-like), or ghrelin (P/D cells).

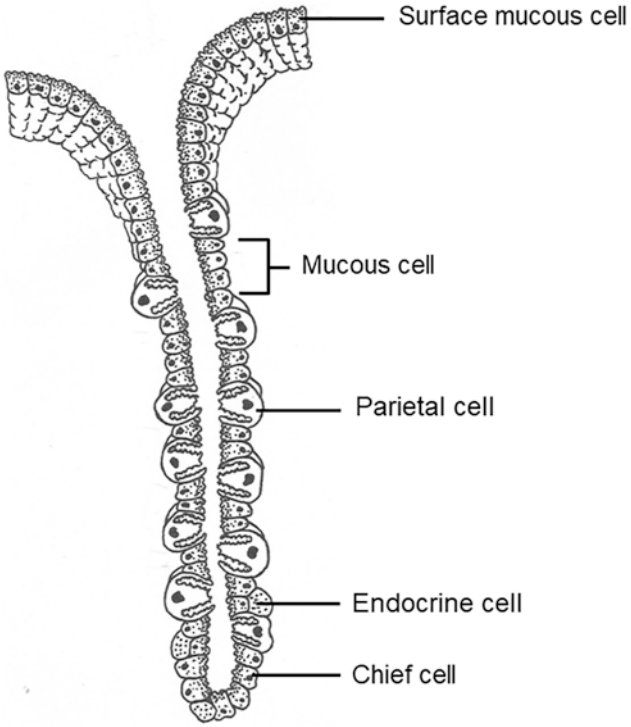


Fig. 2.4 Microscopic anatomy of the gastric mucosa

These different types of epithelial cells are located in the gastric mucosa in a regional distribution consistent with their physiological roles. Parietal cells and chief cells are located in the gastric body where they secrete HCl and pepsin to mix with ingested food, whereas "G" cells and "D" cells are located in the antrum where they can respond to luminal acidity by secreting gastrin and somatostatin, respectively, to regulate acid secretion by parietal cells in the gastric body.

2.3 Embryology

2.3.1 Development

Stomach volume is up to 2 L in adults but is only 30 mL in newborns.

The stomach is recognizable as early as the 4th week of fetal gestation. It develops from the "foregut" which *dilates in an anteroposterior plane* with two concave edges facing anteriorly. The anterior wall will become the lesser curvature, and the posterior wall will become the greater curvature when the stomach will rotate along its longitudinal axis. The embryonic stomach is attached posteriorly by the dorsal mesentery containing branches of the celiac trunk (left gastric artery, hepatic artery, and splenic artery) and anteriorly by the ventral mesentery from which the future liver will develop. The part of the ventral mesentery between the stomach and the liver will become the lesser omentum, while the part between the liver and the anterior abdominal wall will become the falciform ligament.

At about the 6th week of gestation, the stomach *rotates counterclockwise by 90 degrees*. The major development of the liver forward and to the right of the abdomen will cause this first rotation of the stomach along a vertical axis passing through the gastric lesser curvature, while the greater curvature moves to the left, taking with it the splenic artery, the dorsal part of the pancreas, as well as the vagus nerves (the right becomes posterior and the left anterior). The stomach having more space to expand on the left will thus develop asymmetrically, leading to the difference in size between the greater (left) and the lesser (right) curvatures.

The stomach then *rotates a second time*. The liver, still growing, drives the hepatic pedicle to the right, provoking this rotation of the stomach along a horizontal axis: the cardia moves to the left and the pylorus to the right. The first parts of the duodenum, also moved to the right, will join with the posterior plane to form the ligament of Treitz. Thus, the duodenum beyond the gastroduodenal artery is fixed, while the stomach and pylorus remain mobile. The peritoneum between the gastric greater curvature anteriorly and the pancreas posteriorly then develops to form a bursa which will become the greater omentum by joining its different layers.

2.3.2 Developmental Abnormalities

Developmental abnormalities that may occur include the following:

- *Gastric atresia* is relatively rare (3 per 100,000 births). It usually affects the distal stomach, antrum, or pylorus, and is often incomplete, taking the form of membrane over the gastric outlet. It is probably related to developmental abnormalities around the 8th week of gestation. Surgery for membrane removal or for bypass by gastroduodenostomy (anastomosis between the stomach and duodenum) or gastrojejunostomy (anastomosis between the stomach and jejunum) will relieve the child's vomiting caused by this obstruction to gastric emptying.
- *Microgastria* is a small, tubular stomach with incomplete rotation due to developmental abnormalities during the 5th week. It is very rare and is usually associated with other malformations.
- *Gastric duplication* forms a pouch often localized along the greater curvature and rarely communicating with the stomach or GI tract. This gastric pouch may fill with secretory debris and usually presents as a perigastric mass.

- *Hypertrophic pyloric stenosis* is common (3 per 1000 births) and is the most common cause of abdominal surgery in the first 6 months of life. It is caused by hypertrophy of the pyloric muscles causing obstruction to gastric emptying, leading to vomiting. However, it is not a true congenital disorder since the obstruction develops in the postnatal period. Physical examination reveals a palpable pyloric "olive" in the epigastrium, corresponding to the hypertrophied sphincter. Ultrasound confirms the diagnosis. Surgical pyloromyotomy (Ramstedt's operation with a section of the hypertrophic pyloric muscle) corrects the situation.

2.4 Absorption/Secretion

2.4.1 Absorption

Absorption from the stomach is limited. Ingested food is transformed into chyme in the stomach, but nutrients are absorbed mainly in the small intestine. Similarly, most oral drugs are not absorbed until they pass beyond the pylorus; as a result, pyloric obstruction will compromise the absorption of many oral medications. Alcohol and acetylsalicylic acid are among the rare substances that may undergo some gastric absorption.

2.4.2 Secretion/HCl, Pepsin, and Intrinsic Factor

Gastric epithelial cells produce a variety of secretions that are important for the process of digesting food. H*ydrochloric acid* (HCl) and *pepsin* secreted into the gastric lumen will cause the chemical digestion of ingested food and, with the mechanical trituration effected by gastric wall contractions, will reduce the food to small particles that can pass through the pylorus into the intestine where nutrients are absorbed. Exposed to highly acidic (pH 1–2) secretions, the stomach protects itself through the concurrent secretion of *mucus and bicarbonate* which form a protective insulating layer over the gastric epithelial cells.

2.4.2.1 Parietal Cell

Parietal Cells Secrete HCl and Intrinsic Factor

(a) ***Hydrochloric acid.*** Because of its role in the secretion of HCl and in acid peptic diseases (gastric or duodenal ulcer, reflux esophagitis, etc.), the parietal cell (Fig. 2.5) is the best known in human clinical practice, even though it constitutes only 13% of the gastric cell population.

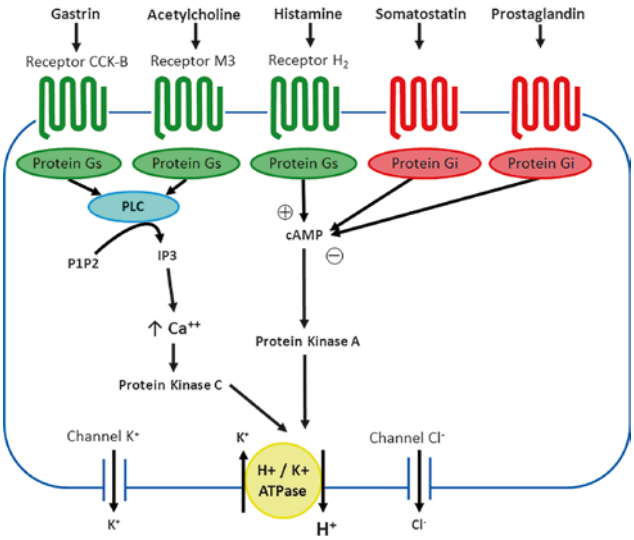


Fig. 2.5 Secretion of HCl by the parietal cell

On the basolateral membrane of the parietal cell, numerous receptors can be activated to stimulate HCl production: histamine H2 receptors, acetylcholine M3 receptors, and gastrin/CCK-B receptors. Membrane receptors for somatostatin and prostaglandins also present there can inhibit the secretion of HCl by the parietal cell.

At the intracellular level, acetylcholine and gastrin use the inositol triphosphate and intracellular calcium pathways as second messengers, while histamine acts via adenylate cyclase (inhibited by somatostatin) to exert their stimulatory effect.

The secretion of H^+ into the gastric lumen involves the activation by the second messengers of an H^+/K^+ ATPase pump located at the apical pole of the cell and allowing the exit of an H^+ ion (proton) into the gastric lumen in exchange for a K^+ ion entering the cell. An associated chloride channel allows the intraluminal secretion of Cl^- which combines to H^+ ions to form HCl. A potassium channel exports outside the cell K^+ ions introduced by the proton pump when secreting H^+ ions.

In humans, several pharmacological tools are known to influence acid secretion by the parietal cell. HCl secretion can be stimulated experimentally by histamine, gastrin, and acetylcholine. In clinical practice, inhibitors of gastric acid secretion are among the most commonly prescribed drugs. HCl secretion may be blocked by antagonists of the stimulatory histamine H2 receptors (e.g., cimetidine, ranitidine, famotidine), or acetylcholine M3 receptors (atropine, etc.), or by agonists of inhibitory membrane receptors such as somatostatin or prostaglandins. We can also block all stimulation by acting on the final common step of the secretory pathway, i.e., the expulsion by the proton pump of H^+ ions out of the parietal cell. Proton pump inhibitors (PPIs) are

benzimidazole derivatives which (by forming disulfide covalent bonds with certain cysteine residues of the H-K ATPase pump) inactivate the proton pump irreversibly (e.g., omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole). Potassium-competitive acid blockers (P-CABs) are novel drugs that compete reversibly with K^+ on the luminal surface to block the H^+-K^+ ATPase pump, resulting in a rapid inhibition of acid secretion; revaprazan, vonoprazan, and tegoprazan are marketed in a few countries in the world for the treatment of peptic disorders.

(b) ***Intrinsic factor.*** The parietal cell is the main site of synthesis of this glycoprotein necessary for the absorption of vitamin B12. Intrinsic factor secretion appears to parallel acid secretion, but it is not affected by PPIs. The absence of parietal cells, after gastrectomy or gastric mucosal atrophy, leads to B12 deficiency and pernicious anemia (Biermer's megaloblastic or macrocytic anemia) (see ► Chap. 3).

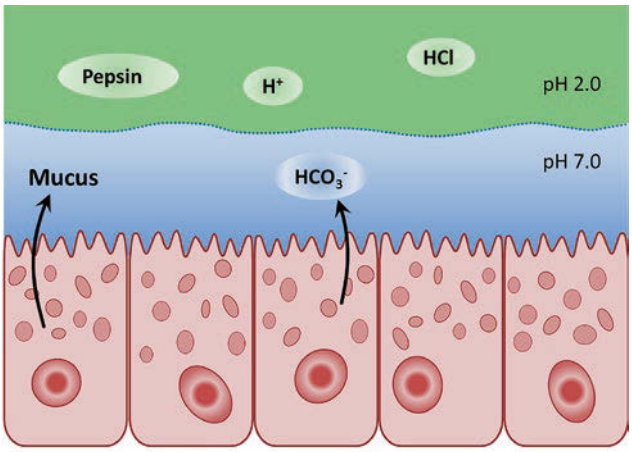
2.4.2.2 Chief Cell

(a) ***Pepsinogens.*** Chief cells synthesize and secrete *pepsinogens*, proenzymes which, in an acidic environment, are transformed into pepsins, proteolytic enzymes that initiate the digestion of food proteins. Pepsin can also potentiate the injurious effects of acid on gastric tissue and is thus probably involved in the pathogenesis of peptic ulcers. Chief cells are the most common gastric cells and secrete substances important to digestion and gastric physiology; however, their practical clinical involvement remains poorly understood and is probably underestimated.

(b) ***Gastric lipase.*** Chief cell also synthesize *gastric lipase*, which is involved in the digestion of lipids, and whose importance is often downplayed (see ► Chaps. 3 and ► 5).

2.4.2.3 Mucous Cell

Mucous cells are distributed in large numbers (40% of gastric cells) in all regions of the stomach. Although they secrete substances such as mucus (made up of 95% water and 5% mucin) and bicarbonates, which play a key role in protecting the gastric mucosa, these cells are still poorly understood. The gastric luminal contents are highly acidic (pH 1–2) and they contain pepsin, a powerful protease. While this environment is important for the digestion of food, it could, also, be very injurious to the gastric mucosa if not protected by the barrier of mucus and bicarbonate produced by the mucous cells. Mucus is a glycoprotein gel that forms a thin mechanical barrier on the surface of the gastric epithelium to protect the underlying cells from injury by intraluminal acid and pepsin. Mucus production is stimulated by the vagus nerve, cholinergic agents, or prostaglandins and can be inhibited, among other things, by drugs such as ASA or NSAIDs. Bicarbonate, also secreted by mucous cells, is another important protective agent that accumulates under the mucus, to form a "micro milieu" (unstirred layer) at pH 7, that isolates the gastric epithelial cells from the more acidic intraluminal contents (pH 1–2) (■ Fig. 2.6).



■ **Fig. 2.6** Protection of the gastric mucosa by the mucus-bicarbonate barrier and the unstirred layer (blue in figure), which provides a thin insulating film of defense for epithelial cells against aggressors from the gastric lumen (green)

2.4.2.4 Endocrine Cells

Endocrine cells secrete a number of hormones or substances that are important for the regulation of gastric functions.

Endocrine cells, previously called APUD (amine precursor uptake and decarboxylation) cells, are recognizable by their cytoplasm rich in secretory granules and their response to silver stains (argentaffin or argyrophil cells). Electronic microscopy allows the recognition of secretory granules specific to each endocrine cell (e.g., G cell, D cell, etc.). More easily, immunochemical staining techniques, using antibodies against specific peptides (e.g., anti-gastrin antibodies), permit ready identification of the peptides contained in the secretory granules and, thus, the type of endocrine cell.

(a) ***G cells,*** located in the antrum, are responsible for the secretion of gastrin into the bloodstream to stimulate secretion of HCl by parietal cells (■ Fig. 2.7). G cells can be activated by enteric nervous system mediators such as acetylcholine, by GRP (gastrin-releasing peptide), and by intraluminal stimuli. The G cell is indeed in contact, via its apical microvilli, with gastric luminal contents such as amino acids, derived from ingested proteins, which will activate the secretion of gastrin postprandially; G cell secretion will be interrupted, at the end of the meal, when

the gastric pH falls below 2 (due to the loss of the alkalizing effect of food). In pathological situations, hypergastrinemia may therefore arise if there is (1) prolonged retention of proteins in the stomach (e.g., due to pyloric obstruction) leading to a continued stimulation of the G cell or (2) hypochlorhydria (e.g., due to pernicious anemia or antisecretory drugs) preventing activation of the secretory brake that would normally be induced (via somatostatin, see below) by a fall in pH.

(b) ***D cells*** secrete somatostatin, a peptide inhibiting many biological functions. Located both in the gastric body, close to parietal and ECL cells, and in the antrum, close to G cells, D cells secrete somatostatin which exerts an important paracrine inhibitory effect on all these cells (G cell, ECL cell, and parietal cell) involved in the secretion of HCl. In the antral mucosa, for example, D cells are activated by luminal acid pH <2 (when food has left the stomach) and secrete somatostatin to inhibit G cells located nearby (paracrine action) to produce gastrin, therefore reducing parietal cell acid production (not required anymore in the absence of food); in hypochlorhydric states, G cells are stimulated continuously to produce gastrin due to the absence of somatostatin inhibition (clinically, the most common cause of hypergastrinemia is hypochlorhydria induced by the use of PPIs).

(c) ***ECL cells*** (enterochromaffin-like cells), initially identified as enterochromaffin cells (secreting serotonin), are now recognized for their histamine content. Located in the vicinity of parietal cells, ECL cells are the key mediators responsible for the effect of gastrin on HCl secretion in human physiology. Indeed, in humans, gastrin does not act directly on the parietal cell, but it acts rather on CCK-B receptors of the ECL cell which, when activated, will secrete histamine to stimulate (paracrine effect) H2 receptors of nearby parietal cells (◘ Fig. 2.7). The activity of the ECL cell can be reduced by various transmitters including somatostatin, galanin, and PYY (peptide YY).

Hyperstimulation of ECL cells may occur in the presence of sustained hypergastrinemia (e.g., pernicious anemia with achlorhydria leading to secondary hypergastrinemia) and may induce polypoid or tumor-like proliferation of ECL cells evoking carcinoid tumors of the stomach (see section on tumor disorders).

(d) ***P/D cells*** are responsible for the secretion of ghrelin from the gastric fundus and body. Ghrelin is a hormone which secretion seems to increase during fasting and decrease after a meal, and which may have a role in appetite regulation.

2.4.3 Regulation of Gastric Acid Secretion

Gastric acid is an important factor of the human health condition: HCl (secreted by parietal cells) facilitates the digestion of ingested food by a direct chemical effect on food particles as well as by converting inactive pepsinogen (secreted by chief cells) into the proteolytic pepsin to digest proteins. The acidic gastric environment is also useful for the transformation of certain substances, such as iron (by conversion from ferric Fe^{+++} to ferrous Fe^{++} form) or calcium (unclear mechanism), and facilitating their absorption by the small intestine. Gastric acid also constitutes a defense against infectious organisms that might attack the body via the digestive tract; the increased risk of *Clostridium difficile* colitis in PPI users supports this hypothesis. However, despite all these important actions, the stomach is not a vital organ (gastrectomy is practiced in various disease conditions), and hypochlorhydria or even achlorhydria (e.g., in autoimmune atrophic gastritis) is, generally, well tolerated, even in the long term, without obvious clinical symptoms or major nutritional deficiency (except for vitamin B12 deficiency).

(a) **Measurement of gastric secretions**. Gastric acid secretion can be measured by collecting gastric secretions, usually using a nasogastric tube. During fasting, the gastric lumen contains secretions with an acidic pH of 1–2; the basal acid output (BAO) is calculated at 2–3 mmol HCl/h. A certain (but marginal) variation in HCl secretion is noted during fasting related to the interdigestive cycle of the migrating motor complex (see ▶ Chap. 3). High gastrin levels, due to an endocrine tumor (gastrinoma or Zollinger-Ellison syndrome), are associated with higher BAO, classically in excess of 10 mmol/h (up to 100–200). The maximum gastric acid secretion (MAO: maximum acid output) measured during pharmacological stimulation by histamine or gastrin reaches 25–35 mmol/h in normal subjects and up to 50–60 mmol/h in patients with duodenal ulcers.

(b) **Regulation of gastric secretion**. Food is the main stimulus for gastric acid secretion. ◘ Figure 2.7 summarizes the process of gastric stimulation by a meal. There are three phases of this postprandial secretion:

1. ***The cephalic phase*** is due to the stimulation by the smell, sight, or taste of food. It is abolished by vagotomy, confirming the major role of the vagus nerve in this stimulation. Atropine blockade confirms the role of cholinergic mediation (M3-type antimuscarinic). In clinic or in the laboratory, to mimic the cephalic phase, the "modified sham feeding" technique can be used to measure the gastric secretion obtained when a

subject smells, sees, and tastes food that he chews but does not swallow (to avoid direct gastric stimulation). Under these circumstances, the vagal cephalic stimulation can reach about 50% of the maximum secretory capacity (MAO; i.e., 10–20 mmol HCl/h). However, in a normal meal, the cephalic phase will be short (as the gastric phase is quickly triggered by the arrival of food in the stomach) and will therefore constitute only about 20% of the meal-related acid secretion. The cephalic pathway can be enhanced by stress or other psychological factors.

2. ***The gastric phase***, triggered by the arrival of food in the stomach, is the main source of postprandial HCl secretion. Food, by virtue of its protein content, high pH, and gastric distension, is responsible for the parietal cell stimulation. Hormonal and neural mechanisms are involved.

Hormonal (Gastrin) Mechanism A cascade phenomenon takes place: (i) amino acids (obtained after protein digestion by HCl secreted from cephalic stimulation as well as from organ distension by the meal) activate the antral G cells directly (via their apical microvilli), causing release of gastrin from their secretory granules into the venous capillaries of the antral mucosa; (ii) gastrin secreted from the gastric antrum then passes from the portal abdominal circulation to the arterial circulation to reach the gastric body; (iii) via this endocrine mechanism (Fig. 2.7), arterial gastrin stimulates CCK-B receptors on gastric body ECL cells to release histamine; (iv) histamine produces paracrine stimulation of histamine H_2 receptors on nearby parietal cells in the gastric body mucosa; (v) this is followed by the stimulation of intracellular adenylate cyclase (Fig. 2.5) and finally activation of the ATPase H/K proton pump with secretion of H^+ ions into the gastric lumen.

The increase in gastric pH which follows food ingestion leads to indirect activation of the parietal cell by inhibiting somatostatin secretion and, hence, promoting gastrin release. Postprandial gastrin secretion stops when food proteins leave the antrum (direct loss of food stimulus) and when the gastric pH, having been raised temporarily to pH 4–7 by ingested food, becomes acidic again (indirect mechanism via somatostatin). The acidic gastric pH stimulates antral D cells to release somatostatin acting via paracrine pathways to inhibit nearby G cells.

Circulating gastrin accounts for about 60–70% of the gastric phase of the postprandial acid secretion. Antrectomy, removing most G cells of the GI tract, reduces by half the daily acid production.

Neural (Vagal) Mechanism The gastric phase of postprandial acid secretion is also regulated by neurological reflexes, most often related to organ distension and involving the vagus nerve (distension → vagal afferents → vagal efferents → HCl secretion). Gastric acid secretion is reduced by 50% after vagotomy (and by 80% after vagotomy + antrectomy).

3. ***The intestinal phase*** of gastric secretion is triggered by the arrival of food chyme in the intestine and is probably under endocrine control via circulating stimulatory hormone(s). However, the nature of this stimulating hormone, tentatively called entero-

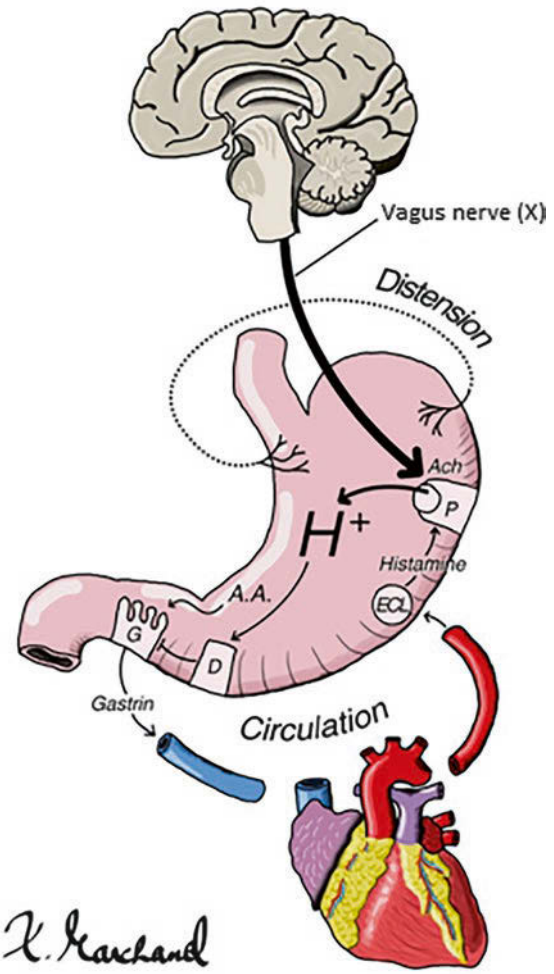


Fig. 2.7 Secretory response of the stomach to a meal. **a** The parietal cell (P) secretes H^+ in response to stimulation by gastrin and the vagus nerve. **b** The vagus nerve is activated by (1) the sight and smell of food (cephalic phase) and (2) by gastric distension by food (vago-vagal enteric reflex). **c** G cells (G) of the antrum secrete into circulation gastrin which will stimulate ECL cells of the gastric mucosa to secrete histamine activating the parietal cell. G cells (1) are activated by meal proteins and (2) will be inactivated by somatostatin released from antral D cells **d** immersed in the acidic pH of an empty stomach

oxyntin, is unknown; most hormones from the small intestine tend to suppress the gastric secretion (GIP, CCK, secretin). The intestinal phase represents less than 10% of total postprandial acid secretion in humans.

2.5 Motility/Sensitivity

2.5.1 Motility of the Stomach

Food is the vital energy supply for all living beings. Nutrients will be assimilated to the body metabolism after their absorption through the small intestine. However, this passage from the external environment to the internal milieu via the intestinal mucosa requires that ingested food be transformed by a combination of mechanical and chemical processes into a molecular form that can be absorbed by the body.

The first step in digestion, after food has been prepared for consumption (cut by utensils, etc.), is mastication or chewing, using the teeth to crush or grind ingested food and mix it with oral secretions, including salivary digestive enzymes. After passing rapidly through the esophagus, food bolus reaches the stomach where they are prepared for final digestion and absorption through the small intestine. Gastric digestion of food involves *chemical alteration* by acid and pepsin and *mechanical trituration* in which contractions of the gastric walls crush and mix the gastric chyme. Gastric motility allows food to be digested in the stomach and then propelled in a gradual regulated manner into the intestine. If gastric motility is impaired (gastric paralysis or gastroparesis), gastric digestion relies solely on chemical digestion, and, above all, the emptying of food particles from the stomach to the small intestine (responsible for their absorption) will be compromised.

Gastric emptying of food into the small intestine is based on the following principles:

- Food particles will pass from the stomach, through the pylorus, to the duodenum when they are less than 2 mm in diameter.
- The passage of gastric chyme from the stomach to the duodenum relies on a pressure gradient between the pre- and post-pyloric regions. Gastric emptying will be facilitated by greater prepyloric forces (antrum, stomach) and lower distal resistance (pylorus, duodenum). Conversely, a decrease in intragastric propulsion and/or an increase in intestinal resistance will slow down the transfer of the gastric chyme toward the duodenum.

Gastric emptying of a meal (illustrated schematically in Fig. 2.8) involves the following steps:

1. **Fundic relaxation/accommodation**. After passage through the esophagus, food enters in the proximal gastric body which gradually expands to receive and accommodate the food as it is processed before being transferred to the duodenum. The walls of the fun-

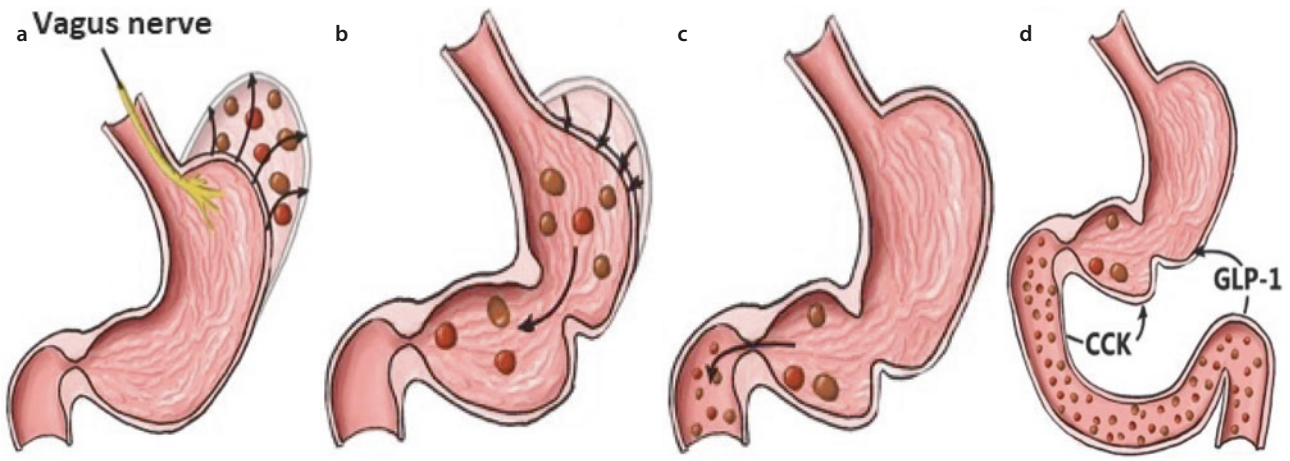


Fig. 2.8 Gastric emptying shown schematically: **a** food arriving in the stomach is stored temporarily in the relaxing fundus (vagal mechanism); **b** food is pushed toward the gastric body by (tonic) contractions of the fundus. Food is pushed from the proximal stomach to the distal stomach (and pylorus) by peristaltic (or phasic) gastric contractions; **c** food particles will pass from the stomach, through the pylorus, to the duodenum, if they are less than 2 mm in diameter. The length of time food will stay in the stomach is influenced by its initial size and consistency; **d** food arriving in the duodenum in high osmotic or lipid concentrations will activate enteric reflexes and intestinal hormones (CCK, GLP-1) to reduce the gastric thrust

dus and proximal gastric body relax and stretch through a process called "adaptive relaxation" allowing the stomach to increase in volume without an increase in intraluminal pressure. The vagus nerve and the neurotransmitters acetylcholine and gamma-aminobutyric acid (GABA) are involved in this enteric reflex. The importance of this accommodative digestive step is evident after surgical vagotomy causes loss of adaptive relaxation and an increase in intraluminal fundic pressure when food arrives in the stomach; this, then, leads to epigastric discomfort and an accelerated transfer of food into the small intestine causing diarrhea and "dumping" (dumping syndrome is discussed later in this chapter).

Impaired adaptive relaxation and accommodation are also implicated in the pathophysiology of functional dyspepsia (discussed in ▶ Sect. 2.8.2).

2. **Emptying of liquid foods**. The stomach, after fundic relaxation, begins to propel food into the duodenum. Tonic contractions of the fundus move food chyme distally toward the gastric body and the antrum. The pyloric sphincter acts as a barrier to the passage of food particles that are too large to be easily digested in the small intestine. Since there is no physical resistance to transpyloric passage of food particles less than 2 mm in diameter, liquids are rapidly drained after ingestion.
3. **Emptying of solid foods**. Peristaltic contractions (circumferential contractions of the gastric circular musculature) are initiated by the "gastric pacemaker," a collection of interstitial cells of Cajal (ICC) in the mid-distal gastric body; these contractions progress from the proximal to the distal stomach to propel chyme distally. However, larger pieces will not pass through the pylorus, which performs a sieving function, restricting the passage of particles larger than 2 mm in diameter. This allows continued intragastric processing of ingested foods by chemical (gastric HCl and pepsin, salivary amylase, gastric lipase, etc.) and mechanical digestion (mixing and grinding by muscular contractions of the gastric walls) until the food particles are small enough to permit transfer to the duodenum.

To optimize delivery of gastric chyme to the duodenum and small intestine, there are several regulatory mechanisms that slow gastric emptying and prevent the digestive and absorptive functions of the small intestine from being overwhelmed.

- *Gastric brake*: The sieving function of the pylorus for particles larger than 2 mm is primarily responsible for this gastric brake which will vary according to the physical characteristics of the food (size, consistency, etc.). Liquid substances will thus be emptied more quickly than solids which require further processing to reduce their size. When the emptying of a meal is measured (Fig. 2.9), liquids are rapidly expelled from the stomach according to an exponential evacuation curve, mainly due to tonic contractions of the proximal stomach (fundus).

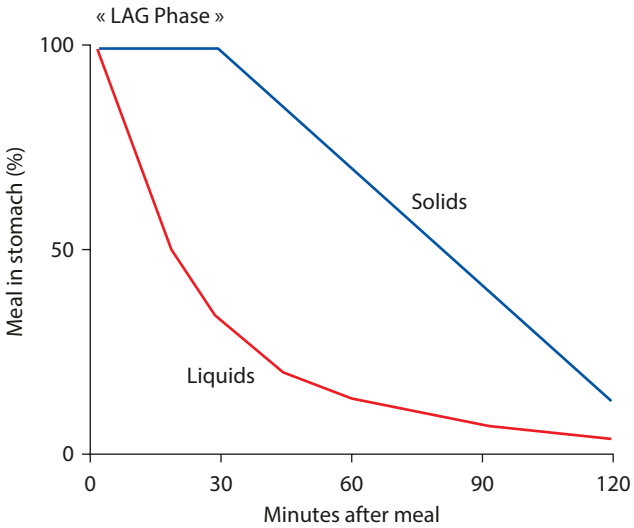


Fig. 2.9 The gastric emptying test in nuclear medicine technique measures, using an external gamma camera, the liquid and solid components of a meal that are present in the stomach in the hours following the test meal ingestion. Liquids are expelled from the stomach through tonic contractions of the proximal stomach propelling them into the duodenum. Solid foods must be reduced, chemically and mechanically, to a volume of <2 mm before passing through the pyloric opening. After a waiting period (lag phase where solid food particles are still too large to pass the pylorus), the solids, once triturated for volume reduction, will exit the stomach when pushed by phasic contractions of the gastric body and antrum

Solid foods greater than 2 mm in diameter will be held up at the pylorus and will be emptied more slowly from the stomach (lag phase; see Fig. 2.9). After digestion and reduction in size to a diameter of <2 mm, solid food particles will pass the pylorus according to a linear evacuation curve, mainly due to contractions of the distal stomach. Postprandial contractile activity will continue until all food particles are sufficiently small to allow passage across the pylorus. Thus, the size and consistency of ingested foods are important factors that determine the speed of gastric emptying; large solid pieces of food (e.g., cubed beef vs. ground beef) or foods of firm consistency (e.g., meat vs. pasta) will be emptied more slowly due to the time required to reduce them to a diameter of <2 mm.

Lipids are also part of the gastric brake. Like solids, they are emptied more slowly than aqueous liquids, in part because when they are in liquid form at body temperature, they float to the top of

the gastric chyme leading to delayed passage from the stomach.

The gastric brake is therefore related to the physical characteristics of the food (size, consistency, lipids, etc.) and to the anatomy of the stomach (pyloric opening).

- *Duodenal brake:* The arrival of food particles in the duodenum is an important mechanism for the regulation of gastric emptying. Duodenal receptors detect the osmotic load (due to carbohydrates and/or proteins) and fat content of gastric chyme that enters the duodenum. If the osmolality or fat content of the duodenal chyme is too high, gastric emptying is inhibited to slow the delivery of nutrients to the small intestine and optimize their absorption.

  Enteric neural reflexes, as well as hormonal mechanisms (postprandial increases in CCK and GLP-1), mediate the duodenal brake by reducing gastric contractile activity to decrease gastric propulsive force and by enhancing pyloroduodenal contractile activity to increase resistance to propulsion, thereby reducing the transpyloric gradient and the speed of gastric emptying.
- *Ileal brake*: Human studies have shown that lipids perfused into the ileum slow gastric emptying (probably via a hormonal mechanism involving GLP-2 and/or PYY released from the ileum). The ileal brake may not be activated under normal conditions, as most nutrients are absorbed proximal to the distal small intestine; this mechanism may be operative if malabsorption caused, for example, by celiac disease or pancreatic exocrine insufficiency results in increased delivery of lipids and other nutrients to the distal ileum.
- *Rectal brake*: In human studies, balloon distension of the rectum can reduce the speed of gastric emptying. The rectal brake probably has limited effect under normal circumstances, but rectal distension, for example, by stools in patients with chronic constipation or by air in those with bacterial fermentation of unabsorbed nutrients, could maybe slow gastric emptying (and explain upper GI symptoms such as nausea commonly reported in these conditions).

4. **Emptying of nondigestible food**. Nondigestible foods will be stopped at the pylorus that constitutes a barrier to the passage of gastric contents which cannot be triturated or reduced to a diameter of less than 2 mm (e.g., dietary fibers, seeds, swallowed foreign bodies, including pills) and which will, therefore, be more difficult to empty from the stomach during normal postprandial gastric motor activity. Once triturable food and liquids have passed the pylorus, the stomach will resume its normal basic fasting motor activity (which is not adynamic as we could imagine) characterized by the cycles of the migrating motor complex (MMC; see ▶ Chap. 3). Every 90–120 min of the interdigestive fasting period, a strong peristaltic contraction (the phase III of the MMC) obliterates the gastric lumen and, with concurrent relaxation (opening) of the pylorus, pushes with force the gastric content across the pylorus into the duodenum. This permits the emptying of larger food particles and even ingested foreign bodies, such as beads or coins, with a diameter of >2 mm from the stomach. If not evacuated from the stomach, fibrous or nondigestible material will tend to clump together or even solidify and form a gastric bezoar.

Food ingestion induces a marked increase in gastric motor activity (fed pattern characteristic of the postprandial period). The contractility of the gastric muscles can be stimulated by cholinergic mediators of the parasympathetic system and by certain intestinal peptides, including motilin. Contractile activity can be diminished by adrenergic moderators of the sympathetic system as well as by several chemical transmitters, including somatostatin, opiate derivatives, and most intestinal peptides such as cholecystokinin (CCK), secretin, glucagon, etc. Under normal physiological conditions, the stomach is under constant autonomic neural (parasympathetic and sympathetic) and hormonal control, ensuring a balance between excitatory and inhibitory influences on gastric contractility. Clinically, gastric emptying may be modulated by various pharmacotherapeutic agents to target these regulatory processes.

2.5.2 Sensitivity of the Stomach

Pain sensation. Vagal and spinal afferent fibers transmit sensory information, including pain, from the stomach to the brain. Disruptions of these physiological mechanisms seem to explain certain pathological states with visceral hypersensitivity such as irritable bowel syndrome (IBS; see ▶ Chap. 4) or functional dyspepsia (discussed later in this chapter).

Reflex activity. As elsewhere in the gastrointestinal tract, sensory afferents transmit information that is not perceived by the central nervous system (CNS), but which is integrated into peripheral reflexes that mediate secretion or motility in the GI tract. For example, secretory and contractile responses of the stomach to gastric distension are based on enteric reflexes. The reflex arc may be limited to the enteric nervous system (e.g., peristaltic reflex; see ▶ Chap. 3) or may involve extrinsic

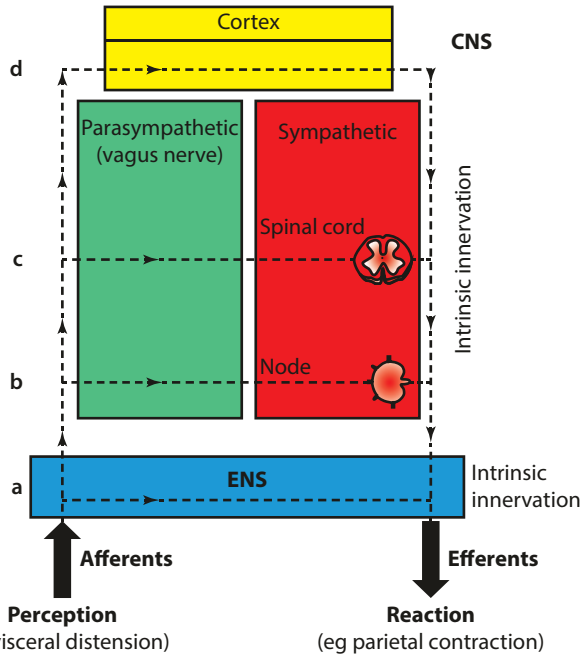


Fig. 2.10 Intestinal reflex: Intestinal stimuli (e.g., visceral distension) are perceived by afferent sensory nerves that transmit information to efferent effector nerves that will stimulate the motor or secretory response of the organ. The reflex arc between the sensory afferent and the effector efferent nerves may **a** be confined to the enteric nervous system (ENS) of the intestinal wall, or involve a sympathetic reflex loop that **b** may be limited to the abdominal level (celiac or mesenteric ganglion), or **c** may require spinal cord neurons, or **d** can even extend up to central structures; at the parasympathetic level, a long vago-vagal reflex may involve the central nuclei of afferent (nodosa ganglion) and efferent (dorsal motor nucleus) structures of the vagus nerve

nervous system structures such as parasympathetic vagal fibers (e.g., postprandial vagal stimulation of gastric acid secretion) or sympathetic ganglia and relays (Fig. 2.10).

2.6 Inflammation Disorders

2.6.1 Peptic Ulcer Disease

Peptic ulcer disease (PUD) refers to two related but distinct conditions: duodenal ulcer (DU) and gastric ulcer (GU).

(a) **Physiopathology of PUD**. The maxim "no acid, no ulcer" has long been a dogma of gastroenterological science and still remains pivotal in understanding the pathophysiology of peptic ulceration:
- Peptic ulcers are exceedingly rare in the absence of acid.
- Acid hypersecretion is a well-documented cause of peptic ulcers.
- Acid suppression is still the most widespread and effective therapy for healing peptic ulcers.

The stomach is exposed to chemical aggression by luminal hydrochloric acid (HCl at pH 1–2) and proteases, such as pepsin, which would not be tolerated by any other organ. Its ability to remain intact is clear evidence for highly effective defense mechanisms that protect the gastric mucosa against such aggression. This *gastric barrier* is made of a number of supra-, intra-, and subepithelial factors:
- *Supra-epithelial factors.* Mucus secreted by the surface mucous cells of the stomach creates a superficial isolation layer above the gastric mucosa to limit direct cellular contact with the acidic and proteolytic luminal environment. The mucus is composed mainly of mucins, large glycosylated proteins, that form a viscous gel that forms a barrier limiting the migration of toxic or irritating substances to the mucosal surface. Intraluminal ulcerogenic substances such as ASA or bile salts can alter the viscosity of the mucus and thus facilitate the back-diffusion of H^+ ions from the lumen to the gastric mucosa.

  Gastric surface cells also secrete bicarbonate which, although it represents only 10% of total gastric secretion, is retained close to the epithelium by the overlying mucus forming the "mucus-bicarbonate barrier" which covers the "unstirred layer" or microscopic milieu at neutral pH on the surface of the gastric cells (Fig. 2.6). Prostaglandins have an important action at this level, regulating the secretion of both bicarbonate and mucus.
- *Intraepithelial factors*. Cell renewal in the epithelium allows rapid restitution or replacement of cells that have been injured by noxious luminal agents.
- *Subepithelial factors.* Mucosal blood flow beneath the epithelium is essential to supply oxygen and nutrients and remove metabolic products in order to maintain the integrity of the epithelium and its defense systems. Nitric oxide (NO) appears to be an important factor in causing capillary vasodilatation and promoting this protective mechanism. Changes in the regulation of the mucosal circulation may be responsible for the decrease in gastric defenses observed with age.

The integrity of the gastroduodenal mucosa is therefore dependant upon a *balance between aggression factors* (HCl, pepsin, etc.) *and defense factors* (mucus, $HCO3^-$, etc.) (Fig. 2.11). A disruption of this balance, created by an increase in the aggressive forces (e.g., hyperchlorhydria) or a decrease in the defensive factors (e.g., decreased prostaglandins due to ASA or NSAIDs), compromises the epithelial integrity, leading to disruption of the mucosa and the development of ulcers. Ulcer healing, therefore, requires a restoration of equilibrium, either by reducing aggressive factors or by strengthening

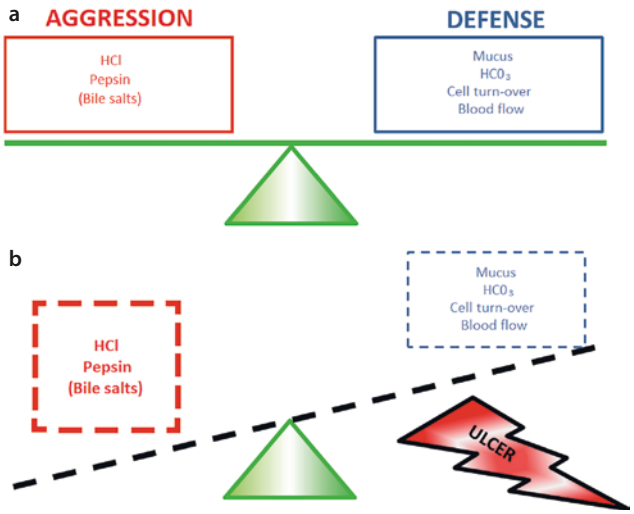


Fig. 2.11 The integrity of the gastric mucosa is normally ensured by a balance between the aggressive and defensive factors **a**. Any disturbance of this balance **b**, by increasing the aggression forces and/or decreasing the defense capacities, can lead to a disruption of the mucosal membrane and to ulcer formation

mucosal defense. The clinician's therapeutic arsenal currently favors the reduction of aggressive factors (e.g., reduction of HCl secretion by PPI) rather than the augmentation of defensive facilities (no medication, such as prostaglandin analogues or sucralfate, is clearly effective) to heal peptic ulcers. This finding could be due simply to the relative therapeutic efficacy of currently available pharmacological tools, and should not be interpreted as a demonstration of the superiority of the aggression theory (over the defense theory) in the genesis of peptic ulcer disease.

(b) **Clinical aspects of PUD**. Peptic ulcer disease is a common affliction that traditionally affected about 10% of the population.

Peptic ulcers manifest mainly with epigastric pain, often in the form of a burning sensation, that typically occurs at distance from a meal (on an empty stomach in the fasting state, between meals or at night, when gastric pH is low) and is diminished by ingestion of food or antacid medication (both elevating gastric pH).

Peptic ulcer is subdivided into duodenal and gastric ulcer (Table 2.1).

- *Duodenal ulcer* (*DU*) is most frequently located in the first part of duodenum or duodenal bulb. It is classically characterized by epigastric pain which occurs when luminal pH is low during fasting and by relief when intraluminal pH rises after the ingestion of food or antacids (Table 2.2). It is often considered to be a disease affecting young adults that, classically, occurs throughout life in recurrent episodes. Duodenal ulcers arise mainly due to an increase in aggressive factors; *Helicobacter pylori* is implicated very frequently, and the eradication of this bacterium has significantly reduced the incidence of DU disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) can also cause DU; 50% of patients with ASA or NSAID-associated ulcers have duodenal bulbar lesions.
- *Gastric ulcer* (*GU*) is located in the antrum or body of the stomach. GU is characterized by epigastric pain which may occur during fasting, as for DU, but also occurs in the postprandial period. It was, classically, considered to be a disease associated with a lower socioeconomic status, often in conjunction with smoking or alcohol ingestion. GUs are considered to arise mainly due to defects in defensive factors. *Helicobacter pylori* is associated with GU, but nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin (ASA) are commonly implicated in its pathogenesis. Unlike DU, a GU in the body or antrum may be malignant and should, therefore, be biopsied at endoscopy and followed closely to confirm healing as failure to heal may be indicative of a malignant lesion.
- *Post-bulbar ulcer* (i.e., located in the second to fourth part of the duodenum, distal to the bulb, or even in the jejunum) is rare, not typical for classic peptic ulcer disease (caused by *H. pylori*

Table 2.1 Peptic ulcer: duodenal and gastric ulcer characteristics

	Duodenal Ulcer	Gastric Ulcer
Epigastric pain	↓ after meal	↓ or ↑ after meal
Mechanism	↑ aggression (HCl-Hp)	↓ defense (NSAIDs)
Hp/NSAID role	Hp (70–90% of cases)/NSAIDs	NSAIDs > Hp
HCl secretion	↑	N or ↓
Response to PPIs	Excellent	Good
Anti-Hp response	Excellent	Variable
Cancer risk	Rare	Possible
Ulcer biopsy required	No	Yes
Follow-up endoscopy required	No	Yes

Table 2.2 Ulceration in stomach or duodenum: causes

General causes
1. *Helicobacter pylori*
2. ASA-NSAIDs
3. Others (rarer):
Hypersecretion (gastrinoma, mastocytosis)
Infectious
Ischemic (arteriosclerosis, cocaine)
Inflammatory (Crohn's)
Location specific causes
a. Gastric ulcer: NSAIDs > *H. pylori*
R/O: adenocarcinoma/lymphoma
b. Bulbar ulcer: *H. pylori* 80–90% of cases (if no NSAIDs)
NSAIDs: 50% = bulbar ulcer
c. Post-bulbar ulcer: Major hypersecretion (e.g., ZES)
R/O: Tumor (cancer of duodenum)
Inflammation: Crohn's

or NSAID), and should suggest other diagnoses such as gastrinoma or Crohn's.

(c) **Causes of PUD**. The causes of peptic ulcer disease are summarized in Table 2.2. *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common causes of stomach or duodenum ulcerations.

1. ***Helicobacter pylori* (*H. pylori* or Hp).** In 1982, a gastroenterologist and a pathologist from Australia identified *Helicobacter pylori* in the human stomach and its involvement in peptic ulcer disease. Barry Marshall and Robin Warren were awarded the 2005 Nobel Prize for their scientific contribution which revolutionized the approach to this disease.

   Bacteriology. *H. pylori* (formerly known as *Campylobacter pyloridis*) is a spiral gram-negative bacterium. Using its flagella (see Fig. 2.12), it can move and migrate through gastric mucus to the gastric epithelium. The bacterium does not penetrate the epithelium, but it produces several enzymes to attack the gastric epithelium (phospholipase, catalase, etc.); enzymes, such as urease, also allow the bacterium to protect itself from acid. Urease is the enzyme with which clinicians are most familiar, as it is the basis for diagnosis with "rapid urease tests" and "urease breath tests," both of which

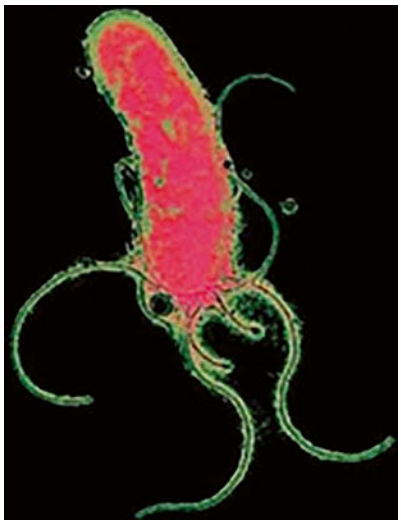


Fig. 2.12 Helicobacter pylori with its flagella allowing movements and penetrance to gastric mucosa

can detect living *H. pylori* in the stomach. Urease, which makes up more than 5% of the protein weight of the bacterium, hydrolyzes urea $\{CO(NH_2)_2\}$ in the gastric lumen to form ammonia (NH_3) which helps neutralize stomach acid and form a protective layer around the bacterium.

Epidemiology of Hp. *H. pylori* is the most common chronic human bacterial infection in the world, estimated to affect 50% of mankind. Its prevalence is inversely proportional to the socioeconomic level of a population [up to 80% of subjects in low or medium Human Development Index (HDI) countries and less than 50% of subjects in high or very high HDI countries are infected] and is proportional to age (10% of 20-year-olds and 50% of 60-year-olds are infected). It appears that *H. pylori* infection is, normally, acquired in infancy or childhood, before the age of 5 years; thus, the increase in prevalence in older individuals is a cohort phenomenon due to lower incidence rates in younger individuals, particularly in high or very high HDI countries, and not the consequence of a persistent constant incidence over time. Very low reinfection rates of less than 1% per year are seen after *H. pylori* eradication.

The mode of transmission is uncertain although both oro-oral and feco-oral routes are plausible. Humans appear to be the most important reservoir of infection. *H. pylori* occurs in both vomitus and diarrheal stools consistent with both modes of transmission, particularly in the context of gastroenteritis. Low socioeconomic status favors transmission due, presum-

ably, to proximity between individuals and suboptimal sanitary conditions.

Pathology of Hp. *H. pylori*, at the time of the primary infectious contact, can lead to acute gastritis that may go unnoticed or may result in abdominal discomfort and vomiting most often attributed to a viral infection.

In the long term, most individuals develop a chronic infection, accompanied by a chronic active gastritis that initially affects the antrum, but that may then migrate proximally to the body or even to the fundus of the stomach.

Hp colonizes only gastric epithelial cells, suggesting a specific recognition of gastric cells by the bacteria (it can also colonize gastric metaplastic epithelium in the duodenum). It binds to the gastric mucosa via adhesion pedestals [using adhesive factors belonging to a large group of outer membrane proteins that bind to factors such as blood group antigen binding adhesin (BabA) and sialic acid-binding adhesin (SabA)]. *H. pylori* also produces various enzymes (e.g., urease, phospholipase, catalase, heat shock protein) that interact with the mucosa, generating host inflammatory and immune reactions mediated mainly by T lymphocytes (and related inflammatory mediators such as IL8, IL1, TNFa).

Physiopathology of Hp. The physiopathology of *H. pylori* ulceration remains poorly understood. Although *H. pylori* infection is highly prevalent, affecting >50% of the population, it remains indolent in most carriers with a peptic ulcer prevalence of about 10%. *H. pylori* infection must, therefore, be considered as multiple, complex interactions between the bacterium and its host which may be modified by various, incompletely understood bacterial, host, and environmental factors. Some factors are considered most likely to play a role in the ulcerative pathogenesis of the infection:

- Bacterial factors: Some bacteria appear to be more virulent and injurious. One well-known toxic factor is the cytotoxin Vac A (vacuolating cytotoxin) which causes clearly identifiable cell damage in vitro. The CagA protein (cytotoxin-associated gene A) regulates the expression of the Vac A gene and could therefore modify the bacterial virulence, as suggested by the finding that the *H. pylori* CagA+ strain is present in 80–100% of patients with duodenal ulcers compared to only 30–60% of asymptomatic Hp-infected subjects.
- Host factors: Differences in host response to *H. pylori* may account for differences in clinical manifestation. It has been proposed that genetic factors may, for example, alter bacterial adhesion to the gastric epithelium, the type or magnitude of the local inflammatory response, and the sensitivity of acid-secreting parietal cells to endogenous stimuli, but these factors are not, currently, well understood.
- Environmental factors: Cigarette smoking and NSAIDs seem to play a role in disrupting the equilibrium between aggressive bacterial factors and defensive host factors and promoting the development of ulcers.

Clinical implication of Hp. *H. pylori* is the main pathogenetic factor in duodenal ulcer disease, but it does also play a role in the pathogenesis of gastric ulcer disease, as well as other gastric diseases including non-ulcer dyspepsia, gastric cancer, and gastric MALT lymphoma.

Hp and duodenal ulcer: The relationship between *H. pylori* and duodenal ulcer is well established. Hp is present in the vast majority (70–90%) of patients with DU not related to NSAIDs, and eradication of Hp heals the ulcer and prevents recurrence of the disease. However, as discussed previously, it is not known why duodenal ulceration develops in only 10–15% of *H. pylori*-infected individuals. The physiopathology of duodenal ulcer encompasses a multistep pathway from *H. pylori* infection to acid hypersecretion and hypergastrinemia:

- *H. pylori* produces ammonia which increases pH in the unstirred layer on the antral epithelial surface and reduces the pH stimulus to somatostatin release; it, also, induces antral inflammation via mediators (e.g., interleukins) which inhibit the activity of antral endocrine D cells responsible for the secretion of somatostatin.
- Hyposecretion of somatostatin decreases its inhibitory influence on antral G cells, leading to increased secretion of gastrin.
- Increased plasma gastrin levels induce parietal cell proliferation and stimulate acid secretion by the parietal cells.
- Increased gastric acid secretion leads to decreased pH and increased peptic activity causing injury to the duodenal mucosa which is more susceptible than gastric mucosa to acid peptic injury.
- Injured duodenal mucosa may heal with replacement of normal duodenal mucosa by metaplastic gastric epithelium which is susceptible to colonization by *H. pylori* and additional bacterially mediated injury.

Hypergastrinemia and acid hypersecretion are well-documented features of duodenal ulcer disease and will regress following the eradication of the bacteria.

Hp and gastric ulcer: *H. pylori* is also involved in the pathogenesis of GU. However, in clinical practice, GUs are more often related to the use of ASA or NSAIDs (see below).

Hp and others: *H. pylori* is also associated with non-ulcer dyspepsia, atrophic gastritis, gastric adenocarcinoma, and gastric lymphoma, as discussed later. However, it is not known why these effects are seen in only a small proportion of *H. pylori*-infected individuals.

2. ***Anti-inflammatory drugs.*** ASA and NSAIDs have well-known to be ulcerogenic for gastric and intestinal mucosa.

Pathophysiology of ASA-NSAIDs-induced gastric damage. The harmful effect of these substances may be due to their direct contact with the gastric mucosa. Ingested ASA is a non-ionized molecule, but following ionization in the gastric acidic environment, it exerts a direct toxic effect on the epithelial cell; some NSAIDs, such as indomethacin, can also injure the gastric mucosa directly. However, the harmful effects of anti-inflammatory molecules are mediated predominantly by their systemic effect on prostaglandin metabolism, whether they are taken orally, rectally, or parenterally.

Prostaglandins play a major role in the defense of the gastric mucosa against peptic injury through their actions in promoting protective factors such as bicarbonate secretion, mucus production, cell renewal, etc. As shown in Fig. 2.13, prostaglandins are synthesized from arachidonic acid by the enzyme cyclooxygenase (COX). COX enzymes exist in two forms in the body (two proteins encoded on two different chromosomes and with a 50–60% identical structure): COX-1 is a so-called constitutive enzyme and is found at relatively constant levels in many cell types, including those of the digestive system; COX-2 is an inducible enzyme, expressed in several cell types in response to inflammatory mediators. The anti-inflammatory and analgesic effects of drugs such as ASA and NSAIDs are attributable to their actions in inhibiting COX-2 enzymes, but, unfortunately, most of these agents also inhibit COX-1 which generates the prostaglandins which protect the gastric mucosa; thus, inhibition of COX-1 is associated with an impairment of the gastric mucosal barrier and

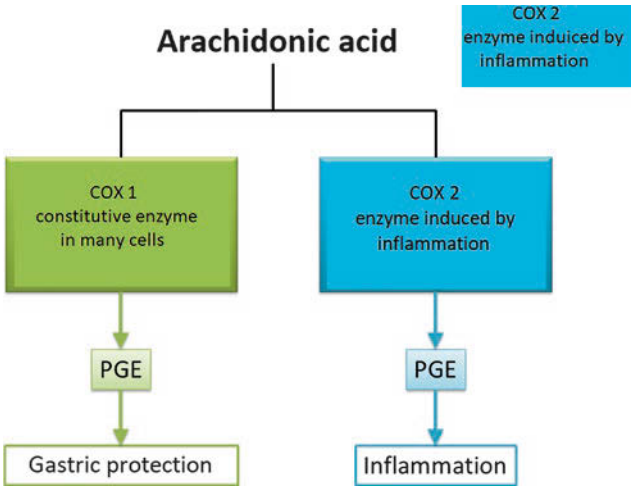


Fig. 2.13 Metabolism of arachidonic acid to prostaglandins (PGEs). Selective inhibition of the enzyme COX-2 would make it possible to decrease pro-inflammatory PGEs (articular or other) without altering gastric protection. Unfortunately, most anti-inflammatory agents currently available inhibit COX-2 as well as COX-1 and therefore compromise mucosal integrity

an increased susceptibility to acid peptic injury. Anti-inflammatory agents acting preferentially on the COX-2 enzyme (with little influence on COX-1 enzyme) have been developed (e.g., celecoxib, rofecoxib) with the goal of producing anti-inflammatory and analgesic effects without accompanying harm to the digestive mucosa. However, many of these agents have been withdrawn due to their cardiovascular side effects.

Clinical implication of anti-inflammatory drugs. ASA and NSAIDs may induce superficial lesions (edema, subepithelial hemorrhages), erosions (mucosal defect superficial to the muscularis mucosa), or deeper, frank ulcerations in the stomach and duodenum (even in the small intestine). They can manifest with typical ulcer symptoms, be silent, and/or cause complications such as perforation or hemorrhage which can be lethal. It is estimated, for example, that 2600 deaths annually in the United States are attributable to these drugs taken by patients with rheumatoid arthritis. The risk of developing ulcer complications from NSAIDs is increased by certain factors:

- Duration of therapy (rare if less than a week)
- Dose of anti-inflammatory drugs (lower doses cause less injury although low doses of ASA (81 mg die) can cause complications)
- Type of NSAID (relative risks of ulceration: ibuprofen 1.4; piroxicam 1.66; diclofenac 1.7; naproxen 1.8; indomethacin 2.25)

- Concomitant therapy with glucocorticoid or anticoagulant drugs
- Age (>60 years of age)
- Previous NSAID complications
- Previous ulcers
- *H. pylori* (patients with NSAIDs are 60 times more likely to develop an ulcer if they are infected with *H. pylori*)

(d) **Complications of PUD**. Peptic ulcer is mainly manifested by epigastric pain, but it can also lead to serious complications as listed in ◘ Table 2.3:

Bleeding. Non-variceal upper gastrointestinal bleeding (NVUGIB) occurs when an ulcer erodes a submucosal blood vessel in the stomach or duodenum. There may be acute, overt blood loss, presenting as hematemesis (vomiting of blood), melena (black stools), or even hematochezia (red blood per rectum), or there may be chronic, occult blood loss, presenting as iron-deficiency anemia. The risk of NVUGIB is increased 1.8-fold in individuals with *H. pylori*, 4.9-fold in NSAID users, and 6-fold if the patient has both risk factors. In 5–10% of overt NVUGIB, bleeding may be severe enough to cause death. The management of GI bleeding is discussed in ▶ Chap. 11.

Perforation. This occurs when an ulcer penetrates beyond the muscularis propria and serosa to form a direct connection between the gastrointestinal lumen and the peritoneal cavity, leading to peritonitis and an acute abdomen requiring urgent treatment. In some cases, signs and symptoms of peritonitis may be diminished if the perforation is sealed by omentum or a nearby organ; if the pancreas is affected, the patient may appear to have acute pancreatitis. The management of gastrointestinal perforations is discussed in ▶ Chap. 16.

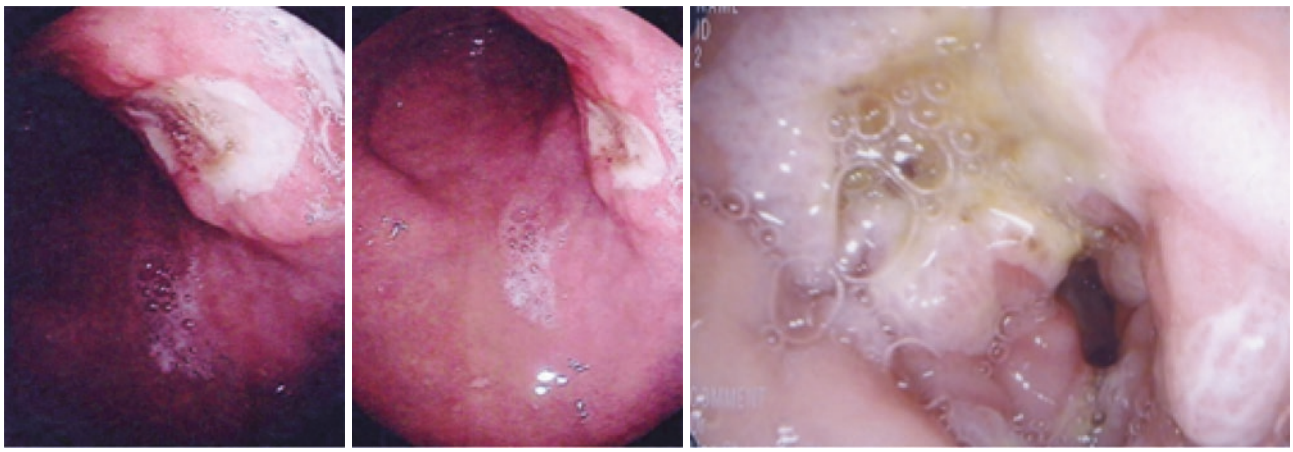
Table 2.3 Peptic ulcer: acute complications and their treatments

(*a*) *Bleeding* → hematemesis, melena, hypovolemic shock
Rx: – Pharmacological therapy: ↓ acid (PPI)
Endoscopy: sclerosis/ulcer coagulation
Arteriography: arterial embolization
Surgery: ligation hemorrhagic vessel
(*b*) *Perforation* → abdominal pain, acute abdomen
Rx: – surgery: oversewing of the perforation
(*c*) *Obstruction* → vomiting
Rx: – IV medication: anti-H2/ PPI
Endoscopy: pneumatic pyloric dilatation
Surgery: pyloroplasty, resection of obstructed segments, bypass (gastrojejunostomy, etc.)

Obstruction. Narrowing of the gastroduodenal lumen by ulcer-related edema and/or scarring, especially if the ulcer is close to the pylorus, may interfere with the passage of food along the upper gastrointestinal tract, causing obstruction, gastric distension, and vomiting.

(e) **Diagnosis of ulcer**. *Endoscopy* is the most accurate way to visualize and diagnose peptic ulcer (◘ Fig. 2.14).

- Duodenal ulcer (DU) is most often located in the duodenal bulb. The differential diagnosis of an ulcerated lesion of the bulb is limited, tumoral or inflammatory conditions being rare at this level. For a typical bulbar ulcer, gastric antral and body biopsies will be taken to diagnose *H. pylori*. Post-bulbar ulcers in the distal duodenum are



◘ **Fig. 2.14** Endoscopy showing an ulcer lesion of the antrum (two photos on the left) or duodenal bulb (photo on the right). (Photos by P. Poitras)

atypical, and hypersecretory (e.g., gastrinoma), inflammatory (e.g., Crohn's), or neoplastic conditions should be considered.

- Gastric ulcer (GU) may be located in the antrum or body of the stomach. It is most often associated with the use of ulcer-causing drugs such as ASA or NSAIDs. All gastric ulcerations must be examined carefully at endoscopy to look for features of neoplasia and differentiate between a benign peptic lesion and a malignant lesion such as adenocarcinoma or, more rarely, lymphoma; multiple biopsies should be taken from around the ulceration to detect the presence of neoplastic cells; and an endoscopic follow-up is usually recommended after 4–12 weeks of medical treatment to document ulcer healing (which usually supports the benign nature of the ulcerative process).

Radiology with ingestion of barium contrast fluid (barium meal) has long been the standard diagnostic procedure for peptic ulcer disease. A benign gastric ulcer generally appears as a "niche" or a "crater" containing barium that extends deep to the gastric contour (whereas a malignant ulcer appear.s as crater, located in a tumoral mass, protruding into the gastric lumen above the normal gastric contour). Barium studies are now rarely performed because they are less accurate than endoscopy and since endoscopic examination, in the case of GU, will be required anyway to exclude a neoplastic process.

(f) **Diagnosis of *H. pylori***: *H. pylori* infection can be diagnosed by various tests (Table 2.4). Most accurate tests of active infection include:

- Biopsy (per endoscopy) of gastric tissue: Microscopic analysis demonstrates *H. pylori* (Fig. 2.15). In "rapid urease tests," gastric biopsies are incubated in a solution of urea and a pH-sensitive indicator which turns red if ammonia is generated by the action of *H. pylori* urease.
- Urea breath test: This requires oral ingestion of urea labelled with a C13 (or C14) isotope which in the presence of urease produced by *H. pylori* will be hydrolyzed to release ammonia and labelled CO_2 then measured in the exhaled breath.

(g) **Treatment of peptic ulcer**. Common pharmacological agents are listed in Table 2.5.

1. ***Acute treatment of ulcer***: Re-equilibrate the aggression/defense balance.

Decrease aggression. Decreasing gastric activity remain the most common therapeutic strategy for peptic ulcer disease (no acid, no ulcer as the classic saying goes).

Antacids, usually incorporating a mixture of calcium, magnesium, and aluminum compounds, quickly neutralize gastric acid to provide rapid pain relief. However, their use is limited by a brief duration of action and side effects at high doses (diarrhea with Mg^+, constipation with Al^-, ion overload, etc.). Calcium (Ca^+), long forgotten, is now increasingly used in antacid preparations; its chronic excess intake (more than 4 g/day in

Table 2.4 Diagnosis of *H. pylori*

Methods	Sensibility/ specificity	Pros-cons	Clinical use
Biopsy (antrum)	Excellent >90%	Needs expertise (endoscopy/ pathology) Invasive test	Very sensitive for Hp detection and follow-up of eradication
Urea breath test	Excellent >90%	Specialized laboratory Well tolerated	Very sensitive for Hp detection and follow-up of eradication False negative results if elevated gastric pH (e.g., by PPI)
Serum tests: dosage IgG anti-Hp	Sensitive 85% Specificity 80% False positive 40%	Routine blood test Limited reliability Unreliable in children	IgG anti-*H. pylori* stay elevated long time: do not allow to verify eradication
Fecal tests: Hp antigen	Sensitive 94% Specificity 97%	Underused Stool manipulation	Useful for detection and eradication

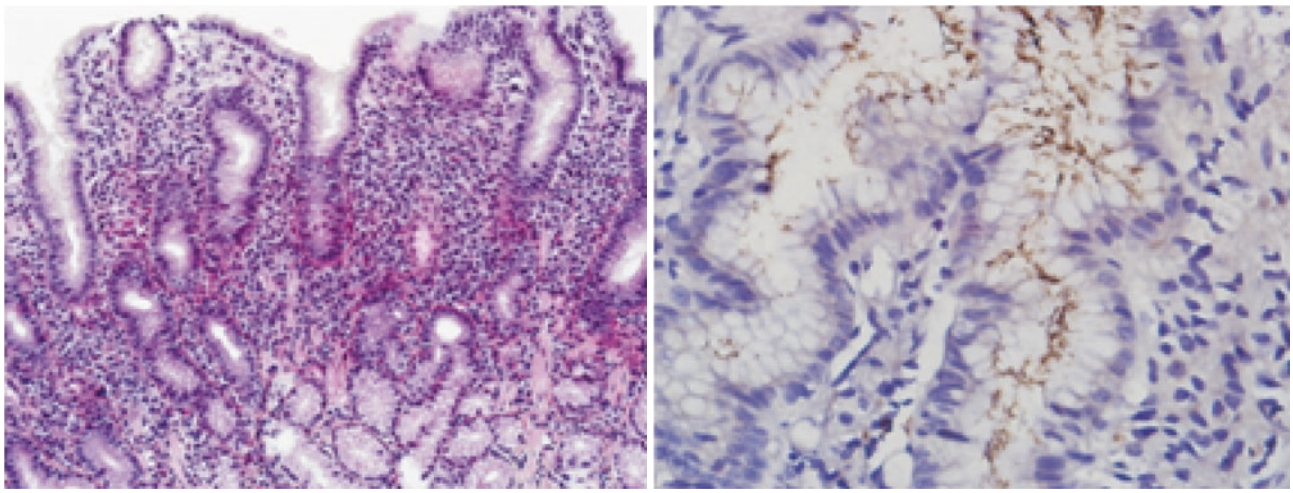


Fig. 2.15 Antral gastritis with a strong inflammatory contingent secondary to H. pylori. At higher magnification (right photo) and with immunohistochemical study, we can clearly see, between the glands, bacteria unable to penetrate the mucosa. (Photos by G. Soucy)

Table 2.5 Pharmacotherapy of peptic ulcer

(A) Antacids	
Al-Mg (15–30 mL q 1–2 h prn) Al Mg (MgOH) Ca	Rapid (but brief) symptom relief by neutralization of endoluminal acid Sold without prescription
(B) H2 receptor antagonists	
Cimetidine (300 mg qid/600 mg bid) Ranitidine (150 mg bid/300 mg hs) Famotidine (20 mg bid/40 mg hs)	Available without prescription. Inhibits HCl secretion
(C) Proton pump inhibitors	
Omeprazole (20 mg id) Pantoprazole (40 mg id) Lansoprazole (30 mg id) Rabeprazole (20 mg id) Esomeprazole (20–40 mg id) Dexlansoprazole (30–60 mg id)	Potent inhibitors of HCl secretion Ulcer healing in 1 month: 60–90% of patients
(D) Cytoprotective agents	
Misoprostol (0.2 mg qid/0.4 mg bid) Sucralfate (1 g 30 min AC + HS)	Misoprostol side effect: diarrhea Sucralfate: poor compliance (qid AC)
(E) Medication IV	
Ranitidine (50 mg q 6–8 h) Famotidine (20 mg q 8–12 h)	H2RA: perfusion over 24 h preferable but rarely done in practice
Pantoprazole (40 mg q 8–24 h or 80 mg bolus + 8 mg/h)	

a prolonged way) provoked the reappearance of a rare but serious complication known as "milk-alkali syndrome" with hypercalcemia, metabolic alkalosis, uremia, and confusion (this complication was well known more than 60 years ago when milk and calcium-based antacids were the only treatment for UD).

Histamine H2 receptor antagonists (H_2RAs), developed in the late 1970s, were the first valid treatment option for peptic ulcers. However, they are now used much less as they are only moderately effective, probably due to the tachyphylaxis with desensitization of the receptors that occurs during long-term use.

Proton pump inhibitors (PPIs), available since the mid-1980s, are efficient and safe. A daily dose of omeprazole 20 mg, pantoprazole 40 mg, lansoprazole 30 mg, rabeprazole 20 mg, esomeprazole 20–40 mg, or dexlansoprazole 30–60 mg completely heals 80–90% of peptic ulcers in 4–8 weeks. PPIs, for maximum efficacy, must act on an activated parietal cell, and it is suggested that they be administered preferably 30–60 min before breakfast (or a meal).

Enhance defense. Enhancing gastric mucosal defenses against acid peptic aggression is, theoretically, a logical strategy for ulcer healing but is rarely used these days.

Sucralfate adheres to fibrinonecrotic tissues, forming a protective layer over the ulcerated site to shield it from luminal acid and promote re-epithelialization of the crater. Its therapeutic efficacy is comparable to that of H_2RAs for both duodenal and gastric ulcers. Compliance with sucralfate treatment can be limited because the medication should be taken four times daily on an empty stomach (30–60 min AC + HS). Sucralfate treatment is only exceptionally used nowadays.

Misoprostol is a prostaglandin analogue with a protective effect on the gastric mucosa by increasing its bicarbonate production. At the therapeutic doses used, misoprostol also inhibits the secretion of HCl. Misoprostol has been found comparable to PPIs in NSAID-induced ulcer disease and should therefore appear as a logical therapeutic approach for ulcers attributed to impaired mucosal defense. However, side effects of misoprostol, especially diarrhea in about 30% of subjects, and an inconvenient dosing schedule (qid or bid) have limited its use.

Duodenal Ulcer (DU) vs. Gastric Ulcer (GU). DU is more commonly due to *H. pylori*, while GU is more often due to NSAIDs or ASA. Eradication of *H. pylori* therefore tends to be more beneficial in duodenal than in gastric ulcer disease. DU is frequently associated with acid hypersecretion and will therefore respond well to acid suppression. In contrast, GU is rather associated with normo-secretion or even hyposecretion of acid and most often involves a disruption of mucosal defense; acid suppression remains nevertheless the treatment of choice to restore equilibrium between aggressive and defensive factors and to heal mucosal breaks (however, GU healing is generally slower than DU).

2. ***Treatment of peptic ulcer disease and prevention of recurrence***: Treating the cause of the ulcer by eradicating *Helicobacter pylori* or stopping the ingestion of ASA/NSAIDs is obviously the best strategy to cure ulcer disease.

***H. Pylori*:** The diagnosis of H. pylori is made using the modalities described in ◘ Table 2.4. Eradication of *Helicobacter pylori* is usually achieved by a combination of antibiotics supplemented by acid suppression therapy. Conventional 7 days' "triple therapies" include a PPI (e.g., omeprazole 20 mg or equivalent) bid with clarithromycin 500 mg bid, and metronidazole 500 mg bid or amoxicillin 1 g bid will eradicate the bacteria in about 75% of cases; prolonging administration to 14 days increases therapeutic efficacy. However, antibiotic resistance to clarithromycin or metronidazole is increasingly common, and new therapeutic regimens are proposed (see ◘ Table 2.6). One report suggested that vonoprazan, a potassium-competitive acid blocker (P-CAB), could provide better results than PPIs (triple therapy with vonoprazan vs. PPIs: eradication rate of 91% vs. 76%, respectively). The benefit of eradicating *H. pylori* in duodenal ulcer disease is clear, but the benefit is less clear for other diagnoses (as summarized in ◘ Table 2.7).

ASA-NSAIDs: Strategies for prevention and treatment of drug-induced ulcer disease are summarized in ◘ Table 2.8.

As a general rule, NSAID therapy should use the least harmful agent, at the lowest effective dose, for the shortest possible duration.

If the patient has a history of duodenal ulcer, testing for H. pylori and eradication is recommended, given the increased risk of ulcer complications observed when NSAIDs are taken in presence of *H. pylori* gastritis.

Prophylactic acid suppression therapy is suggested for a patient taking NSAIDs if there is a history of ulcers; if there is concomitant therapy with antiplatelet, anticoagulant, or steroid medications; or if the patient is over 65 years of age or has significant comorbidities (heart disease, etc.).

◘ **Table 2.6** Pharmacotherapy of *H. pylori*

PPI	AB 1	AB 2	AB/others	Use
Bid	Clarithromycin 500 mg bid	Amoxicillin 1 g bid	–	Acceptable in areas where AB resistance is weak
Bid	Clarithromycin 500 mg bid	Metronidazole 500 mg bid	–	Acceptable in areas where AB resistance is weak
Bid	Clarithromycin 500 mg bid	Amoxicillin 1 g bid	Metronidazole 1 g bid	1st line treatment
Bid	Metronidazole 500 mg bid	Tetracycline 500 mg qid	Bismuth 2 co qid	
Bid	Amoxicillin 1 g bid	Levofloxacin 250 mg bid	–	2nd line treatment
Bid	Amoxicillin 1 g bid	Rifabutin 150 mg bid	–	3rd line treatment

Duration of treatment suggested = 14 days. Recommendations from Toronto consensus (Gastroenterology, 2016). IPP: usual dose bid (omeprazole 20 mg, esomeprazole 20, lansoprazole 30, pantoprazole 40). Bismuth in Canada: PeptoBismol® 262 mg/co

Table 2.7 *H. pylori* eradication: indications and benefits

Duodenal ulcer treatment (without NSAIDs)
Obvious benefit = cures the disease and its recurrences
Gastric ulcer treatment
Potential benefit but limited in practice by NSAIDs frequently involved in gastric ulcer
Prevention of NSAID ulcer and its complications
Eradication suggested but more effective against low-dose ASA (80 mg) than standard NSAIDs
Treatment of functional dyspepsia
Attempted but marginal chance of success (probably <10% of treated subjects)
Treatment of MALT lymphoma
Efficacy is evident in early cases, but this disease is very rare
Prevention of gastric adenocarcinoma
Logical therapeutic strategy supported by cohort studies; benefit for all? (possible to alter cancer risk if exposure for several years?)
Gastroesophageal reflux disease (GERD)
No indication; no benefit to be seen
Other indications: unexplained iron-deficiency anemia, idiopathic thrombocytopenic purpura (ITP)
Pathophysiological mechanism uncertain but therapeutic benefit documented

Table 2.8 NSAID/ASA ulcers: therapeutic strategies

General measures:
NSAIDs at the lowest possible dose
NSAIDs with the lowest possible toxicity
Consider "selective" COX-2 inhibitors (but cardiac risk of COX-2 inhibitors)
Ulcer prevention:
Indications for preventive treatment in patients with:
History of ulcers
Age >65 years old
Comorbidity (heart disease, kidney disease, etc.)
Concurrent Rx: steroids, anticoagulants, antiplatelet agents
Preventive treatments:
Eradicate Hp if positive
Drugs:
.PPI usual dose
.Misoprostol 0.2 mg–0.4 mg bid
Ulcer treatment:
Stop ASA-NSAIDs (if possible)
Ulcer without current treatment: PPI (usual dose)
Ulcer occurred under preventive treatment: double-dose PPI ± misoprostol?

Drug prevention of NSAID or ASA ulceration can be done with different medications. Anti-H2 drugs are weak hypo-secretors and seem to be ineffective in this context. Misoprostol, a prostaglandin analogue that inhibits acid secretion and enhances gastric mucosal protection, appears to have a protective effect; in a pivotal study of patients taking NSAIDs, gastric ulcers occurred in 16% of patients on placebo and 8% of patients on misoprostol 200 µg bid or 4% if qid, and the incidence of duodenal ulcer of 8% on placebo was reduced to 2.6% on misoprostol 200 µg bid and 1.4% if qid. PPIs are effective in preventing NSAID-associated ulcers. A typical study showed that after 6 months of NSAID use, peptic ulcers occurred in 16.5% of patients on placebo versus 3.6% on omeprazole 20 mg daily. There are no comparative studies between misoprostol or PPIs. In practice, PPIs are often preferred, in part because of their ease of administration (once daily) and their favorable side effects profile (frequent diarrhea with PGEs). PPIs (mainly omeprazole), however, through their action on cytochrome P450, may reduce the bioavailability of the antiplatelet drug clopidogrel; the use of a PPI other than omeprazole that is less likely to interact (e.g., dexlansoprazole, pantoprazole) is recommended. Other long-term disadvantages of PPIs (Table 2.9) should also be considered, although overall they are considered as safe medications for chronic long-term use.

3. ***Surgical treatment of peptic ulcer***: Before the advent of effective pharmacological treatments in the late 1970s, surgery was the standard treatment for peptic ulcer disease. The decrease in gastric HCl production of about 50% achieved by interrupting vagal stimulation (vagotomy) or by removing circulating gastrin (antrectomy) cured about 90% of DUs; more refractory cases, such as GU or major hypersecretory states, could benefit from an 80% reduction in HCl secretion when vagotomy was combined with antrectomy. However, surgical treatment also modifies gastric motor activity leading to significant, even disabling, aftereffects in about 10% of patients.

Table 2.9 PPIs: potential side effects

Drug interaction (cytochrome metabolism): omeprazole/warfarin, phenytoin, clopidogrel
Increased risk of enteric infections (related to hypochlorhydria): *Clostridium difficile* (RR2), *Salmonella* (RR3)
Increased risk of lung infection (related to hypochlorhydria): pneumonia (RR4), aspiration pneumonia
Reduced absorption of certain substances (potential risk; related to hypochlorhydria): calcium, iron, vitamin B12
Increased risk of osteoporotic fractures (uncertain risk; calcium-related?)
Diarrhea (rare; mechanism unknown; may be associated with microscopic colitis)
Hypomagnesemia (rare; mechanism unknown)

Complications of vagotomy (see below) are rare today given the now exceptional use of this surgical procedure, but they can occur following injury to the vagus nerves suffered during anti-reflux surgery, lung transplantation, etc.

Post-vagotomy gastroparesis: Section of the vagus nerves impairs fundic relaxation, gastric contractions, and pyloric relaxation. The reduction in peristaltic contractions prolongs gastric emptying of food, especially solids. Stomach drainage was facilitated by pyloroplasty (a surgical procedure to reduce the pyloric sphincter tone) or gastrojejunostomy (a bypass anatomy created by an anastomosis between the stomach and a proximal jejunal loop) and was performed systematically in all subjects operated upon for truncal vagotomy. Subsequent developments led to selective or highly selective vagotomy which, generally, denervated the gastric body while preserving pyloric and fundic relaxation to minimize the risk of post-vagotomy gastroparesis and its symptoms of early satiety, postprandial fullness, vomiting, and, in some patients, nutritional compromise.

Post-vagotomy dumping: Decreased fundic relaxation after vagotomy prevents the stomach from expanding to accommodate ingested food, and this, combined with the loss of the pyloric brake after pyloroplasty or gastrojejunostomy, can lead to excessively rapid, uncontrolled delivery of gastric contents, especially liquids, to the small intestine causing dumping syndrome.

Early dumping occurs within the first hour after eating (Fig. 2.16). It is due to the premature arrival of unprepared, hyperosmolar chyme in the small intestine. This leads to a rapid increase in water secretion by the small intestine and a commensurate decrease in intravascular volume. As a result, the patient may experience abdominal pain or discomfort (caused by distension of the small intestine and a reflex transit acceleration) with or without symptoms of hypotension (caused by a reduction in intravascular volume by displacement of intravascular water into the intestinal lumen), including generalized weakness, hot flashes, and syncope. Early dumping will generally respond to an anti-dumping diet with small meals and avoidance of concentrated, hyperosmolar sugar solutions.

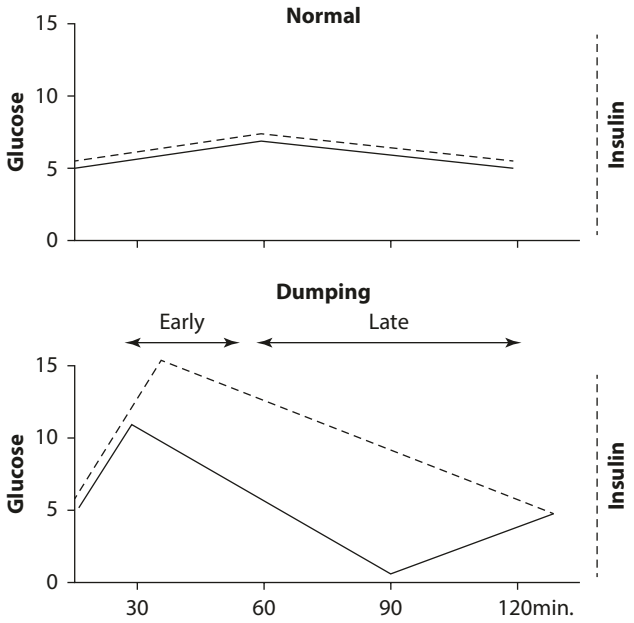


Fig. 2.16 Early dumping (30–60 mm PC) is due to the rapid delivery of hyperosmolar sugars into the duodenum, resulting in transfer of water from the circulation into the intestine, with secondary circulatory hypovolemia and hypotension. Late dumping (60–120 mm PC) is due to an imbalance in the blood sugar/insulin ratio; rapid emptying of carbohydrates from the stomach into the intestine generates a rapid increase in blood glucose and an inappropriate increase in incretins (GLP-1, GIP) leading to an exaggerated insulin secretion (dotted red line) and secondary hypoglycemia (blood sugar: solid green line)

Late dumping occurs about 2 hours after eating (Fig. 2.16) due to the rapid arrival of large sugar load in the small intestine. This leads to rapid, massive sugar absorption and a rapid rise in blood glucose levels, followed promptly by the release of insulin to control the hyperglycemia; however, the insulin response may be too important and poorly synchronized causing symptomatic hypoglycemia with weakness, sweating, convulsions, and, even, loss of consciousness. If late dumping does not respond to an anti-dumping diet, it may respond to treatment with a somatostatin analogue (octreotide) to slow gastric emptying and inhibit insulin secretion either directly (by action on the islet cells) or indirectly (by

slowing gastric emptying and, thereby, reducing the intestinal stimulus to insulin secretion).

Post-vagotomy diarrhea observed in some patients after truncal vagotomy is most often due to accelerated intestinal transit caused by hyperosmolar intraluminal contents. It can be controlled by an anti-dumping diet and/or by intestinal transit modulators (opiates, loperamide).

Nowadays, surgery is very exceptionally used for the control of peptic ulcer disease. Its role is limited to the management of ulcer complications by ligating hemorrhagic vessels or suturing a perforated ulcer. Vagotomy is now an exceptional procedure, but its complications are observable after vagus nerve injury occurring mainly during surgery involving the esophagus.

2.6.2 Gastritis and Gastropathies

Strictly, the term "gastritis" refers to the histological finding of an inflammatory gastric infiltrate (e.g., lymphocytes, neutrophils, eosinophils), but, in practice, it is often used by patients and physicians to describe digestive symptoms that are attributed to the stomach. Histologically, gastric mucosal injury caused by irritants, such as bile, alcohol, or NSAIDs, is not inflammatory but, rather, a reactive chemical gastropathy (often characterized by foveolar hyperplasia and loss of surface mucus-containing cells). Gastritis, in its broadest sense, has multiple causes (Table 2.10).

(a) **Infectious gastritis**. Acute food poisoning with organisms such as *Staphylococcus*, *Bacillus cereus*, *Clostridium perfringens*, etc. usually presents with vomiting a few hours after ingestion of the infected food (e.g., buffet with food kept at the wrong temperature, oysters and other molluscs which filter and concentrate toxic bacteria, etc.). Viral infections (e.g., rotavirus) often lead to gastric disorders with vomiting, which spontaneously improve after a few hours. The most well-known infectious gastritis is the chronic active antral gastritis caused by *H. pylori*.

(b) **Inflammatory gastritis**. Inflammatory gastritis is usually confirmed by histology, which may reveal granulomas, lymphocytes, or eosinophils infiltrates; these conditions are rare but specific.

Reactive, chemical gastropathy: Irritation of the stomach by NSAIDs, alcohol, or bile (usually due to postsurgical duodenogastric reflux) is frequently blamed for dyspeptic symptoms. However, the relationship between symptoms and the findings at endoscopy and histology remains unclear.

Gastropathies are frequently encountered in liver disease. Portal hypertension gastropathy, which mainly affects the corpus and fundus regions, as well as GAVE (gastric antral vascular ectasia) lesions, does not usually produce GI symptoms, but rather present with symptoms of chronic blood loss and iron-deficiency anemia.

(c) **Atrophic gastritis and gastric atrophy (with pernicious anemia)**. Atrophy of the gastric mucosa is characterized by the loss of parietal cells and secondary achlorhydria.

Type A gastritis affects the gastric body and is an autoimmune condition with antibodies against parietal cells, often in association with other autoimmune conditions such as hypothyroidism or vitiligo. Type B gastritis is due to an *H. pylori* infection that extends from the antrum to the proximal stomach.

Table 2.10 Gastritis and gastropathies

(a) Infectious diseases
Virus (CMV, rotavirus, etc.)
Bacteria (the best known is *H. pylori*; phlegmonous or emphysematous gastritis due to *Staphylococcus* or *Escherichia coli* is serious but rare)
Parasite: rare
(b) "Chemical" or "irritant" products
Ethanol, NSAIDs, ASA
Bile (post-surgery)
(c) Inflammatory
Granulomatous (tuberculosis, syphilis, Crohn's, sarcoidosis)
Lymphocytic: rare and associated with celiac disease
Eosinophilic: with eosinophilic enteritis
(d) Related to portal hypertension and liver disease
Portal hypertensive gastropathy (affecting body and fundus)
Gastric antral vascular ectasia (GAVE)
(e) Atrophic
Type A: autoimmune
Type B: secondary to *H. pylori*

Clinical: Atrophic gastritis does not, usually, cause GI symptoms, but is well known for its hematological and neurological consequences. The absence of parietal cells leads to the loss of the intrinsic factor necessary for vitamin B12 absorption and to megaloblastic pernicious anemia that can also be accompanied by peripheral or central neurological dysfunctions. The absence of acid secretion seems to have surprisingly little clinical impact on nutrient digestion or absorption; however, it is probably responsible for some iron-deficiency anemias by compromising the digestion of heme proteins into ferrous iron (Fe++) to be absorbed. Decreased gastric acid also appears to impair the defense function of the stomach and predispose to enteric or pulmonary infections, as it has been reported for PPIs (e.g., *Salmonella* (RR, 3); *Clostridium difficile* (RR, 2); pneumonia (RR, 4)).

Diagnosis: The diagnosis of gastric atrophy can be confirmed by documenting that gastric secretions have a neutral pH. Endoscopy may reveal a transparent atrophic mucosa and at biopsies the parietal cells will be absent. The Schilling test, which measures the urinary excretion of absorbed vitamin B12, has limited reliability and is now rarely performed. Marked hypergastrinemia (more than 1000 μg/L) can occur in response to achlorhydria (in absence of acid, G cells are continuously active since never inhibited by somatostatin). Circulating antibodies against parietal cells or intrinsic factor can be detected.

Treatment: IM or SC injection of vitamin B12 (1 mg q 1–3 months) or oral intake (1 mg/day) corrects the B12 vitamin deficiency. Per oral iron supplements can correct iron deficiency.

Complications of gastric atrophy: Gastric achlorhydria is associated with an increased risk of neoplasia. Progression to adenocarcinoma is probably related to *H. pylori* infection. Hyperplasia of endocrine ECL-type cells, in response to the persistent stimulation by reflex hypergastrinemia (due to absence of acid as discussed previously), may lead to carcinoid tumors (most often benign). Despite the risk for gastric neoplasia, the cost-effectiveness of endoscopic surveillance for patients with gastric atrophy remains uncertain.

2.7 Tumor Disorders

2.7.1 Adenocarcinoma

(a) **Incidence**. Gastric adenocarcinoma is the most common neoplasia of the stomach and accounts for 10% of all cancers in general. It is much more prevalent in Asian countries than in Africa or the West; in the United States, it is seen twice as often in black, Spanish-speaking, or native communities than in Caucasians.

Gastric adenocarcinoma occurs commonly in the 7th decade; it is twice as common in men as in women and is more prevalent in economically disadvantaged areas. The incidence of cancers of the distal part of the stomach is declining worldwide, while there is an increase in proximal (cardia and fundus) cancers.

(b) **Etiology of gastric adenocarcinoma**. Various factors have been proposed:

- Dietary factors have been suggested in many retrospective studies: salted, smoked, and poorly preserved foods, as well as tobacco, have been incriminated, and a protective role for fresh fruits and vegetables was advocated. Nitrites, widely used for food preservation, are considered to be gastric carcinogens; it has been suggested that the replacement of nitrite preservatives by refrigerated and frozen foods may account for the worldwide decrease in the incidence of gastric adenocarcinoma.
- *H. pylori* is considered a carcinogen based on animal studies, on the increased risk (RR 1.9) of developing gastric adenocarcinoma in *H. pylori*-infected individuals, and the finding of *H. pylori* in 71–95% of gastric cancer cases. According to the Correa hypothesis, gastric carcinogenesis is a cascade evolving from normal gastric mucosa to superficial gastritis (induced by *H. pylori* infection), atrophic gastritis, intestinal metaplasia, dysplasia, and finally cancer. On this basis, *H. pylori* eradication should be carried out in all infected subjects; the positive impact of its eradication on carcinogenesis is now supported by several cohort studies.

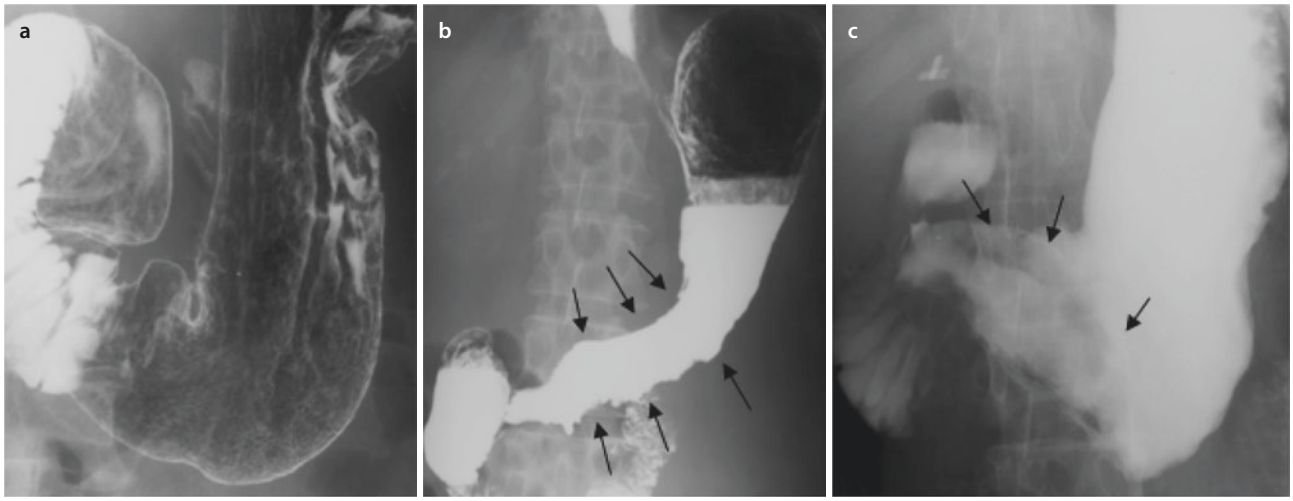
In Africa, the apparently low prevalence of gastric cancer compared to the very high prevalence of *H. pylori* infection remains an enigma (but this apparent discrepancy may be no more than an epidemiological artifact).

- The decreased gastric acidity, observed in patients who have atrophic *H. pylori* gastritis, autoimmune atrophic gastritis, or gastric resection (e.g., Billroth II gastrojejunostomy), is thought to facilitate the transformation of dietary nitrates into carcinogenic nitrites, thereby leading to an increased risk of neoplasia.
- Genetic factors are, also, important in some cases. The risk of gastric cancer is about two to three times higher in first-degree relatives of a gastric cancer patient than in the general population. Although this may reflect familial exposure to environmental factors such as *H. pylori*, abnormalities of the E-cadherin CDH1 gene, a suppressor gene for gastric carcinogenesis, have

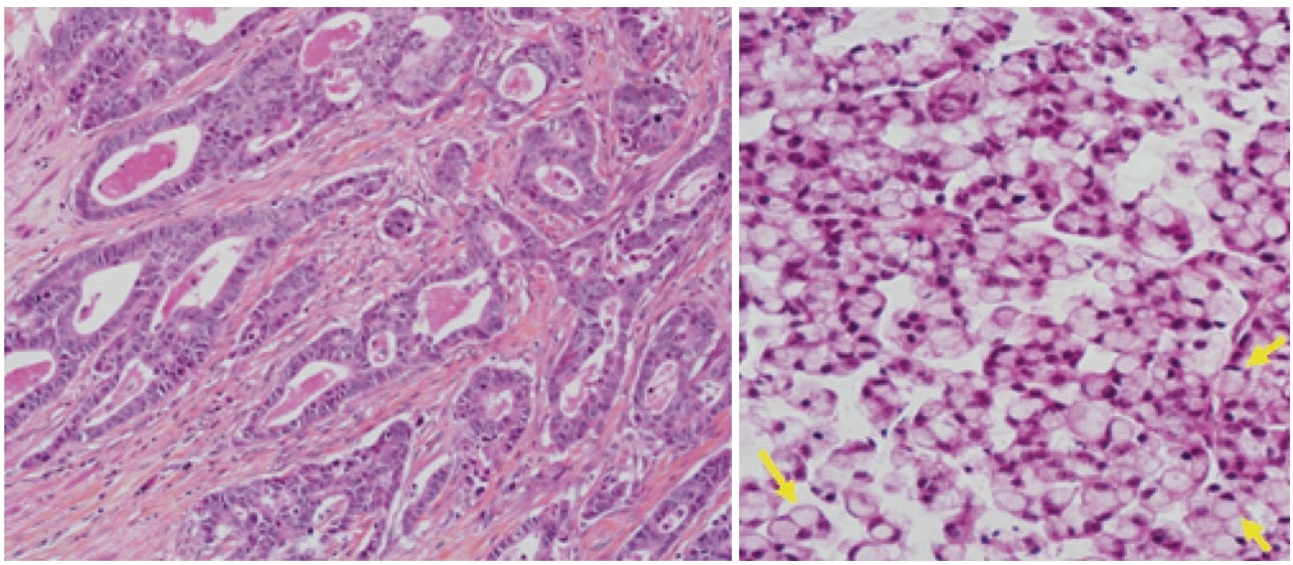
been identified in some families that have an exceptionally high frequency of gastric adenocarcinoma.

(c) **Macroscopic pathology**. Adenocarcinoma represents 90% of all gastric cancers. It occurs in the proximal, middle, and distal third of the stomach in 32%, 17%, and 39% of cases, respectively. It may present as a polypoid endoluminal mass, as an ulcerated crater (hence the importance of biopsy for all gastric ulcerations), or as a submucosal infiltrate typical of a "leather bottle stomach" with rigid gastric walls (radiological aspects are shown in ◘ Fig. 2.17).

(d) **Microscopic pathology of gastric adenocarcinoma**. Two main types of epithelial tumor are recognized in the WHO classification: the tubular-/papillary-type carcinoma (formerly called intestinal-type carcinoma in Lauren classification) forming glandular structures (◘ Fig. 2.18a) and the poorly cohesive carcinoma (formerly called diffuse-type carcinoma) without glandular formation and sometimes showing signet-ring cells containing abundant mucus (◘ Fig. 2.18b). The poorly cohesive cell-type adenocarcinoma seems to have a poorer prognosis.



◘ **Fig. 2.17** Barium meal X-ray images to visualize **a** a normal stomach and to recognize the different forms of gastric neoplasia: **b** a narrowed, non-distensible, infiltrating adenocarcinoma (leather bottle stomach) of the antrum; **c** an ulcerated crater positioned in a tumoral mass of the antrum. (Photos from R. Déry)



◘ **Fig. 2.18** Left figure: adenocarcinoma (tubular type) of the stomach. Right figure: gastric adenocarcinoma of poorly cohesive type with signet-ring cells (arrows in the figure); the nucleus is pushed at the periphery of the cell by mucus mimicking a ring appearance. (Photos by G. Soucy)

(e) **Clinical aspects**. Gastric adenocarcinoma may manifest with epigastric discomfort or pain (often increased by meals), nausea, vomiting, weight loss, and anemia (due to blood loss). However, the clinical symptoms are usually late, and the cancer is often unfortunately well-advanced when it is diagnosed. On examination, a mass may be palpable if the tumor is large or if there is invasion of the omentum or adjacent organs. Lymphatic spread most often involves the abdominal lymph nodes (celiac, etc.) or may result in metastases to the left supraclavicular fossa (Troisier's or Virchow's lymph node), the periumbilical region (Sister Mary Joseph's nodule), the ovary (Krukenberg's tumor), or the pouch of Douglas (Blumer's shelf). Hematogenous metastases can reach the liver, lung, bones, brain, etc.

Diagnosis Gastric cancer is confirmed by endoscopy and biopsy. The neoplastic lesion may present as an ulcerated mucosal lesion with obvious proliferative features (located on an infiltrating mass, having irregular and hard edges, etc.), but it may resemble a benign gastric ulcer (hence the need to biopsy all gastric ulcers)and present as a submucosal diffuse infiltrate (leather bottle stomach in radiology; see ◘ Fig. 2.17) that can be difficult to recognize before it spreads over a large area. Tumor spread is evaluated most often by CT scan or endoscopic ultrasound (EUS), having high specificity but suboptimal sensitivity.

Treatment of Gastric Cancer Surgical resection of the tumor remains the treatment of choice, but in practice it is often not feasible because the disease is too advanced. In Japan, the high prevalence of gastric cancer has prompted the implementation of screening methods to allow early detection of tumors and curative surgical treatment. In the West, less than 50% of patients are diagnosed at a stage that is early enough to allow curative surgical resection. Survival at 5 years is about 50% in the absence of regional nodal spread at the time of surgery, but it decreases to 25% in the presence of such metastatic nodes.

Distal gastric tumors may be amenable to more limited surgery (subtotal gastrectomy), sparing the proximal part of the stomach. Infiltrative cancers, however, have a worse prognosis. Proximal tumors seem to have a poorer prognosis than distal tumors and often require very extensive surgery such as total gastrectomy.

Pre- or postoperative chemotherapy can be beneficial. It is now considered in many patients.

Approximately 20% of gastric cancers, especially those of the tubulo-papillary type, will possess, like breast cancer, receptors for epidermal growth factor (HER2 identified in histopathology) and may respond to therapy with a monoclonal antibody against this receptor (e.g., trastuzumab).

With recent developments in targeted therapies for cancers, a new molecular classification of gastric cancers was proposed. Gastric carcinoma with microsatellite instability that results from impaired DNA mismatch repair (see ▶ Chap. 25) is an important subtype since it may benefit from immunotherapy (designed to enhance the patient's immune system which then can more effectively recognize, target, and eliminate cancer cells).

2.7.2 Lymphoma

Gastric lymphoma accounts for 5% of gastric neoplasia. The clinical and endoscopic presentations are similar to those of the adenocarcinoma, and biopsies will confirm the diagnosis. The majority of gastric lymphomas originate from B cells.

- *Nodal lymphoma:* Occasionally, lymphomas may originate from lymphatic nodes and spread to various organs, including the bone marrow, stomach, etc.
- *Extra-nodal lymphoma*: Most often, gastric lymphomas are of non-nodal origin, arising, instead, from the lymphoid tissue of the mucosa; they are called MALT (mucosa-associated lymphoid tissue) lymphoma. These lymphomas are probably the result of clonal B cell proliferation during chronic *H. pylori* gastritis.

Limited and early stages of MALT lymphomas may respond to *H. pylori* eradication. The majority of lymphomas will be treated with chemotherapy, and surgical resection is now limited to special cases.

2.7.3 Neuroendocrine Tumors (NET)

Most commonly, NET of the stomach represent polypoid proliferation of endocrine ECL cells ("ECLome" or carcinoid) in response to hypergastrinemia. ECL cells (enterochromaffin-like cells) normally secrete histamine to act on the parietal cell and are stimulated by gastrin; severe and prolonged hypergastrinemia can cause hyperplasia and lead to tumor development. Hypergastrinemia may be secondary to the achlorhydria caused by gastric atrophy (type I gastric carcinoid) or, less often, to the tumoral production of gastrin by a gastrinoma (type II gastric carcinoid seen in Zollinger-Ellison tumor). These ECL cell tumors are often multiple and have low malignant potential. Type III gastric carcinoid is rarer and represents malignant proliferation of enterochromaffin (EC) cells (rather than ECL cells; but EC and ECL cells cannot be differentiated on normal histology). These

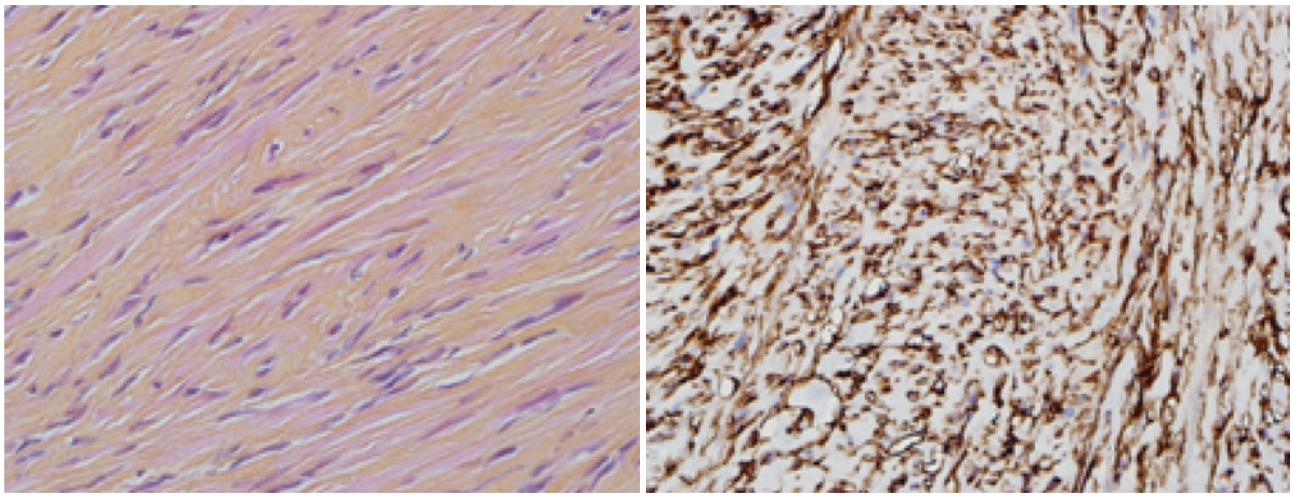


Fig. 2.19 Stromal tumor; histochemical analysis (photo on the right) reveals the CD117 antigen (brownish coloration). (Photos by G. Soucy)

tumors may be invasive and metastatic and may lead to carcinoid syndrome, etc. (see ▶ Chap. 3).

2.7.4 Stromal Tumors

Stromal tumors, or GIST (gastrointestinal stromal tumor), are mesenchymal tumors with muscular or neuronal-like features (Fig. 2.19). These tumors are rare (less than 1% of gastric tumors) and in 70% of cases are localized to the stomach. Previously designated as leiomyomas, leiomyosarcomas, neurofibromas, schwannomas, etc., these tumors are now known to arise from interstitial cells of Cajal (ICC), mesenchymal cells located between the muscle layers of the gastric wall to act as a pacemaker in the electrophysiology of muscle contraction. Tumor differentiation will lead to the muscular or neurological appearance of these cells, initially of mesenchymal origin.

These submucosal tumors are slow-growing and provoke few symptoms before reaching a large volume. Their malignant potential is often difficult to establish, and their treatment was typically obtained by surgical excision (although limited by their infiltrative nature) before our basic knowledge of cell biology led to a new therapeutic option of targeted chemotherapy.

Cajal's cells are indeed recognizable histochemically by their ability to express the CD117 antigen, which is part of the Kit membrane receptor, a tyrosine kinase receptor involved in trophic responses. GISTs arise from mutations in the Kit protein that increase tyrosine kinase activity and tumor cell growth. Tyrosine kinase inhibitors (such as imatinib) are able to block this inappropriate trophic response and to inhibit tumor growth and metastases. This targeted chemotherapy has revolutionized the treatment of GISTs.

2.7.5 Polyps

Polypoid lesions may be discovered during endoscopic or radiological examinations.

Fundic gland polyps are the most common polypoid lesions found endoscopically. They are made of hyperplastic fundic glands located exclusively in the secretory portion of the stomach. They are most often associated with PPI therapy. They can disappear spontaneously and have no significant malignant potential.

Adenomatous polyps make up 10% of gastric polyps. Their risk of malignant transformation is proportional to their size and will justify their excision (usually endoscopic).

Hyperplastic or regenerative polyps are often associated with *H. pylori* gastritis, and their potential for malignant transformation is rare.

Other polypoid lesions can be seen at endoscopy. They are usually submucosal: the lipoma, often yellowish in appearance, is of no clinical significance; the ectopic pancreas, recognizable by its umbilicated appearance (pancreatic duct), is usually found in the prepyloric region and is asymptomatic; stromal tumors (GIST) were discussed above.

2.8 Function Disorders

2.8.1 Motor Disorders

2.8.1.1 Hypomotility/Gastroparesis

1. ***Etiology:*** Decreased contractions of the stomach will delay gastric emptying of food. Various conditions (Table 2.11) which affect gastric musculature or its innervation can lead to impaired motility and delayed gastric emptying that may present, clinically, as gastroparesis.
   The most common conditions include:
   - Post-vagotomy gastroparesis: The physiological role of the vagus nerve to gastric emptying is evident from the decrease in gastric contractile activity and the increase in pyloric tone that occur almost systematically when the vagus nerves are severed (until 1980, truncal vagotomy was the treatment of choice for acid peptic ulcer disease) or traumatized (e.g., during lung surgery, antireflux surgery, etc.). To overcome this condition, surgeons had learned to combine vagotomy with a drainage procedure, such as a pyloroplasty or gastrojejunostomy, to avoid the physical obstacle and facilitate gastric evacuation of food. However, despite these ancillary drainage maneuvers, some individuals may still have incapacitating post-vagotomy gastroparesis.
   - Diabetic gastroparesis: Long-standing, poorly controlled diabetes mellitus can be complicated by microvascular injury to peripheral or central nerves. Subjects suffering from diabetic gastroparesis, arising from injury to the vagus nerve or interstitial cells of Cajal, usually suffer from other autonomic neuropathies leading to orthostatic hypotension and erectile dysfunction. In addition, hyperglycemia has a direct effect on gastric motor function leading to markedly delayed gastric emptying when blood glucose concentrations exceed 12 mmol/L. Good blood sugar control is, therefore, key to the short- and long-term maintenance of normal gastric motor function.
   - Muscular gastroparesis: The gastric musculature can be affected by "infiltrative" systemic disorders such as scleroderma (usually involving other organs such as the esophagus) or amyloidosis (often with renal damage) or be affected by hereditary myopathies (usually in a context of chronic intestinal pseudo-obstruction).
   - Drug-induced gastroparesis: Anticholinergic and opioid drugs are most commonly involved.
   - Idiopathic gastroparesis: In practice, in almost 50% of cases, no cause can be identified to explain this condition. Some of these patients seem to present psychogenic disorders (depression, anxiety, etc.), suggesting that central mechanisms may play a role here.
2. ***Clinical manifestations of gastroparesis:*** As the stomach does not empty properly, patients may experience postprandial symptoms such as early satiety preventing them from eating a normal meal, exaggerated post-meal fullness, nausea, vomiting, weight loss, or, in more severe cases, denutrition.
3. ***Diagnosis of gastroparesis***: Nuclear medicine scintigraphy, using radio-labelled food markers, is the standard technique for evaluating gastric emptying (see Fig. 2.9). The subject ingests a test meal consisting of solid foods (liver or eggs) labelled with technetium-99 and liquids labelled with indium-111. Using an external camera periodically positioned on the subject's abdomen, the radioactive counts emitted by labelled food in the gastric area are measured over 2–4 h to calculate the rate of disappearance of radioactive counts from the stomach (gastric emptying rate).

   Gastric emptying can also be estimated by breath tests or radiological markers.

Table 2.11 Gastroparesis: causes

A. Muscle causes
Scleroderma
Myopathic chronic intestinal pseudo-obstruction (often familial)
B. Neurological causes
Post-vagotomy
Diabetes
Various neurological pathologies (Parkinson's disease, multiple sclerosis, amyloidosis, etc.)
Cerebral hypertension or tumor
Neurogenic chronic intestinal pseudo-obstruction
C. Drug causes
Opiates
Anticholinergics
D. Metabolic causes
Increase or decrease in serum calcium, magnesium, or potassium levels
Blood glucose greater than 12 mmol/L
E. Idiopathic gastroparesis

4. ***Treatment of gastroparesis.***
   (a) General measures can be used to reduce the work of the stomach:
   - A "gastroparesis diet" comprises foods that are easy for the stomach to "digest"; patients are advised to take smaller, more frequent meals that consist of liquids or semisolid foods that are soft and low in fiber and fat contents to reduce the symptoms of gastroparesis;
   - PPIs can reduce the volume of gastric secretions by about 50%, thereby reducing the gastric load.

   (b) To stimulate gastric contractility, various pharmacological treatments can be used:
   - Cholinergic: Cholinergic receptor agonists (such as Urecholine) or cholinesterase inhibitors (e.g., neostigmine IV, or SC, or po) would be logical candidates, but they are not widely used clinically.
   - Antidopaminergics: Metoclopramide 5–10 mg (po, SC, IV) 30 min before meals or domperidone 10 mg po 30 min before meals is the usual strategy.
   - Motilin receptor agonists: The antibiotic erythromycin 1–3 mg/kg po or IV is used here; but these agents are often subject to tachyphylaxis which limits their long-term benefit.
   - 5-HT4 receptor agonists: Cisapride and tegaserod were effective drugs but have been withdrawn from the market in many countries. Prucalopride can be tried.

   (c) Antinauseants (dimenhydrinate, 5-HT3 antagonist ondansetron or granisetron, NK-1 antagonist aprepitant) are used to relieve nausea (often an incapacitating symptom).

2.8.1.2 Hypermotility Disorders

Dumping syndrome: Rapid gastric emptying or "dumping," described earlier, is attributed to hypercontractility or impaired relaxation of the fundus. Accelerated gastric emptying is a complication of surgical vagotomy, but it can occur also in the early stages of diabetes gastropathy (probable vagal involvement).

Accommodation disorder: Impaired fundic relaxation is also implicated in functional dyspepsia (see below). This pathology could therefore, in some individuals, be considered as a form of hypermotility disorder.

2.8.2 Sensory Disorders/Functional Dyspepsia

Gastric hypersensitivity has been recognized since the end of the twentieth century for its involvement in functional dyspepsia (FD, also called non-ulcer dyspepsia, nonorganic dyspepsia, Moynihan syndrome, etc.).

(a) **Definition of FD**. Functional dyspepsia is recognized by chronic pain or discomfort (i.e., >3 months) that is attributed to the stomach and manifests itself in the absence of structural abnormalities that can be identified by standard tests such as X-rays, gastroscopy, biopsies, etc. There are two main forms of this disorder:
- Functional dyspepsia of the ulcer type [epigastric pain syndrome (EPS) according to the Rome IV classification], characterized by ulcer-like symptoms (i.e., burning, cramping epigastric pain that is diminished or increased by meals), in the absence of an identifiable peptic ulcer or other lesion on investigation
- Functional dyspepsia of the motor type [postprandial distress syndrome (PDS) according to Rome IV; see ▶ Chap. 4] characterized by early satiety, belching, postprandial eructation, postprandial fullness, slow digestion, or nausea in the absence of obvious abnormalities affecting, among other things, the rate of gastric emptying

Functional dyspepsia is present in men or women (prevalence of 7.2% or 8.7%, respectively) and is more frequent in young subjects (prevalence of 9.2%, 6.6%, and 3.8%, respectively, in subjects 18–39, 40–64, and >65 years).

(b) **Pathophysiology of FD**. Symptoms of motor-type functional dyspepsia often suggest a diagnosis of gastroparesis. However, slow gastric emptying is found in only 20–30% of such patients (and these patients may therefore be characterized as having idiopathic gastroparesis). In the remaining subjects, gastric distension studies, most often using expandable balloons positioned in the proximal stomach and simulating gastric distension with a meal, indicate that the symptoms are due to distension intolerance. This inability to normally tolerate gastric distension appears to be due to (1) visceral hypersensitivity (35% of patients) and/or (2) impaired fundic relaxation (hypermotility mentioned above; present in 45% of cases).

Visceral hypersensitivity remains of unknown etiology. Normal sensory perception mechanisms may be disrupted at various stages: (a) at the peripheral level, sensitization of the visceral organ itself would lead sensory sympathetic fibers to transmit enhanced pain signals to centers of conscious perception in the CNS; or (b) visceral signals that were normal at origin could be amplified when peripheral sympathetic afferents synapse with the spinal cord ascending nerves; or (c) the normal afferent signal could be amplified at the level of the central nervous

system where sensations or pains are integrated and perceived; or (d) a central suppression of the normal compensatory downward inhibition of a normal afferent signal could lead to visceral hypersensitivity. Extensive discussion on gut hypersensitivity mechanisms can be found in ▶ Chap. 4 in the section on irritable bowel syndrome.

Acid hypersensitivity, especially in the duodenum, has also been documented and may probably explain ulcer-like functional dyspepsia and the symptomatic benefit of PPI therapy to reduce gastric acid secretion in 50% of these patients.

H. pylori gastritis has been suspected as a causal factor for functional dyspepsia. However, this hypothesis appears marginal since eradication therapy provides benefit in only about 10% of patients.

Duodenal inflammation has recently been suggested as a causal factor for functional dyspepsia.

(c) **Diagnosis of FD**. The diagnosis of functional dyspepsia is based on the clinical history of chronic symptoms attributable to the stomach, usually without impairment of general condition, and often aggravated by stress, fatigue, etc. in a patient with normal physical and biological examinations.

Not everyone needs further investigation (see ▶ Chap. 12).

- Exclusion of lesional abnormalities will be necessary if the patient has alarm features: (a) new or recent onset symptoms, (b) age over 50 years, (c) impaired general health, and (d) abnormalities on physical or laboratory examinations.
- Esophago-gastroduodenoscopy is the most commonly performed test. The exclusion of ulcers in cases of ulcer-type dyspepsia is a determining factor. In patients with symptoms suspected of a gastroduodenal origin, endoscopy is positive in only 30% of cases.
- Abdominal ultrasound, Doppler ultrasound, and axial tomography of the abdomen may be required in some cases to exclude pancreatic (e.g., chronic pancreatitis, neoplasm, etc.), vascular (e.g., mesenteric angina), or other pathologies.
- Motor dysfunction tests (gastric emptying study) or sensory tests (balloon distension test) are usually reserved for a more specialized investigation.

(d) **Treatment of FD**. Functional dyspepsia is a common condition that leads many patients to self-treatment through dietary modifications (reduction of offending foods, reduction of fat, etc.) or self-medication (over-the-counter antacids, natural products, etc.). Therapeutic options are presented in ● Table 2.12.

Table 2.12 Functional dyspepsia: therapeutic options

(A) General measures: avoid offensive foods or precipitating factors (stress, fatigue, etc.)
(B) Eradicate *H. pylori* if + (chance of success: 10% of treated subjects)
(C) If symptoms of delayed gastric emptying: prokinetics (anti-D2: domperidone 10 mg ac po, metoclopramide 5–10 mg ac po)
(D) Reduce acid secretion with PPI
Effective in 50% of patients (mostly ulcer-like dyspepsia)
Due to ↓ of aggressive factor (acid or secreted volume)
(E) Improve fundus relaxation
Anticholinergic (dicyclomine, etc.)
5-HT1 agonists (buspirone, mirtazapine)
(F) Visceral analgesics
Tricyclic (amitriptyline, desipramine, imipramine)
SSRIs (citalopram, venlafaxine, etc.)
(G) Psychogenic treatment (essential if psychogenic condition)
Psychotherapy
Psychotropic drugs (SSRIs, etc.)

Pharmacotherapy: Reduction of gastric secretion with PPIs appears to be effective in about 50% of patients with functional dyspepsia, especially those with ulcer-like dyspepsia (EPS).

Pharmacological modulation of fundic relaxation (e.g., by anticholinergics) or of visceral sensitivity (e.g., by amitriptyline 10–30 mg in HS) is a logical strategy considering the previously discussed pathophysiological concepts (specially in relation to PDS). Buspirone (5-HT1 agonist) and mirtazapine have, also, been reported to provide symptomatic benefit in some cases.

Psychotherapy: As with most functional diagnoses, psychogenic conditions or stress may be aggravating factors in many patients. Various psychotherapeutic strategies have been shown to relieve the discomfort of functional dyspepsia. Pharmacological agents such as serotonin reuptake inhibitors (e.g., fluoxetine, citalopram, paroxetine at standard doses such as 20 mg die, etc.) may be beneficial in some subjects.

2.8.3 Cyclic Vomiting Syndrome

Cyclic vomiting syndrome (CVS) is characterized by acute episodes of vomiting that last from a few hours to a few days and recur every few weeks or months. The usual causes of nausea (see ► Chap. 10) must of course be eliminated. Both migraine (about 25% of those suspected of CVS) and cannabis abuse (probably 50% of cases) are still to be considered. CVS is of unknown etiology, and its treatment remains uncoded and symptomatic.

2.8.4 Aerophagia/Belching/Excessive Belching Syndrome

Aerophagia – swallowing air – is a normal phenomenon. It is estimated that for every sip of liquid swallowed, 15–30 cc of air is swallowed. Eructation is a central reflex triggered by gaseous distension of the fundus, leading to relaxation of the lower esophageal sphincter and release of gas from the stomach. It is most often unconscious and can occur three to four times per hour. Burps, or belches, may, also, be a sign of gastro-esophageal reflux or functional dyspepsia.

Excessive belching may become bothersome and, as such, it may be considered pathological. In the vast majority of cases, it is not gastric eructation involving gastric air, but rather supragastric eructation where air is ingested into the esophagus and immediately expelled by diaphragmatic contraction. It is a voluntary, often unconscious, action, related to a behavioral disorder. Behavioral therapies are therefore indicated.

2.8.5 Rumination Syndrome

Rumination (or merycism) – the repeated return of ingested food into the mouth – is physiological and necessary for digestion in multi-gastric animals such as sheep or cattle, but it is abnormal in humans where it is induced voluntarily. Rumination differs from regurgitation, which refers to spontaneous involuntary return of ingested food in the mouth without accompanying abdominal contractions. Rumination also differs from vomiting which refers to the forced oral expulsion of gastric (or even intestinal) contents by retroperistaltic digestive contractions aided by abdominal and/or thoracic muscle contractions.

Rumination is triggered by relaxation of the lower esophageal sphincter associated with fundic contraction. Rumination is achieved effortlessly; although it is voluntary, it is usually an unconscious act which, like excessive belching syndrome, is related to a behavioral disorder.

2.9 Miscellaneous

2.9.1 Gastrinoma (Zollinger-Ellison Syndrome)

Gastrinoma is a neuroendocrine tumor (NET) arising from ectopic gastrin-secreting cells (G cells) that leads to gastric acid hypersecretion, severe peptic ulceration, and diarrhea known as Zollinger-Ellison syndrome (ZES).

■■ Pathology

Most gastrinomas arise in the pancreas or duodenum; in 80% of cases, they are sporadic, and, in 20% of cases, they are due to multiple endocrine neoplasia type I (MEN-1) syndrome, an autosomal dominant inherited disorder that is, also, associated with parathyroid tumors causing hyperparathyroidism and pituitary tumors causing hyperprolactinemia. Gastrinomas are usually malignant tumors, but they are often indolent, progressing very slowly over periods of more than 10 years.

■■ Clinical

Hypergastrinemia causes clinical manifestations which were first attributed to gastrin secreting tumors by two surgeons, R.M. Zollinger and E.H. Ellison, after whom the syndrome was named:

(a) Severe acid peptic disease: Hypergastrinemia leads to excessive stimulation of the parietal cells with major hypersecretion of HCl resulting in an exceptional and severe peptic ulcer disease with peptic ulcerations often located in atypical areas such as the distal duodenum or even the jejunum (unable to resist to a high acid load), prone to complications such as perforation or hemorrhage, and resistant to standard acid suppression treatments.

(b) Diarrhea is a classic of the Zollinger-Ellison syndrome (ZES). It resolves if gastric acid hypersecretion is controlled; the following three physiopathological mechanisms are retained:

- Secretory diarrhea: The increased volume of gastric secretion (10 L per day rather than the usual 1–2 L) poured into the duodenum overwhelms the absorptive capacity of the small and large intestines.
- Malabsorption: The large quantity of acid secreted by the stomach cannot be entirely neutralized by alkaline secretions from the duodenal and pancreas, leading to post-bulbar peptic ulcerations (as discussed above), but also to intestinal villi injury (similar in some cases to villous atrophy of celiac disease; see ► Chap. 3), and, possibly, malabsorption of the nutrients to be assimilated.
- Maldigestion: In acidic duodenal pH, bile salts for micellar formation and pancreatic enzymes such as lipase are inactivated, causing fat maldigestion (see ► Chaps. 3 and ► 5).

Diagnosis of ZES

Direct measurement of gastric HCl secretion, usually by collecting these secretions through a nasogastric tube, confirms a very high basal acid secretion [typically greater than 10 mmol/h (for a normal 3–5 mmol/h) and up to 100 mmol/h].

Serum gastrin is very high. However, other factors may be responsible for hypergastrinemia as shown in Table 2.13. In physiological situation, gastric acid inhibits gastrin secretion by antral G cells, and any process resulting in decreased gastric acid secretion will result in hypergastrinemia, usually proportional to the hypoacidity. Normally, ingested food stimulates the secretion of antral G cells; any condition where nutrients are retained in the antrum (e.g., duodenal obstruction, etc.) may lead to hypergastrinemia.

A stimulation test with secretin may identify a gastrinoma; normally the injection of secretin (1–2 mg/kg IV) decreases gastrin serum levels, but in ZES it will cause a paradoxical increase in gastrinemia. However, the sensitivity and specificity of the secretin test are questionable.

Upper endoscopy may reveal prominent, enlarged gastric folds, resulting from the proliferation of parietal cells in response to sustained hypergastrinemia; ulcers are often post-bulbar, and esophagitis is frequent.

Endoscopic ultrasonography, labelled somatostatin scintigraphy, axial tomography, nuclear magnetic resonance, angiography, and ultrasound, will be used to locate the tumor and its metastatic extension

Table 2.13 Hypergastrinemia

Serum gastrin	Causes	Mechanisms	Clinic
Marked elevation			
(>1000 µmol)	Gastrinoma (ZES)	Tumor production of gastrin	Gastric acid secretion ↑↑
	Gastric atrophy	No suppression of gastrin by HCl	Gastric acid secretion = 0
Moderate elevation			
(200–500 µmol)	Digestive obstruction	Continuous G cell stimulation by food	Stomach filled with food/ distended
	Kidney failure	No gastrin excretion	Kidney failure
	Extensive bowel resection	No gastrin suppression (by somatostatin ?)	Post-op intestinal resection
Mild elevation			
(<200 µmol)	*H. pylori*	Hp inflammatory mediators ?	
	Anti-ulcer surgery	Low gastric acid	
	Antacid Rx (PPI)	Low gastric acid	

Treatment of ZES

Involves first controlling the effects of hypergastrinemia and, afterward, if possible, eliminating the source of hypergastrinemia.

(a) Control of acid secretion: PPI doses three to four times higher than normal are usually required, and patient compliance to drug administration is critical. Total gastrectomy, previously used to control exaggerated acid secretion, is now rarely necessary.

(b) Treatment of the tumor: This will usually involve surgery, and sometimes chemotherapy. Surgical cure is rare due to the high prevalence of metastases by the time of diagnosis; however, cancer progression can be very slow with survival rates in excess of >50% at 10 years.

2.9.2 Ménétrier's Hypertrophic Gastritis

Ménétrier's hypertrophic gastritis is a very rare condition characterized by enlarged gastric folds and hypoalbuminemia caused by an exudative gastropathy.

The differential diagnosis for prominent gastric folds, usually observed on endoscopic or radiological examinations, includes gastrinoma, lymphoma, and Ménétrier's disease.

The pediatric form of Ménétrier's hypertrophic gastritis is very different from that of Ménétrier's disease in adults. The evolution will be benign with a resolution generally after 5 weeks. It is often due to an acute cytomegalovirus infection.

2.9.3 Volvulus

The volvulus corresponds to a rotation or a twist of an organ on itself. Most commonly, the gastric torsion will occur along the luminal axis of the stomach (organoaxial volvulus) in the presence of diaphragmatic abnormalities (post-traumatic or paraesophageal hernias). In 1/3 of the cases, the gastric volvulus will occur along the mesenteric axis (mesenterico-axial volvulus) and will

often be incomplete. A volvulus occurs spontaneously and requires emergency surgery to prevent ischemia of the twisted organ secondary to the vascular compromise caused by the torsion of the blood supply.

In pediatrics, the most common presentation of gastric volvulus is non-bilious vomiting, epigastric distension, and abdominal pain in children under 5 years of age. Unlike adults, the volvulus is often mesenterico-axial.

2.9.4 Bezoars

Bezoars form when gastric residues clump together or solidify. Bezoars are, most commonly, made of fibrous plant substances (phytobezoars) that are difficult to evacuate from a stomach affected by gastroparesis. Trichobezoars are composed of hairs swallowed compulsively by some people.

Bezoars can cause early satiety, gastric fullness, vomiting, etc. The management strategies include the treatment of the underlying conditions (gastroparesis, psychological disorders, etc.), removal of the bezoar by chemical dissolution (acetylcysteine, papain, etc.), mechanical dissection (endoscopy), or even surgical extraction.

Lactobezoar can also be found in infants. It is a pathological agglomeration of milk and mucus that often obstructs the pylorus.

2.9.5 Perforations

Perforation of the gastric wall can occur following trauma or be secondary to penetrating mucosal lesions such as ulcer, cancer, etc. The spillage of gastric contents into the abdominal cavity will lead to a "surgical" abdomen as discussed in ▶ Chap. 16.

2.9.6 Gastric Bleeding

Any erosive or ulcerated lesion of the stomach can lead to vascular breakdown and acute or chronic bleeding. Digestive hemorrhage is discussed in the chapter on upper digestive tract hemorrhage.

2.9.7 Dieulafoy's Lesion

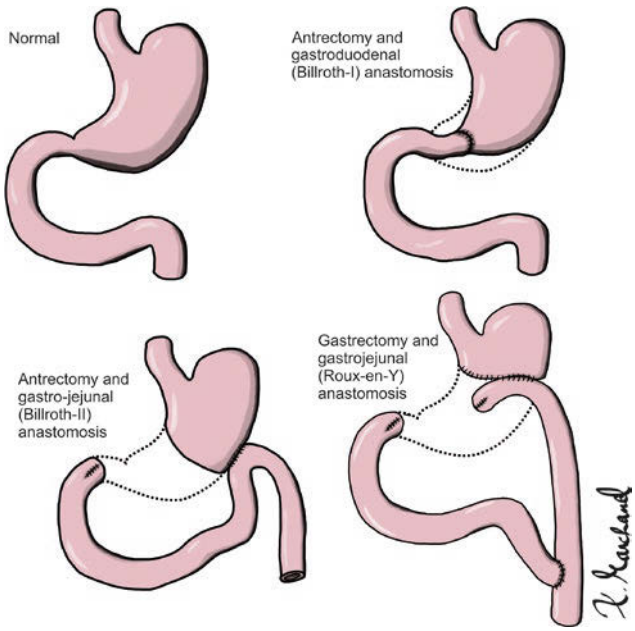
Dieulafoy's lesion identifies a particular condition seen endoscopically where active bleeding appears to come from the gastric mucosa but in a normal, healthy, ulcer-free mucosa. Micro-perforation of a vessel of the gastric mucosa not detectable in endoscopy or dilatation of aberrant submucosal vessels eroding the surface epithelium may explain this anomaly. Occurring without any known causative factor, Dieulafoy's lesion should be suspected in any upper GI bleeding for which no cause can be found. Given the difficulty in identifying the hemorrhagic vessel (not visible in the absence of active bleeding), the digestive bleeding may be prolonged and significant before the pathology can be identified and treated (endoscopic coagulation, etc.).

2.9.8 Gastric Surgery

After resection of a portion of the stomach, for ulcer disease or, most often, for a neoplastic lesion, continuity between the residual gastric pouch and the intestine will have to be restored. Various anastomoses have been described by now famous surgeons (see ◘ Fig. 2.20).

The most physiological and most desirable reconnection to ensure optimal digestive function after antrectomy is certainly the gastroduodenal anastomosis (known as Billroth I or Péan). However, gastric resection may be too extensive to allow a gastroduodenal anastomosis, and various other reconnection strategies are possible: gastro-jejunal anastomosis (known as Billroth II, or Finsterer or Polya) is the most common; in some cases, a jejunal loop may be mobilized and anastomosed to the stomach (Roux-en-Y anastomosis).

The most common gastric surgery at present is the cancer gastrectomy with Roux-en-Y anastomosis.



◘ **Fig. 2.20** Gastrointestinal anastomosis techniques following surgical gastric resection

PS: For complementary lectures on the stomach, see ▶ Chaps. 10, 11, 12, 25, and 29.

The Small Intestine

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Contents

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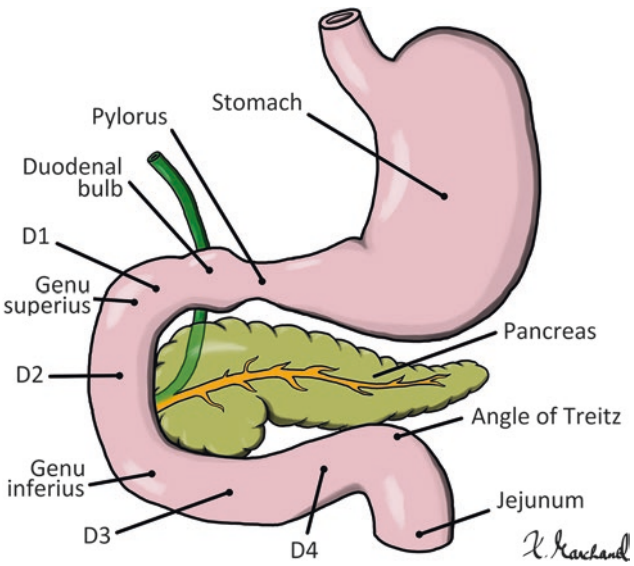
The small intestine is the most important organ of the digestive tract. You can live without a stomach or colon, but you cannot live without a small intestine. Its main function is to absorb nutrients, fluids, and electrolytes necessary for our life. The small intestine is also the largest endocrine organ in the body. We sometimes forget that the small intestine has an important role in immune function since it is acting as a barrier to various agents (bacteria, toxins, etc.) that, along with the absorbed nutrients, could pass from the outside world to the inside of the human body.

3.1 Macroscopic Anatomy

3.1.1 Shape and Structure

The small intestine is located between the stomach and the colon. It is a long tube (3–4 m long and 2–4 cm in diameter) that starts at the pylorus and ends at the ileocecal valve (or Bauhin valve). Three portions are recognized: the duodenum, the jejunum, and the ileum.

The *duodenum* begins immediately after the pylorus and ends 25–30 cm further at the angle (or ligament) of Treitz (◘ Fig. 3.1). Wrapped around the pancreas, one distinguishes successively the bulb (dilated room where occur most of the peptic ulcers known as duodenal ulcers described in the ▶ Chap. 2), D1 (first portion of the duodenum), the angle of the genu superius, D2 (vertical portion around the pancreatic head where the bile duct and the pancreatic duct terminate at the ampulla of Vater), the genu inferius, D3 located horizontally under the corporal pancreas, and D4 close to the caudal pancreas and going up toward the angle or Treitz. The anterior part of the duodenum is covered by visceral peritoneum, but the posterior part is retroperitoneal.



◘ **Fig. 3.1** Anatomy of the duodenum and the most clinically useful anatomical landmarks

The *jejunum* starts after D4 at the angle of Treitz. Treitz's ligament consists of peritoneal folds which at this point firmly attach the intestine to the retroperitoneum; after Treitz's ligament, the intestinal loops become free in the abdominal cavity. Even if there is no obvious anatomical delineation along the intestine, the first third after the duodenum will be called the jejunum (about 1 m long), and the next two-thirds will correspond to the ileum.

The *ileum* measures about 2 m. The term distal ileum most often refers to the last meter of the ileum (which has the unique functional characteristic of absorbing bile salts and vitamin B12); the term terminal ileum (often affected in Crohn's disease) refers to the ileal region located just upstream to the colon.

Bauhin's ileocecal valve is an area of high pressure at the last cm of the terminal ileum and acts as a barrier to prevent reflux of material from the colon into the small intestine.

The *mesentery* is an anatomical structure connecting the intestinal loops and the aorta. It is composed of two layers of peritoneum surrounding arterial and venous vessels, lymphatics, and nerves and containing fatty tissue.

3.1.2 Vascular Supply

Arteries The abdominal viscera are irrigated by three arteries coming from the aorta: the celiac trunk, the superior mesenteric artery, and the inferior mesenteric artery (◘ Fig. 3.2).

The proximal part of the duodenum is vascularized by the gastroduodenal artery (coming from the common hepatic artery, therefore from the celiac trunk) and by its pancreaticoduodenal branches (see ▶ Chap. 5). The distal part of the duodenum is vascularized by the pancreaticoduodenal branches issued from the superior mesenteric artery (SMA) joining the pancreaticoduodenal branches coming from the celiac trunk. This vascular connection ensures protection in case of thrombosis; indeed, in the event of an SMA thrombosis, the duodenum and the first 20–30 cm of the jejunum are spared from ischemia thanks to the blood flow coming from the celiac trunk. Conversely, the arterial supply of the liver can be ensured by the SMA (via the pancreaticoduodenal arteries and then the gastroduodenal artery) in case of obstruction of the celiac trunk.

The SMA ensures the vascularization of the entire small intestine via the jejunal and ileal branches distrib-

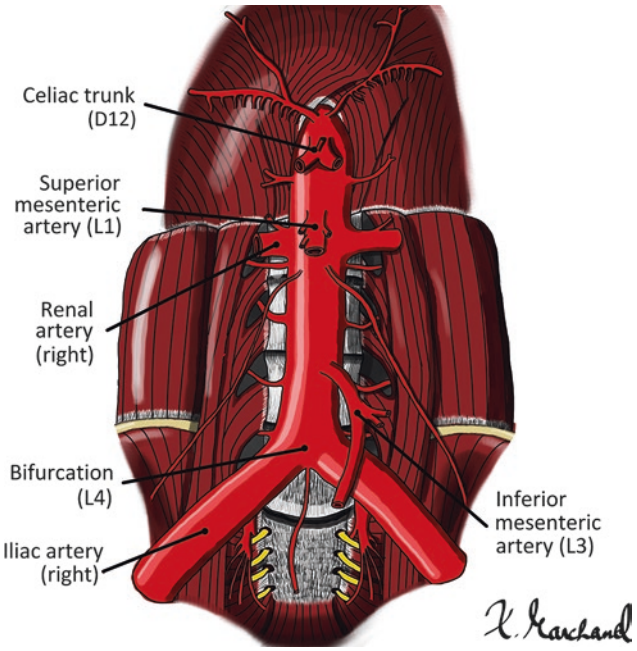


Fig. 3.2 Abdominal aorta and abdominal arteries: the celiac trunk (CT) originates from under the diaphragm at the level of the vertebral body of T12; the superior mesenteric artery (SMA) starts in front of L1, just above the renal arteries; the inferior mesenteric artery is issued in front of L3, just above the aortoiliac bifurcation at L4

uted in a fan-shaped arc along the edge of the intestine (Fig. 3.3a). The SMA also gives branches to the proximal colon.

Veins Venules draining from the intestinal wall run in the mesentery and converge toward the superior mesenteric vein which, joining the splenic vein, gives rise to the portal vein (where the gastric veins also drain; Fig. 3.3b). All venous blood originating from the intestine, and therefore containing the nutrients absorbed through the wall of this organ, flows to the liver (which will play a central role in the metabolism of several absorbed substances). After passing through the liver, the abdominal blood returns to the systemic circulation via the hepatic veins draining into the inferior vena cava, which in turn drains into the right atrium of the heart.

Lymphatics Lymphatics from the intestinal mucosa (including Peyer's lymphoid follicles; see Microscopic Anatomy) join regional mesenteric lymph nodes (in the mesentery close to the intestinal loops) before emptying into the more proximal lymphatic vessels running through the abdomen and converging into the lymphatic nodes and the cisterna chyli (also called Pecquet's cistern) located at the root of the superior mesenteric vessels,

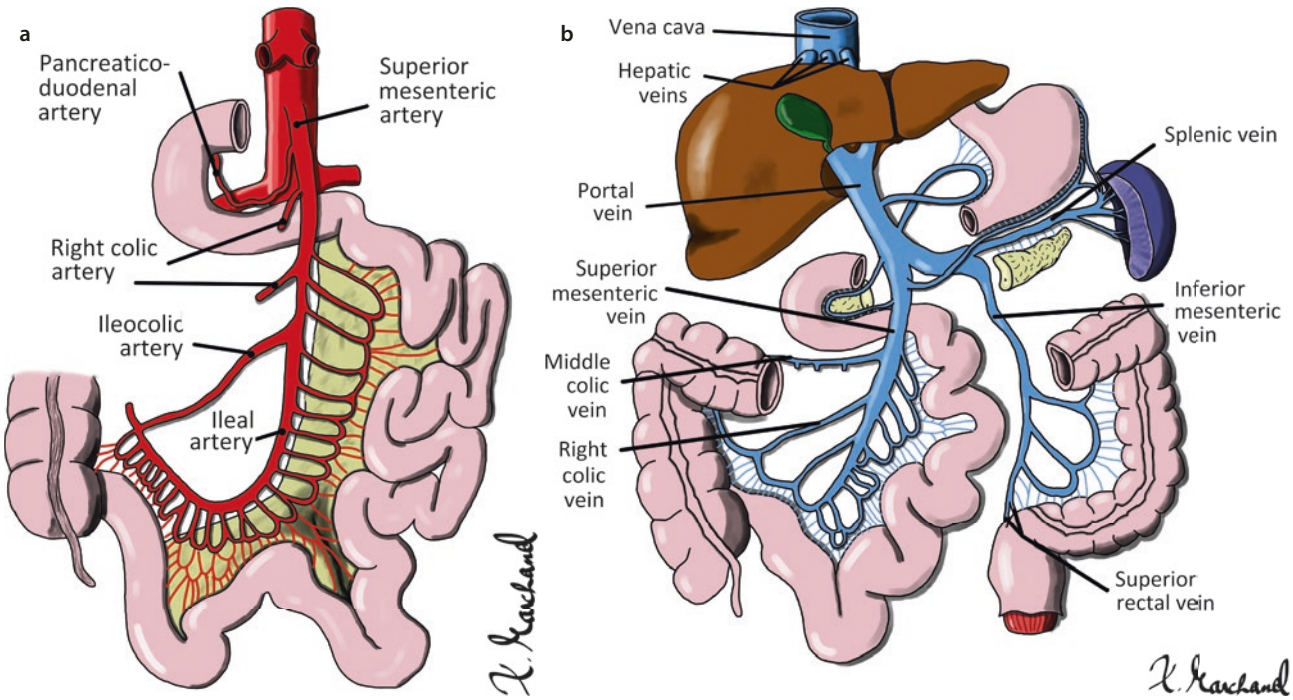


Fig. 3.3 **a** Arterial vascularization of the small intestine through the superior mesenteric artery. **b** Venous drainage from the intestine to the portal vein

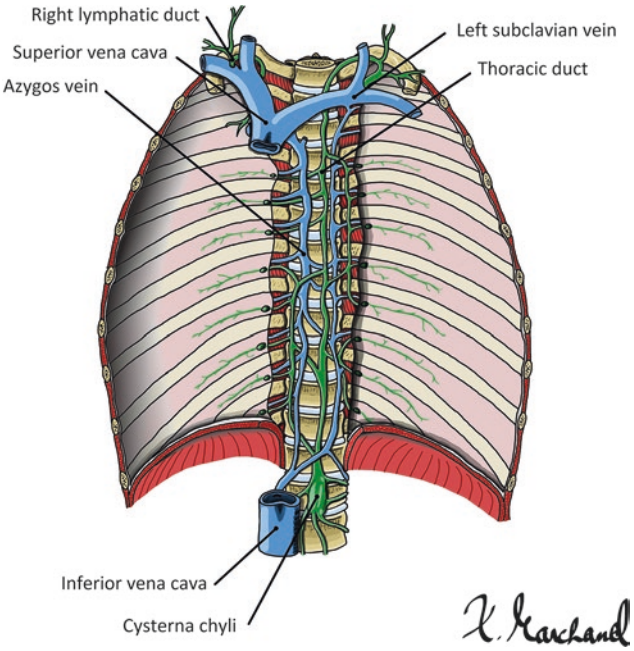


Fig. 3.4 Abdominal lymphatic circulation: lymphatics of the abdomen converge toward the cisterna chyli, a subdiaphragmatic lymph node structure draining into the left thoracic duct that ascends along the spine to the left jugular and subclavian veins to join the venous systemic circulation

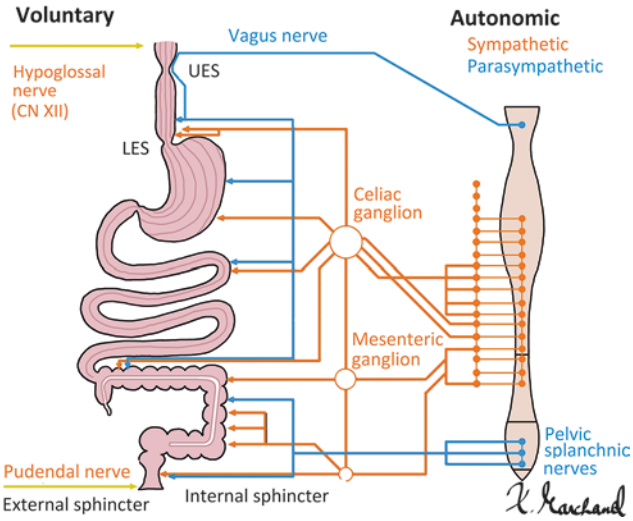


Fig. 3.5 Small bowel innervation. **a** The parasympathetic innervation (*in blue in the figure*) of the gastrointestinal tract depends on the vagus nerve for the stomach and small intestine, as well as on pelvic splanchnic nerves influencing the anorectal region. **b** Sympathetic nerves (*in orange in the figure*) (1) join the paravertebral ganglia when coming out of the spinal cord between two vertebrae; (2) they will then reach the celiac or mesenteric ganglia, before (3) spreading toward the intestinal loops. **c** Somatic nerves do not influence the digestive smooth muscles, affecting only striated sphincter muscles of the digestive upper and lower extremities to allow voluntary regulation of swallowing and defecation

behind the pancreas. These abdominal lymphatic vessels then pass through the diaphragm and join the thoracic duct (where the lymphatics of the left thorax also flow), which runs up along the spine (next to the azygos vein) until the left subclavian vein after having circled around the left jugular vein (Fig. 3.4). A disturbance in this complex lymphatic pathway may impact on the intestinal absorption of fatty acids normally carried via these lymphatic vessels.

3.1.3 Innervation

Intrinsic nervous system As elsewhere in the gastrointestinal tract, the intrinsic nervous system is made up of the enteric nervous system (ENS) consisting of Auerbach's myenteric plexus, located between the layers of circular and longitudinal muscles to control the contractile activity of the intestinal wall, and of Meissner's submucosal plexus, located between the muscle layer and the mucosa to regulate the functions of secretion and absorption by the mucosal cells.

Extrinsic nervous system The extrinsic nervous system consists of the ramifications of the parasympathetic and sympathetic autonomic nervous system (Fig. 3.5).

The *parasympathetic system* reaches the small intestine through the vagus nerve = X^e cranial nerve (cranial nerve number 10) or pneumogastric nerve issued from the vagal dorsal motor nucleus located on the floor of the IV^e ventricule = fourth ventricule. After running down along the esophagus and innervating the stomach, it gives branches to the intestinal loops either directly or via the celiac ganglion. The pneumogastric nerve is most often called the vagus nerve because of its complex ramifications and influences in the abdomen. The vagus nerve contains efferent (cholinergic) fibers whose influence is evident in the stomach and seems (from a clinical point of view) to taper more distally. Vagal afferents are important, among other things, in many reflexes regulating abdominal visceral functions.

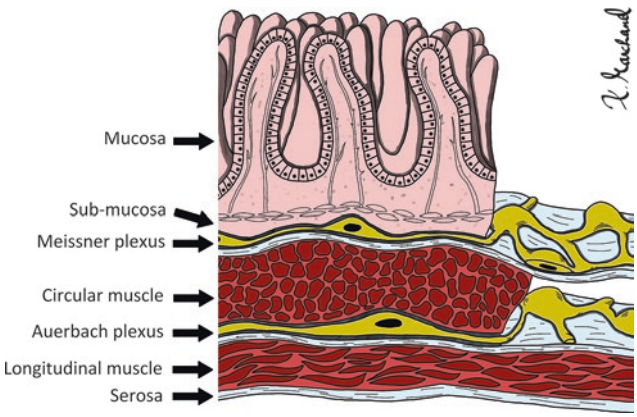
Sympathetic regulation is provided by the sympathetic nerves that originate from the spinal cord. These nerves are grouped together in abdominal ganglia such as the celiac or mesenteric ganglia (Fig. 3.5). From these nodes (which also receive parasympathetic nerves), nerve fibers leave toward the intestinal loops. Sympathetic afferent fibers convey painful sensations from the abdominal viscera to the central nervous system. The efferent sympathetic system mainly uses adrenaline as a mediator, which has an inhibitory influence on the motor or secretory functions of the small intestine.

However, given the complex anatomical structure of sympathetic innervation where 10–15 medullary nerves converge to 1–2 ganglionic structures (celiac and mesenteric nodes) receiving also parasympathetic influences and redistributing multiple efferent fibers to various abdominal organs, the role of the sympathetic system in digestive physiology is difficult to identify. Its clinical involvement appears as relatively minor (in comparison with the major health consequences noted following vagal disturbances); sympathectomy, or any deficit in sympathetic regulation, may decrease the adrenergic brake function leaving the way clear for parasympathetic cholinergic stimulation to generate an acceleration of intestinal transit and diarrhea.

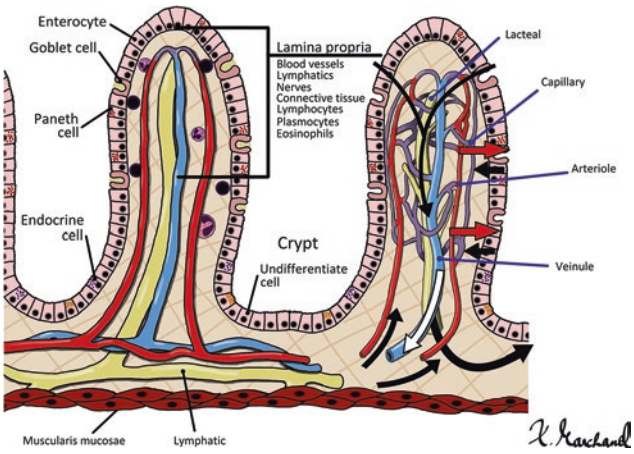
3.2 Microscopic Anatomy

The small intestine is a tube of 3–4 m long with a diameter of 2–4 cm and an anatomical surface area of about 0.5 m^2. The numerous folds of the intestinal wall triple this surface area. Microscopically, digitiform mucosal projections, called villi, increase the absorption surface by about ten times. At the ultramicroscopic scale, microvilli increase the absorptive surface area by 20 times, resulting in a total absorptive surface area of approximately 300 m^2 (more than the surface area of a double tennis court).

The wall of the intestine is made up of different superimposed and functionally different structures (◘ Fig. 3.6). On the outside, the serosa surrounds the muscularis made of a layer of external longitudinal muscles and separated by Auerbach's myenteric plexus from the internal circular muscles. Above the muscularis, the submucosa contains blood and lymphatic vessels, as well as nerve fibers of Meissner's submucosal plexus. The mucosa, facing the intestinal lumen, takes the form of digitiform projections called "villi." These villi (◘ Fig. 3.7) contain, in their center, an arteriole perfusing/oxygenating the surface cells and giving rise



◘ **Fig. 3.6** Intestinal wall: transverse view



◘ **Fig. 3.7** Small intestine mucosa. Intestinal villi are covered by a layer of enterocytes. Inside the villi are arterioles (red) that oxygenate and "feed" the enterocytes, as well as venules (blue) and lymphatics (yellow) that carry absorbed substances (transported from the intestinal lumen through enterocytes) to the systemic circulation. The villus on the right shows the vascular network at higher magnification

to capillaries permeable to absorption (of ions, sugars, etc.) draining to a venule carrying absorbed nutrients to the mesenteric venous circulation. At the center of the villus, the lacteal, a lymphatic capillary with a blind end, constitutes the starting point for the lymphatic transport of lipids.

3.2.1 Mucosa

The intestinal mucosa is composed of three layers: the epithelium, the lamina propria (connective tissue), and the muscularis mucosae. The villi are finger-like folds of the epithelium projecting into the lumen on an axis of lamina propria. The crypts (of Lieberkühn) are invaginations of the epithelium into the mucosa down to the muscularis mucosae. Villi and crypts represent, respectively, about 2/3 and 1/3 of the mucosal thickness (◘ Fig. 3.8). At the bottom of the crypts, the stem cells give rise to enterocytic cells which, as they proliferate and migrate up along the villus, differentiate into their four subtypes: enterocyte (absorption cell), goblet cell (mucus-producing), Paneth cell (involved in defense against intestinal bacteria), and endocrine cells (synthesizing hormones). Complete cell renewal takes place over 3–5 days. While the villi mainly ensure intestinal absorption, the crypts are mainly used for the secretion process.

Enterocyte The enterocyte is the most abundant cell (90% of the cells) of the intestinal epithelium. Rather rectangular in shape, its apical membrane, known as the brush border, is made up of microvilli (◘ Fig. 3.9) that increase the absorptive surface area by about 20 times and contain

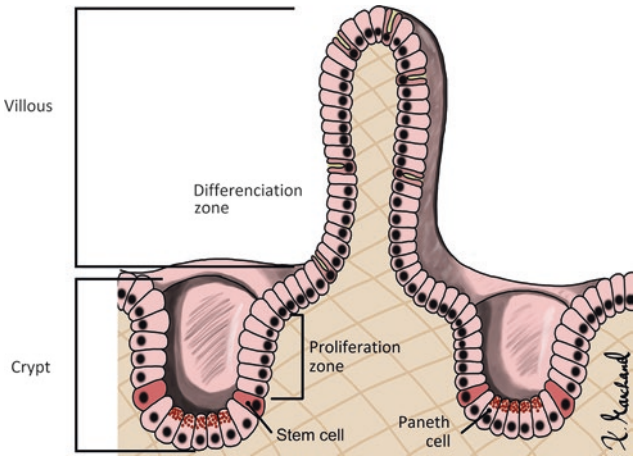


Fig. 3.8 Small intestinal mucosa: crypts and villi

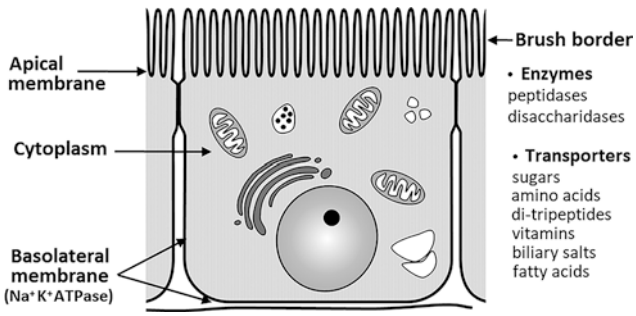


Fig. 3.9 Enterocyte: schematic illustration

various digestive enzymes (disaccharidases, etc.) and specific transporters.

The apical membrane will be the site where the nutritive molecules pass from the intestinal lumen to the interior of the cell, while the basolateral membrane of the enterocyte will allow these absorbed substances to pass from the cell to the blood or lymphatic vessels of the lamina propria (then to the submucosa and, subsequently, to the mesentery, etc.). The apical and basolateral membranes have different functions and have a different composition in lipids and proteins.

The enterocytes are placed side by side and are joined at their apical portion by bonds called "tight junctions" (Fig. 3.10). These junctions appear under the electron microscope as a continuous network of branched and anastomosed fibers surrounding the apex of each cell. These fibers consist of the membrane proteins claudin, occludin, and JAM (junction adhesion molecules) which bind to cytoplasmic proteins, such as zonula occludens and cingulin, attached to the cytoskeleton (actin filaments) of the enterocyte. These tight junctions, therefore, leave only a restricted space of 10–15 angstroms between two cells, closing the access to most molecules (except H_2O and ions). It is now known that these tight junctions are however dynamic and flexible structures that can respond to certain physiological or pathological stimuli to open up and allow certain substances to penetrate into the paracellular space.

The functional capacities of enterocytes will be discussed extensively in the ▶ Sect. 3.6.4.

Goblet cells Goblet cells (term referring to the cell's goblet-like shape) secrete mucus that lines the intestinal epithelium to protect and lubricate it. The presence of these highly glycosylated mucoproteins contributes to the formation of an unstirred layer between the apical membrane of the cell and the intestinal fluid medium itself, which limits the diffusion of solutes.

Paneth cells Paneth cells remain at the bottom of the crypts. They are attributed a protective role against infection by secreting defensins, TNF, lysozymes, etc. In addition, Paneth cells play a crucial role in the proliferation and differentiation of intestinal cells from the crypt to the villus.

Endocrine cells These cells are histologically recognizable by their ability to capture silver and are called argentaffins or argyrophils (depending on their need for a reducing agent for this capture); they are identifiable under microscopy by their specific secretory granules. These cells, derived from the neural crest and previously called APUD (amine precursor uptake decarboxylation) cells, secrete amines or peptides which, when released into the bloodstream, may have a remote endocrine action (e.g., secretin, CCK, GIP, motilin secreted from the proximal small bowel or PYY, enteroglucagon, neurotensin from the ileum) or may have an effect via the paracrine pathway (e.g., serotonin, somatostatin) on nearby cells. Digestive "hormones" are essential to the process of nutrient assimilation (e.g., gastrin, secretin, CCK) but also to other functions such as carbohydrate homeostasis (e.g., insulin, glucagon, GIP, GLP-1) and appetite (e.g., ghrelin, CCK, leptin, etc.). The different endocrine cells are shown in Fig. 3.11. Digestive peptides can also come from nerves or other cells in the digestive tract (Table 3.1).

"Immune" cells Specialized M cells (microfold cells-enterocyte looking cells but with shorter villi) of the brush border can take up antigens from the lumen of the intestine (via endocytosis) and deliver them to immune cells of the mucosa. In the epithelium, one can also see cells of the immune system, such as the dendritic cell, which, as the name suggests, can form extensions (dendrites) to infiltrate between enterocytes; the cell recognizes antigens (toxins, bacteria, etc.) of the intestinal chyme to start the defense process of the intestine against these aggressors by presenting them to the immune cells of the chorion.

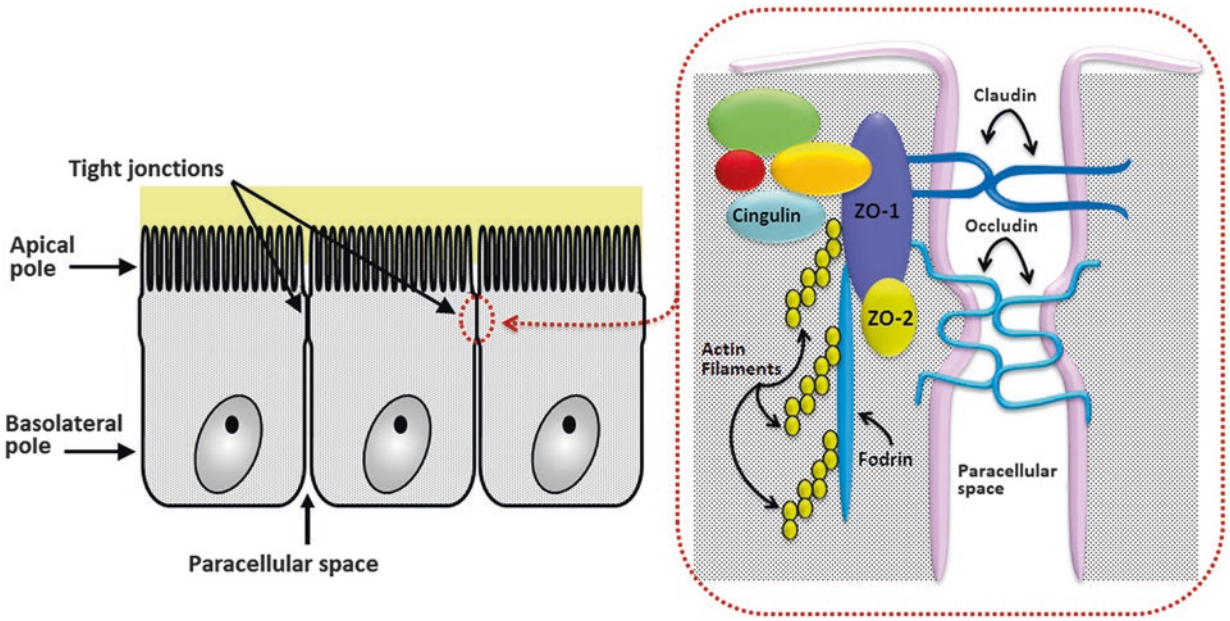


Fig. 3.10 Enterocyte wall. Enterocytes are joined by tight junctions that delimit the apical and basolateral poles of the cell. Tight junctions are described schematically at high magnification: membrane proteins claudin and occludin are bound to actin filaments of the cell cytoskeleton by cytoplasmic proteins such as zonula occludens (ZO) proteins, cingulin, fodrin, etc

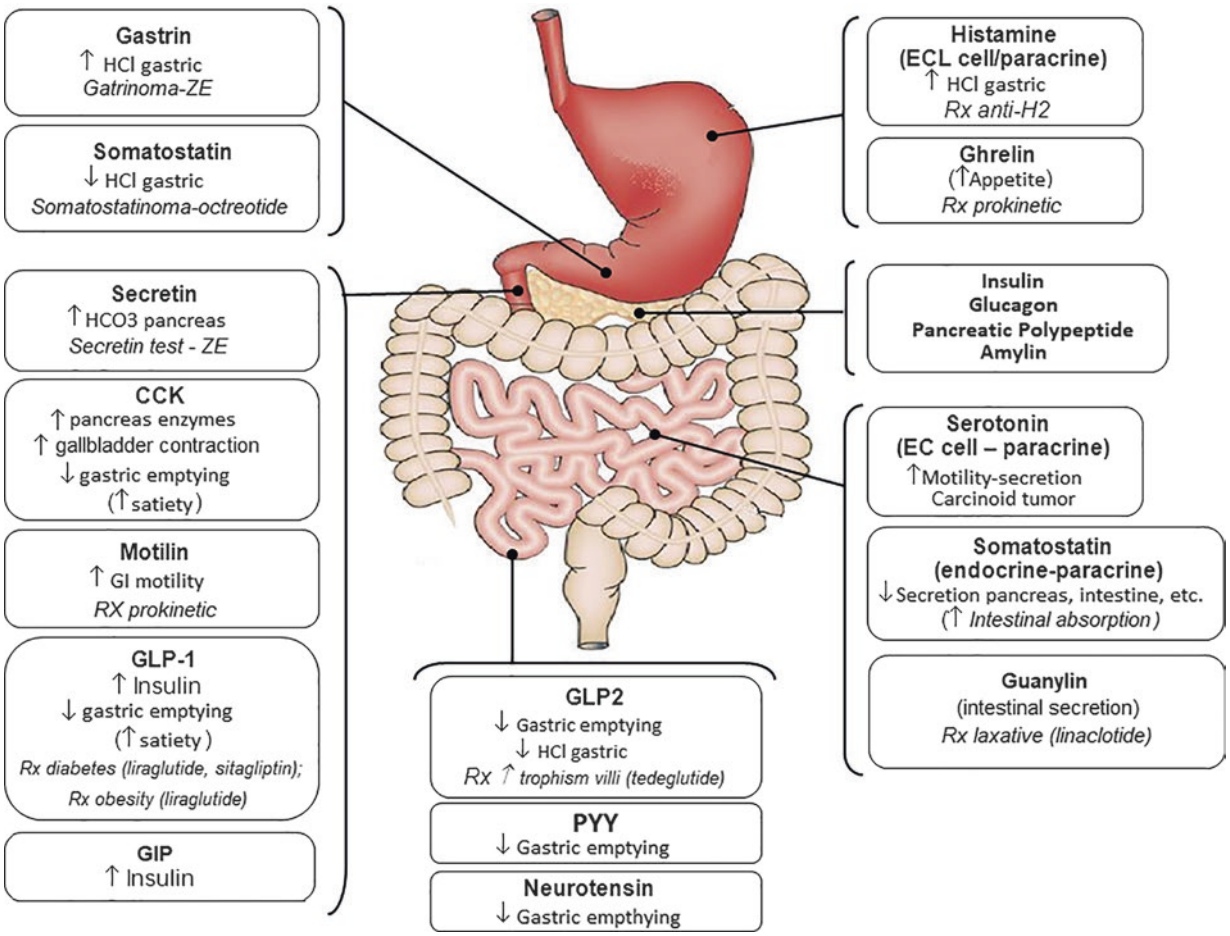


Fig. 3.11 Peptides (and other substances) from endocrine cells of the gastrointestinal tract. The name of the substance appears in bold characters, and its recognized biological actions are listed in regular fonts (presumed biological actions are in brackets). Clinical, diagnostic, or therapeutic impacts are in italics

Table 3.1 Non-endocrine regulatory substances from GI tract

Substance	Action	Clinic
(a) Produced in enteric nerves (and acting as neurotransmitters)		
Subst P/neurokinins	Muscle contraction	Rx: aprepitant (antinausea drug)
VIP	Muscle relaxation	VIPoma
Enkephalins	Secretion/motility GI	Rx: opiates/anti-opiates
Somatostatin	Motility/secretion	Octreotide – somatostatin
CGRP	Peristaltic reflex	
Galanin	↓ inflammation?	
GRP	↑ HCl gastric	
PACAP	Peristaltic reflex	
5HT	Motility GI/secretion	Rx: 5HT4 agonists, 5HT3 antagonists
Acetylcholine	Secretion/motility GI	Rx: anticholinergic/cholinergic drugs
(b) Produced in non-endocrine cells of GI tract		
Leptin (stomach chief cells)	↑ satiety (endocrine pathway?)	–
Guanylin (intestinal goblet cells)	↑ cGMP → ↑ secretion	Rx: linaclotide (laxative)
Defensin (intestinal Paneth cells)	Mucosal protection	–
Trefoil peptide (intestinal mucus cells)	Cytoprotection?	–

The chorion (or lamina propria) is a layer of connective tissue located between the epithelial cells described above and the muscularis mucosae (thin muscular layer separating the mucosa from the submucosa). The chorion contains various immune cells (lymphocytes, mast cells, macrophages, etc.) acting as a defense system against aggressive agents that could have crossed the epithelial surface. The lymphocytes of the lamina propria are mainly T lymphocytes expressing CD8, and the plasma cells secrete mainly immunoglobulin A. The chorion also contains Peyer's patches (see below).

3.2.2 Submucosa

The submucosa is an area of fibroelastic connective tissue with various structures:

- Blood and lymphatic vessels of the intestinal wall mainly circulate in the submucosa before inserting themselves upward into the chorion of the villi and exiting at the other end of the intestinal wall toward the vessels of the mesentery.
- Nerve fiber web constitutes Meissner's submucosal plexus, an important component of the enteric nerve system and intended primarily to regulate the absorption and secretion functions of the surface epithelium.
- Peyer's patches are made of aggregates of lymphatic follicles of the mucosa and submucosa that contain precursors of B and T lymphocytes. Peyer's patches play a primary role in the protective function of the intestine by producing and regulating immune cells that will attack potential aggressors in the intestinal lumen.
- In the proximal duodenum, Brunner's glands present in the submucosa secrete mucus and bicarbonates to protect the surface epithelium from the acid found in large quantities there.

3.2.3 Muscularis

The muscularis of the small intestinal wall contains the following:

- It has two layers of smooth muscles: The *inner layer* is made up of circularly oriented muscle fibers important in intestinal peristaltic contractions; the *outer muscle layer* is made up of smooth muscle fibers oriented in the longitudinal axis and assisting in the intestinal propulsive movements.
- Between these two muscle layers is Auerbach's *myenteric plexus*, a component of the enteric nervous system, which controls the contractile motor activity of the intestine, as discussed later in ► Sect. 3.6.5.

- Also found between these two muscle layers are the Cajal mesenchymal cells, which appear to act as a pacemaker in the enteric contractile activity (and which can proliferate to give rise to stromal tumors (GIST) discussed later in the ▶ Sect. 3.7).

While absorption through the mucosa of ingested nutrients is the primary function of the small intestine, the muscularis is critical for mixing and propelling nutrients to be absorbed along the small intestine.

3.2.4 Serosa

The serosa consists of a layer of mesoepithelial cells constituting the visceral peritoneum which encircles the small intestine in its jejunal and ileal portion and which covers the anterior portion of the duodenum.

3.2.5 Summary

Knowledge of the anatomy of the small intestine is essential to understand its role in the absorption of nutrients, or in the immune defense of the organism (◘ Fig. 3.12).

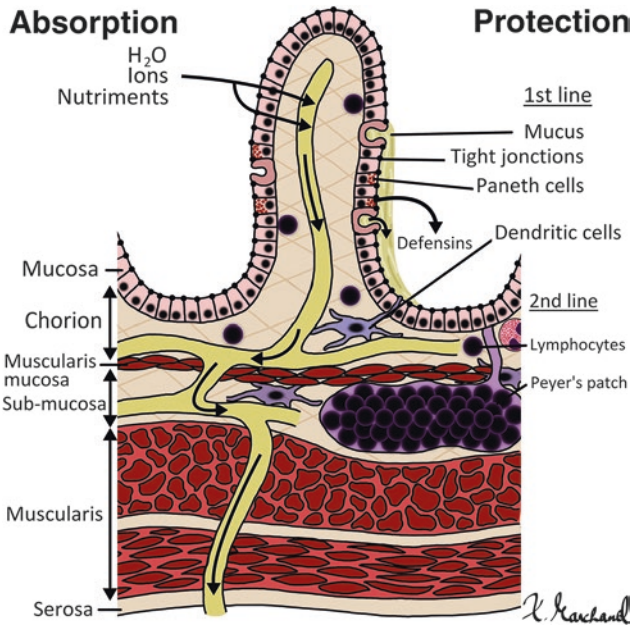
3.3 Embryology/Developmental Abnormalities

The main malformations of the small intestine are Meckel's diverticulum, malrotations, omphalocele, and stenoses. They involve errors in the development of the embryo.

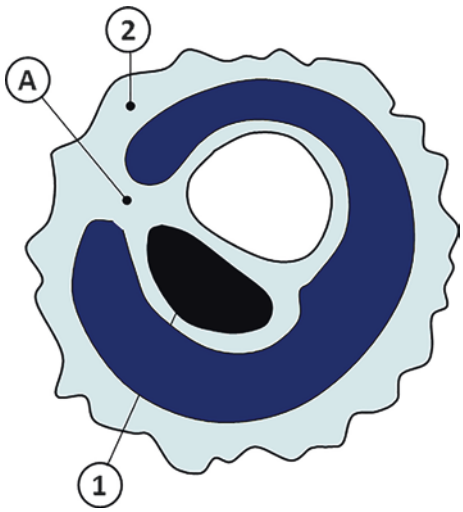
On day 0, fertilization occurs when a sperm that has migrated into the fallopian tube penetrates the egg. On day 1, the first chromosomal fusion and the first cell division take place in the oocyte. On day 4, the cells have multiplied to form a cluster of 16–32 mulberry-like cells called a morula. On day 7 or 8, the morula nests, as it continues to grow, having migrated from the fallopian tube into the uterus and implanted into the lining of the uterus.

As it continues to grow, the cells outside the morula will transform to eventually become the placenta and the amniotic membrane lining the uterine walls, while the cells inside the morula will transform to become the fetus itself. These two internal and external structures will be united for a certain time by the embryonic pedicle which, fusing with the yolk canal, will ultimately become the umbilical cord (◘ Fig. 3.13).

The embryo then differentiates into three layers. The internal leaflet, the endoderm, will give rise to the internal viscera such as the digestive and respiratory systems.



◘ **Fig. 3.12** Summary of anatomical characteristics for the absorptive and protective functions of the small intestine
Absorption: "Nutritive" substances to be absorbed will pass through the enterocyte layer of the mucosa to reach chorion venules draining into mesenteric veins toward the portal vein and systemic circulation (fat will go through lacteals to join mesenteric lymphatics, the thoracic duct, and left subclavian vein)
Protection: The intestine protects the body organism against penetration of toxic substances from the intestinal lumen. First-line or superficial defense mechanisms (mucus, tight junctions, Paneth cells, dendritic cell extensions, etc.) prevent the penetration of a "foreign" substance through the enterocyte barrier. A second line of defense can intervene to attack "toxic" substances that could have crossed the first line and penetrated the mucosa; B and T lymphocytes (and their products, such as immunoglobulins, TNF, interleukins, cytokines, etc.) from intestinal lymphoid organs (Peyer's patches) or from systemic lymphoid organs may then come into action



◘ **Fig. 3.13** Embryo at about week 3. The internal cells (**1**) of the morula differentiate toward the formation of the embryo. The external cells (**2**) will form the placenta. The two structures are connected by the embryonic pedicle (**A**)

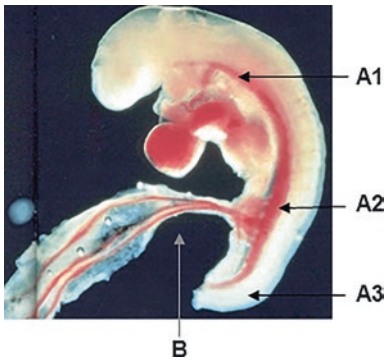


Fig. 3.14 Human embryo at 4–5 weeks. Starting from the endoderm, the digestive tract of the embryo begins to form as a tube (**A1**, **A2**, **A3**) with the yolk pedicle (**B**) in its center and after fusion with the embryonic pedicle will give the future umbilical cord. The upper part of the tube (**A1**) will give the anterior intestine (foregut = stomach + duodenum); the middle part (**A2**), where the yolk pedicle comes from, will give the middle intestine (midgut = small bowel); the distal portion (**A3**) will give the posterior intestine (hindgut = distal colon and rectum). Photo Lennartt Nilsson

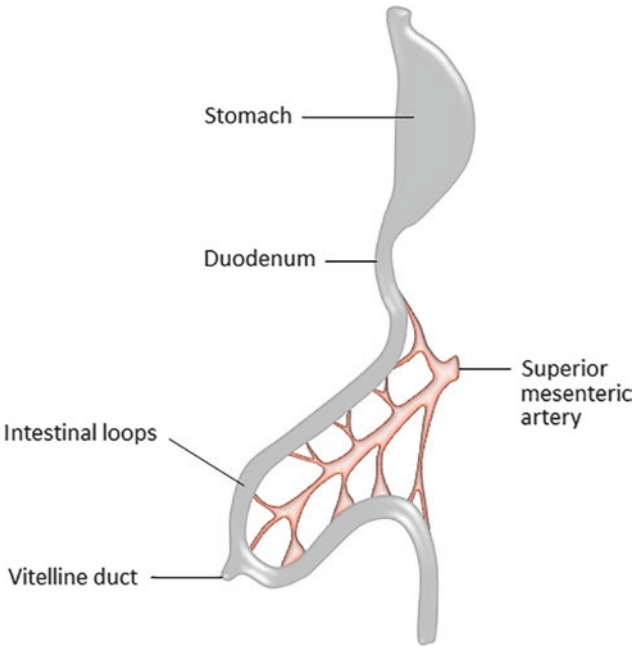


Fig. 3.15 Development of the midgut and Meckel's diverticulum. (1) The embryo was attached to the placenta through the vitelline duct located in the center of the fetal intestinal tract. (2) The midgut proliferates around the push by the superior mesenteric artery. (3) Communication between the fetus and the mother will now take place via the umbilical cord, (4) while the vitelline duct will close; incomplete closure of this vitelline duct may leave a diverticular structure (Meckel's diverticulum) in the center of the midgut

The intermediate layer, the mesoderm, will give rise to the heart, vessels, kidneys, and gonads. From the outer layer, the ectoderm, the skin, the nervous system, the nose, the eyes, the ears, and also the rectum will develop (see ► Chap. 7 in this manual).

By the fourth week (see ◘ Fig. 3.14), the intestine, which originates from the endoderm, is a tube (closed at both ends) that is divided into three parts: the foregut, the midgut, and the hindgut. The three parts of the digestive tract will then grow more or less in isolation along their respective vascular axes, i.e., the celiac trunk for the foregut (stomach and duodenum), the upper mesenteric artery for the midgut (small bowel), and the lower mesenteric artery for the hindgut (colon and rectum).

From day 32 onward, the midgut lengthens forming crescent shape toward its middle as if attracted by the yolk duct and pushed by the mesenteric artery (◘ Fig. 3.15). Its growth at this time is so rapid that the digestive tract then leaves the embryonic structure and continues to grow in the amniotic cavity outside the fetus.

Communication between the fetal intestine and the uterine wall normally closes before the 8th week, when the yolk canal (together with the embryonic canal) gives birth to the umbilical cord that unites the vascular systems of the mother and the fetus. However, the closure of the yolk canal may be imperfect and may give rise to a diverticular formation along the middle intestine corresponding to the insertion site of the old yolk canal. *Meckel's diverticulum* is the most common malformation of the small intestine (1–3% of the population; see ► Sect. 3.9.6 of this chapter). It is usually located 50–100 cm from the ileocecal valve and is a true diverticulum, i.e., it contains all three layers of the intestine (in contrast to the much more frequent false diverticulum, which is made up of herniation of the mucous layers through a muscular defect). Meckel's diverticulum may contain ectopic gastric mucosa which, by secreting HCl, may become ulcerated and bleed.

Starting on day 44, the intestines (which had developed outside the fetus, in the amniotic cavity) seek to reenter the fetal abdominal cavity. By rotating on the axis of the mesenteric artery, the proximal intestine will then position itself from the right to the left of the abdomen, and by day 56, the cecum will have migrated from the upper abdomen to the right iliac fossa region. Different developmental defects will explain various malrotations (see example in ◘ Fig. 3.16) where, for example, the proximal intestine may end up on the right side of the abdomen or the cecum may end up free at the right hypochondrium without being fixed. These *anomalies of rotation or fixation* may, in some cases, lead to obstructions (on the volvulus, etc.) or be asymptomatic.

Once reintegration has been achieved, as in the case of the duodenum, the peritoneal folds of the peritoneum will form. The posterior face of the ascending and descending colon will merge with the posterior plane, forming the right and left Toldt's fascias. As a result, these parts of the colon are fixed, while the whole of the small intestine, the transverse colon, and the sigmoid colon remain mobile. The result is that the entire small

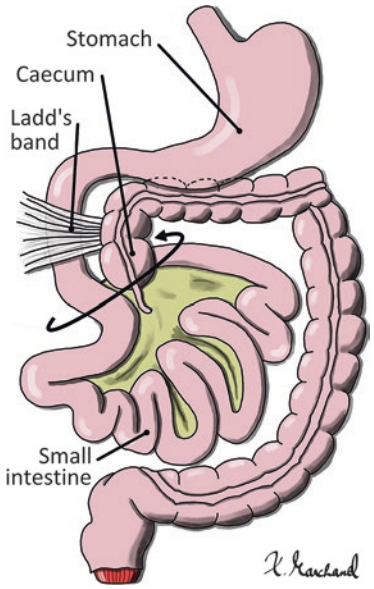


Fig. 3.16 Example of a malrotation where the cecum has not been fixed normally to the right iliac fossa and takes place at the right hypochondrium. Here, also shown are "Ladd's bands," embryonic vestiges that may obstruct by compressing the duodenum

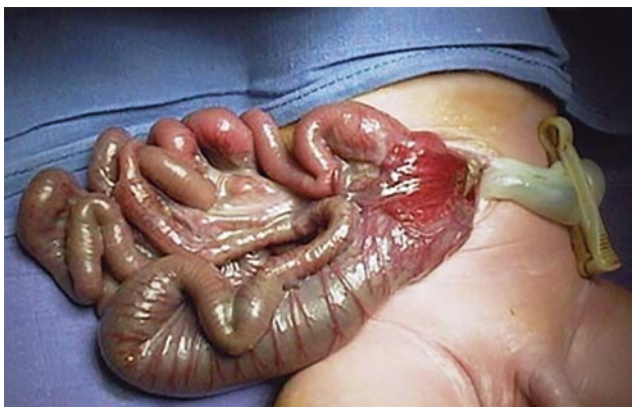


Fig. 3.17 Example of a laparoschisis where abdominal viscera protrude outside the abdominal cavity. (Image from ► vision.variousforum.com)

intestine, transverse colon, and sigmoid colon remain movable.

By the 9th week, the intestine should have migrated into the abdomen, and the abdominal wall should have closed. Failure to close the abdominal wall will result in an *omphalocele* (visceral hernia through an umbilical defect) *or laparoschisis* (intestinal hernia through a para-umbilical defect; see Fig. 3.17), rare malformations (2.5/10,000 births) where the abdominal viscera protrude through the deficient abdominal wall.

During fetal growth, mucosal proliferation is very abundant inside the intestinal tract, and the digestive tract will have to recanalize to form the visceral lumen around the 9th week. Defects in the luminal recanalization may result in various malformations in the form of *stenosis or atresia* (i.e., complete stenosis of the intestinal lumen). Intestinal atresia occurs in the case of 1 in 1000 births and affects the duodenum in half of the cases.

3.4 Absorption/Secretion

3.4.1 Absorption by the Small Intestine

The intestine is an interface, like the skin, between the outside world and the inside of our body. This barrier must allow the entry of nutritive substances essential for survival.

Absorption through the small intestine is a vital function. The intestine absorbs (a) water and electrolytes, essential for fluid balance; (b) macronutrients (carbohydrates, lipids, proteins) for energy; and (c) other substances (vitamins, minerals, etc.) essential for metabolism.

3.4.1.1 General Mechanisms

The process of digestion and absorption, from ingestion to excretion, is complex. Ingested food goes through the esophagus relatively unaltered, except for the first trituration by chewing and the initial digestion of sugars by the salivary amylase. It then reaches the stomach where it is subjected to a chemical and mechanical transformation. Acid and enzymes such as pepsin and lipase will continue the chemical digestion, while the stirring movements of the stomach wall contractions will mechanically reduce the size of food particles, facilitating further digestion. Through this process, food particles will be reduced from a few cm in size during swallowing to 2 mm particles that will pass through the pylorus. The passage through the pylorus (and stomach emptying) is regulated by several mechanisms that control the size and amount of nutrients entering the small intestine; it is important for optimal digestion and absorption, since a too rapid transit of food would compromise these processes. Bile and pancreatic secretions as well as certain intestinal enzymes will then take care of the final transformation of the food macromolecules to more simple substrates that will be presented to the small intestinal enterocytes for absorption.

Substrates will then pass, through the intestinal epithelial barrier, into the blood and lymphatic circulation of the mucosal lamina propria (or chorion). The epithelial barrier consists of enterocytes that are placed side by side (Figs. 3.7, 3.8, 3.9, and 3.10) with microvilli on the outer surface or luminal side (apical membrane)

and the lower surface (basolateral membrane) facing the chorionic blood and lymphatic vessels that collect the absorbed substances waiting to reach the systemic circulation and be distributed into the whole body.

The passage of substrates from the intestinal lumen to the chorion vessels can therefore take place through the enterocyte cell (transcellular route) or between two enterocyte cells (paracellular route).

Transcellular pathway It depends on numerous transport mechanisms, specific or not, energetically dependent or not, that will be used by numerous substrates that will pass first through the apical membrane and then through the basolateral membrane of the enterocyte.

Various mechanisms are available for the passage through the enterocyte (Fig. 3.18):

(a) *Simple diffusion* allows a substrate to pass through the lipidic bilayer by following a concentration difference (the substrate moving from the area of high concentration to the area of lower concentration), or according to an electrochemical gradient (e.g., Cl^- passage to follow the Na^+ passage). Small, uncharged, fat-soluble substrates can thus be absorbed by simple diffusion through the lipidic membrane of the enterocyte.

(b) *Facilitated diffusion* (or passive transport) follows a concentration gradient but involves a transmembrane protein serving as a transporter or a channel to create a hydrophilic pore allowing the passage of ions or molecules through the lipid bilayer.
- Channels are protein pores in the lipidic membrane that are often specific for a given ion (e.g., the Na^+ channel excludes K^+ ions); the channels close and open very quickly to allow large amounts of substrates to pass through (e.g., more than 10^6 ions per second). However, the channels are of little importance in the small intestine.
- Facilitated transporters are proteins of the membrane which are less efficient than channels in terms of transport speed but which exhibit substrate selectivity; they ensure the passage of hydrophilic molecules through the membrane according to their concentration gradient (e.g., GLUT2 transporter for glucose or GLUT5 transporter for fructose).

(c) *Active transport* allows the passage of nutrients against a concentration gradient. Depending on the energy source used to do this work, active transport of primary or secondary nature is identified: (1) primary active transporters are pumps that require the expenditure of energy in the form of ATP to allow the transport of ions against a gradient. For example, the Na^+/K^+ ATPase pump of the basolateral membrane uses ATP to expel three Na^+ ions from the enterocyte against the entry of two K^+ ions; (2) secondary active transporters will use the electrochemical gradient produced by the pumps (or ATPases) to carry out the transfer of a substance against its concentration gradient (e.g., glucose transport by the SGLT-1 transporter of the apical membrane). The transporters operate in symport (transport of the substrate and co-substrate in the same direction; e.g., Na^+/glucose, Na^+/amino acid) or in exchanger system (the substrate exchanged against a co-substrate; e.g., Na^+/H^+ exchanger, Cl^-/$HCO3^-$ exchanger).

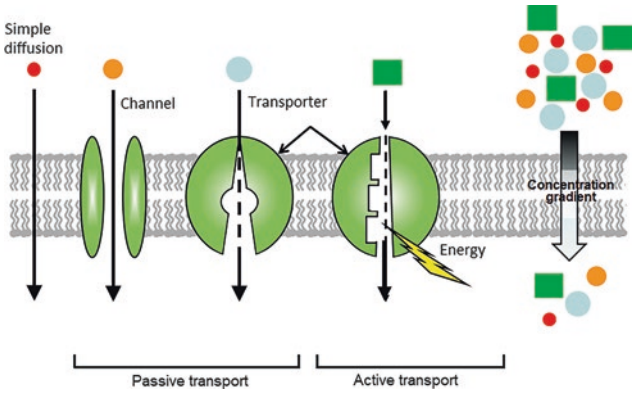


Fig. 3.18 Transport mechanisms through the enterocyte lipid apical membrane

Paracellular pathway Substances can be inserted at the tight junction (zonula occludens) which leaves only a space of 10–15 angstroms between two cells and ensures the sealing of the mucosal epithelium by preventing the passage of large molecules. Only 4–5 kd molecules such as water and ions are small enough to infiltrate this small space. Water can use this paracellular pathway to infiltrate in response to an osmotic charge; for example, glucose expelled from the basolateral membrane of the enterocyte into the paracellular space increases the osmolarity there and draws water from the lumen. This movement of water can carry in its flow certain ions such as sodium or potassium that are small enough to fit through the tight junction; this is the "solvent drag," i.e., a call for substrates in a liquid flux (Fig. 3.19).

Space between cells is a potential weakness area through which undesirable substances such as bacteria that thrive in the gut could enter, and the tight junctions therefore play an essential protective role in ensuring the tightness of the epithelium. These tight junctions are made of the membrane proteins occludin, claudin, and JAM, which bind to cytoplasmic proteins such as ZO-1 (zonula occludens protein 1) that attach to the

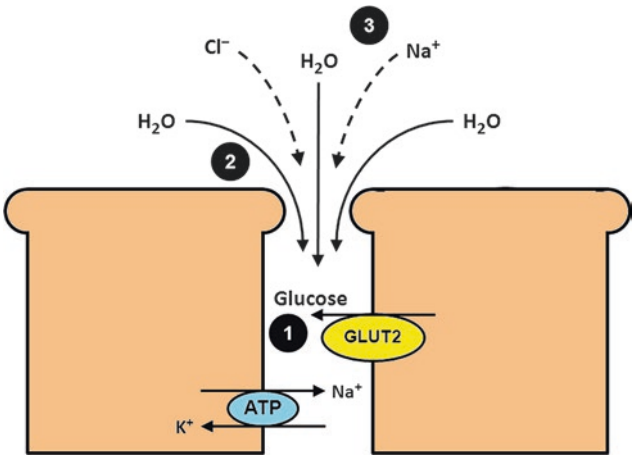


Fig. 3.19 Paracellular passage and solvent drag. (**1**) In paracellular space, an osmolar charge is established by receiving glucose and Na^+ secreted from basolateral membranes of the enterocytes. (**2**) In response to this increased osmolarity, water infiltrates through apical tight junctions. (**3**) Flow of H_2O from the intestinal lumen to the paracellular space drags with it small ions: the "solvent drag"

cytoskeleton of the cells to force contact at their apex (Fig. 3.10). It is now known that, by means of these membrane proteins, the opening of these tight junctions can be modulated physiologically as well as during pathological processes. Infectious toxins such as ZOT (zonula occludens toxin) can attack these tight junctions; the zonulin protein is believed to cause a decoupling of the ZO-1/occludin-claudin bond, thus opening the tight junctions. In the case of food allergies, infections, autoimmune diseases, or inflammatory bowel diseases, zonulin secretion would be increased, which could allow the entry of bacteria and/or toxins that contribute to the maintenance of inflammation. Zonulin antagonists, such as larazotide, are clinically tested to improve cellular barrier function.

Intestinal absorption mechanisms are heavily solicited since they must ensure the daily absorption of 7–8 l of H_2O and several grams of carbohydrates, amino acids, and lipids, as shown in Table 3.2. However, these absorption mechanisms have a much greater functional capacity, so they are never saturated under physiological conditions and they can increase their absorption capacity if necessary. A defect in intestinal absorption will be seen mainly when enterocytes are in insufficient quantity (e.g., during a short bowel after extensive intestinal resection or during villi atrophy as encountered in celiac disease) or, more rarely in the clinic, will be attributable to qualitatively nonperforming enterocytes (e.g., SGLT-1 transporter deficiency).

Table 3.2 The intestine absorbs large amounts of ions and nutrients on a daily basis and can significantly increase its capacity

	Absorption	
	Normal daily	Maximum capacity
Sugars	200–800 g	>kg
Proteins	50–100 g	500–700 g
Lipids	>100 g	500 g
Ions	50–100 g	>100 g
Water	7–8 l	20 l

3.4.1.2 Water and Electrolyte Uptake

(a) Absorption of H_2O Large quantities of H_2O have to be reabsorbed by the intestine on a daily basis. The exogenous supply of liquid ingested (and to be absorbed) is usually 2–3 l in humans; the intestine will also need to reabsorb endogenous secretions such as saliva (1–2 l), gastric (about 2 l), biliary (about 1 l), pancreatic (1–2 l), and intestinal (about 1 l) secretions that enter the intestine daily. The small intestine will therefore in total have to deal with ≈ 9–10 l of water daily. Only 1–2 l of liquid is not reabsorbed in the small intestine and reaches the colon, which will reabsorb about 90% of it. Gut absorption of exogenous as well as endogenous fluids is illustrated in Fig. 3.20. Water absorption is therefore a very efficient phenomenon throughout the small intestine from the duodenum to the ileum (as well as in the colon).

Crossing of the intestinal barrier by H_2O molecules is done both by transcellular (e.g., via the aquapo-

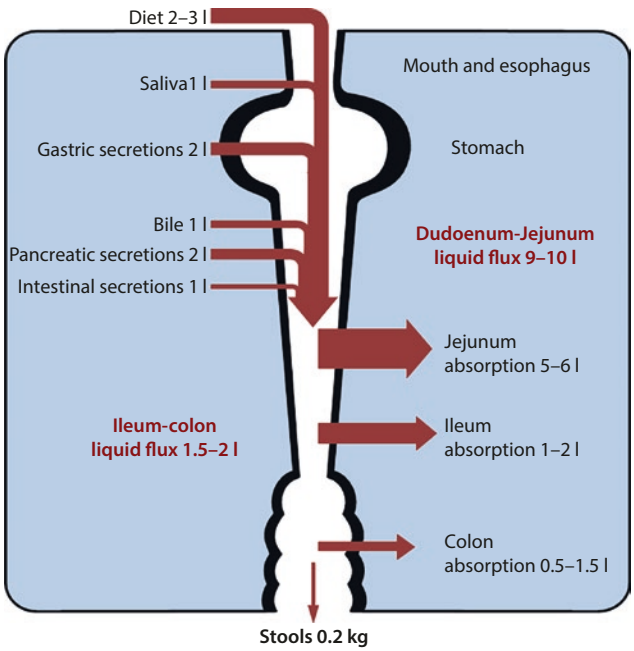


Fig. 3.20 Daily absorption and secretion in the digestive tract. Ingested exogenous solutions (water, juice, etc.) as well as endogenous secretions (saliva, gastric juice, etc.) must be absorbed from the intestine

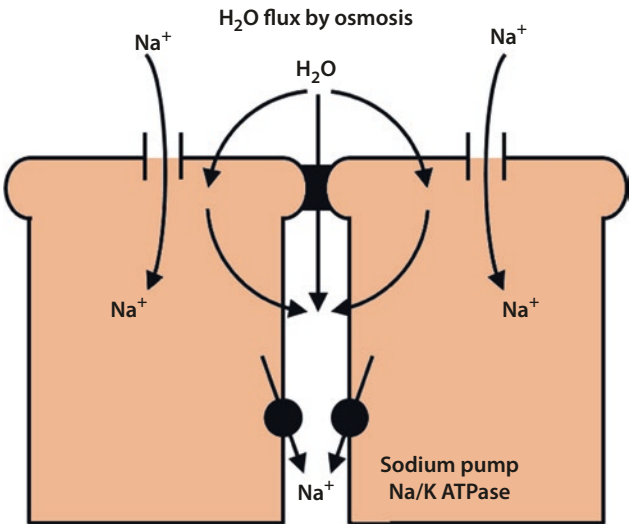


Fig. 3.21 Entry of H_2O follows an osmolar gradient and ion movements: ions such as Na^+ (as shown here in the figure) or Cl^-, etc. are absorbed by various mechanisms (simple diffusion, facilitated diffusion, active transport, etc.) through the enterocyte barrier; H_2O follows the osmotic gradient generated by these ions. H_2O can enter via transcellular or paracellular routes

rin, a channel transporting H_2O and small molecules through the membranes) and paracellular routes. As a vital phenomenon, the movement of H_2O from the gut lumen into the organism is mainly based on simple osmotic diffusion mechanisms and is linked essentially to ionic movements and mostly to the movement of Na^+ (Fig. 3.21) and Cl^-.

(b) Sodium absorption The absorption of Na^+ is vital, among other things, because it also conditions the transparietal movements of H_2O. Na^+ is absorbed at all levels of the digestive tract, mainly in the jejunum (where there are very active cotransporters for many substrates) but also in the duodenum or ileum (Na^+/H^+ exchange) or in the colon through sodium channels (sensitive to amiloride).

Creation of a concentration gradient The Na^+/K^+ ATPase pump of the enterocyte basolateral membrane is the key element in the movement of Na^+. By driving three Na^+ ions out of the cell against the entry of two K^+ ions, the pump maintains in the intracellular milieu of the enterocyte a low concentration of Na^2. This lowered Na^+ concentration serves as the essential basis for the concentration gradient that will subsequently lead to the movement of Na^+ from the intestinal lumen (area of high concentration) to the enterocyte milieu (area of low concentration).

Transcellular passage of Na+ When the concentration gradient from the intestinal lumen to the enterocyte (created by the ATPase pump expelling Na^+ from the cell) is established, various transport mechanisms can then intervene to move Na^+ from the intestinal lumen into the enterocyte:

- Passive input (or simple diffusion) of Na^+ through the membrane is possible.
- Na^+/H^+ exchangers NHE-2 and NHE-3 (also called SLC9A2 and SLCA3 or solute carrier 9) are very active agents in the absorption of Na^+, specially during the interdigestive period when Na+ is absorbed in the absence of nutrients.

Na^+/H^+ exchanger 3 (NHE-3) is an essential factor in the absorption of sodium (and consequently of water) and is an important player in diarrhea. A mutation in the NHE-3 gene is responsible for congenital sodium diarrhea (a lethal condition for untreated newborn, as described at the end of this chapter). NHE-3 is inhibited by various secretion mediators such as cAMP (mode of action of secretin, VIP, cholera toxin), cGMP (guanylin peptide or its pharmacological derivative linaclotide, *E. coli* enterotoxin), and intracellular Ca++ (*Clostridium difficile* toxin, rotavirus). On the other hand, its activity is stimulated by alpha-2 adrenergic agonists, opiates, somatostatin, and certain products under development for the treatment of diarrhea. A NHE-3 inhibitor, tenapanor, is now available for the treatment of constipation.

NHE/SCL9 transporter mediating sodium-hydrogen exchange is functionally coupled to the apical transporter SCL26 mediating Cl^--HCO_3^- exchange discussed below. This coupled and synchronized action of SCL9 and SCL26 transporters favors entrance of ions in the cell and enhances the secondary process of H_2O absorption (linked to osmotic and ionic gradient).

- Active carriers use the cotransport Na^+ with another substrate (such as glucose or galactose, various amino acids, certain vitamins, bile salts, etc.). These transporters are very active after a meal (when these nutrient substances are present in the intestinal lumen). The SGLT-1 transporter (sodium-glucose cotransporter 1) at the apical surface of the enterocyte co-transports simultaneously sodium and glucose (two ions of Na^+ and one molecule of glucose) which is very powerful and vital. Its physiological contribution is obvious since the congenital absence of this receptor (fortunately an exceedingly rare disease) leads to a malabsorption of glucose and Na^+ that is not compensated by any other absorption mechanisms and that is a fatal condition by diarrhea and dehydration (unless all glucose is removed from the newborn diet)

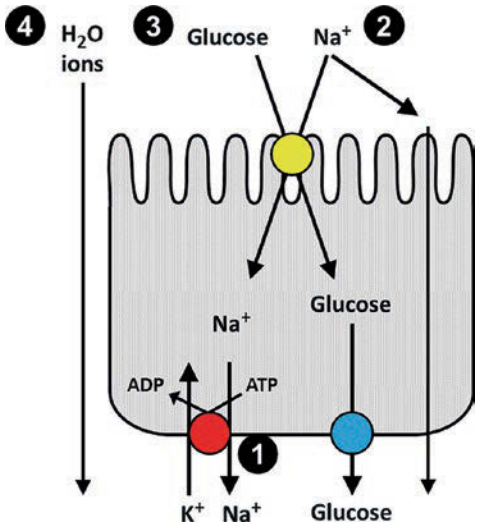
Understanding of the physiological mechanism of sodium-glucose coupled transport (discovered by Robert Crane in 1960) has enabled the development of a therapeutic solution (WHO solution popularized by the

World Health Organization) that has saved many lives, especially in Africa, by countering the deadly dehydration of severe infectious diarrhea (cholera diarrhea can reach 3–4 l per day). The replacement of water and ions essential for survival was indeed often insufficient with oral treatments and required their administration intravenously. By simply adding glucose to oral rehydration solutions of salt and water (WHO solution contains Na^+ 90 meq (NaCl 2.6 g or ≈1 teaspoon of cooking salt) and glucose 20 g (≈8 teaspoons of sugar), with if possible KCl 1.5 g (juice of ≈2 oranges), in 1 l of H_2O), the Na+/glucose cotransporter (not affected by cholera toxin) is activated, and the intestinal absorption of orally administered Na^+ and water is optimized, thus avoiding the need for intravenous infusion to correct dehydration.

Sodium-glucose cotransporters (SGLT-2) are also present on kidney tubules; SGLT-2 antagonists (glifozins inhibiting renal reabsorption of glucose) are well known to treat hyperglycemia in diabetic patients. A SGLT-1 inhibiting agent, Mizaglifozin, is being investigated for the treatment of constipation.

Paracellular passage of Na+ After their expulsion from the enterocyte cell via the basolateral membrane, the high concentrations of Na^+ and other substrates (including glucose) present in the paracellular space will generate an osmotic gradient drawing water from the intestinal lumen through the tight junctions (paracellular passage). This flux of H_2O through the tight junctions will carry with it molecules in suspension such as ions Na^+, Cl^-, K^+, etc. (this is called solvent drag).

Absorption on Na+ is summarized in ◘ Fig. 3.22.



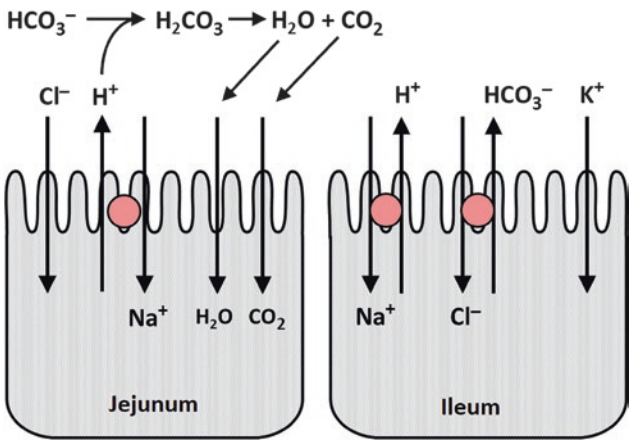
◘ **Fig. 3.22** Na^+ Absorption: (**1**) The Na^+/K^+ ATPase pump of the basolateral membrane drives Na^+ out of the cell and lowers the intracellular concentration of Na^+. (**2**) Na^+ from intestinal lumen follows the concentration gradient by simple diffusion or via exchangers through the apical membrane. (**3**) Various transporters allow movement with Na^+ of various substrates such as glucose (shown here), amino acids, and vitamins. (**4**) The increase in paracellular space of Na^+ and substrates driven out of the enterocyte draws water and ions from the lumen through the tight junctions

(c) Chloride absorption Cl^- is absorbed throughout the digestive tract. At the jejunal level, it is absorbed passively, following Na^+ according to an electrical gradient Na^+-Cl^-. In the distal ileum, as in the colon, a Cl^-/HCO_3^- exchanger (SCL26 or CLD) allows the absorption of Cl^- and the secretion of HCO_3^- (see below).

A mutation of this CLD transporter (chloride anion exchanger) explains congenital chlorinated diarrhea (described at the end of this chapter).

Chloride, after its absorption at the apical membrane, can be exported out of the enterocyte cell across the basolateral membrane via a potassium/chloride cotransporter (KCC1).

(d) Bicarbonate absorption HCO_3^- is the only ion that is absorbed in the proximal small bowel but secreted distally (as in the colon). In the jejunum, as shown in ◘ Fig. 3.23, intraluminal HCO_3^- is absorbed indirectly following a transformation into H_2CO_3 (H^+ secreted by the enterocyte for Na^+/H^+ exchange) itself transformed into H_2O + CO_2, which will thus cross



◘ **Fig. 3.23** HCO3⁻ is absorbed in the jejunum; it is secreted in the ileum to allow the entry of Cl^- and H_2O

the intestinal membrane (CO_2 will be eliminated later by the lungs). At the ileum (and colon), the HCO_3^- ion is expelled out of the cell in exchange for a Cl^- ion (and secondarily H_2O) by CLD (SCL26) anion transporter. This mechanism is physiologically very active since the congenital deficiency of CLD-SCL26 exchanger (a very rare condition) is a lethal disease where chlorinated diarrhea (high presence of Cl^- ions in the stool) and metabolic alkalosis (lack of HCO3⁻ excretion through the intestine) are encountered.

(e) Potassium absorption K^+ is passively absorbed throughout the small intestine, probably as a result of H_2O entry. However, it is secreted in the colon (Fig. 3.24)

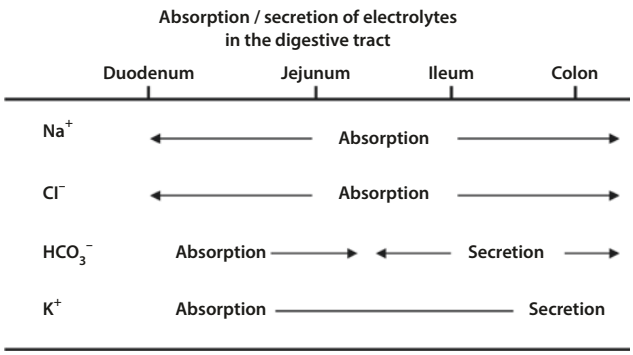


Fig. 3.24 Movements of the most important ions along the digestive tract, i.e., the duodenum, jejunum, ileum, and colon

via two mechanisms: a passive transcellular component due to a potential difference between the lumen and blood (−15 to −25 mV) and a potassium channel sensitive to aldosterone.

Potassium, after its absorption at the apical membrane, can be exported out of the enterocyte cell across the basolateral membrane via a K^+/Cl- cotransporter (KCC1).

Hypokalemia is a phenomenon to be feared during diarrhea compromising the movement of water and ions from the intestinal lumen to the body environment.

(f) Summary Absorption of water and various electrolytes is summarized schematically in Fig. 3.25.

The importance of the transporters involved in water absorption is evidenced by the clinical conditions resulting from an abnormality of these transporters

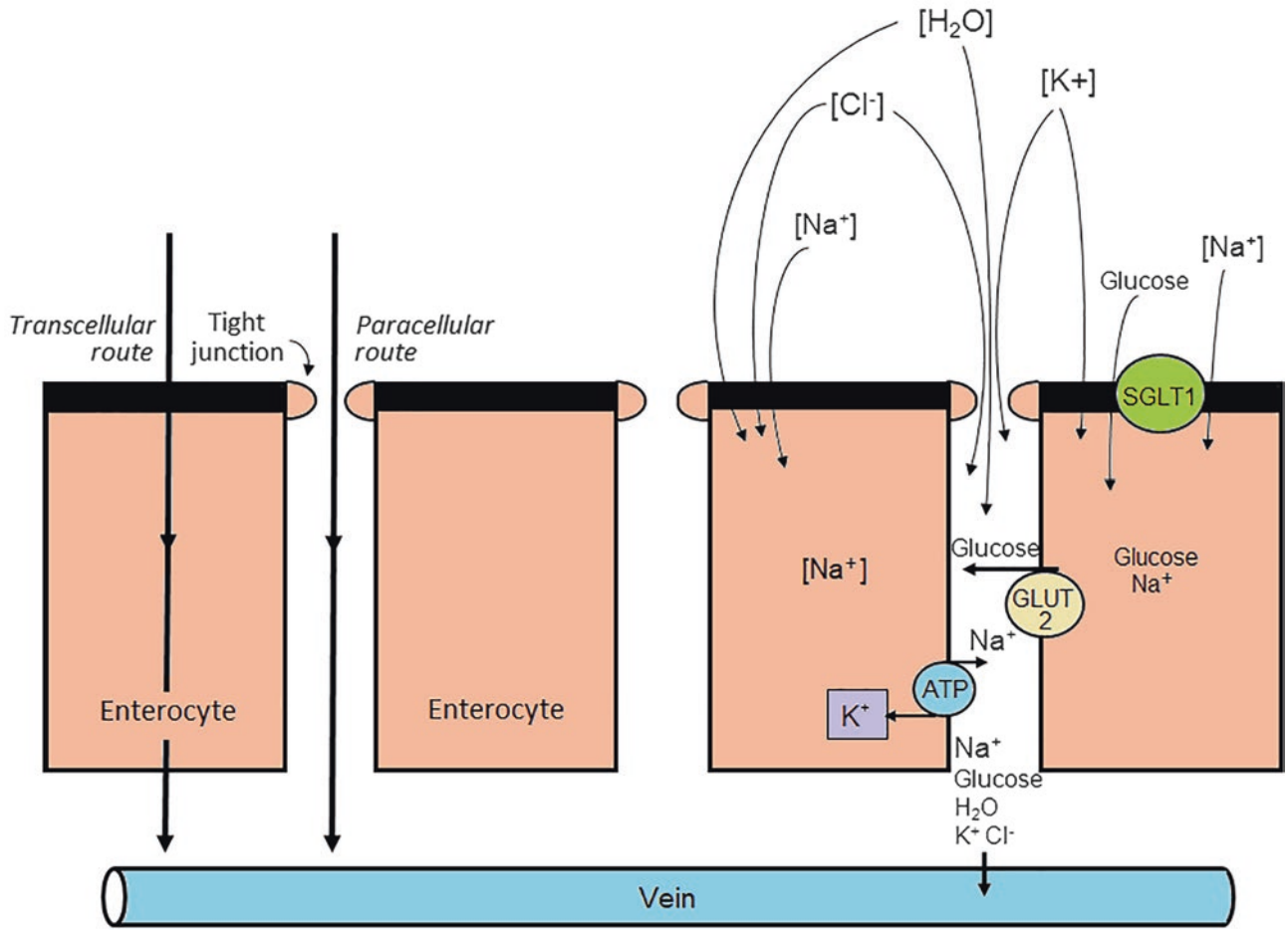


Fig. 3.25 H_2O absorption and electrolytes in proximal small bowel by trans- and paracellular pathways: (1) in response to a low intracellular Na^+ concentration due to the Na^+/K^+ ATPase pumping Na+ out of the enterocyte; (2) Na^+ from the lumen diffuses within the cell or is co-transported with various substrates including glucose (transporter SGLT-1); (3) Cl^- will follow the transmembrane movement of Na^+, attracted by an electrochemical gradient; H_2O follows the movement of ions through the cell membrane; (4) Na^+ and glucose are driven out of the cell, respectively, by the Na^+/K^+ ATPase pump and by the GLUT2 transporter of the basolateral cell membrane to enter the paracellular space, creating a hyperosmolar space with high concentration of Na^+ and glucose; (5) H_2O is attracted by an osmolar gradient through the tight junctions toward the intercellular space; (6) H_2O flux through the tight junctions drags along small ions such as K^+, Cl^-, etc. ("solvent drag") paracellularly

Table 3.3 Transporters involved in water absorption: clinical impact

Transporter	Action mechanism	Pathological impact	Therapeutic use	Gene disease
NHE-3	Absorb Na+ → absorb H_2O	Inhibited by diarrhea agents (VIP, cholera toxin, *E. coli*)	Inhibitor tenapanor (Rx constipation)	Congenital sodium diarrhea
	Important in absence of food	Stimulated by opiates, somatostatin		
SGLT-1	Absorb Na+/glucose→absorb H_2O		Inhibitor gliflozin (Rx constipation)	Glucose-galactose malabsorption (severe diarrhea)
	Important in presence of food		WHO solution for rehydration	
CLD (SLC26A3)	Absorb Cl^-/secrete HC03- → absorb H_2O in ileum + colon			Congenital chloride diarrhea
CFTR/ClC2	Secrete Cl^- → secrete H_2O	Stimulated by diarrhea agents (VIP, cholera toxin, *E. coli*)	Stimulated by laxative lubiprostone, linaclotide	Cystic fibrosis
			Inhibited by antidiarrheal crofelemer	

(congenital chlorinated diarrhea, etc.; see Table 3.3). Modulation of these transporters by pharmacotherapeutic agents is now possible.

3.4.1.3 Absorption of Macronutrients

The assimilation of nutrients by the body is based on two steps: (1) digestion by enzymes (salivary, gastric, pancreatic, intestinal) to reduce the ingested nutrients to a molecular form acceptable to the enterocyte and (2) subsequent absorption by the intestine requiring passage of digested nutrients through the enterocyte cell and to the venous or lymphatic vessels.

(a) Carbohydrates digestion and absorption Sugars make up about 50% of our dietary caloric intake. They are mainly in the form of polysaccharides, such as amylose, amylopectin, or starch (a long chain of glucose molecules and constituting about 60% of ingested carbohydrates), or disaccharides such as sucrose (also called saccharose: a dimer of glucose and fructose constituting about 30% of the consumed sugars), lactose (dimer of glucose and galactose), maltose (glucose dimer linked by α-1,4), and more rarely trehalose (glucose dimer linked by α-1,1) (Fig. 3.26). Other sugars are also present in the diet such as sorbitol, cellulose, hemicellulose (insoluble fibers), and pectins (soluble fibers).

Polysaccharides such as starch (glucose chains α1–4 and α1–6) are rapidly digested by salivary amylase (digestion of about 5% of the polysaccharides in the mouth and about 30–40% in the stomach) and pancreatic amylase (in the duodenum and/or jejunum) to produce maltose (a disaccharide consisting of two molecules of glucose) but also maltotriose (made of three glucose molecules) or α-limit dextrin (chain of about eight glucoses). In practice, salivary insufficiency or pancreatic insufficiency has few clinical consequences for the absorption of sugars, since one of the two organs will probably be able to compensate for the other and since dietary disaccharides (40–50% of ingested sugars) are not affected by amylase deficiency and can be directly digested in the intestine (below).

Disaccharides (ingested as such or obtained by the digestion of polysaccharides) consist of two sugars and are not absorbable as such; they will have to be reduced by enzymes (disaccharidases) of the intestinal brush border to generate monosaccharides absorbable by the enterocyte. Maltase transforms maltose (from starch) into two glucose molecules; lactase transforms lactose into glucose and galactose molecules; saccharase (sucrase) transforms saccharose (sucrose) into glucose and fructose molecules, while trehalase transforms the trehalose molecule (glucose-glucose α1–1, contained in mushrooms or wine or as an additive in some foods such as ice cream) into two glucose molecules. Glucoamylase and isomaltase hydrolyze α-limit dextrins and maltotriose into glucose.

Insufficient membrane disaccharidases leave in the intestinal lumen carbohydrate molecules that have not been reduced to monosaccharides and are therefore not absorbable, thus generating an osmotic load provoking H_2O transfer into the intestinal lumen and diarrhea; these non-absorbed sugars, when they reach the colon, are partially metabolized by the colonic bacteria into volatile gases (such as CO_2, methane, volatile fatty acids, etc.) resulting in flatulence and abdominal bloating. Disaccharidase deficiency may be congenital (e.g., lactase deficiency common in adult non-Caucasians) or acquired

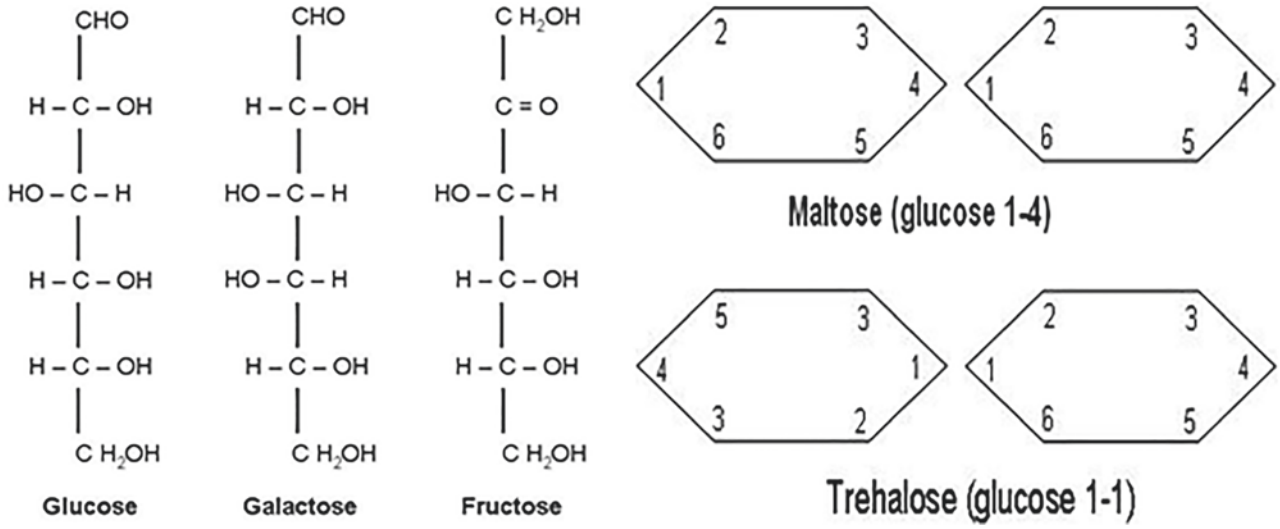


Fig. 3.26 Structure of monosaccharides (glucose, galactose, fructose) on the left and disaccharides (maltose and trehalose) on the right (Lactose (glucose-galactose) and sucrose (glucose-fructose) are not shown here)

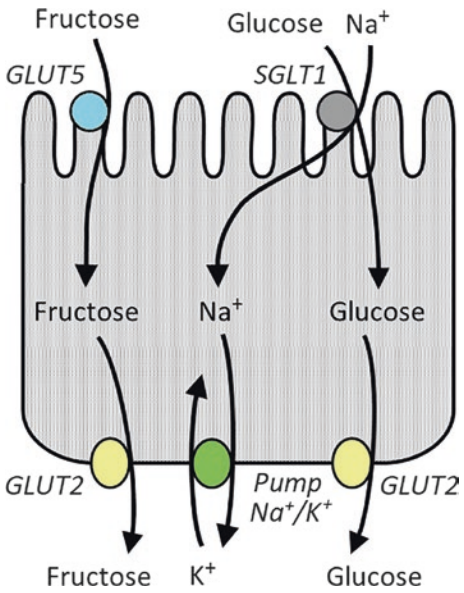


Fig. 3.27 Small intestine and absorption of monosaccharides. Glucose passes from the intestinal lumen to the interior of the enterocyte via SGLT-1, which simultaneously transports one molecule of glucose and two molecules of Na^+ through the apical membrane. Galactose also uses SGLT-1. Fructose enters the enterocyte via GLUT5 transporter. To exit from the cell to the extracellular space (before reaching the blood vessels), monosaccharides will have a facilitated transport by GLUT2 transporter of the basolateral membrane

(secondary to any disease affecting the growth of intestinal villi normally containing these disaccharidases).

Monosaccharides, glucose, galactose, and fructose, will be absorbed by the enterocyte (Fig. 3.27). The passage of these carbohydrates from the intestinal lumen to the interior of the enterocyte cell is ensured by specific transporters located at the apical membrane of the enterocyte: SGLT-1 (sodium-glucose cotransporter 1) transports glucose, just like galactose, within the cell; it is coupled, as we have seen previously, to the transport of the Na^+ ion. GLUT5 (glucose transporter 5) transports fructose through the apical membrane to the interior of the enterocyte. Other transporters such as GLUT2 (normally expressed at the basal membrane; see below), GLUT7, SGLT-4, and SGLT-6 have also recently been identified at the brush border membrane of the enterocyte, but their physiological roles remain to be demonstrated.

Once introduced into the enterocyte, glucose, galactose, and fructose will be expelled from the cell by GLUT2 (glucose transporter 2), a transporter located on the basolateral membrane (Figs. 3.27 and 3.28). Although it is only a glucose facilitated transporter (and not an active transporter like SGLT-1), GLUT2 has a high functional capacity and is practically unsaturable. Once in the intercellular space, these monosaccharides will be able to reach the submucosal veins and travel via the portal circulation from the intestine to the liver.

In the intercellular space, carbohydrates, by their osmotic charge, will contribute to the paracellular flux going through the tight junctions, drawing water and subsequently ions into the flow (solvent drag).

The sequence of digestion of polysaccharides into monosaccharides to be absorbed is summarized in Fig. 3.28.

(b) Proteins digestion and absorption Proteins constitute about 25% of our caloric ingestion. The sequence of digestion of proteins into dipeptides and amino acids for absorption at the enterocyte is illustrated in Fig. 3.29.

- *In the stomach,* proteins are first digested by pepsin, secreted by the gastric chief cells, which hydrolyzes polypeptides into oligopeptides.

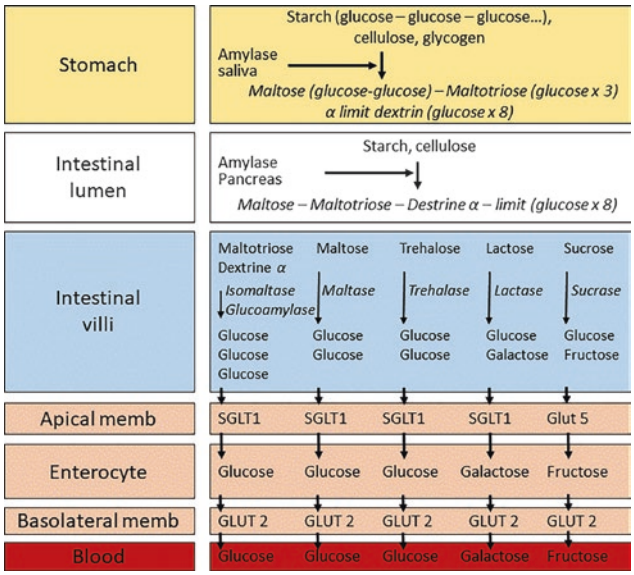


Fig. 3.28 Digestion and absorption of carbohydrates. (1) Ingested polysaccharides (starch, cellulose, glycogen) are transformed by salivary and pancreatic amylases into disaccharides. (2) Disaccharides, whether transformed (e.g., maltose) or ingested (e.g., sucrose, lactose, trehalose), are reduced by villi disaccharidases into monosaccharides. (3) These simple sugars (glucose, fructose, galactose) are absorbed into the enterocyte by specific brush border membrane (BBM) transporters. (4) They are then released from the absorbent cell (into the paracellular space toward blood vessels) using a transporter (GLUT2) of the basolateral membrane (BLM)

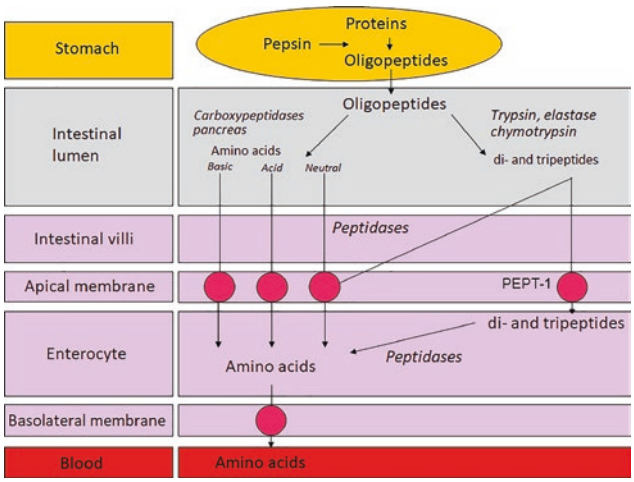


Fig. 3.29 Digestion and absorption of proteins. (1) Ingested polypeptides are digested by gastric pepsin and pancreatic peptidases into oligopeptides and amino acids. (2) Villi peptidases can then reduce oligopeptides into amino acids. (3) Amino acids will cross the apical membrane (BBM) of the enterocyte using specific transporters; di- or tripeptides can use the very fast pathway of the apical transporter PEPT-1 to enter the enterocyte where they will then be reduced into amino acids by cytoplasmic peptidases

- *In the intestinal lumen*, pancreatic enzymes (endopeptidases, trypsin, chymotrypsin, and elastase, and exopeptidases: carboxypeptidase, etc.) reduce oligopeptides to di- or tripeptides or amino acids.
- *At the intestinal villi*, aminopeptidases and DPP IV (dipeptidyl peptidase IV) may complete the final digestion of di- or tripeptides into free amino acids to be absorbed by the enterocyte.
- *The enterocyte* will be able to absorb the protein products using different transporters of the apical membrane: di- or tripeptides can be absorbed as such by PEPT-1 (peptide transporter 1), while amino acids can be absorbed by various transporters more or less dedicated to each class of amino acid.

PEPT-1 is a transporter that can move di- or tripeptides very efficiently into the intracellular milieu where they will then be transformed into amino acids by cytoplasmic peptidases. PEPT-1 is very efficient, i.e., it has a high absorption capacity and is able to treat all di- or tripeptides. PEPT-1 is even used for the passage of various drugs into the cell (various cephalosporins, penicillins, ACE inhibitors, antivirals such as acyclovir, etc.). PEPT-1 is a cotransporter coupled to a H^+ proton gradient.

Amino acids can also be absorbed as is. Conveyors (Na^+ coupled or not) exist for most of the major classes of amino acids (e.g., a transporter for acidic amino acids, a transporter for basic amino acids, etc.), but these are usually nonexclusive and may carry other amino acids than their typical substrates. Tryptophan transporter deficiency (expressed primarily in the kidney and leading to Hartnup disease with secondary niacin deficiency and hypercalcemia) is one of the few conditions where deficiency of an amino acid transporter has important clinical consequences. Carrier deficiency (e.g., histidine, or methionine, or cysteine, etc.) most often results in mild clinical abnormalities (e.g., mild mental retardation) or may even induce asymptomatic biochemical abnormalities (e.g., aminoaciduria). Indeed, a defect in an amino acid carrier can often be compensated by other carriers that can take over to allow the transport of the amino acid that may have been affected by the loss or deficiency of its carrier, as well as by PEPT-1, which may allow the entry of di- or tripeptides containing the amino acid in question.

- *At the basal membrane,* the transfer out of the enterocyte cell to the paracellular space of the amino acids will be carried out using membrane transporters for neutral, acidic, or basic amino acids.

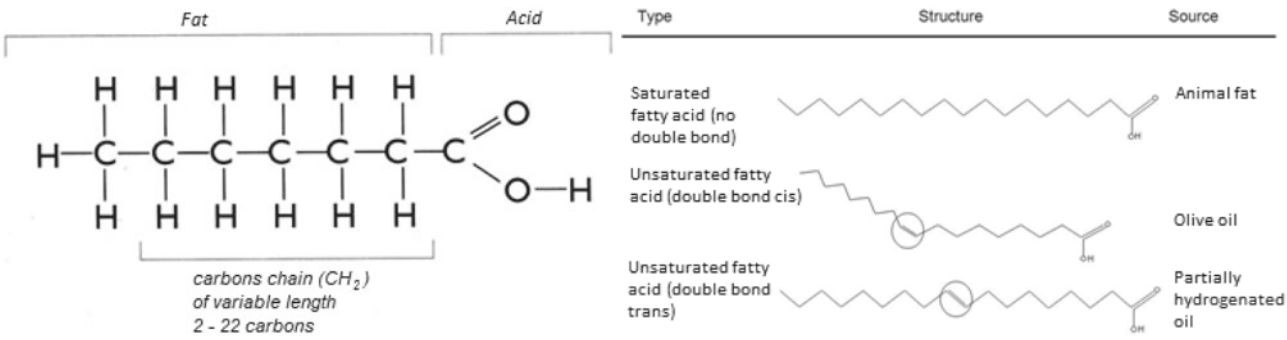


Fig. 3.30 Fatty acid structure. Left: the carbon chain is of variable length (2–22). Right: the double bond (circle) can angulate (cis form) or keep linear (trans form) the unsaturated fatty acids

(c) Lipids digestion and absorption Lipids account for approximately 25% of our caloric intake, and 95% of lipids are ingested in the form of triglycerides, i.e., a glycerol molecule to which three fatty acid molecules are attached. Fatty acids are made up of a chain of carbon atoms of different lengths (2–22 carbons), such as butyric acid (C_3 H7 COOH) found in butter, octanoic acid (C8) in vegetable fats, palmitic acid (C15) or stearic acid (C17) in animal and vegetable fats, and arachidic acid (C19) in peanuts. Fatty acids can be saturated (i.e., without a double bond between the carbon atoms) or unsaturated (i.e., with one or more double bonds); the double bond can lead to the trans form (linear structure of the C atoms) or to the cis form angulating the structure of the molecule (Fig. 3.30). The fluidity of fatty acids is influenced by these structural changes (cis FA > trans FA > saturated FA).

- The first step of lipid digestion aims at transforming triglycerides into monoglycerides and free fatty acids. This process is partially carried out in the mouth by salivary lipase, continues in the stomach by gastric lipase, and is completed in the intestine by pancreatic lipase. Gastric lipase, secreted by the chief cells of the stomach (together with pepsinogen), can take up to 40% of the fat digestion process, which probably explains the persistence of some lipid digestion even in the presence of a total pancreatectomy. Pancreatic lipase, unlike gastric lipase, is acid-sensitive and therefore requires the joint secretion of bicarbonates (mostly pancreatic but possibly also duodenal), as well as of a colipase, to be active.

Other dietary lipids include phospholipids (lecithin and phosphatidylcholine) which will be hydrolyzed by phospholipase A2. Cholesterol esters are hydrolyzed by cholesterol esterase into absorbable free cholesterol.

- Fatty acids released in the proximal small bowel then combine with cholesterol, phospholipids, and fat-soluble vitamins (A, D, E, K) to form micelles, small aggregates made water-soluble by the addition of bile salts (Fig. 3.31).

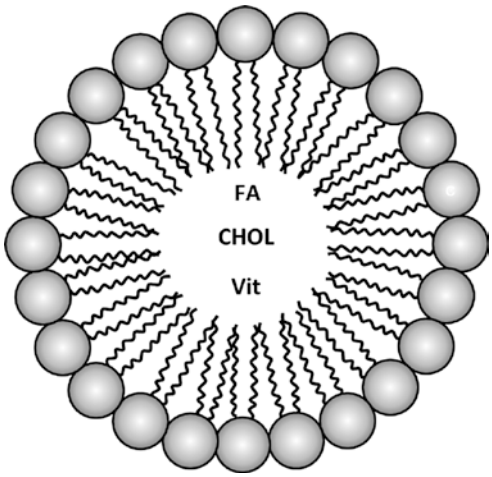
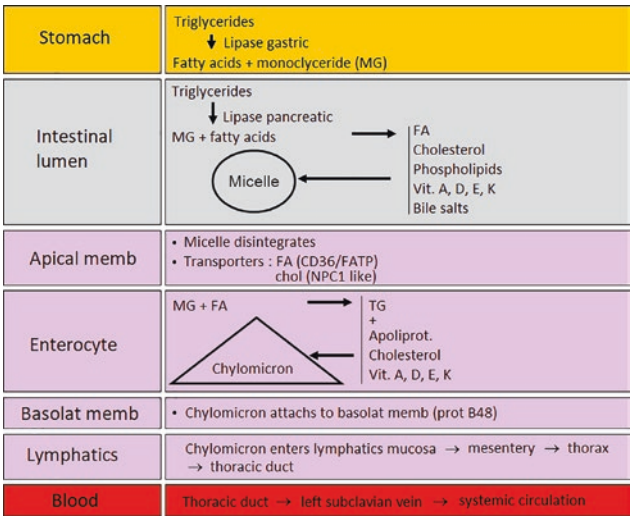


Fig. 3.31 Micelle: spherical-shaped structure made of 20–40 molecules of bile salts with a fat-soluble center (where fatty acids, cholesterol, and fat-soluble vitamins A, D, E, and K can be found) and a hydrophilic exterior side (allowing dissolution in the intestinal aqueous liquid)

- Micelles, which are water-soluble, can pass through the mucus layer lining the intestine and reach the apical mucosa of the enterocyte. At this point the micelle will progressively "disintegrate," and while the bile salts will remain in the intestinal lumen to be ultimately absorbed at the ileum, the other components of the micelle will then enter the cell. Until recently, it was believed that the passage into the enterocyte was a passive entry. It is now known that there are many proteins on the apical membrane of the enterocyte that are involved in this absorption process: CD36/FATP (fatty acid transport protein) acts as a fatty acid transporter through the apical pole; other specific transporters are involved in the entry of cholesterol (Niemann-Pick C1-like; inhibited by ezetimibe, a drug used as a cholesterol-lower-

ing agent) or vitamin E (scavenger-receptor class B type 1).

- Inside the cell, the rare short-chain (less than eight carbon atoms) or medium-chain (C10–C12) fatty acids can travel directly to the venous system (superior mesenteric vein → portal vein) and reach the liver. But the fatty acids in the diet are mostly long-chain (C16, etc.) and will require a more laborious route: in the smooth endoplasmic reticulum, the fatty acids are re-esterified with glycerol to re-form a triglyceride that will join apolipoproteins, cholesterol, and fat-soluble vitamins to form a chylomicron. The chylomicron, thanks to the B48 protein (deficient in *chylomicron disease* where lipids accumulate in the enterocyte), attaches itself to the basolateral membrane to be expelled from the enterocyte and thus reaches the lymphatics (lacteals) of the villi.
- Chylomicrons circulate in the intestinal lymphatics (and lymph nodes) toward the thoracic lymphatics and the thoracic duct draining into the left subclavian vein. Any obstacle to the passage of lymph from the intestine to the upper venous circulation (e.g., obstruction of the abdominal lymphatic system by lymphoma, compression of the lymphatics of the upper retroperitoneum by pancreatitis, surgical or traumatic interruption of lymphatic flow at the thoracic duct or left subclavian vein) can compromise lipid assimilation (except for short-chain fatty acids that use the portal venous rather than the lymphatic pathway to integrate into the body's systemic functions). The stages of lipid digestion and absorption are illustrated in ◘ Fig. 3.32.



◘ **Fig. 3.32** (1) In the stomach and intestine, lipids are digested by gastric and pancreatic lipases into fatty acids. (2) Bile salts will allow fatty acids to be solubilized into water-soluble micelles. (3) After "disintegration" of the micelles at the apical membrane (BBM) of the enterocyte, fatty acids will penetrate the enterocyte via the CD36/FATP transporter. (4) Inside the enterocyte, fatty acids will be integrated into chylomicrons. (5) Chylomicrons are expelled through the basolateral membrane (BLM), via B48 protein, out of the cell into the paracellular space (6) toward the lymphatic and (7), ultimately, the venous system

(d) Summary Assimilation of food into the organism thus includes (1) its digestion by different enzymes in the gastric and intestinal lumen (◘ Fig. 3.33, next page) and (2) its absorption by the enterocyte (◘ Fig. 3.34).

3.4.1.4 Vitamin Absorption

Fat-soluble vitamins A, D, E, and K are absorbed via micelles and chylomicrons as described above in the (see ► Sect. 3.4.1.3) on lipids.

Water-soluble vitamins B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), and C, biotin, and pantothenic acid are absorbed in the proximal small bowel by various transport mechanisms, sodium dependent or not.

Folic acid is a nonabsorbable molecule in its original polyglutamate form. A mucosal enzyme, folate hydrolase, allows the release of glutamates that can be absorbed by three transporters including PCFT (or proton-coupled folate transporter identical to heme carrier protein 1 which may carry the heme molecule for iron absorption as discussed later). Certain substances, such as alcohol or some medications (e.g., sulfasalazine or methotrexate), inhibit folate hydrolase and therefore can reduce folate absorption.

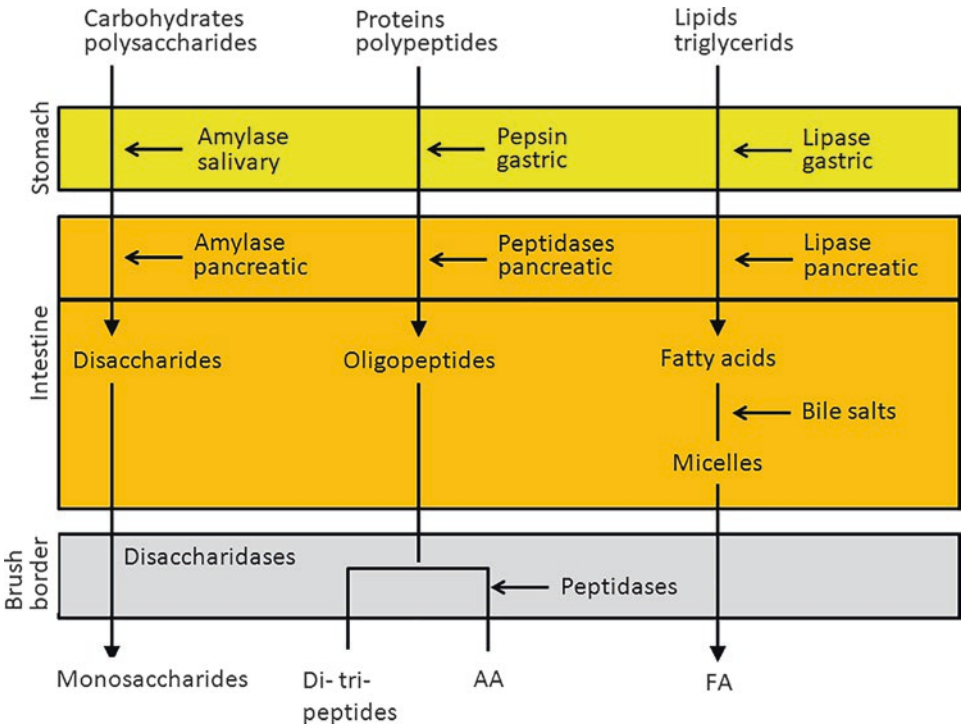
Vitamin B12 is absorbed in the ileum, as discussed later in point 7.

3.4.1.5 Mineral Absorption

Calcium is absorbed by active transport in the duodenum and jejunum. Its absorption is finely regulated according to circulating Ca^{++} levels (mainly by a metabolite of vitamin D, 1–25 vitamin D_3, whose renal production increases in response to the rise in plasma parathyroid hormone following blood hypocalcemia).

Calcium absorption is normally transcellular; in presence of high concentrations of calcium in the lumen, the paracellular pathway (solvent drag) may also be mobilized.

Magnesium is clinically important (neurotransmission, muscle relaxation, bone metabolism, etc.). Magnesium absorption seems to be maximal in the ileum. Paracellular pathways by solvent drag are involved, as well as cellular pathways via active transporters (TRPM6 and TRPM7: transient receptor potential melastatin) in the form of channels permeable to divalent cations and sen-



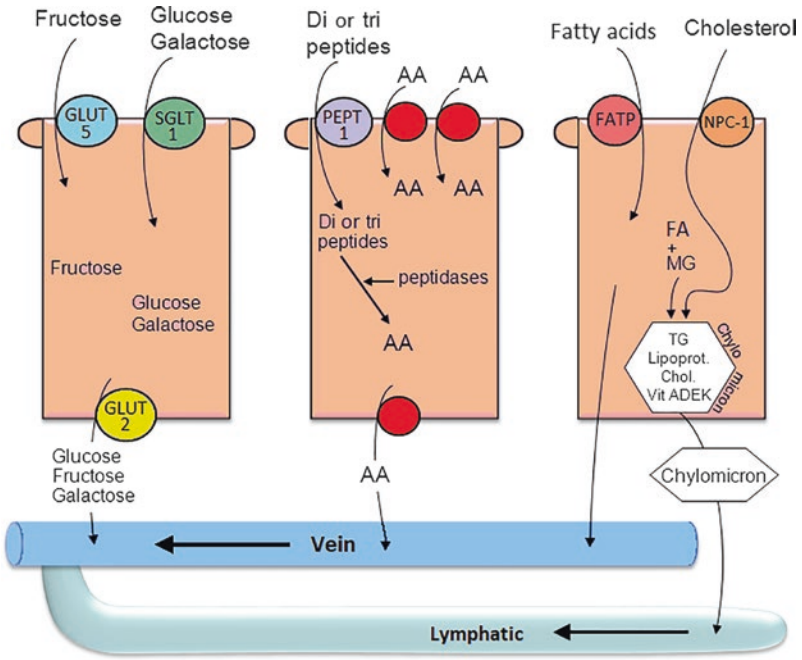


Fig. 3.33 Food digestion in the stomach cavity, intestinal lumen, and brush border microvilli to allow absorption by enterocytes

Fig. 3.34 Nutrient absorption through the enterocyte barrier. After digestion by salivary (amylase), gastric (pepsin/lipase), pancreatic (amylase/peptidases/lipase), and villi (disaccharidases/peptidases) enzymes, simple sugars, amino acids or oligopeptides, and fatty acids enter the enterocyte cell via specific apical membrane transporters. The expulsion from the enterocyte into the intercellular space of the intestinal mucosa will take place via different transporters of the basolateral membrane of the absorbent cell. Simple sugars, amino acids, as well as short-chain fatty acids will then reach the venules of the intestinal villi to join the mesenteric and the portal veins to the liver; long-chain fatty acids, integrated into chylomicrons, meet the lymphatics of the intestinal villi and then, via the mesenteric and thoracic lymphatics, travel to the peripheral venous circulation

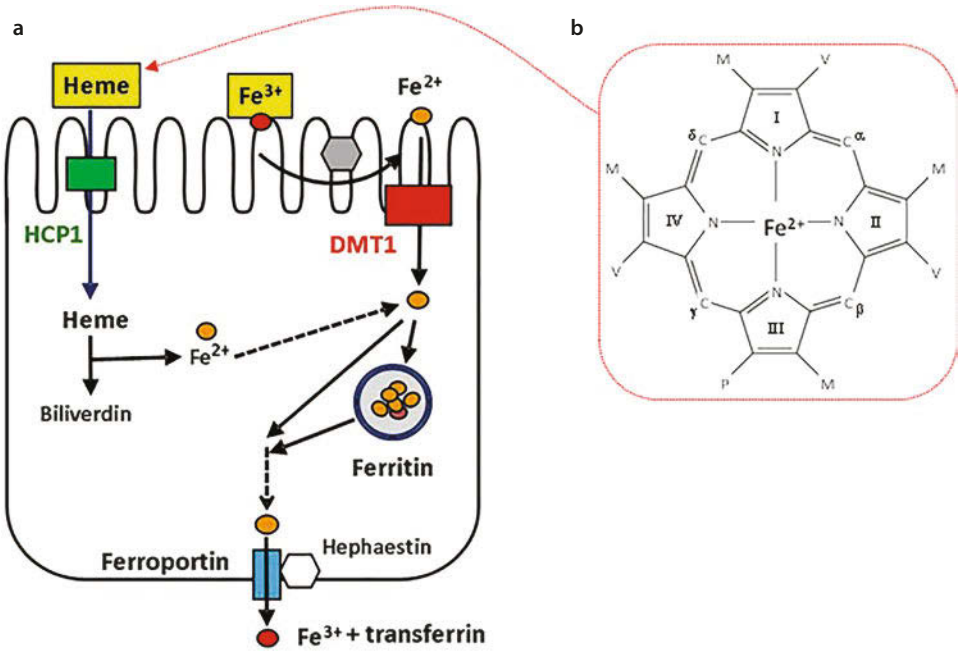


Fig. 3.35 Intestinal iron uptake: **a** Iron contained in the heme of red blood cells, myoglobins, etc. from animal meats is absorbed by HCP-1 (heme carrier protein 1), transporter of the heme molecule; **b** Iron existing in other foods as Fe^{+++} is transformed by a membrane reductase into Fe^{++} to be absorbed by the transporter DMT-1. Iron is expelled from the cell by the transporter ferroportin

sitive to various factors such as angiotensin II, aldosterone, estrogens, etc. as well as to certain drugs such as PPIs (hypomagnesemia is a rare but potentially severe complication of proton pump inhibitors).

Iron Only 10–20% of ingested iron is absorbed, mostly by the proximal small bowel and via two specific routes of absorption (Fig. 3.35). Heme iron (i.e., contained in the heme of red blood cells, myoglobins, etc., from animal meats) is absorbed by HCP-1 (folic acid transporter). Nonheme iron (vegetal iron) is nonabsorbable as such and has to be transformed, in an acid milieu and with the help of a reductase of the enterocyte membrane, from ferric iron (Fe^{+++}) into ferrous iron (Fe^{++}) to be absorbed via DMT-1 (divalent metal ion transporter-1). Once in the enterocyte, Fe^{++} may join ferritin, an intracellular reserve protein; or it can be transported to the basolateral membrane to be expelled via ferroportin, and then reoxidized to Fe^{+++} by hephaestin, before binding to transferrin for blood transport to target organs.

The absorption of iron is regulated by its body concentrations; a molecule produced by the liver, hepcidin, inhibits the ferroportin transporter of the basolateral membrane and slows down the apical absorption of iron by the enterocyte. In the event of iron deficiency, hepcidin production is reduced, and the enterocyte, released from its brake, increases its absorption of iron. Hepcidin deficiency (either directly by defect of the HAMP (hepcidin antimicrobial peptide) gene coding for hepcidin or indirectly by defect of the HFE protein regulating hepcidin production) explains the exaggerated iron absorption and iron overload of hemochromatosis (abnormalities of the HFE gene are used clinically to diagnose hereditary hemochromatosis; see ▶ Chap. 8).

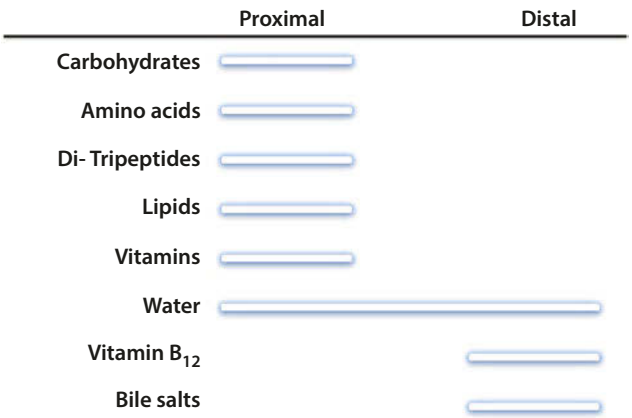


Fig. 3.36 Absorption of ions, fluids, and nutrients along the small intestine

3.4.1.6 Distal Small Intestine

Most substances are absorbed throughout the small intestine (Fig. 3.36) but, in fact, are already absorbed during their transit in the proximal half of the intestine. However, the distal ileum is essential for the absorption of two substances: vitamin B12 and bile salts.

3.4.1.7 Vitamin B12 Absorption

Vitamin B12 (or cobalamin) is a complex vitamin (Fig. 3.37) that is absorbed from the ileum and undergoes several stages of processing that can lead to various causes of B12 deficiency (Fig. 3.38).

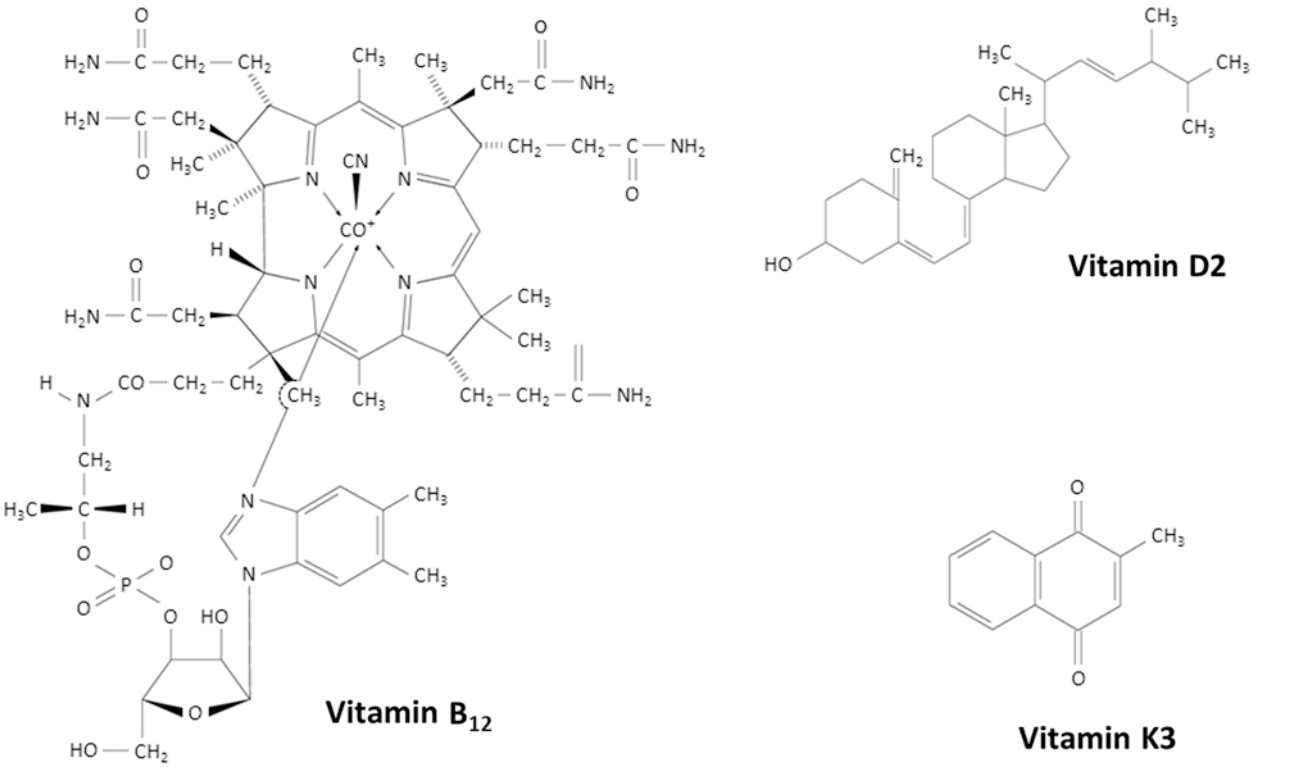


Fig. 3.37 Complex structure of vitamin B12. Other vitamins, shown here as examples, have a much simpler chemical structure

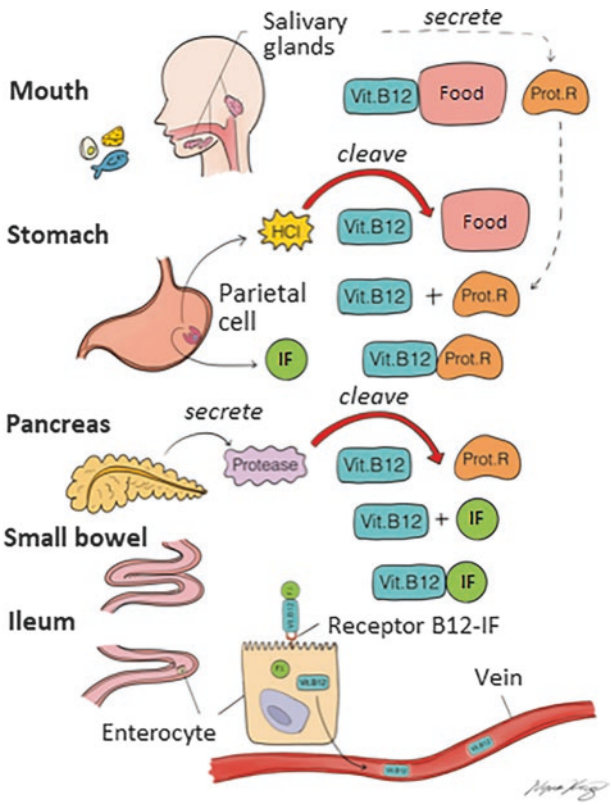


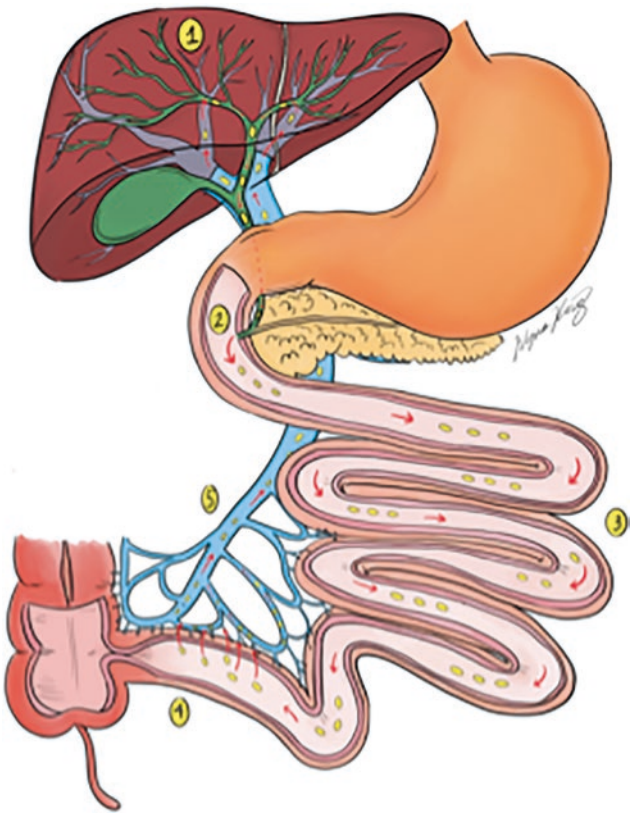
Fig. 3.38 Absorption of vitamin B12

1. Ingested vitamin B12 is protein-bound and requires the action of acid and pepsin to be released in the stomach. Hypochlorhydria (e.g., PPI) may decrease the absorbed amount of B12.
2. Vitamin B12 then binds to protein R (haptocorrin or transcobalamin), produced mainly by the salivary glands to protect itself from hydrolysis by pepsin and stomach acid. However, no vitamin B12 deficiency is known in clinic to be related to a deficiency of this R protein.
3. The intrinsic factor (IF) secreted by the gastric parietal cell is absolutely necessary for absorption of vitamin B12 from the ileum. Intrinsic factor deficiency occurs mainly after gastrectomy or with gastric atrophy (see ▶ Chap. 2) and leads to vitamin B12 deficiency with its hematological consequences (Biermer's megaloblastic anemia).
4. Binding of vitamin B12 to the intrinsic factor is however impossible in acidic pH and can therefore only occur in the alkaline duodenal environment; important gastric acid hypersecretion (e.g., gastrinoma) with duodenal acidification could compromise this binding.
5. Vitamin B12 must first be dissociated from the R protein by pancreatic trypsin (hence possible vitamin B12 deficiency in case of pancreatic insufficiency) and will then be bound to the IF.

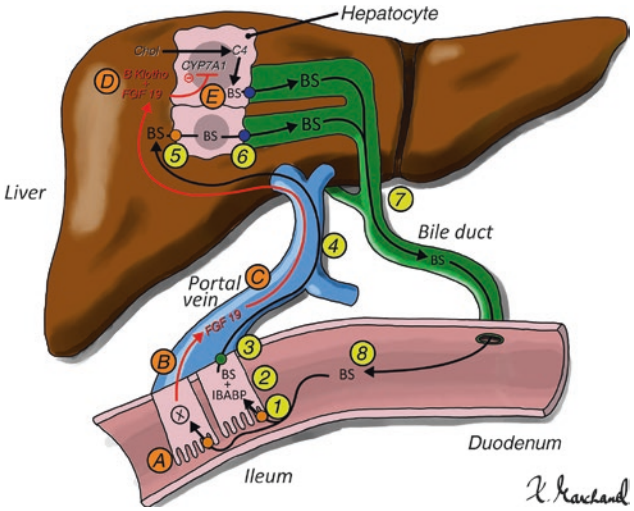
6. Once bound to the IF, vitamin B12 will travel from the small intestine to the terminal ileum. Bacteria in excessive numbers (small intestinal bacterial overgrowth syndrome discussed later in the ▶ Sect. 3.6) can attack vitamin B12 and reduce its concentration.
7. At the distal ileum (over the last 100 cm or so), a receptor (cubilin) allows binding of the FI/vitamin B12 complex to the enterocyte and its transport into the cell. FI will then be degraded in the lysosomes; B12 (cobalamin) will be released into the bloodstream and transported, bound to the transcobalamin protein, to the bone marrow and to the liver (where it can be stored for 3–5 years). Any alteration of the distal ileum (e.g., surgical resection of the distal intestine, Crohn's disease affecting the mucous membrane of the terminal small intestine, etc.) may therefore significantly compromise vitamin B12 absorption and leads to a deficiency with its clinical consequences.

3.4.1.8 Bile Salt Absorption

For an extensive description of bile salts, see ▶ Chap. 8. Bile salts are known to be essential for the absorption of lipids, and to understand their role in this process, please refer to ◘ Figs. 3.39 and 3.40.



◘ **Fig. 3.39** Schematic journey of bile acids that are (**1**) synthesized in the liver, (**2**) excreted in the bile ducts, (**3**) and then excreted in the small bowel, (**4**) absorbed in the distal ileum, and (**5**) recirculated via the portal vein to the liver



◘ **Fig. 3.40** Recirculation of bile salts (BS)/acids: (**1**) the BS penetrates into the enterocyte via the apical sodium-dependent bile acid transporter (ASBT), (**2**) binds to the ileal bile acid binding protein (IBABP), and (**3**) is then expelled from the enterocyte via the basolateral organic solute transporter (OST) to (**4**) the portal vein. (**5**) Once in the liver, BS enters the hepatocyte, via an apical transporter called NTCP (Na^+-taurocholate cotransporting polypeptide), and (**6**) is then exported out of the hepatocyte by an ATP-dependent pump to (**7**) the bile duct (**8**) and ultimately reaches the duodenum

Regulation of bile salts (BS)/acid synthesis: BS absorbed from the intestine (**A**) stimulates the farnesoid X nuclear receptor (FXR) which (**B**) causes the enterocyte to secrete FGF-19, (**C**) which is then expelled into the portal vein. (**D**) At the hepatocyte, FGF-19 and beta-Klotho protein bind together to the FGFr4 receptor, (**E**) to inhibit the transformation (by cytochrome CYP7A1 (7α-hydroxylase)) of serum cholesterol into 7a-hydroxy-4-cholesten-3-one (C4) and ultimately into BS (to be evacuated in the bile ducts en route to the duodenum)

Step 1 In the liver, bile salts are synthesized, using more than 16 enzymes, from blood cholesterol (the primary bile acids are then conjugated with glycine or taurine) or are obtained from circulating bile salts after their absorption at the terminal ileum (as discussed below). Any liver disease that prevents liver synthesis (hepatocyte failure in cirrhosis, etc.) or excretion from the liver of synthetized materials (e.g., intrahepatic cholestasis in primary biliary cirrhosis) may result in bile salt deficiency compromising diet lipid absorption.

Step 2 Once synthesized by the hepatocyte, bile salts enter the bile ducts and exit the liver to the extrahepatic bile ducts and the common bile duct before reaching the duodenum at the ampulla of Vater. Any obstruction of the bile ducts (by stones, inflammation, neoplasia, etc.) preventing bile salts synthesized in the liver from reaching the duodenum will compromise the absorption of lipids.

Step 3 In the small intestine, conjugated bile salts play a major role in the absorption of lipids by emulsifying lipids into droplets for lipase action and by generating the for-

mation of micelles that allow fatty acids to "melt" into a water-soluble structure (micelle) and thus approach the enterocyte for absorption. At the intestinal level, the formation of micelles can be vulnerable to various aggressors: (a) intestinal bacteria in too large quantity (intestinal bacterial overgrowth syndrome) can deconjugate the bile salts, making them unsuitable for micellar formation; (b) an overly acidic environment (e.g., gastric hypersecretion in gastrinoma (see ▶ Chaps. 2 and 5)) compromises micellar formation; (c) certain pharmacological substances, such as cholestyramine-type resins used in some cases of diarrhea, can bind bile salts and thus reduce the concentration required for micellar formation.

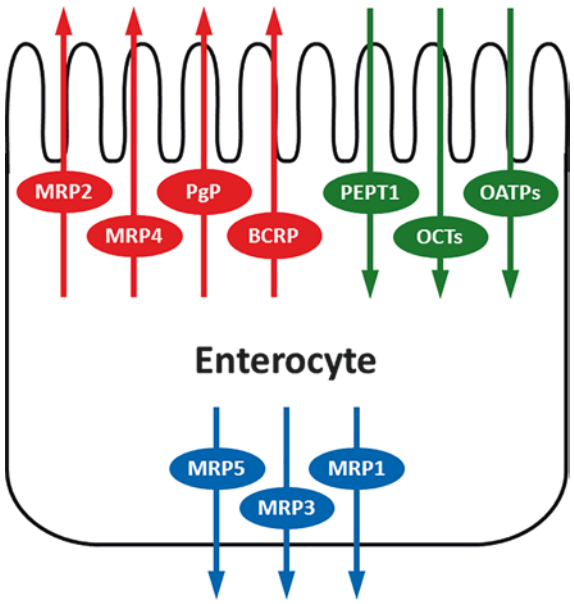
Step 4 At the enterocyte surface, the micelle will "dissolve"; fatty acids and vitamins are then transported into the enterocyte, while bile salts are released free in the intestinal lumen. Driven with the intestinal flow by the motor contractions of the small intestine walls, bile salts reach the terminal ileum where are located enterocyte specific receptors (apical sodium-dependent bile acid transporter (ASBT)], proteins (cytoplasmic ileal bile acid binding protein (IBABP)), and transporters (basolateral organic solute transporter (OST)) allowing 95% of the bile salts to be reabsorbed from the intestine. Any pathological condition (e.g., Crohn's disease inflammation, surgical resection, etc.) affecting the last meter of the ileum compromises the absorption of bile salts (as well as vitamin B12); unabsorbed bile salts will then pass directly into the colon and, by activating the secretion of the colonocyte, via a cAMP-dependent mechanism, will cause diarrhea. Choleretic diarrhea can be treated by binding luminal bile salts to a cholestyramine-type resin to reduce the quantity of free bile salts stimulating colon secretion. Inhibitory drugs against ileal receptors for bile salt absorption are being investigated to increase colonic secretion and treat constipation.

Step 5 After their absorption at the terminal ileum, bile salts enter the mesenteric venous circulation and travel via the portal vein to the liver where they are absorbed by hepatocytes to join the newly synthesized (from blood cholesterol) bile salts for excretion into the bile ducts. This "enterohepatic recirculation" is essential to maintain the "pool of bile salts" in the body. In the event of decreased enterohepatic recirculation (e.g., failure to absorb bile salts after resection of the terminal ileum), the liver increases the synthesis of new bile salts from cholesterol in an attempt to maintain adequate bile salt secretion for intestinal absorption of lipids. The hepatic synthesis of new bile salts is regulated by FGF-19 (fibroblast growth factor-19) secreted from the enterocyte into the portal vein to inhibit the activity of the hepatic enzyme 7α-hydroxylase, which converts cholesterol into bile acid. A defect in FGF-19 secretion has been identified in patients with idiopathic (or primary) choleretic diarrhea (see ▶ Sect. 3.9.4) and probably explains diarrhea by increased colonic secretion due to overproduction of bile salts that will reach the small intestine in excess quantity overriding the ileal absorptive capacity and then spilling into the colon.

3.4.1.9 Drug Absorption/Biotransformation

The vast majority of oral medications are absorbed through the small intestine. Prolonged passage through the stomach (e.g., diabetic gastroparesis) can delay the absorption of a drug and even modify its kinetics. Too rapid passage through the intestine (e.g., dumping syndrome, short bowel syndrome, post-ileostomy, etc.) may result in an insufficient contact time with the enterocyte to provide optimal absorption. Such physical factors are clinically important causes of altered drug absorption and bioactivity.

Drug absorption mechanisms have been clarified and characterized in recent years. As for nutrients, there is less and less belief in their strictly passive absorption, and the notion of membrane transporters is becoming more and more important. To cross the apical membrane of the enterocyte, most drugs use transporters such as PEPT-1 (also used for the transport of di- or tripeptides). To cross the basolateral membrane into the bloodstream, other transporters (e.g., MRP1, MRP3, etc.) come into action (◘ Fig. 3.41). Transporters



◘ **Fig. 3.41** Drug transport by the enterocyte: at the apical membrane, transporters (called influx transporters, such as PEPT-1, shown here in green) allow a drug to enter the enterocyte; transporters (called efflux transporters, such as PgP, shown here in red) are also present to cause a drug (perceived as toxic) to exit the cell back into the intestinal lumen. At the basolateral membrane, transporters (in blue) allow the passage of drugs from the enterocyte to the bloodstream

expressed in the enterocyte, as well as in other organs (such as the hepatocyte, blood-brain barrier, etc.), are usually capable of transporting various drug molecules.

Faced with drug molecules, which are probably more or less perceived as "foreign material," the body seems to have provided "protective" mechanisms. At the apical membrane, efflux transporters (such as P-glycoprotein, BCRP, MRP) can transport molecules absorbed by the influx transporters back to the intestinal lumen (Fig. 3.41). In other systems, the importance of these efflux transporters has been well demonstrated; thus, the increase of BCRP (breast cancer resistance protein) or MRP (multidrug resistance protein) transporters has been implicated in the phenomenon of drug resistance to treatment by preventing the passage of the therapeutic agent to the target cell. The anticoagulant dabigatran, a substrate with an affinity for P-glycoprotein (PgP or PGP), may have increased systemic bioavailability if used with a potent P-glycoprotein inhibitor such as ketoconazole, or even with more modest inhibitors such as verapamil and quinidine; its plasma concentrations can also be lowered in presence of P-glycoprotein inducers such as rifampin, carbamazepine, and St. John's wort.

Biotransformation is another protective mechanism. Enterocytes contain P450 cytochromes (well known in the liver) and can thus transform certain drugs. Vincristine (anticancer agent), verapamil (anticalcic agent), dexamethasone (corticosteroid), cyclosporine (immunosuppressant), statins, etc., after they have passed through the apical membrane, are transformed by the cytochrome CYP3A4 of the enterocyte. The metabolites (active or inactive) of these substances can then be transported to the basolateral pole and to the circulation or can be redirected out of the cell by the P-glycoprotein of the apical membrane into the intestinal lumen (Fig. 3.42).

The clinical impact of this intestinal biotransformation is illustrated by grapefruit juice, which can alter the bioavailability of many drugs absorbed by the intestine. A single glass of grapefruit juice irreversibly inhibits cytochrome 3A4 (for 3–5 days until synthesis of a new enterocyte cell) and thus markedly increases circulating levels (Fig. 3.43) and pharmacological activity of many drugs such as calcium blockers that would normally be transformed into inactive metabolites by this enteric cytochrome.

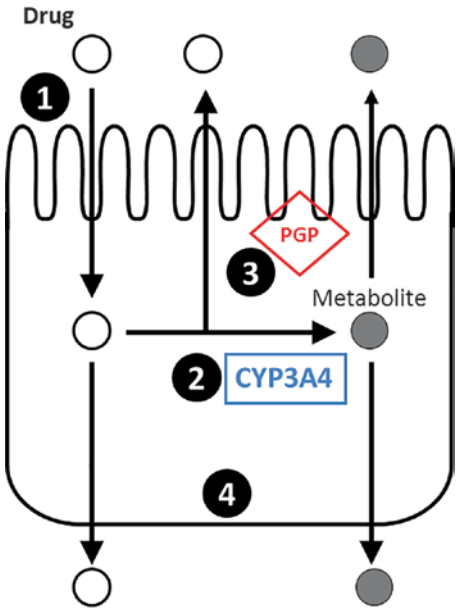


Fig. 3.42 Biotransformation of drugs by the enterocyte. A drug absorbed at the apical membrane (**1**) can be expelled intact at the basolateral membrane (**4**). Or it may be released at the apical membrane (**1**) via PGP (**3**). Or it can be transformed by a cytochrome (**2**) into a metabolite that can be taken out of the enterocyte via apical PGP (**3**) or transported to the basolateral pole (**4**) and to the bloodstream

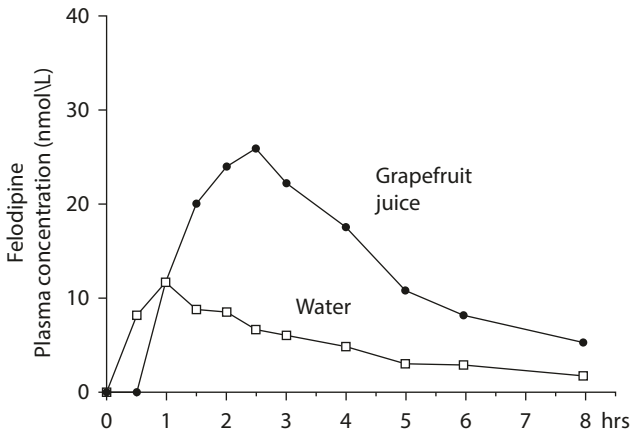


Fig. 3.43 Increased plasma levels of felodipine when absorbed in the presence of grapefruit juice rather than water (according to Wilkinson GR. NEJM 2005)

3.4.2 Secretion by the Small Intestine

The small bowel is vital for its absorption function (7–8 l/day), while its secretion process is often neglected. It is estimated that the small intestine, especially the proximal one, secretes about 1 l of fluid daily. This secretion is mainly intended to balance the osmolarity of the intraluminal contents.

3.4.2.1 Water and Electrolyte Secretion

The entry of hyperosmolar food into the duodenum triggers water secretion. The luminal content then becomes isoosmotic and will remain so throughout the small bowel. This secretion may be simply due to a reflex

flow in response to an osmolar gradient, as it may be due to an active secretory process triggered by digestive hormones (gastrin, secretin, CCK, GIP, etc.) secreted during the meal.

Hyposmolar duodenal chyme can generate in the proximal small bowel an adaptative secretion of ions in order to correct the luminal osmolarity, but this ionic flux is accompanied by a passive movement of H_20 from the body toward the intestinal lumen. This apparently paradoxical response, reinforcing the duodenal hyposmolarity, is normally compensated in the distal intestine; but the situation can be problematic in patients missing their distal small bowel. In patients with short bowel syndrome (< 100 cm jejunum left after extensive surgical resection; see ▶ Sect. 3.9 in this chapter), drinking water in trying to improve their fluid balance will in fact increase their digestive losses and worsen dehydration. The addition of sodium (NaCl 1 g 1–4 co/glass of water to correct hyposmolarity) and of sugar (to activate Na+-glucose transporter SGLT-1) in drinking fluids is necessary to optimize H20 absorption in the proximal intestine.

3.4.2.2 Bicarbonate Secretion

The secretion of HCO_3^- is a very important function to protect the intestinal mucosa from gastric acid. Insufficient bicarbonate secretion contributes to the genesis of the duodenal peptic ulcer (as discussed in ▶ Chap. 2). Brunner's glands secrete an HCO_3^--enriched mucus, and their marked presence in the duodenum (including the bulb) probably explains the greater capacity of the proximal intestine to protect itself from acid aggression than the distal intestine. Surgical modifications (e.g., gastrojejunostomy) that expose the jejunal or even ileal mucosa to gastric HCl are ulcerogenic, i.e., conductive to ulcer formation in this area of the intestine that is normally not intended to cope with acidic aggression. In the ileum, HCO_3^- is actively secreted via a specific transporter (SCL26) exchanging HCO_3^- for an absorbed Cl^- ion.

3.4.2.3 Mucus Secretion

Secretion of mucus by goblet cells distributed along the intestinal epithelium is, as in the stomach, part of the defense mechanisms of the intestine against any aggression. The inhibition of mucus secretion (and/or HCO_3^-) by nonsteroidal anti-inflammatory drugs (inhibition of prostaglandin synthesis by inhibition of COX-1) probably explains the presence of intestinal ulcers with these drugs.

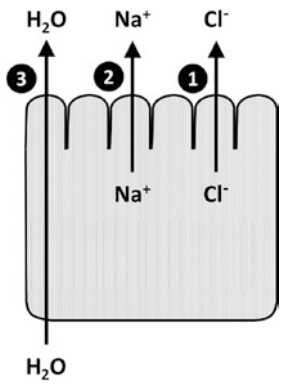
3.4.2.4 "Endocrine" Secretions

Intestinal "endocrine" cells are well known for their secretion of hormones in the circulation (e.g., CCK, secretin) or of paracrine substances (histamine, 5HT, somatostatin). Exocrine intraluminal secretion also appears to exist (e.g., trefoil peptide, defensins).

3.4.2.5 Chloride Secretion and Pathological Conditions

Intestinal secretion is important in pathological situations. Secretions of VIP (vasoactive intestinal polypeptide) by a neuroendocrine tumor (VIPoma) or of toxin by *Vibrio cholerae* or by enteropathogenic *E. coli* are examples of intestinal secretion (usually involving Cl^-) triggered by a pathological process. The secretion of Cl^- is due to the activation (via adenylate cyclase) of the CFTR (cystic fibrosis transmembrane regulator) or the ClC-2 channel of the enterocyte apical membrane. As shown in ◘ Fig. 3.44, the secretion of Cl^- ion in the lumen will cause (on an electrochemical gradient) the passage of a Na^+ ion from the cell to the lumen, then attracting H_2O (osmotic gradient) to the intestinal lumen. The secretion of water during cholera induces a very important diarrhea which can quickly lead to fatal dehydration. Since only the secretory cells in the crypts are affected by the cholera toxin, the enterocytes in the villi remain available for normal absorption (role of the WHO rehydration solution discussed earlier).

The chloride channels responsible for secretion are now therapeutic targets for new pharmacological agents. Lubiprostone, a laxative recently used in the USA, is analogous to prostaglandins and activates ClC-2 channels of the enterocyte, forcing the transport of a Cl− ion into the intestinal lumen and the above-described cascade of Na+ and H2O secretion. Linaclotide, a guanylin analogue and chloride channel activator (CFTR), is also available as a therapeutic agent for constipation. A chloride channel inhibitor, crofelemer, is available for



◘ **Fig. 3.44** Secretion of Cl^- leads to a cascade of events generating the accumulation of liquid in the intestinal lumen: (**1**) secretion of the Cl^- anion (via a CFTR or ClC-2 channel) causes (**2**), according to an electrochemical gradient, migration of the Na^+ cation out of the cell, (**3**) in turn creating an osmolar gradient to attract H_2O to the intestinal lumen

the treatment of secretory diarrhea; it is purified from the latex of the Croton lechleri tree, a sap used in traditional South American medicine (called dragon's blood) against diarrhea, insect bites, etc.

3.4.2.6 Miscellaneous

Table 3.4 presents various agents capable of stimulating secretion or absorption from the small intestine.

Table 3.5 shows some drug-induced disturbances in the absorption physiology.

Table 3.4 Agents stimulating intestinal absorption or secretion

Absorption stimulants	Secretion stimulants
Aldosterone	Prostaglandins
Corticoids	VIP/secretin
α-Adrenergics	Acetylcholine
Opiates and endorphins	Serotonin
Somatostatin	Guanylin
PYY – NPY	Gastrin
	Toxins (*Vibrio cholerae*, *E. coli*, *Salmonella*)
	Bile salts, long-chain fatty acids

Table 3.5 Examples of pharmacological handling of normal assimilation mechanisms

Agent	Action	Result
Somatostatin (octreotide)	Inhibition of pancreatic secretions	Steatorrhea
Orlistat	Inhibitor of gastric and pancreatic lipases	↓ lipid caloric intake (Rx obesity)
Cholestyramine	Bile salt-binding resin	Malabsorption of fats (Rx hypercholesterolemia)
Ezetimibe	Inhibitor of the cholesterol transporter NPC1-like	Malabsorption of cholesterol (Rx hypercholesterolemia)
Acarbose	Inhibitor of glucoamylase, maltase, sucrase	Malabsorption of sugars (Rx diabetes)
Opiates (and somatostatin)	Inhibits intestinal transit	↑ absorption (Rx diarrhea)

3.4.3 Other Functions of the Small Intestine

3.4.3.1 Protection

Like the skin, the small intestine has the essential function of protecting the body against external aggression. In this case, the aggression comes from the billions of bacteria that inhabit the intestine and that can have harmful consequences if they penetrate the human body (e.g., septicemia during translocation of pathogenic bacteria). The intestine, therefore, serves as a barrier to the entry of these aggressors into the body:

(a) An anatomical barrier is constituted by the enterocytes aligned side by side and forming a "wall" to the aggressors. Tight junctions play an essential role in closing the intercellular space, just as mortar blocks the space between the bricks of a wall.

(b) A chemical barrier is present thanks to the mucus secreted by the goblet cells and forming a protective film above the enterocyte wall, as well as by the defensins secreted by Paneth cells from the bottom of the crypts to counter certain aggressors.

(c) The immunological barrier is important:
- Immunoglobulin A (secretory IgA) secreted by plasma cells of the intestinal wall into the intestinal lumen provides a first line of immunological defense.
- M cells (microfold cells-enterocyte looking cells but with shorter villi) of the brush border can take up antigens from the lumen of the intestine (via endocytosis) and deliver them to the immune cells of the mucosa.
- Dendritic cells of the mucosa form, as their name indicates, extensions (dendrites) which are inserted between the enterocytes into the intestinal lumen in order to recognize, thanks to their receptors (TOLL, NOD, etc.), the aggressors and then activate T lymphocytes (Th1, etc.).
- T lymphocytes of Peyer's patches are activated (naive T → effector T) by dendritic cells to secrete interleukins (IL-1, IL-8, IL-23, etc.), TNF, IFN gamma, etc. against the aggressors.
- Mast cells residing in the intestinal wall can phagocytize "intruders" that could squeeze through the surface barrier.
- Neutrophils can be recruited from the periphery and migrate to the intestinal wall to participate in the defense reaction against aggressors.

3.4.3.2 Digestive Regulation

The small intestine, being at the center of the essential process of nutrient absorption, plays a major role in the regulation of digestion processes by other organs such as the stomach or the pancreas.

The stomach (see ▶ Chap. 2) dissects and triturates ingested food into particles less than 2 mm in

size which can be transformed by digestive enzymes into substrates that can be absorbed by the enterocyte. To allow nutrient arrival in the intestine at a reasonable rate for their absorption, gastric emptying of food is slowed down by brake mechanisms coming from the proximal and distal small intestine and involving neurohormonal phenomena. The duodenal brake is ensured by neural reflexes and by hormones (e.g., CCK, GLP-1) secreted from the duodenal mucosa into the bloodstream; the distal brake (ileal brake) involves hormones PYY, neurotensin, etc.

The pancreas (see ► Chap. 5) secretes bicarbonates and enzymes necessary for luminal digestion of nutrients. The arrival of food in the duodenum induces the activation of neurological reflexes as well as the secretion of hormones such as secretin and CCK to stimulate pancreatic secretion.

The incretins GIP and GLP-1 increase the secretion of pancreatic insulin essential for the metabolism of absorbed carbohydrates.

Appetite is subject to regulatory mechanisms that are still poorly understood but which most probably involve substances from the small intestine such as CCK, galanin, PYY, GLP-1, etc. (see ► Chap. 24).

3.5 Motor/Sensory Functions

The small intestine can be seen as a long thin tube along which food is mixed and propelled for absorption. The movement of food through this tube from top to bottom (or from proximal to distal, i.e., from pylorus to cecum) depends on the contractions of the intestinal walls that ensure the transit of food along the intestine (a movement often referred to as peristalsis). The basic mechanism for this peristalsis is based on annular contractions of the circular muscles of the intestinal wall that propel the contents of the intestine forward a few centimeters; the advancement or migration of sequential circular contractions along the intestinal tract will generate the coordinated forward propulsion of the intestinal content. The digestive motility discussed in this chapter applies specifically to the small intestine, but the general concepts apply to other digestive organs, such as the esophagus, stomach, or colon.

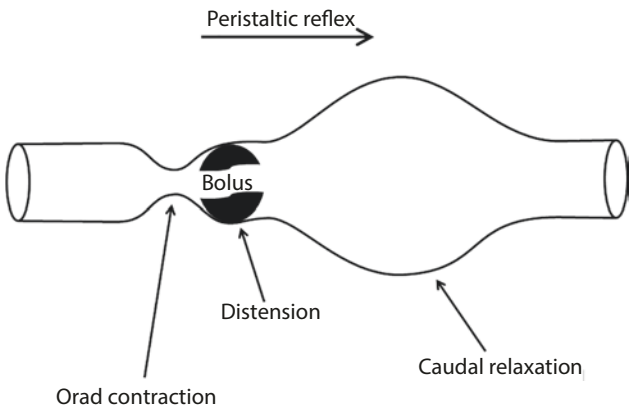
3.5.1 Intestinal Muscle

Contraction (or relaxation) of the intestinal smooth muscle cell will occur in response to stimulators (or inhibitors) acting on cell membrane receptors to increase (or decrease) the intracellular calcium concentration and thereby generate cell contraction (or relaxation). Contractile agents such as acetylcholine or substance P usually act via diacylglycerol and inositol triphosphate to increase intracellular calcium by facilitating the entry of extracellular Ca^+ into the cell or by mobilizing intracellular Ca^+ from the endoplasmic reticulum into the cytosol. Relaxing agents usually act via adenylate cyclase (e.g., VIP) or guanylate cyclase (e.g., nitric oxide) to reduce intracellular Ca^+ concentrations.

The increase in intracellular Ca^+ allows the activation of a cascade mechanism involving calmodulin and myosin light chain kinase to induce actin and myosin interactions leading to muscle cell shortening and, consequently, muscle contraction.

3.5.2 Peristaltic Reflex

The peristaltic reflex is the basic mechanism of peristaltic contractions generating the movement and the advance of the luminal contents along the digestive tract. The peristaltic reflex (◘ Fig. 3.45) involves, following the perception of a content or a bolus in the intestinal lumen, an annular contraction of the intestinal wall upstream of the bolus (upward or oral contraction) with a relaxation of the intestinal walls downstream of the bolus (distal or caudal relaxation) to "chase" the food bolus from top to bottom (or from proximal to distal, from the mouth to the anus).



◘ **Fig. 3.45** The peristaltic reflex: in response to a luminal distension by a food bolus, the intestine responds by contracting upstream of the bolus and relaxing downstream to promote forward movement of the bolus

This complex movement of the internal circular smooth muscle, i.e., contraction upstream of the bolus and relaxation downstream, is accompanied by a paradoxical movement of the external longitudinal muscle of the intestinal wall. Indeed, during oral contraction, to facilitate and optimize the contractile movement of the internal circular muscle, the external longitudinal muscle relaxes (therefore without opposing forces on the movement of luminal narrowing); while during caudal relaxation, the longitudinal muscle contracts to main-

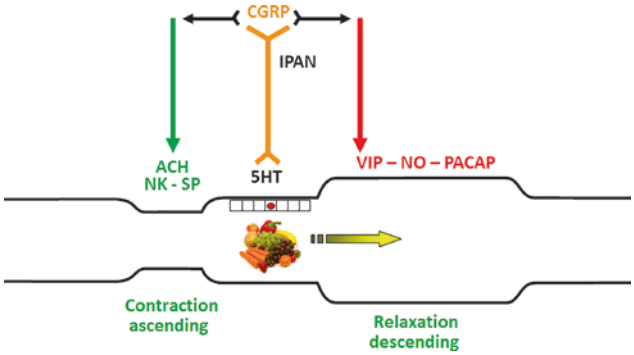


Fig. 3.46 Neurological and ENS neurotransmitter pathways involved in the peristaltic reflex = afferent sensory pathway as well as efferent motor pathways for stimulation (upstream contraction) or inhibition (downstream relaxation) of intestinal contraction

tain a certain overall tonus to the intestinal tube (otherwise lowered by decreased circular muscle activity).

This peristaltic reflex, taking place entirely in the intestinal wall, relies on the enteric nervous system (ENS) and particularly on Auerbach's myenteric plexus. The sequence of the peristaltic reflex can be summarized as follows (Fig. 3.46):

(a) Afferent neurons (IPAN: intrinsic primary afferent neuron), with endings close to the intestinal surface, detect the presence of food bolus in the intestinal lumen. Food contact with the mucosa and/or intestinal distension caused by the bolus stimulates enterochromaffin cells of the intestinal mucosa to release serotonin (5HT) which will paracrinally activate 5HT1 and 5HT4 receptors of a neighboring IPAN nerve. Activation of this sensitive afference releases its neurotransmitter (CGRP: calcitonin gene-related peptide) which in turn activates interneurons to begin the motor phase of the reflex.

(b) Interneurons are neurons of the myenteric plexus located between sensory neurons originating from the mucosa and motor neurons reaching the parietal muscles. These interneuron circuits are complex and have yet to be precisely identified. It is known that the interneurons of the ascending contraction loop involve mainly cholinergic nerves, while the interneurons of the descending relaxation loop involve neurotransmitters such as enkephalins, GABA, and somatostatin.

(c) Upward (or oral) contraction occurs in response to the activation of stimulatory motor neurons releasing neurotransmitters acetylcholine and kinins (substance P, neurokinin 1, neurokinin 2) which act directly on the membrane receptors of the smooth muscle cell to generate (as previously discussed), via the second messenger IP3, an increase in intracellular calcium causing the actin/myosin interaction inducing cell contraction.

(d) Descending (or caudal) relaxation occurs in response to the activation of inhibitory motor neurons releasing neurotransmitters VIP (vasoactive intestinal polypeptide), NO (nitric oxide), and PACAP (pituitary adenylate cyclase activator peptide) acting on the smooth muscle cell membrane receptors to decrease, via cyclic AMP and cyclic GMP as second messengers, the concentration of intracellular calcium leading to relaxation of the smooth muscle cell.

3.5.3 Enteric Nervous System

The enteric nervous system (ENS) thus constitutes the brain (little brain compared to the central nervous system called big brain) of intestinal peristalsis. As shown in Fig. 3.47, the nerves of the ENS are primarily intended for local action such as the peristaltic reflex managed by Auerbach's myenteric plexus or for secretion/absorption activities managed by Meissner's submucosal plexus. Sympathetic and parasympathetic extrinsic nervous systems regulate intestinal motility by acting on the intrinsic neurological pathways of the ENS. The parasympathetic nervous system mainly uses the vagus nerve and cholinergic neurotransmitters to stimulate intestinal motility. The sympathetic nervous system, derived from medullary fibers via the celiac and mesenteric ganglia, will counterbalance the parasympathetic influence by its adrenergic transmitters having an inhibitory action on the intestinal motility. Intestinal reflexes (see ► Chap. 2) may therefore be based on reflex loops confined to the ENS (such as the peristaltic reflex), or on reflex loops that may extend from the intestinal wall to the abdominal neurological ganglia (e.g., celiac ganglion), or even to the central nervous system (e.g., vagal dorsal nucleus).

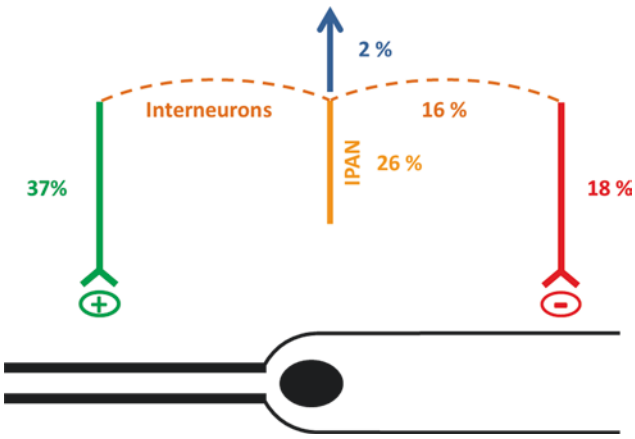


Fig. 3.47 Enteric nervous system: 98% of the nerve pathways in the ENS are confined to the intestine for sensory or motor actions; only 2% communicate with the extrinsic nervous system

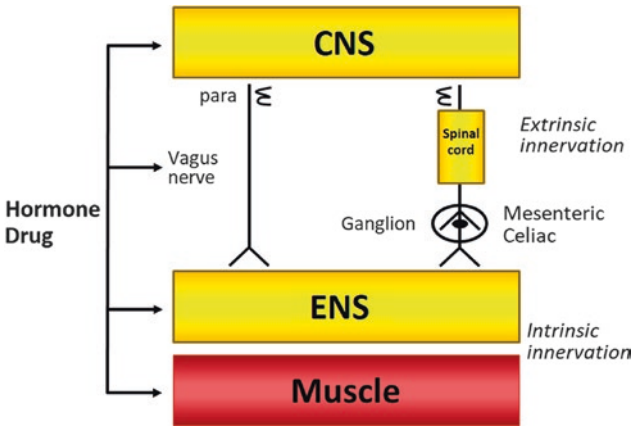


Fig. 3.48 The intestinal muscle is regulated by intrinsic nerves of the enteric nervous system (ENS), which in turn are influenced by extrinsic sympathetic or parasympathetic nerves from the central nervous system (CNS). Substances circulating in the blood (hormones, drugs, etc.) can influence the intestinal muscle directly or indirectly via an action on intrinsic or extrinsic nerves

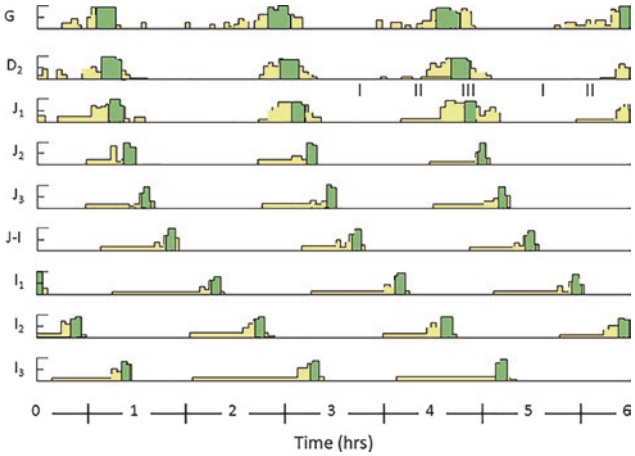


Fig. 3.49 The migrating motor complex (MMC) is composed of three phases of contraction (phases I, II, and III) recurring cyclically every 80–120 min and migrating progressively from the stomach (G) to the duodenum (D), the jejunum (J), and the ileum (I) (according to Code and Marlett 1975). On the graph, phase I is illustrated by the black line, phase II by the orange "box," and phase III by the green "box"

Blood-borne substances, such as regulatory hormones or pharmacological substances administered as drugs, may influence intestinal contractility by acting either directly on the intestinal smooth muscle cells, as well as indirectly on the intrinsic nerves of the ENS, or on the extrinsic nerves of the autonomic nervous system (parasympathetic or sympathetic pathways) (Fig. 3.48).

It is thus understood that the intestinal transit of the food nutrients may be disturbed by pathological mechanisms affecting the intestinal wall muscles (e.g., myopathy, scleroderma, etc.) or the nerves of the ENS or ANS (e.g., complications of diabetes, amyloidosis) that regulate the contractility of these intestinal muscles.

3.5.4 Interdigestive Motility/MMC

The contractile response of the intestinal smooth muscle cell and its regulation by neurological and hormonal mechanisms are organized to generate two different motor profiles which will be specific for the digestive (or postprandial) period or for the interdigestive (or fasting) period.

During the interdigestive period, the small intestine (like the stomach) is submitted to a pattern of irregular and cyclical contractions designed as the migrant motor complex (MMC; see Fig. 3.49). Each MMC lasts 80–120 min and is made up of three successive phases: Phase I, lasting 20–60 min, contains no contractile movement. Phase II then follows, and for 20–60 min, the bowel will be animated by contractile movements of moderate amplitude stirring the intraluminal contents in a back and forth motion to slowly make it move forward. Phase III, which lasts 3–5 min, is characterized by a very powerful peristaltic muscle contraction that migrates from the stomach (it begins even at the lower esophagus) to the ileum (some contractions even cross to the colon). During phase III, the very strong circumferential muscle contraction obliterates the digestive lumen to force the entire intraluminal contents forward. This cycle of intermittent contractions (MMC) returns periodically every 80–120 min during the fasting period and will be interrupted by food intake to make way for digestive-type motility.

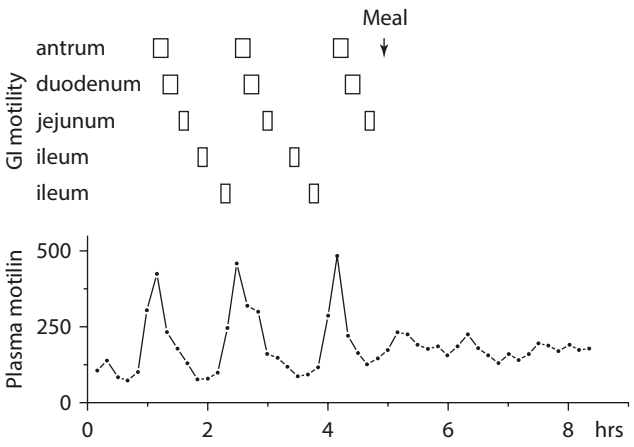
Phase III of the MMC is used to cleanse the digestive tract of nondigestible foods (e.g., fibers) and of bacteria that may accumulate. The absence of fasting intestinal contractions (e.g., muscular or neurological damage to the intestine) leads to stagnation and a bacterial overgrowth responsible for secondary food malabsorption. Phase III involves, in order to cleanse the intestine, a very rapid and complete displacement of the intraluminal contents along the intestinal tract. This transit is too fast to allow an optimal absorption of the nutrients thus propelled, and this is why, in the postprandial period, the type III intestinal contraction must disappear to make way for a digestive motility profile optimizing the absorption of ingested nutrients.

3.5.5 Postprandial or Digestive Motility

While eating, the digestive tract will be at work to move food from the mouth to the small bowel, as discussed in the previous chapters on peristalsis of swallowing and on gastric emptying. In the small bowel, the digestive motor system must therefore push nutrients while allow-

ing their absorption. The intestine cannot be immobile as in phase I or too active as in phase III of the MMC. The postprandial motor activity resembles the interdigestive motor activity of phase II; the muscles of the intestinal wall are animated by moderate and irregular contractions which generate a mixing of the food substances with the digestive secretions and a back and forth movement which ends up in a slow transit of the intraluminal chyme from the proximal to the distal region. This contractile activity (also described as rhythmic segmentation) is optimal for intestinal absorption since it allows (a) food to be mixed with digestive secretions (biliary, pancreatic, etc.) to facilitate intraluminal digestion and (b) food to move along the intestine at a slow enough speed to allow adequate contact and absorption by the enterocytes.

Regulation of interdigestive and digestive motor patterns relies on neurological (e.g., vagus nerve) and hormonal mechanisms. During the fasting period, motilin, a hormone synthesized in the endocrine Mo cell of the duodenojejunal mucosa, is released into the blood every 80–120 min (◘ Fig. 3.50) to induce phase III MMC in the stomach, which then will migrate along the intestine through intrinsic neural mechanisms. It is also known that the vagus nerve participates in this induction of phase III in the stomach. Transition from interdigestive to digestive motor function occurs with meals. Food, whether by circulating hormones released after a meal (e.g., gastrin, CCK, etc.), extrinsic and intrinsic neurological mechanisms, or local actions (e.g., inhibition of the Mo cell by intraluminal substances), leads to the transfer of the interdigestive/fasting motility, essential for basic intestinal homeostasis (e.g., to avoid bacterial overgrowth), to the digestive-postprandial motility essential for intestinal propulsion and absorption. When food disappears from the digestive lumen, the digestive motility profile fades to make way, until the next meal, for the interdigestive motility.



◘ **Fig. 3.50** Motilin regulation of MMC: serum motilin increases cyclically during the fasting period to trigger MMC phase III; meal ingestion inhibits cyclic increases in motilin (and releases other hormones such as gastrin, CCK, etc.): MMC is interrupted and interdigestive motility profile is replaced by a postprandial motor activity

3.5.6 Sensitivity

Sensitivity-reactivity The functions of sensitivity (or perception) of the intestine intervene in the regulation of physiological phenomena such as the peristaltic reflex as discussed above. The function of perception is obviously essential to the triggering of a reflex arc, whether its effective outcome is motor or secretory.

Sensitivity-pain Perception by the intestine can also give rise to the transmission of painful phenomena perceptible by the central nervous system. The gut is normally not a very sensitive organ (see ▶ Chap. 16); however, it can transmit pain sensations during distension (e.g., pain from intestinal obstruction) or inflammation. The small intestine may be the site of diffuse hypersensibility as demonstrated in functional digestive disorders affecting mainly the colon (irritable bowel syndrome) or the stomach (functional dyspepsia).

3.6 Inflammation Disorders

3.6.1 Celiac Disease/Gluten Enteropathy

Celiac disease will be discussed extensively, as it is the most typical example of the clinical consequences of loss of villous enterocytes and food malabsorption in intestinal disease.

Celiac disease, also called gluten enteropathy or nontropical sprue, is an intestinal inflammation generated by immune mechanisms due to sensitivity to alimentary gluten. The clinical disease was first reported in 1888, its relationship to cereals was described in 1941, and the more specific involvement of gluten was identified as early as 1953. The characteristic histological picture of villous atrophy was recognized in 1954.

Long seen as a rare disease affecting only 1/4000–8000 people, celiac disease is now considered a common condition that affects nearly 1% of the population.

(a) Histology Celiac disease is identifiable by the typical histological picture of villous atrophy (total (then pathognomonic) or partial (other diagnoses are then possible)), with crypt hyperplasia and intraepithelial lymphocyte infiltration of the intestinal mucosa (◘ Fig. 3.51). The abnormalities are more pronounced in the proximal than in the distal small intestine (due to the higher gluten concentrations in the proximal bowel). These histological

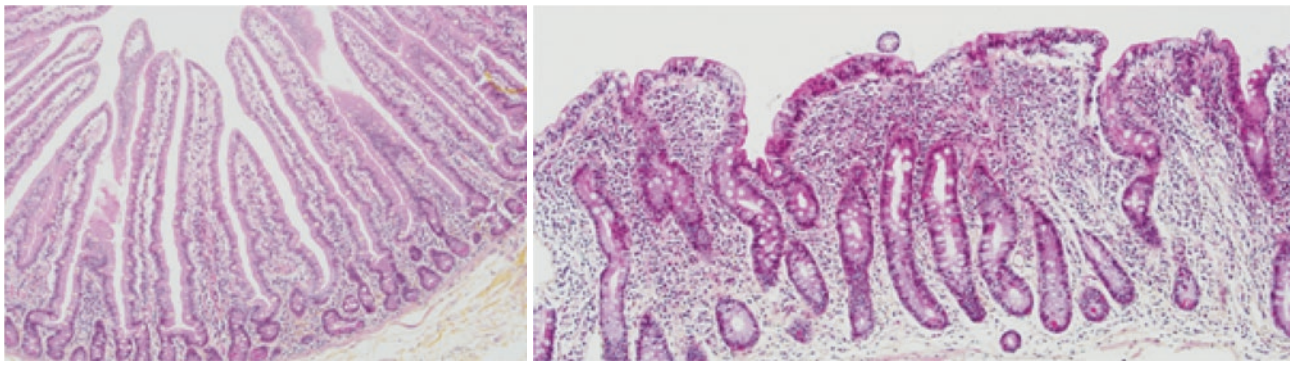


Fig. 3.51 Left photo: normal intestinal mucosa with sharply tapered, elongated, digitally formed villi. Right photo: In celiac disease, atrophic villi, hyperplastic crypts, and inflammatory infiltrate are seen. (Photos by G. Soucy)

abnormalities disappear when gluten is excluded from the diet, and the mucosa may return to normal in the absence of gluten exposure.

(b) Pathophysiology of celiac disease Gluten is a sticky proteinic substance present in certain cereals (including wheat) that gives the dough (especially bread) a malleable consistency, but is not essential to the human diet (we can live very well on a gluten-free diet).

Gluten, like its two derivatives, gliadin and glutenin, is poorly digested in the stomach or small intestine and is normally found in the stool since it is very poorly absorbed.

The gliadin absorbed, weakly by transcellular route but mainly by a paracellular route (in case of mucosal breaks with loss of the tight junctions of the enterocyte barrier), will usually be rapidly degraded in the intestinal lamina propria by tissue transglutaminase (TTG, a nonspecific "detoxifying" enzyme), and its metabolites will be excreted in urine.

In the individual with celiac disease, the gliadin metabolites (derived from TTG) will be submitted to an "abnormal" T cell response. Activated CD4s with HLA DQ2 or DQ8 receptors (an essential condition for the development of celiac disease) then generate a cascade of inflammatory mechanisms (release of inflammatory cytokines such as alpha or gamma interferon, interleukins IL-17 and IL-15, etc.) with migration of CD8, NK cells, etc., leading to destruction of the intestinal epithelium. Activation of B lymphocytes leads to the production of antibodies against gliadin, anti-TTG, etc.

The understanding of pathophysiological mechanisms involved in celiac disease, although still imperfect, allows us to foresee various therapeutic solutions (other than the gluten-free diet) such as the production of gluten-free modified cereals, the neutralization or digestion (e.g., by glutenase enzymes) of gluten in the stomach, the reinforcement of intestinal tight junctions (e.g., by zonulin antagonists such as larazotide), the inactivation of TTG, the inhibition of lymphocytes or of their pro-inflammatory products (IL-15, etc.), and the modification of the immune response (by vaccines, parasites, etc.). Several of these putative solutions are already being tested in clinic.

(c) Aggravating factors The familial predisposition for celiac disease is obvious: the frequency of celiac disease is 3/4, 1/20, or 1/40 individuals, respectively, in homozygous twins, first-degree relatives, or second-degree relatives.

Some diseases are associated with celiac disease; dermatitis herpetiformis (85% of patients with DH have celiac disease), Down's syndrome (16% of patients have celiac disease; RR20), diabetes, immunoglobulin A deficiency, and Turner's syndrome may be associated with celiac disease in 2–7% of patients (RR 3–10); microscopic colitis and certain autoimmune diseases such as thyroiditis or primary biliary cirrhosis also are associated with celiac disease.

HLA genetic markers DQ2 and DQ8, although not very specific, are always present in patients with celiac disease. In practice, the absence of HLA DQ2 or DQ8 allows the clinician to eliminate the presumptive diagnosis of celiac disease.

(d) Clinical presentation Celiac disease can manifest under various forms:

Classical form: The absence of villi and enterocytes leads to nutrient malabsorption with (a) digestive manifestations, such as diarrhea, steatorrhea stools, abdominal bloating, and abdominal discomfort and (b) systemic consequences due to macro- as well as micronutrient deficiencies: weight loss, growth retardation in children, edema (due to hypoalbuminemia), anemia (due to iron, folate, or B12 deficiency), neurological damage (such as polyneuritis due to B12 or vitamin E deficiency, etc.), bone diseases (such as osteoporosis or osteomalacia due to calcium or vitamin D deficiency), etc. This overt spectacular presentation of celiac disease with malabsorption is however infrequent and for a long time led to the belief that celiac disease was a rare disease (which

was confirmed then with intestinal biopsies obtained by complex technical procedures).

Atypical form: It is now known that the digestive and systemic symptoms of malabsorption may be lacking and that celiac disease may manifest itself in more discrete patterns, often indicative of a selective nutritional deficit. Iron-deficiency anemia and bone diseases such as osteoporosis or osteomalacia became, in the 1980s, the most common forms of the disease which could now be diagnosed by duodenal biopsies that were readily available by endoscopy. In the last 10–15 years, the even easier identification of celiac disease by serological tests (such as the anti-transglutaminase assay discussed below) has led to the recognition that celiac disease can be manifested by even more frustrating symptoms such as abdominal bloating (that was tentatively attributed to irritable bowel syndrome), fatigue, etc. and that it is actually present in about 1% of the Western population.

Silent or subclinical form: Screening tests then led to the diagnosis of celiac disease but in the absence of apparent clinical signs. However, it is not uncommon that gluten-free diet improves in these people symptoms (e.g., nausea, fatigue) that they had not previously recognized as abnormal.

Latent or potential form: Celiac disease detected in childhood may become asymptomatic in adolescence or adulthood even in the presence of gluten. Disease recurrence is possible.

Non-celiac gluten sensitivity (*NCGS*) is the diagnostic term used to designate patients who experience symptomatic benefit while following a gluten-free diet even if medical investigation (intestinal biopsies and celiac disease serologies are negative) does not identify celiac disease. Gluten-free diet is currently very popular; it is estimated that 20% of Americans use gluten-free foods and that gluten intolerance is five times more common than celiac disease. Since the 1970s, several publications have provided various arguments to support the existence of this entity still debated and of unknown physiopathology. There are no strict diagnostic criteria for NCGS, and in clinic the "diagnosis" is often made by observing a beneficial effect of the gluten-free diet and, if possible, a reappearance of symptoms with it gluten re-exposure. However, it remains unclear whether the benefit of the diet is due to the exclusion of gluten, wheat, or other nutrients (including FODMAP fermentables) or even to a placebo effect. In practice, one can only be happy that the patient has found an effective therapeutic solution to his (or her) ailments.

(e) Manifestations associated with celiac disease

- Diarrhea is common, but its absence should in no way rule out a diagnosis of celiac disease. It is of osmotic type (i.e., it stops with fasting; see ▶ Chap. 13). In severe cases, malabsorption can be obvious (floating, fatty stools).
- Abdominal pain is usually moderate. Severe pain should lead to suspicion of associated conditions such as irritable bowel syndrome, neoplastic transformation, etc.
- Gas and flatulence are common. Sugars, lipids, or proteins, not absorbed by the small intestine, are digested by colonic bacteria into gas (methane, volatile fatty acids, etc.).
- Lactose intolerance is very common, villous atrophy leading to a deficiency in disaccharidases. It may disappear with the resumption of villi following gluten exclusion.
- Relative pancreatic insufficiency may exist due to villous atrophy leading to a decrease in CCK cells stimulating pancreatic secretion or to a decrease in enterokinase activating pancreatic enzymes (see ▶ Chap. 5).
- Microscopic colitis (lymphocytic or collagen) may occur in some cases.
- Abnormalities in liver function tests are common, affecting up to 40% of patients. They can be caused by a coexisting autoimmune disease (e.g., primary biliary cirrhosis), by hepatic steatosis related to weight loss and undernutrition, or, most often, by mechanisms that are not yet understood (e.g., bacterial translocation through an atrophic intestinal mucosa).
- Extra-gastrointestinal manifestations: Nutritional and vitamin deficiencies described in ◘ Table 3.6 (iron-deficiency anemia, bone diseases, etc.) are the mode of presentation in many patients.

(f) Complications of celiac disease Nutritional (weight loss, undernutrition, etc.) or vitamin deficiencies (◘ Table 3.6) related to deficient absorption must be monitored.

Neoplastic development has been reported. However, recent studies that take into account the increasing prevalence of celiac disease suggest that the risk of cancer is only modest (RR 1.3) and that it is most prevalent for lymphoma disorders (RR 5–6). Intestinal lymphoma type T is a rare condition in itself and is found almost exclusively in patients with celiac disease. Adenocarcinoma of the small intestine is also a rare pathology and, if present, is most often associated with celiac disease. The benefit of the gluten-free diet in the prevention of neoplasia in patients with celiac disease has been reported in some studies. It is a strong argument for the use of gluten-free diet even in patients with discrete symptoms (where there may be a temptation to neglect the diet treatment), but its effectiveness remains uncertain.

Table 3.6 Nutrient deficiencies and overload: clinical manifestations

	Deficiency	Overload/excess
Macronutrients		
Generalized (carbs/fats/proteins)	Marasmus: Weight loss Growth retardation (child) Muscle wasting Susceptibility to infections Delayed wound healing	Obesity Refeeding syndrome
Proteins	Kwashiorkor: Peripheral edema, ascites Nails: transverse lines Hair loss	
Lipids	Skin: dry/thick/eczematous	
Carbohydrates	Hypoglycemia	
Fat-soluble vitamins		
A	Skin: follicular hyperkeratosis Eyes: loss of nyctalopia/blindness	Intracranial hypertension Skin exfoliation Liver necrosis
D	Child: rickets Adult: osteomalacia Bone fractures Bone pain Lower limb weakness	"Metastatic" calcifications Urinary lithiasis
E	Fragile red blood cells/hemolytic anemia Neuropathies (peripheral, ophthalmoplegia, posterior cords)	
K	Hemorrhages – hematomas	
Water-soluble vitamins		
B1 (thiamine)	Beriberi: "wet", heart failure "dry": nystagmus/ophthalmoplegia/ataxia	
B2 (riboflavin)	With other vitamin deficiencies	
B3 (niacin)	Pellagra: dermatitis/diarrhea/dementia	
B6 (pyridoxine)	With other vitamin deficiencies	
Folate	Macrocytic anemia Glossitis Diarrhea (villi atrophy)	

(continued)

Table 3.6 (continued)

	Deficiency	Overload/excess
C (ascorbic acid)	Scurvy: Fatigue Depression Gingival inflammation Perifollicular petechiae Internal bleeding	
B12 (cobalamin)	Megaloblastosis: macrocytic anemia, glossitis Demyelination: peripheral nerves – posterior cords – CNS	
Trace elements		
Chrome	In patients with TPN (total parenteral nutrition) Hyperglycemia Neuropathy/encephalopathy	
Copper	Patients with TPN Skin depigmentation "Iron-deficiency" anemia	
Iron	Microcytic hypochromic anemia Glossitis Koilonychia (spoon nails)	Hemochromatosis
Fluoride	Tooth decay, osteoporosis (?)	Fluorosis
Iodine	In places without salt supplementation Adult: goiter Child: fetal hypothyroidism/cretinism	
Manganese	Not demonstrated	
Molybdenum	Not demonstrated	
Selenium	Patients with parenteral nutrition Cardiomyopathy	
Zinc	Patients with parenteral nutrition Enteropathic acrodermatitis: Periorificial dermatitis Diarrhea Hair loss Behavioral change	

Some refractory states may develop despite continuous treatment with gluten-free diet. These may include collagen sprue, ulcerative jejunitis, or lymphoma.

(g) Diagnosis of celiac disease *Duodenal biopsy*, obtained by simple gastroduodenoscopy, confirms the villous disease and is the "gold standard" diagnostic tool. Total villous atrophy with crypt hyperplasia usually establishes the diagnosis; however, villous atrophy is often partial and will then force to consider other conditions since any mucosal aggression by infection (e.g., giardia, bacterial overgrowth), inflammation (e.g., Crohn's disease), irritation (e.g., gastric HCl), etc. may alter the villous profile. Absolute confirmation of the diagnosis of celiac disease may be obtained when observing correction of histological abnormalities following treatment with a gluten-free diet. In practice, this confirmatory duodenal biopsy is rarely necessary, and the diagnosis will be assured by the correction of biochemical and/or clinical abnormalities in response to treatment by gluten-free diet.

Serum antibodies against transglutaminase (gliadin-degrading enzyme; anti-TG) have a sensitivity and specificity superior to 90% and are currently the most useful screening tool (in patients without IgA deficiency). Anti-endomysial antibodies have near-perfect sensitivity and specificity, but are not readily available clinically. Antigliadin antibodies have lower sensitivity and specificity and should no longer be used. Whether the diagnosis of celiac disease can be established solely by serologic tests (without histological analysis) remains debated.

(h) Treatment of celiac disease Gluten-free diet (GFD) is the treatment for this condition. T is diet requires the exclusion of foods that contain gluten: wheat, barley, oats, and rye. Rice, corn, soy, and quinoa are allowed, as are meats, fish, fruits, and vegetables. A dietary consultation is therefore required to guide the patient. This therapeutic diet must be continued for life and is, for many patients, difficult to follow since it excludes many foods that are often appreciated (e.g., bread, pasta, regular beers, etc.). GFD, over months, may restore the intestinal villous architecture. It improves clinical symptoms (diarrhea, discomfort, etc.) as well as manifestations of vitamin deficiencies within a few weeks or months. Many people believe that GFD protects against certain cancers associated with celiac disease, which would be an argument for treating all patients, even those who are asymptomatic.

Vitamin replacements (e.g., iron, calcium, etc.) are often required, especially at the beginning of treatment, before the GFD can fully restore villi architecture and intestinal function. In many patients, some vitamin deficiency may persist (probably secondary to some degree of persistent villi atrophy due to an imperfect adhesion to GFD) and will require chronic replacement. Annual clinical and biochemical follow-up is desirable for patients with celiac disease in order to correct and prevent nutrient or vitamin deficiencies.

Clinical management of celiac disease is summarized in Table 3.7.

Discovering the pathophysiology of celiac disease could lead to future pharmacological solutions. Certain therapeutics are currently being explored, such as the ingestion of enzymes (PEP proteases such as TAK-062) to digest the gluten molecule, the administration of zonulin antagonists to block the permeability of the tight junctions of the intestinal mucosa to gluten, TTG blockers to prevent deamidation of gluten and production of immunogenic derivatives, or therapies (such as TAK-101) to reduce gluten immunogenicity.

Table 3.7 Celiac disease

Who to investigate?	
Investigation required:	Manifestation "classic":
	Chronic diarrhea/malabsorption
	Manifestation "atypical" with high probability:
	Iron-deficiency anemia (without bleeding)
	Folic acid/vit. B12 deficiency
	Bone diseases with Ca/vit. D deficiency
Investigation to be considered:	Manifestation atypical with weaker probability:
	Abdominal gas/IBS
	Fatigue
	Infertility/miscarriages
	Migraine
	High-risk groups: relative with celiac/diabetes I/trisomy
How to investigate?	
Duodenal biopsies per endoscopy = "Gold standard" (always necessary?)	
Serum tests: antibodies anti-transglutaminase/anti-endomysium (enough for diagnosis?)	
How to treat?	
Gluten-free diet (No: wheat, barley, oat, rye. Yes: rice, corn, soya, quinoa)	
Replacement vitamins, etc.	

3.6.2 Crohn's Disease

Crohn's disease is a chronic granulomatous inflammation of the small intestine (and entire digestive tract). Crohn's disease is the most important disease of the small bowel, in terms of both frequency and severity, in the specialized medical practice of gastroenterology. Of unknown origin, it often affects the colon, and together with ulcerative colitis (UC), it constitutes what is generally known as inflammatory bowel diseases (IBDs). For convenience, Crohn's disease and IBDs will be discussed more extensively in the ▶ Chap. 4.

(a) Diagnosis of Crohn's disease Crohn's disease is characterized by an inflammation often resulting in intestinal stenosis and/or fistulas, which can affect the entire small intestine and typically involves mainly the terminal ileum. Ileitis is typically revealed by X-ray imaging of the small intestine after ingestion of a barium contrast substance (small bowel follow-through exam): terminal ileitis (◘ Fig. 3.52) can vary in length (from a few centimeters to more than 1 m), can be seen with skipped area of normal mucosa, and can take various forms such as intestinal wall edema, or ± deep and ± serpiginous ulcers giving the typical "cobblestone" image (◘ Fig. 3.52b), or fistulas with neighboring organs (entero-enteric, entero-colic, entero-bladder fistulas, etc.; ◘ Fig. 3.52c), or ± long and ± tight stenoses of the intestinal lumen (with the classic "string sign").

Ileitis is now often revealed by other imaging techniques such as axial tomography (CT scan, enteroscan; ◘ Fig. 3.53), endoscopy (ileoscopy per colonoscopy or by video capsule), magnetic resonance (MR enterography), or ultrasonography.

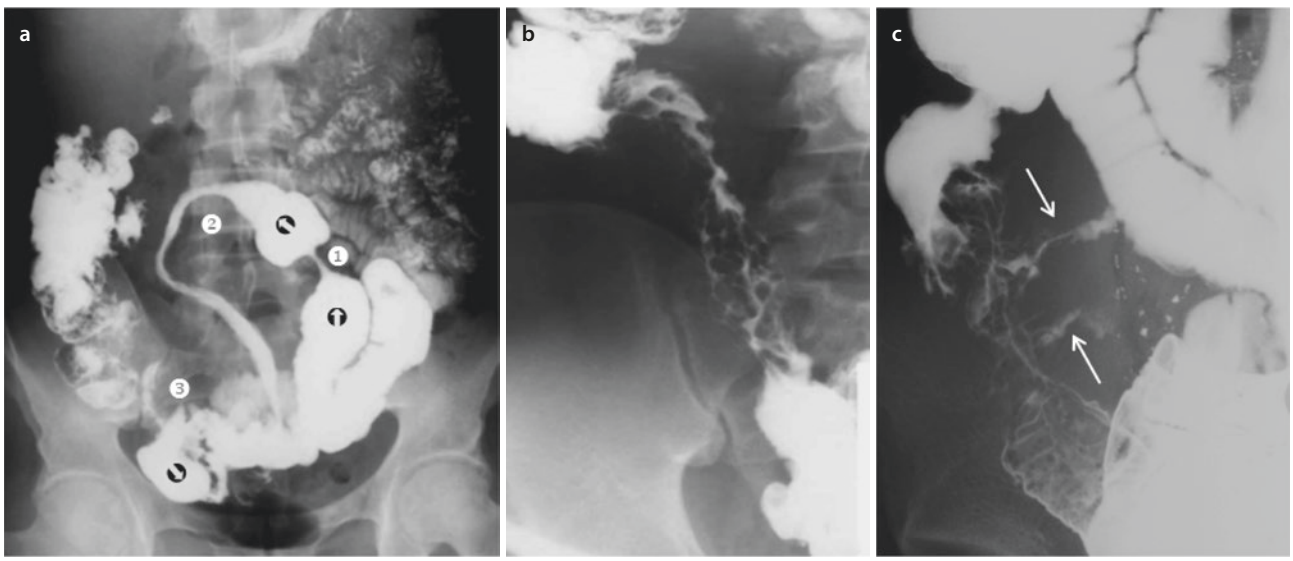
Terminal ileitis is most often caused by Crohn's disease in Western patients, but its differential diagnosis includes (1) infection with *Yersinia enterocolitica* or (2) tuberculosis, as well as (3) lymphoma and (4) radiation enteritis.

(b) Clinical manifestations of Crohn's ileitis Clinical manifestations include abdominal pain (most often postprandial and due to stenoses of the intestinal lumen restraining the passage of food) and diarrhea (due to multiple factors (◘ Table 3.8), and often related to the length and severity of the inflammation in the small intestine as well as in the colon).

Acute complications may occur: intestinal occlusion (by inflammatory or fibrotic stenosis), intestinal perforation (perforation of a deep ulcer with abscess, peritonitis, etc.), or, more rarely, intestinal bleeding.

On clinical examination, an inflammatory mass (± tender depending on the inflammatory character) is often palpated in the right iliac fossa.

(c) Treatment of Crohn's disease The treatment to eradicate and cure the inflammation is unfortunately unknown, and the disease is chronically progressive. Various therapeutic strategies exist to control the inflammation and its complications. Reduction of inflammation can be achieved with topical anti-inflammatory drugs (5ASA), antibiotics, corticosteroids, immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate), or various biological agents (anti-TNF, anti-integrin), as discussed in ▶ Chap. 4.



◘ **Fig. 3.52** X-rays of the small bowel obtained after ingestion of barium substance that "colors" in white the luminal content. **a** Crohn's disease with three stenoses ((**1**), (**2**), (**3**)), including a long narrowed segment of the ileum (**2**), with dilation of the upstream intestinal loops (arrows indicate the direction of transit). **b** Ileitis in cobblestone appearance. **c** Terminal ileitis with two fistulas (arrows) penetrating other intestinal loops. (Photos from R. Déry)

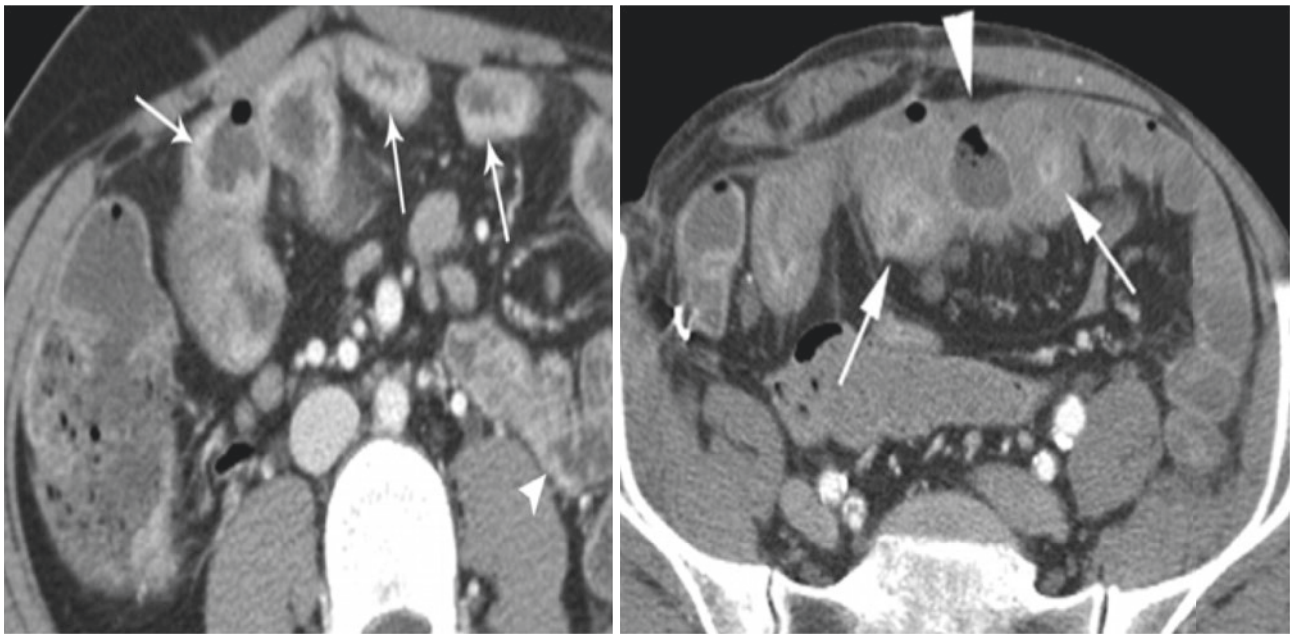


Fig. 3.53 Crohn's ileitis on CT scans: thickened intestinal walls (left image) or with abscesses (right image). (Photos from R. Déry)

Table 3.8 Crohn's disease diarrhea = multifactorial and often related to the length and severity of intestinal inflammation and of concomitant colon involve ment

Inflammatory: erosions, ulcerations of intestinal (and colonic) mucosa → transudation of proteins, liquids (lymph, plasma), etc.

***Osmotic*:** with malabsorption or maldigestion

- Loss of villi surface area (malabsorption) through inflammatory mucosal disease, or postsurgical resection of intestinal segments, or "short circuit" by enteric fistula
- Reduction of villous disaccharidases (maldigestion) by inflammatory mucosal damage
- Intestinal bacterial overgrowth (and secondary malabsorption) due to intestinal stenosis or fistulas

Secretory: malabsorption of bile salts by the ileum (altered by inflammation or surgically resected) and stimulation of colonic secretion = choleretic diarrhea

Motor:

- Increased motor activity to "overcome" an obstacle (stenosis) to transit
- Acceleration of intestinal transit through "loss" (surgical or functional due to inflammation) of ileocecal valve

Surgery can be used to remove intestinal segments that are stenosing, perforating, or fistulizing. However, surgical resection of diseased segments does not prevent the recurrence of inflammation, and must therefore be limited to protect the essential intestinal function of food absorption.

3.6.3 Infections

The small intestine can be affected by acute (lasting a few hours to a few days) or chronic (lasting more than 2 weeks) infections due to viruses, bacteria, or parasites.

Infection is usually acquired through the ingestion of contaminated food (foodborne infection) or by fecal/oral transmission. Infectious agents generate diarrhea through various mechanisms: (a) invasive, such as the destruction of the enterocyte by the germ (e.g., *Campylobacter*); (b) irritating, such as the destruction of the brush border (e.g., virus); and (c) toxic, such as the stimulation of cell secretion by a toxin (e.g., *Vibrio cholerae*). More advanced knowledge of intestinal physiology now allows us to more precisely identify the mechanisms of infectious diarrhea. Thus, we know that *Vibrio cholerae* toxin stimulates enterocyte secretion by activating the Cl^- CFTR channel while reducing Na^+

absorption by inhibiting NEH-2 and NEH-3 exchangers; rotavirus toxin inhibits the activity of brush border disaccharidases (hence the temporary lactose intolerance common in children with viral gastroenteritis) and inhibits the absorption activity of SGLT-1 transporters; zonula occludens toxin (ZOT) secreted by various bacteria attacks tight junctions (and thus probably facilitates the passage of toxins, aggressors, etc.).

Diarrhea is the most common clinical manifestation of small bowel infections and is often associated with abdominal pain, cramping, vomiting, and fever. Some of the infectious agents discussed below may affect other digestive organs such as the stomach or the colon; for organizational reasons, they will be included in this section of the manual.

(a) Viral infections Rotaviruses (found throughout the world but prevalent during winter in temperate countries), noroviruses (e.g., Norwalk virus transmitted during epidemics or by food poisoning), as well as some adenoviruses or astroviruses can be transmitted by fecal/oral routes and contaminated food or even through the respiratory tract. Diarrhea can also exist with HIV or coronavirus.

Viral gastroenteritis (often with diarrhea and vomiting) is usually short-lived (<72 h) and resolves spontaneously. Viral identification is not a clinically available test, and the diagnosis of viral enteritis is usually based on the clinical and epidemiological context.

(b) Bacterial infections Food poisoning with undercooked or improperly preserved food by toxins of bacterial pathogens such as *Staphylococcus aureus*, *Clostridium perfringens*, or *Bacillus cereus* generates diarrhea, often with vomiting, which starts early (2–12 h after ingestion) and resolves spontaneously within a few hours.

Diarrhea that persists for more than 48 h is rare with virus and most often due to bacteria, the most common being *Campylobacter jejuni* (50% of bacterial diarrhea in Quebec), *Salmonella*, and *Shigella*.

Many bacterial diarrheas disappear spontaneously in less than a week before the causal factor can be identified. The diagnosis of infectious enteritis is usually confirmed by stool examination (stool culture or parasite test). However, it is estimated that an infectious cause is identified in only about 3% of infectious diarrhea. The indication to perform a stool culture (which usually takes 2–4 days for results) is not universal and is usually based on severe and/or prolonged diarrhea beyond 3–4 days and/or bloody diarrhea and/or epidemic. A negative stool culture does not rule out the diagnosis of bacterial enteritis; some studies have shown that out of five successive samples, only one may be positive for the causative organism. A positive culture is not always an indication for treatment since some patients will already be cured by the time the culture results are received and since some bacteria, such as *Salmonella*, do not necessarily require specific treatment. The various bacterial agents of diarrhea with their characteristics and treatments are presented in Table 3.9 in next page.

The presence of blood is due to colonic damage most often caused by *Campylobacter*, *Shigella*, *Salmonella*, or enteropathogenic *E. coli*.

The term dysentery refers to a severe infection with fever, mucus, or blood. It is caused by bacteria (*Shigella*, etc.) or amoeba and can be lethal (many famous historic people died of dysentery: King St Louis during the Holy Crusades, Suleiman the Magnificent, Sir Francis Drake, etc.)

The most common bacterial enteritis is caused by the following agents:

- *Campylobacter jejuni* (gram-positive bacteria) is the most common causative agent (50% of cases) of bacterial enteritis in Quebec. The contamination most often occurs after ingestion of chicken (chickens are widely contaminated with *Campylobacter* or *Salmonella*) that has been undercooked, or by cross-contamination (via preparation, utensils, etc.) of other foods (e.g., lettuce, uncooked food, etc.) contaminated by chicken. In addition to diarrhea, *Campylobacter* can sometimes cause severe abdominal reactions (rebound tenderness, abdominal defense, etc.) that can mimic an "acute abdomen." Since long treated with quinolones, campylobacter has developed a growing resistance to this antibiotic (> 30% of cases in Quebec and > 80% if the bacterium is contracted in Asia).
- *Salmonella paratyphi* is most often acquired through contaminated chicken or through contact with "exotic" animals (turtles, lizards) and produces a diarrhea similar to *Campylobacter*.

  Salmonella typhi is rarer and will be responsible for typhoid: an enteric disease often without diarrhea but severe with fever, abdominal pain, intestinal inflammation (especially ileal), and hepatosplenomegaly. *Salmonella* bacteria can be found in the gallbladder, and patients who remain carriers can suffer disease relapse and infect others; cholecystectomy may be required to eradicate the source of chronic infection.

  Typhoid fever is a septicemia originating from mesenteric lymphatics. It is common in tropical areas and is diagnosed in industrialized countries almost exclusively in travelers returning from endemic areas. Clinical manifestations are associated with early headaches, insomnia, vomiting, dizziness, epistaxis, and a progressively increasing fever. By the second week, fever reaches 40 degrees with pulse/temperature dissociation, accompanied by lenticular pink spots (erythematous macules scattered on the trunk),

Table 3.9 Bacterial diarrhea: pathogenic agents, causes, treatments

Pathogens	Causes	Treatments
Campylobacter jejuni	Contaminated food (chicken) International travel	Azithromycin 500 mg id 3 days Ciprofloxacin 500 mg bid 7 days
Salmonella	Contaminated food (chicken)	No Rx Azithromycin 500 id 7 days Ciprofloxacin 500 bid 7 days
Shigella	Travel Per-person transmission	Azithromycin 500 id 3 days Ciprofloxacin 500 bid 3 days
Enteropathogenic *E. coli*	Traveler's diarrhea	No Rx Azithromycin 1000 id 1 day Ciprofloxacin 500 bid 1–3 days Rifaximin 200–600 mg die-tid 3 days
Clostridium difficile	Antibiotics/hospitals/PPI	Metronidazole 500 tid 10 days Vancomycin 125 qid 10 days Fidaxomicin 200 mg bid 10 days Fecal transplant
Enterohemorrhagic *E. coli*	Ground beef	No Rx (avoid AB)
Yersinia enterocolitica	Nordic countries (Canada) Cattle, pigs	Ciprofloxacin 500 bid 7–14 days
Clostridium perfringens	Food poisoning (8–14 h)	No Rx
Staphylococcus aureus	Food poisoning Duration <12 h; incubation: 2–7 h	No Rx
Bacillus cereus	Food poisoning; incubation: 2−14 h	No Rx
Aeromonas	Tropics	Azithromycin 500 id 3 days Ciprofloxacin 500 bid 3 days
Plesiomonas	Seafood International travel	Azithromycin 500 die 3 days Ciprofloxacin 500 bid 3 days
Vibrio (non-cholera)	Seafood, shellfish	No Rx Azithromycin 500 id 3 days Ciprofloxacin 500 bid 3 days
Vibrio cholerae	Endemic countries	Azithromycin 500 id 3 days Tetracycline 500 qid 3 days

splenomegaly, hepatomegaly, and disturbance of consciousness. At paraclinical level, the diagnosis is evoked by the absence of hyperleukocytosis in a context of septicemia and is confirmed by isolation of the germ from blood and/or stool cultures. Intestinal perforations of typhoid ulcers constitute 1/10 of all intestinal perforations seen by surgeons in Black Africa. Fluoroquinolones are the treatment of choice.

- *Shigella* is more rare. However, the toxin is acid-resistant and highly virulent, so that small amounts of bacteria are sufficient to lead to epidemic outbreaks. Risk factors outside of these outbreaks usually include travel abroad and/or homosexual intercourse.
- *E. coli* O157:H7 is the most famous of the *E. coli* bacteria capable of causing disease by producing enteropathogenic toxins (shiga toxin). It is most often acquired through contamination of ground beef (hence its popular name "hamburger disease") that is undercooked. The typical presentation includes bloody stools due to colitis (mimicking ischemic colitis on histological analysis) of the transverse colon. Shiga toxin can lead to the hemolytic uremic syndrome (HUS) with hemolysis and vascular complications affecting the kidneys, brain, etc. Antibiotics appear to be associated with increased production of shiga toxin and are therefore not recommended for the treatment of this infection.

- *E. coli*, enterotoxigenic, etc. represent different strains of *E. coli* that will cause "travelers' diarrhea" by secreting toxins that activate intestinal adenylate cyclase or guanylate cyclase. Traveler's diarrhea is usually of moderate intensity (three to six bowel movements per day) and of limited duration (24–72 h). It is common among travelers from "southern" or "exotic" countries such as Mexico (Montezuma's revenge), the West Indies, India, etc. It is usually caused by *E. coli*-type bacteria (characterized only by ultra-specialized microbiological techniques and not identifiable by routine analysis) contracted by drinking contaminated water or eating food washed with contaminated water. Fever or bloody stools are exceptional and must lead to the suspicion of other infectious agents (*Campylobacter*, *Salmonella*, etc.). For treatment and prevention, see ◘ Table 3.10.
- *Yersinia enterocolitica* is relatively rare. However, some clinical points are worth mentioning: (a) acute forms may mimic appendicitis (pseudoappendicitis), (b) while the disease may also evolve in a chronic way, like Crohn's ileocolitis.
- *Clostridium difficile* can colonize the human intestine like a commensal agent. However, the use of antibiotics, most probably by unbalancing the normal digestive flora, can cause its proliferation and release of toxins (A or B) with toxic actions on the colon and also the small intestine. In recent years, particularly virulent strains of *C. difficile* have appeared in Quebec and elsewhere in North America, and *C. difficile* colitis can be lethal in patients who contract this iatrogenic infection. The infection is, in the vast majority of cases, related to the use of antibiotics (all antibiotics are likely to be involved, but clindamycin and quinolones seem to be more frequently involved) in the preceding days or weeks. Other risk factors include hospital stay (contamination in a "closed" environment where virulent strains are present), PPI use, and impaired immunity. *C. difficile* colitis can be recognized on endoscopy by pseudomembranes (pseudomembranous colitis) that are almost pathognomonic, but not essential. Stool examination confirms the presence of the toxin.

Table 3.10 Traveler's diarrhea

Food precautions:
- Drink "Bottled" water
- Eat cooked or peeled food (cook it, peel it, or throw it)

Drug prevention:
- Pepto-Bismol 2 co qid
- Dukoral vaccine
- Prophylactic antibiotics (in rare selected cases)

Treatment:
- Hydration (WHO solution or equivalent)
- "Enteritis" diet (bananas, rice, apple sauce, toast, chicken noodle soup, soda cookies, potatoes, light meals)
- Loperamide if necessary (i.e., travel, comfort, etc.) and if no signs of severe infection (temperature, rectal bleeding)
- Antibiotics (possible in selected cases; see ◘ Table 3.9)

Complications of infectious diarrhea The main consequence of infectious diarrhea during its acute phase is dehydration, and its correction by oral (e.g., WHO solution) or intravenous fluids should be the main initial therapeutic goal.

Other less frequent complications may be associated with bacterial enteritis:
- Megacolon and colonic perforation can occur in severe forms of bacterial colitis. Ileal perforation is a complication of typhoid fever.
- Hemolytic uremic syndrome is characterized by hemolysis with renal failure (that may require hemodialysis, etc.) or cerebrovascular accidents (stroke, etc.). It is due to a shiga toxin produced by some *Escherichia coli*, the most common being the O157:H7 type.
- Seronegative arthritis, or Reiter's syndrome, is due to an immunological reaction occurring a few weeks after infectious enteritis and leading to inflammatory arthritis with sometimes ureteral damage. Usually affecting people HLA-B27 positive, this condition can occur after *Campylobacter*, *Salmonella*, *Shigella*, or *Yersinia* infections.
- Ascending paralysis or Guillain-Barré syndrome is another autoimmune manifestation that can sometimes be seen after *Campylobacter* infection.
- Post-infectious irritable bowel syndrome can develop in some individuals (see ▶ Chap. 4).

(c) Parasitic infections Some parasites can cause acute diarrhea:
- *Cyclospora* has been linked to epidemic food infections (strawberries, raspberries, lettuce), or to travel (e.g., Nepal).
- *Giardia lamblia* is the most common parasitic infection encountered in North America. It may be acquired through ingestion of contaminated (among other things, by beavers) spring water from the Adirondack or Rocky Mountains. This infection is prevalent in certain environments such as daycare

centers and can also be acquired during trips to the South or even in certain northern countries such as Russia (especially in St. Petersburg area).
- Amoebae can affect mainly the colon and are usually found in travelers of African or Asian countries.

Chronic parasitic infections can also occur. The most frequent infections encountered in Quebec are due to *Giardia lamblia*, *Entamoeba histolytica*, or *Blastocystis hominis*.

In tropical areas, particularly in Africa south of the Sahara, infection by certain intestinal parasites will be responsible for abdominal pain and/or transit disorders (diarrhea, constipation, vomiting, nausea) associated with blood hypereosinophilia (except for protozoa). The main parasites involved are:
- Nematodes or roundworms (*Ascaris lumbricoides*, *Ancylostoma duodenale*, *Necator americanus*, *Strongyloides stercoralis*, *Enterobius vermicularis*, etc.)
- Taenias or flatworms (*Taenia saginata*, *Solium*, *Hymenolepis nana*, etc.)
- Protozoa (giardia, *Entamoeba histolytica*, etc.)

The diagnosis of these parasitoses is made by stool examination which finds the parasite or its eggs.

Treatment uses benzimidazoles (mebendazole, albendazole) for nematodes, niclosamide for tapeworms, and metronidazole for protozoa.

(d) Mycotic infections *Candida albicans* is found in the normal intestinal or fecal flora. The involvement of candida in septicemia or in esophagitis (and possibly some gastritis) is well documented; however, no pathogenic role for candida is recognized in the small intestine (or colon).

Stool examination is discussed in ◘ Table 3.11. Less common pathogens are presented in ◘ Table 3.12.

Table 3.11 Stool examination for pathogens

Stool tests = "gold standard" to confirm enteric infections and identify causal agents

Viral tests
- Analysis rarely available in routine clinical laboratory
- Not very useful in clinic given the rapid and spontaneous healing of most viral enteritis

Bacterial detection by stool cultures
- Limited sensitivity (30–70%????): routine culture tests focus on bacteria known to cause diarrhea (salmonella, shigella, etc.); sensitivity is limited by intermittent fecal excretion of pathogenic bacteria
- Time to results: 2–4 days
- High specificity; but many germs (e.g., *Campylobacter*, *Salmonella*) may not require treatment

Stool parasite search
- Microscopic identification: uncertain sensitivity (50%?) related to local expertise and intermittent fecal excretion of parasites
- PCR test: new test with higher sensitivity. Specificity?: detects nonpathogenic parasites (*Entamoeba dispar*, etc.) or parasites of uncertain pathogenicity (*Blastocystis hominis*)

Table 3.12 Pathogens encountered in special or specific circumstances

Raw or undercooked food	
Diphyllobothrium latum: parasite (ad 12 m long!) contracted in raw fish from northern waters (Scandinavia, Russia, Alaska)	
Capillariasis: raw fish (Philippines, Thailand, Japan). Disease may be severe with diarrhea/malabsorption/death within 1 month	
Anisakis simplex: raw fish (sushi). Stomach, stomach pain/nausea/vomiting few hours after ingestion; intestine, ≈ ileitis/appendicitis; allergic reaction (rash, etc.)	
Trichinosis: uncooked pork (rare now), uncooked bear (Inuits)	
Travel	
Giardia (Appalachians, Rocky Mountains, Russia)	
Amoebae (Africa, Asia):	Diarrhea/colitis Liver abscess
Ascaris: roundworm 25–50 cm long:	Intestinal obstruction: pain Biliary obstruction: jaundice
Hookworm (Africa)/*Necator americanus* (America): contacted by barefoot in contaminated soil; iron-deficiency anemia (parasites in duodenal mucosa)	
Taenia: flatworm 4–10 cm long – *T. saginata* (beef)/*T. solium* (pork)	
Schistosomiasis: bathing in contaminated water	*S. mansoni* (Africa): colitis/portal vein hypertension / *S. japonicum* (Asia): hemorrhagic bladder
Immunodeficiency – HIV	
Opportunistic infections (CD4 ↓):	Cytomegalovirus (CMV) Cryptosporidium/*Isospora belli* Mycobacterium avium complex (MAC)

3.6.4 "Special" Infections of the Small Intestine

Intestinal tuberculosis Tuberculosis (TB) bacilli can infect the digestive tract after swallowing of contaminated pulmonary secretions or, more rarely, through the ingestion of infected food (e.g., milk from a TB-infected cow). Inflammation of the distal ileum, similar to Crohn's disease ileitis, is the most common clinical presentation.

Intestinal TB is exceedingly rare in industrialized countries. However, this diagnosis should be considered in patients from countries where it may be common (India, Africa, Haiti, etc.). Biopsy of the lesions reveals giant cell granuloma with caseum. The infection evolves in a context of weight loss, anemia, asthenia, anorexia, and amenorrhea associated with nocturnal fever.

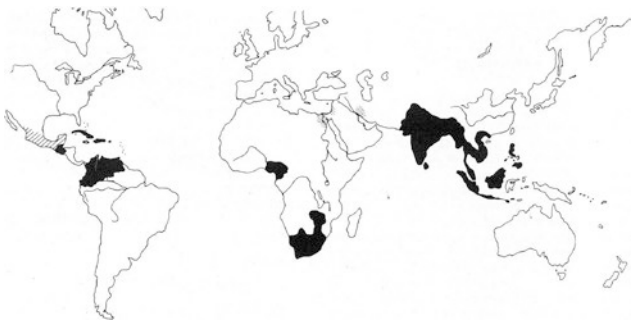
Tropical sprue Tropical sprue causes chronic diarrhea and even malabsorption. Intestinal histology reveals partial villous atrophy that can be quite comparable to that of celiac disease (also called nontropical sprue) . Tropical sprue should be suspected in people with chronic diarrhea who reside or have resided for some time in developing countries as shown in ◘ Fig. 3.54 (Haiti, India, etc.).

No specific germ has been identified yet to cause tropical sprue, but its geographical distribution, and especially its treatment with tetracycline (combined to folic acid), clearly supports an infectious origin.

Whipple's disease Whipple's disease is a multisystemic disease whose infectious origin was revealed in 1992 by the identification of a new bacterium *Tropheryma whipplei*, a gram-positive bacillus related to *Actinomyces* and responsible for the disease.

Whipple's disease is rare, but it can affect several systems. Classic presentation of the disease includes digestive symptoms (diarrhea, weight loss due to malabsorption, abdominal pain) and arthralgia. However, it is now known that it can also affect the nervous system (with oculomasticatory myorhythmia, i.e., contraction of the ocular and masticatory muscles that is pathognomonic for the disease, or cerebellar atrophy, or dementia), as well as the heart or lungs (endocarditis, pulmonary hypertension), etc.

Its diagnosis is established by intestinal biopsies revealing partial atrophy of the villi with infiltration of the lamina propria by organisms staining positively with PAS. It is treated with antibiotics, usually for several months.

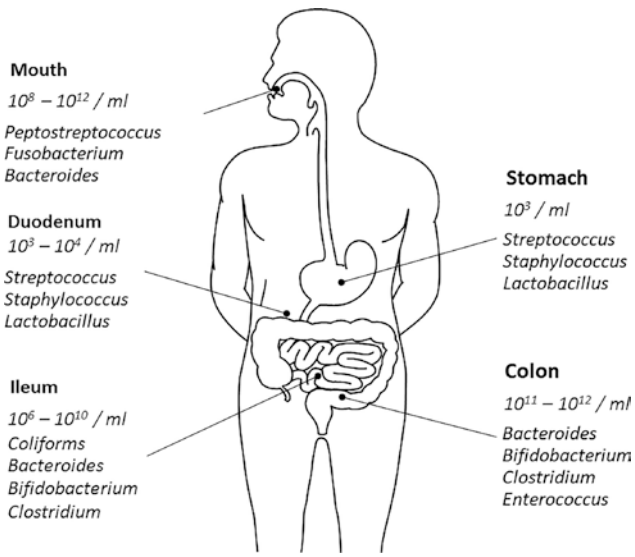


◘ **Fig. 3.54** Worldwide distribution of tropical sprue: black areas indicate where the disease is found

3.6.5 Small Intestinal Bacterial Overgrowth (SIBO)

SIBO is a peculiar "infectious" condition since it is not due to the proliferation of a specific pathogen, but rather to the exaggerated proliferation in the proximal small bowel of bacteria normally present in the gastrointestinal tract.

(a) Normal intestinal flora (microbiota) At birth, the gastrointestinal tract is sterile, but it will be rapidly colonized by maternal and foodborne bacteria (◘ Fig. 3.55). Genomic studies of the intestinal microbiota (microbiome) indicate the presence of 36,000 different species of bacteria in the human intestine, which are classified into four main phylogenetic groups: Firmicutes ((64%) *Clostridium*, lactobacilli, enterococci, *Staphylococcus*, streptococci, etc.); Bacteroidetes ((23%) bacteroids, flavobacteria, etc.); Proteobacteria ((8%) enterobacteria,



◘ **Fig. 3.55** Distribution and types of bacteria in the human digestive tract (concentration expressed in colonies/mL)

Escherichia coli, pseudomonas, fusobacteria, etc.); and Actinobacteria ((5%) corynebacteria, etc.).

The mouth contains a very large number of bacteria (10^8–10^{12} bacteria/ml of saliva, which corresponds to the concentration found in the colon!). There are a very large number of anaerobic bacteria (*Fusobacterium*, *Peptostreptococcus*, *Actinomyces*, *Eikenella corrodens*, *Bacteroides*), as well as gram-positive aerobic bacteria (*Streptococcus*, *Staphylococcus aureus*, etc.).

The esophagus, by its rapid transit, offers little opportunity for swallowed oral bacteria to stay there.

In the stomach, only few rare bacteria such as *Helicobacter pylori* can survive in its acidic environment.

In the small intestine, the concentration of bacteria, especially gram-negative bacteria, will gradually increase throughout the intestine, as will the proportion of anaerobic bacteria.

In the colon, bacteria are found in very high numbers: anaerobic bacteria (*Bacteroides*, Lactobacillus, *Clostridium*), as well as some aerobic bacteria (*Enterobacter*, *Escherichia coli*).

Sixty percent of stools' weight is made up of bacteria. Fungi, such as *Candida*, are also natural inhabitants of the human intestine.

(b) Role of the normal intestinal flora Although bacteria are most often associated with a harmful effect, intestinal bacteria may play a beneficial role in the body. They contribute in energy intake since colonic bacteria will be able to metabolize sugars and dietary fibers that were not absorbed by the small intestine into short-chain fatty acids that will be absorbed by the colon to provide up to 10% of usable calories. Colonic bacteria also play a role in the digestion of exfoliated epithelial cells, as well as in many immune responses. The growing popularity of probiotic or prebiotic solutions for the treatment of various conditions is an illustration of the presumed beneficial role of intestinal bacteria.

(c) Protection of the host against bacteria The hyper-abundance of bacteria can however be harmful (below), and their over-multiplication must therefore be controlled by various mechanisms, including acid pH in the stomach and bile salts in the small intestine. However, the dysfunction of these natural defense mechanisms (e.g., during gastric achlorhydria) seems to have only a relative impact.

On the other hand, the ability of the small intestine to get rid of stagnant bacteria through its peristaltic contractile movements seems to be a determining factor. Phase III of the MMC allows the stomach and small intestine to clear superfluous bacteria that could stagnate and grow in excessive numbers. MMC is so called the "intestinal housekeeper," and any condition hindering its normal presence may lead to an exaggerated intestinal bacterial outbreak.

(d) SIBO The proximal small intestine normally contains a small amount of bacteria (less than 10^3 bacteria/ml of duodenal fluid), usually of aerobic type. An increase in the number of bacteria (>10^5 bacteria/ml) and the proliferation of anaerobic bacteria may have a detrimental effect on normal absorption mechanisms.

Mechanisms for malabsorption due to *SIBO* involve the following:

- Bile salts of the intestinal chyme are deconjugated, thus preventing the formation of micelles and compromising the absorption of lipids and liposoluble vitamins.
- Inflammation of the intestinal mucosa with partial villous atrophy reducing disaccharidases and other mucosal digestive enzymes.
- Vitamin B12, carbohydrates, and proteins are consumed by bacteria.

Causes of SIBO Any disturbance in the "clearance" process of intestinal bacteria from the small bowel by peristaltic contractions of the intestinal walls (Fig. 3.56) can lead to bacterial accumulation:

- Stenosis (benign or malignant) preventing transit of intestinal chyme essential for bacteria clearance
- Saccular formation (e.g., diverticula) or excluded segments (e.g., blind loop after surgery) compromising cleaning in some intestinal segments

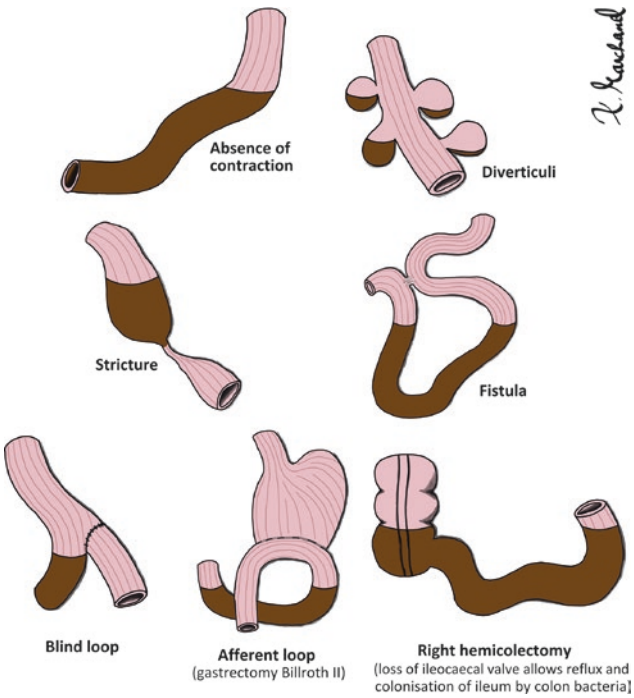


Fig. 3.56 Conditions that can lead to bacterial overgrowth, in which the intestine is unable to clean itself adequately (from Frexinos 2003)

- Deficient intestinal peristalsis due to parietal damage (e.g., intestinal scleroderma) or due to a muscular or neurological disease (e.g., intestinal pseudo-obstruction) preventing the normal presence of the MMC
- Exaggerated discharge of bacteria exceeding normal clearance limits (e.g., colo-gastric fistula)

Clinical presentation of SIBO includes diarrhea, malabsorption, weight loss, abdominal discomfort, bloating, and distension.

Diagnosis of SIBO It is best made by duodenal fluid collection (via tubing or endoscopy) and counting of the number of bacteria. This is the "gold standard" method, but in practice it is a complex procedure for both the patient and the medical team. Therefore, indirect functional tests are used. These are based on the abnormal catabolism, by over-accumulated bacteria, of certain substances not normally absorbed by the proximal small intestine (e.g., bile salts absorbed at the ileum or nonabsorbable sugars such as lactulose). Absorption of an orally ingested labelled bile salt (C^{13} cholylglycine or, more rarely, radioactive C^{14} cholylglycine) can be monitored with a CO_2 breath test, where an increase in lung-exhaled C^{13} (or radioactive C^{14}) can normally be detected 3–5 h post-ingestion (i.e., when the bile salt has reached the ileum and has been absorbed). During bacterial overgrowth in the proximal bowel, the peak of C^{13} or C^{14} excretion occurs as early as 1–2 h post-ingestion (when the bile salt is deconjugated in the duodenum by overabundant bacteria). Similarly, lactulose which normally gives a peak of exhaled hydrogen (hydrogen breath test not requiring radioactive compounds) after 3–5 h (when the nonabsorbable sugar is metabolized by colonic bacteria) will give an early peak after 1–2 h (when the sugar is metabolized by overabundant bacteria in the proximal small bowel).

Treatment of SIBO

- Correct, if possible, the causal factor, i.e., intestinal stenosis, blind loop, fistula, dysmotility, etc.
- Reduce the abundance of intestinal bacteria with antibiotics (e.g., tetracycline, metronidazole, amoxicillin, ciprofloxacin, etc.) which are often used at low doses (e.g., tetracycline 250 mg bid), in rotation (e.g., tetracycline for 1 week, then metronidazole for 1 week, etc.) and intermittently (one week out of 2−3)

3.7 Tumor Disorders

Neoplasias of the small intestine are rare. They represent only 2% of digestive tumors and 0.4% of all tumors.

Table 3.13 Small bowel primary malignancies and their frequency (%)

Duodenum	Jejunum	Ileum
AdenoCa 64%	AdenoCa 46%	Carcinoid 63%
Carcinoid 21%	Lymphoma 21%	AdenoCa 19%
Lymphoma 10%	Carcinoid 17%	Lymphoma 15%
Sarcoma 4%	Sarcoma 17%	Sarcoma 5%

3.7.1 Malignant and Benign Tumors

Types of intestinal tumors

Primary malignancies of the small intestine are described in Table 3.13.

Adenocarcinoma (adenoCa) of the small intestine seems to follow the same sequence of development known for colon carcinoma, i.e., to develop from an adenoma. The risk is increased in patients with genetic conditions such as HNPCC (hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis, and Peutz-Jeghers polyposis (see ▶ Chap. 4) or with chronic inflammation such as Crohn's disease or celiac disease.

Primary digestive lymphoma affects the stomach in 75% of cases but also the small intestine in 25%. Lymphoma type B (MALT, etc.) is more common; it is prevalent in HIV immunodeficiency states or under post-transplant immunosuppressive treatment. Lymphoma can also be of type T in refractory celiac disease.

Sarcomas include gastrointestinal stromal tumors (GIST; see ▶ Chap. 2) in 80% of cases and more rare tumors such as sarcoma, leiomyosarcoma, schwannoma, etc.

"Secondary" tumors of the small intestine: Tumors originating from other organs can reach the small intestine. The invasion can be continuous and is most often associated with peritoneal carcinomatosis due to ovarian, colonic, or gastric neoplasms. Hematogenic metastatic invasion can occur from melanoma (the small intestine is the main site of melanoma metastasis), lung, or breast cancers.

Benign tumors of the small intestine: Adenoma of the small intestine has malignant potential as in the colon. Often located in the duodenum, they have a predilection for Vater's ampulla. In some cases (e.g., familial polyposis), multiple adenomas may be found.

Other benign tumors include leiomyoma, lipoma, desmoid tumor (in familial polyposis), or hamartomatous polyps as in Peutz-Jeghers polyposis.

Clinical presentation of intestinal tumors Tumors of the small intestine may progress for a long time prior to developing clinical symptoms:

- Cramp-like abdominal pain associated with an occlusive or sub-occlusive syndrome
- Nausea and vomiting related to the occlusion
- Weight loss due to eating difficulty (occlusion) or to malabsorption (lymphoma)
- Acute (rectorrhagia) or chronic (occult iron-deficiency anemia) bleeding
- Palpable abdominal mass

Diagnosis of intestinal tumors Tumors of the small intestine are usually revealed by imaging tests. However, the small intestine is difficult to investigate. Endoscopy, which is useful for visualizing the proximal (esophagus, stomach, duodenum) and distal (colon, terminal ileum) GI tract, is more difficult to perform deep in the small bowel, considering its length of 3 meters. Radiological procedures that include small bowel follow-through with barium ingestion, abdominal CT scan (enteroscan with ingestion of contrast fluid), or MR enterography can be performed. Push or double-balloon enteroscopy with an endoscope inserted via the mouth or rectum, as well as enteroscopy by video capsule, can be used to investigate the small intestine.

Treatment of intestinal tumors Depending on the type of tumor, surgery or chemotherapy may be used. However, tumors of the small intestine can evolve for a long time without symptoms and can therefore, unfortunately, be very advanced at the time of diagnosis.

3.7.2 Neuroendocrine Tumors (NETs)

NETs originating from neuroendocrine cells of the gastrointestinal tract are mostly malignant, but their malignant potential is often less aggressive than that of adenocarcinomas. Their clinical expression varies according to amines or peptides synthesized by these cells and released into the circulation. NETs are common in the pancreas (pNET; see ▶ Chap. 5) where they can secrete insulin (insulinoma), glucagon (glucagonoma), gastrin (gastrinoma or Zollinger-Ellison syndrome), and vasointestinal polypeptide (VIPoma). Intestinal NET (iNET), previously known as carcinoid tumor, involves enterochromaffin cells involved in serotonin synthesis and found in large numbers in small intestinal mucosa.

The intestinal tumor (like all NETs) is characterized histologically by small, round, uniform cells with secretory granules that may be stained with silver, either directly (argentaffin cells) or after application of a reducing agent (argyrophil cells). Further histochemical studies may reveal their serotonin or peptide content.

Carcinoid tumors (or iNET) are located mainly in the ileum (30%), lung (25%), appendix (20%), rectum (10%), colon (10%), or stomach (5%). The malignant potential of iNET is proportional to its size; the incidence of metastases is only 2% for 1 cm tumors, 50% for 1–2 cm tumors, and 80% when the tumor is larger than 2 cm. However, NETs are less aggressive than adenocarcinomas, and patients can often have prolonged survival even with metastatic disease.

Ileal NET (carcinoid tumor) may be revealed by abdominal pain related to intestinal obstruction which may be due to the tumor itself (having reached a certain volume) but most often caused by a wrapping and narrowing of the intestine by mesenteric fibrosis secondary to "sclerosing" products secreted by the tumor (as described below).

Carcinoid syndrome is due to the release of products secreted by the tumor cells (here enterochromaffin cells with serotonin, histamine secretion, etc.) into circulation, and having effects on various organs. Carcinoid syndrome is found in approximately 10% of intestinal NETs and most often involves the presence of liver metastases. It is recognized by:

- Diarrhea due to an excess serotonin (5HT) released into circulation causing hypermotility and hypersecretion of the intestine. It is present in 80% of patients and can be reduced by serotonin antagonists.
- Flushing characterized by brief episodes (30 s to 30 min) of vasodilatation with hot flash, purplish red coloration affecting the face, neck, and trunk. Flushing may be triggered by eating, alcohol, and liver palpation. It can be associated with telangiectasia or cyanosis. Episodes of bronchoconstriction with asthma-like symptoms are also frequent. Histamine and/or kinins released by the tumor are responsible for the symptoms of flushing and bronchoconstriction.
- Fibrosis of different organs seems to be due to different "sclerosing" substances (TGF-β (transforming growth factor-β)? and serotonin?) secreted by the tumor. Two anatomical sites (◘ Fig. 3.57) are especially vulnerable: (a) the mesentery next to the tumor and hosting the venous toxic drainage of the tumor and (b) the tricuspid valve of the right heart irrigated by fibrotic substances secreted from hepatic metastases into the hepatic veins and the inferior vena cava. Mesenteric fibrosis wrapped around the intestinal loop will cause luminal occlusion, while tricuspid fibrosis may lead to right heart failure which may be fatal in a large number of patients.

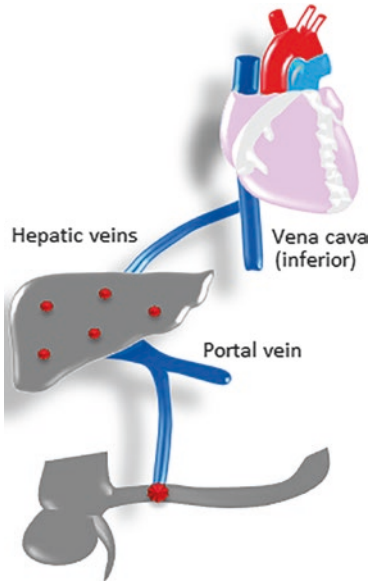


Fig. 3.57 The carcinoid ileal tumor releases fibrosing substances (5HT, TGF-B) that generate mesenteric fibrosis in the vicinity of the tumor, as well as other substances (serotonin, kinins, etc.) that (via the portal vein (PV)) reach the liver where most of them are destroyed. Carcinoid liver metastases secrete substances that enter the systemic circulation to cause diarrhea (serotonin) , flushing (kinins), bronchoconstriction (histamine), etc.; fibrosing substances secreted toward the hepatic veins (HV), the inferior vena cava (IVC), and the right heart may attack and destroy the tricuspid valve

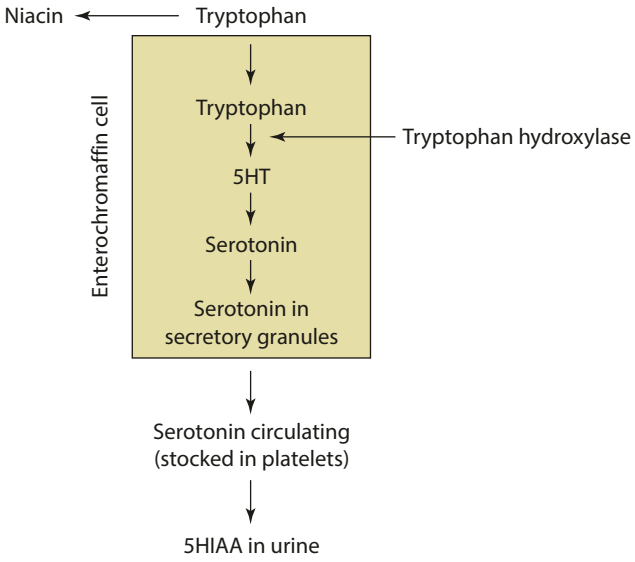


Fig. 3.58 Serotonin metabolism. Tryptophan (essential amino acid) is normally used as a precursor to both serotonin and niacin; excessive synthesis of serotonin depletes tryptophan stores required for niacin synthesis, leading to niacin deficiency with, possibly, pellagra. A metabolite of serotonin, 5HIAA, can be readily measured in urine to detect excess production of serotonin by carcinoid tumor

Pellagra skin lesions may be present with carcinoid syndrome and niacin deficiency. This niacin deficiency is due to a lack of tryptophan (precursor of niacin and serotonin) caused by excess tumor synthesis of serotonin (using tryptophan and depleting the reserves of tryptophan normally used for niacin synthesis) (Fig. 3.58).

Diagnosis of intestinal NET is based on imaging techniques (CT scan, MRI, nuclear scan, or PET scan with tumor-binding somatostatin analogues (Octreoscan, PET-DOTA)) revealing the location of the tumor and its metastases, as well as by biochemical methods to evaluate the production of tumor products. Measurement of plasma serotonin is not a diagnostic tool readily available in the clinic, and hyperproduction of serotonin will be assessed by the urinary excretion of 5HIAA (5-hydroxyindoleacetic acid), a serotonin metabolite (Fig. 3.58).

Carcinoid syndrome can be controlled by serotonin or histamine antagonists but often only partially. Treatment with the hormone somatostatin or synthetic analogues (octreotide, etc.) is the most effective way to reduce humoral secretion of NETs.

Treatment of NET will involve surgical resection and/or chemotherapy. Carcinoid syndrome will be treated by reducing tumor mass and/or by administering hormonal inhibitors (discussed above).

NET of the appendix NET is found in approximately 1/300 appendices resected for appendicitis. This is often an incidental finding. In 95% of the cases, the tumor is less than 2 cm in size and is healed by an appendectomy. Larger or invasive tumors must be treated by extensive oncologic resection.

Duodenal NET NET, especially gastrinoma and somatostatinoma, can occur in the duodenum. They will be discussed with the pNETs in ► Chap. 5.

3.8 Function Disorders

Absorptive and secretive functions of the intestine can be disrupted by inflammatory or tumoral disorders that have been discussed beforehand and can be easily recognized by usual laboratory or imaging techniques. Motility and sensitivity functions may also be abnormal and are often difficult to identify

3.8.1 Intestinal Pseudo-obstruction

Chronic pseudo-obstruction of the intestine is the most apparent and severe form of functional dysfunction of the small bowel. This disease took its name from the observations that patients with signs of intestinal occlusion (abdominal cramps, no passage of stools or gas, abdominal distension, X-ray of the abdomen showing enlarged intestinal loops with air-fluid levels) have no findings when operated by laparotomy (undertaken to remove an obstructive lesion (tumor, inflammation, or others) and to restore normal intestinal transit) and where no cause is identified to explain the apparent intestinal obstruction. Impairment of intestinal motility by a disease affecting intestinal muscles (e.g., infiltration by scleroderma, amyloidosis, or muscular diseases such as Steinert's dystrophy, etc.) or nerves (diabetic neuropathy, paraneoplastic neuropathy, etc.) regulating intestinal transit is responsible for intestinal pseudo-obstruction disease.

Intestinal pseudo-obstruction can be a very severe condition preventing oral nutrition. Its treatment will include (1) control of the causal disease (if possible); (2) stimulation of digestive motility by various pharmacological agents (cholinergic, anti-dopaminergic, 5HT4 agonists, motilin agonists, etc.); (3) control of bacterial overgrowth by antibiotics; and (4) nutritional support via an enteral or parenteral route.

3.8.2 Rapid Transit

Accelerated transit can, in certain circumstances, reduce the contact time of ingested substances (nutrients or medication) to enterocytes and limit their absorption. Conditions most frequently encountered to explain rapid intestinal transit are presented in ◘ Table 3.14.

3.8.3 Slow Transit/Ileus

Slow intestinal transit, as explained above, may be severe enough to mimic intestinal obstruction. Other conditions compromising bowel movements are shown in ◘ Table 3.14. The patient with an obstructed bowel, or ileus, suffers from painful abdominal distension, often with fecaloid vomiting; X-ray of the abdomen shows distended bowel loops with air-fluid levels (◘ Fig. 3.59). The ileus may be of mechanical origin, i.e., by blockage, or of "paralytic" origin (◘ Table 3.15).

Paralytic ileus is most often transient. It is common after abdominal surgery with bowel manipulation; it may be reactive to any intra-abdominal condition (visceral perforation, abscess, etc.); it is common with drugs such as opiates or anticholinergics that inhibit intestinal contractility.

3.8.4 Irritable Bowel Syndrome (IBS)

IBS is a very frequent pathology responsible for abdominal pain and colonic manifestations of constipation/diarrhea, etc. (see ▶ Chap. 4). However, motor and sensory abnormalities of the small intestine are also identifiable: exaggerated ileal contractions have been associated with cramping pain in some patients (leading to the clinical use of "antispasmodic" drugs to reduce intestinal contractions); abdominal bloating, common in these patients, appears to be partly related to motor dysfunction and abnormal intestinal gas transit; visceral hypersensitivity well documented in the rectum of IBS patients can also be found in the small intestine.

Table 3.14 Small intestine: transit variations

Rapid transit

- Loss of ileocecal "brake": ileocecal resection, ileostomy
- Neurological dysfunction: post-vagotomy dumping, abdominal sympathectomy (celiac/mesenteric ganglion), neuropathy (diabetes, amyloidosis, etc.)
- "Hormonal" stimulation: serotonin (carcinoid tumor), thyroxine (thyrotoxicosis), thyrocalcitonin (thyroid medullary carcinoma)
- Pharmacological stimulation: cholinergic agents, 5HT4 agonists, prostaglandins, laxatives (lubiprostone, castor oil, osmotic laxatives)
- Intestinal "irritation": infection (bacteria, giardia), "toxic" (strong spices, radiotherapy, etc.)

Slow transit

- Postoperative ileus (post-laparotomy)
- Reflex ileus = possible with any abdominal infection or inflammation (appendicitis, pancreatitis, abdominal abscess, visceral perforation, etc.)
- Drugs: anticholinergics (including tricyclic antidepressants, etc.), opiates

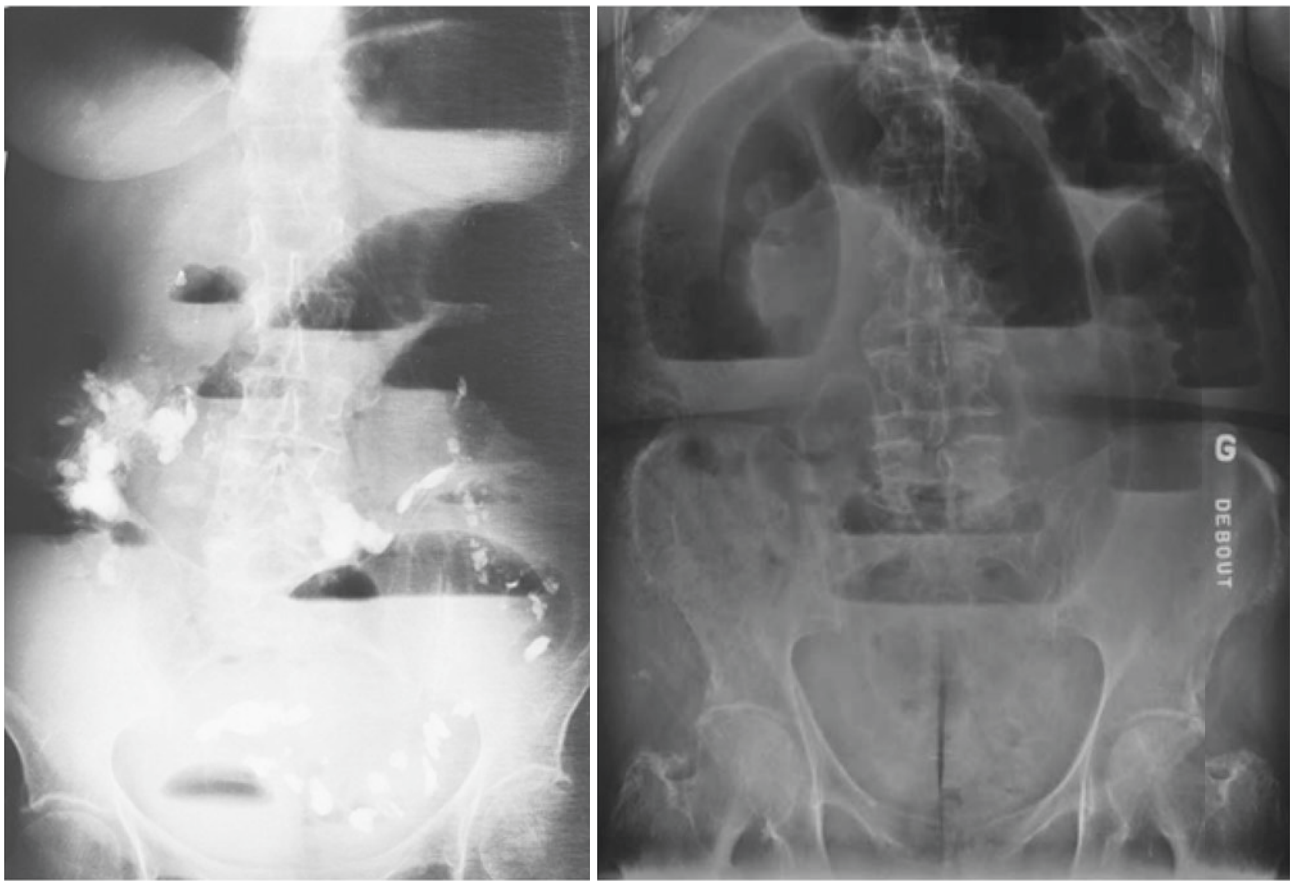


Fig. 3.59 Intestinal ileus as seen on plain X-rays of the abdomen: enlarged intestinal loops with air-fluid levels. (Photos from R. Déry)

Table 3.15 Intestinal ileus

Mechanical ileus	Paralytic ileus
Blockage by stricture, tumor, adhesion, etc.	Slowing down by motor paralysis
Examination: hyperactive bowel sounds (struggling to overcome the obstacle)	Examination: decreased bowel sounds (hypocontractility, paralyzed intestine)
Localized intestinal loop distension upstream of the obstruction site with normal loops downstream	Diffuse GI tract distension

3.9 Miscellaneous

3.9.1 Ulcerations

Small bowel ulcerations can occur during infection (most often acute such as *Campylobacter*), inflammation (e.g., Crohn's disease), and ischemia (vasculitis, arteriosclerosis, etc.). Peptic ulcerations are exceptional (due to the rare Zollinger-Ellison syndrome) in the small bowel.

Ulcerations, most often, are caused by medications such as aspirin (ASA) or nonsteroidal anti-inflammatory drugs (NSAID). Painless and without consequences on intestinal absorption or transit, ASA or NSAID ulcers are usually revealed by evidence of blood loss (sometimes acute but most often chronic), frequently aggravated by concomitant treatment with anticoagulant or antiplatelet drugs.

ASA/NSAID-induced ulcerations are usually superficial and only a few millimeters in size. They usually escape radiological diagnostic techniques such as small bowel follow-through, CT enteroscan, MR enterography, etc. They can be identified during specialized and complex endoscopies using long "enteroscopes" that can be introduced, via oral or anal route, at varying distances along the jejunum or terminal ileum, or during visualization of the small intestine by a video capsule (pill camera orally ingested and spontaneously traveling along the digestive tract while transmitting images from intestinal lumen).

Treatment involves, if possible, discontinuation of the causative agent (ASA or NSAID) and/or agents

that may promote bleeding (anticoagulants, antiplatelet agents, etc.). Proton pump inhibitors (PPIs), while useful in the treatment of gastric ulcers, have no effect on intestinal ulcers; in fact, some animal studies even suggest that PPIs increase intestinal ulcers (possibly by alteration of intestinal microbiota). It is tempting to speculate that the pathophysiology of these intestinal ASA/NSAID-induced ulcers involves reduced production of protective mucosal prostaglandins; synthetic prostaglandin drugs such as misoprostol may be effective in treating these ulcers.

3.9.2 Vascular Abnormalities (Angiectasias, Etc.)

Vascular abnormalities of the small intestine can be either benign (hemangioma) or malignant (Kaposi's sarcoma, angiosarcoma), be part of congenital or systemic disorders (Rendu-Osler-Weber disease, scleroderma), or be acquired and sporadic and then called angiectasia, angiodysplasia, arteriovenous malformation, vascular ectasia, etc.

Angiectasias are the most common vascular lesions and account for 40% of bleeding in the small intestine. They occur most often in patients over 60 years of age who are anticoagulated and suffer from renal failure, von Willebrand disease, or aortic stenosis (Heyde's syndrome).

3.9.3 Intestinal Ischemia

Intestinal ischemia can be acute or chronic (40% of cases), of arterial or venous (5% of cases) origin.

Chronic ischemia Mesenteric angina can occur when arterial supply to abdominal viscera is insufficient. As with angina pectoris, symptoms of mesenteric angina appear during exercise, which for the intestine corresponds to the period of food digestion. Blood supply to the intestine corresponds to about 20% of the cardiac output in the basal period but can increase up to 35% after meals.

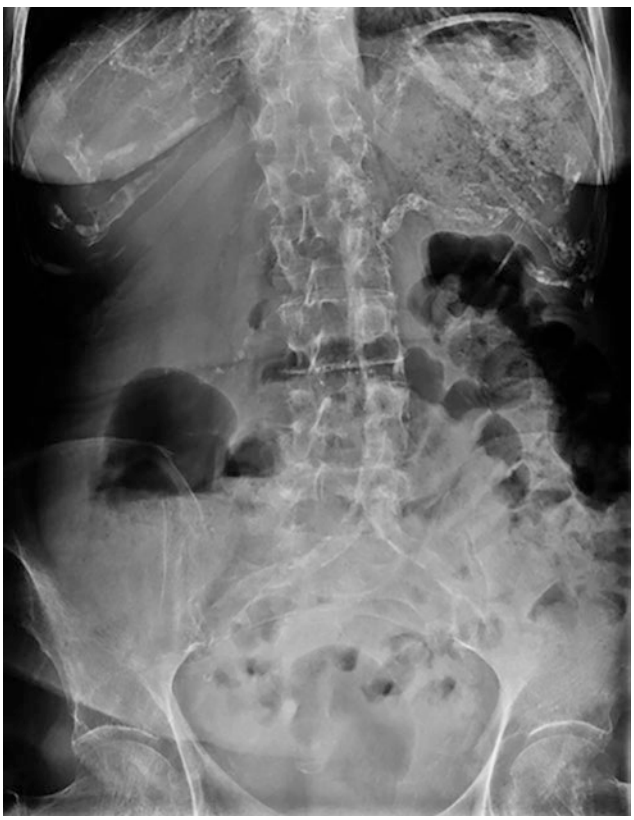
Symptoms of mesenteric angina include pain (a) periumbilical or epigastric, (b) occurring in the postprandial period (30–120 min pc), (c) of intensity proportional to the size of the meal (i.e., in relation to the intensity of the effort required), (d) resulting in eating difficulty (among other things, due to fear of pain) and secondary weight loss. Diarrhea can also occur in the case of ischemic damage to intestinal villi. Oxygenation of the digestive viscera relies on three main vessels, the celiac trunk, the superior mesenteric artery, and the lower mesenteric artery (especially for the colon), thus ensuring great possibilities for collateral irrigation. Atherosclerotic narrowing of two of the three main arterial trunks is the main cause of mesenteric angina. On physical examination, an epigastric murmur can be perceived.

Vascular damage (◘ Fig. 3.60) is best identified by Doppler ultrasonography of the abdominal arteries or by angiography via CT scan, magnetic resonance, or arterial catheter.

Restoration of arterial flow, either by endovascular stenting or bypass surgery, improves the symptoms of mesenteric angina.

Acute ischemia Acute obstruction of the arterial vessels irrigating the intestine (most often the superior mesenteric artery) or of the drainage veins (i.e., superior mesenteric vein and portal vein) results in clinical situations that are, most of the time, severe and, unfortunately, difficult to diagnose.

Vascular insufficiency may be due (a) to thrombotic phenomena (e.g., with hypercoagulability, atheroscle-



◘ **Fig. 3.60** Plain X-ray of the abdomen showing severe atherosclerosis with calcifications (making the vessels here very visible) of the aorta, mesenteric artery, and iliac arteries in a patient with mesenteric angina. (Photo from R. Déry)

rosis, vasculitis), or (b) embolic (via atrial fibrillation, aortic atheroma plaque, etc.), or (c) be related to nonocclusive ischemia due to a decrease in the intestinal perfusion flow (heart failure, dehydration, hemodynamic shock), etc.

The clinical picture is one of acute abdominal pain, most often diffuse, often evolving rapidly in a few hours to signs of peritoneal irritation (rebound tenderness on examination) and ultimately of intestinal perforation (localized abdominal guarding → diffuse rigidity).

Diagnosis Acute intestinal ischemia is a vital emergency. Diagnosis is often difficult given the rather nonspecific signs. Blood lactates rising in response to intestinal ischemia are, unfortunately, a late indication of the severe condition. Abdominal CT or angioscan reveals vascular defects (clots, thromboses) and the state of the intestine (edema, perforation, etc.).

Treatment Repermeabilization of the vessels (by heparin, thrombectomy, etc.) can be effective if performed before the development of intestinal necrosis from severe and prolonged ischemia. Intestinal necrosis will require urgent laparotomy with resection of necrotic intestinal segments (most often in the territory of the superior mesenteric artery, i.e., middle and distal intestine as well as proximal colon). Mortality and morbidity rates associated with this surgery are very high. Intestinal resection after intestinal ischemia is a major cause of short bowel syndrome (discussed below) requiring artificial feeding.

3.9.4 Bile Salt Diarrhea

Bile salt diarrhea (or choleretic diarrhea) is due to the stimulation of colonocytes by bile salts arriving in excess to the colon. Neutralization of these excess bile salts with cholestyramine (or other similar binding agents) is a good therapeutic solution (and serves as a diagnostic test). Choleretic diarrhea occurs secondary to the following conditions: (a) after resection of the terminal ileum, or with a disease affecting the terminal ileum (most often Crohn's ileitis) causing bile salts to be malabsorbed from the ileum and to reach the colon, and (b) after cholecystectomy (10% of cases) where loss of gallbladder reservoir function results in bile salts entering the intestine (and colon) continuously and no longer synchronized with meals. It can also be idiopathic (or "primary"), often in a patient that has been previously identified as suffering from functional diarrhea or irritable bowel syndrome; recent work has shown that ileal bile salt transporters (ASBT, IBABP, OST, etc.) are normal, but there is a deficit in enterocyte secretion of FGF-19 which leads to overproduction of bile acids by the liver and an increased secretion of bile salts in the intestine exceeding the ileal reabsorption capacity and thus reaching the colon where they stimulate H_2O secretion.

3.9.5 Lactose Intolerance

Lactose intolerance is due to a lack of lactase in intestinal villi which leaves in the intestinal lumen lactose molecules that have not been reduced to monosaccharides glucose and galactose and are therefore not absorbable. An osmotic load then provokes H_2O transfer into the intestinal lumen and diarrhea; these non-absorbed sugars, when they reach the colon, are partially metabolized by the colonic bacteria into volatile gases (such as CO_2, methane, volatile fatty acids, etc.) resulting in flatulence and abdominal bloating.

Lactase deficiency may be congenital (lactase is present in newborns but decreases when growing older; lactase deficiency in adults affects 10–15% of Caucasians and up to 80–90% of non-Caucasians) or acquired (secondary to any disease affecting the growth of intestinal villi normally containing lactase and other disaccharidases).

Treatment relies on lactose-free diet. Lactase supplements (Lactaid®, Lacteeze®) can help. In patients with secondary lactose intolerance, symptoms can resolve after intestinal villi recovery (e.g., patients with celiac disease treated by gluten-free diet).

3.9.6 Meckel's Diverticulum

Meckel's diverticulum is the most common intestinal malformation. It is characterized by the mnemonic "rule of 2": (a) found in 2% of the population; (b) male-female ratio of 2:1; (c) located within 2 feet (60 cm) of the ileocecal valve; (d) measures 2 inches (5 cm) long; (e) symptomatic in 2% of carriers; (f) affects children under 2 years of age (60% of clinical cases); and (g) has two types of ectopic tissue: gastric and pancreatic. Clinical manifestations include rectal bleeding, abdominal pain, intussusception, and pseudoappendicitis. The presence of ectopic gastric tissue in the diverticulum allows the capture of various isotopic markers that can be visualized by nuclear medicine tests.

3.9.7 Short Bowel Syndrome/Intestinal Failure

Short bowel syndrome refers to a small intestine that is too short to maintain sufficient absorption of fluids,

electrolytes, and nutrients, resulting in dehydration, electrolyte imbalance, and weight loss (intestinal failure). It illustrates the physiological importance of the small intestine which is an essential vital organ.

(a) Causes Extensive surgical resections secondary most often to Crohn's disease, acute intestinal ischemia, internal events (hernia, volvulus, malformation, etc.), or traumatic accidents (motor vehicle, gunshot wound, etc.) are responsible for short bowel syndrome and intestinal failure.

(b) Consequences Intestinal loss can have consequences in the immediate period after the "accident" and weeks, months, or years later.

▪▪ Acute reaction

During the acute period after extensive intestinal resection, severe hypersecretion of gastric acid may occur and put the patient at risk of peptic complications such as GI hemorrhage, ulcer perforation, etc. The sudden loss of intestinal hormones normally capable of inhibiting gastric secretion (enterogastrones, such as enteroglucagon, PYY, neurotensin, somatostatin, etc.; ◘ Fig. 3.11) seems to be responsible for the hypersecretion of gastric acid not submitted anymore to inhibitory mechanisms. This phenomenon is transient and must be controlled by gastric secretion inhibitors such as PPIs or H2 blockers.

▪▪ Medium and long-term effect

Resumption of oral intakes may increase diarrhea or ostomy output due to malabsorption and result in an inability to maintain nutritional status and normal fluid and electrolyte balance (intestinal failure).

In practice, intestinal resection is more often limited to the distal intestine and compromises mainly the absorption of (a) vitamin B12 (compensated by parenteral administration; 1 mg B12 subcutaneous or intramuscular q 1–3 months), (b) bile salts (choleretic diarrhea, as discussed above, may be improved by cholestyramine-type resins), and (c) magnesium (oral or IV replacement).

Extensive intestinal resections compromise the general absorption of nutrients, electrolytes, and fluids. A proximal small intestine of less than 100–115 cm from Treitz's ligament, in the presence of an ileostomy, will rarely allow autonomy on oral nutrition and will often require intravenous nutrition. In the presence of the colon in continuity (jejuno-transverse anastomosis), a small intestine of more than 60 cm will usually be sufficient to ensure oral nutritional autonomy, as the colon can increase its capacity to absorb not only liquids and ions but also energy from certain nutrients (see ▶ Chap. 4). If the entire colon is present with its ileocecal valve and some ileum (jejuno-ileal anastomosis), a minimum 35 cm of small bowel length may be sufficient to avoid artificial intravenous nutrition.

(c) Treatment The treatment of short bowel syndrome is based on the following principles which can be adjusted according to the final anatomy of the intestinal remnant and progressive intestinal adaptation:

- Reduction of the GI transit speed with antimotility agents like opiates (loperamide, codeine, etc.) may be needed. This results in better absorption due to the increased contact time of nutrients with the intestinal mucosa. Rapid transit may limit the absorption of drugs administered as solid tablets, and a liquid or parenteral form may be used to optimize treatment.
- Separation of solids from liquids when eating (liquids will accelerate transit and decrease the absorption of solid nutrients).
- Avoidance of hyperosmolar foods (e.g., concentrated sugars, elementary diets) that draw fluids into the intestinal lumen and increase enteric losses.)
- Limitation of fluid intakes and avoidance of hypoosmolar solutions (e.g., H_2O) are required since they can increase enteric fluid losses by promoting ionic flow (and then of water) from the body to the intestinal lumen to compensate for osmolarity. The addition of NaCl (1 g tablets) and sugar (to activate Na^+/glucose transporters) may be helpful.
- Reduction of endogenous secretions to be handled by the intestine. Proton pump inhibitors can reduce the usual 2 l of daily gastric secretion by more than 50%.
- Enhancing absorption: Somatostatin, which reduces transit speed as well as digestive secretions and output, can stimulate directly the mechanisms of absorption. It may sometimes be helpful, but on a long-term basis, it may also compromise intestinal adaptation by inhibiting trophic gut hormones.
- Promoting villi development and intestinal adaptation: After intestinal resection, the intestine will seek to increase its absorptive capacity by increasing its enterocyte population and villi surface area. This adaptation is favored by oral feeding (which should be resumed as soon as possible in the postoperative period). GLP-2 analogues (teduglutide) are new drugs able to stimulate intestinal trophism and decrease the need for intravenous nutrition.
- Using intravenous nutrition (TPN, total parenteral nutrition) may be necessary to compensate for a small intestine that is unable to absorb nutrients and/or life-essential fluids and ions. Artificial solutions of glucose, amino acids, lipids, vitamins, and minerals are available for IV use; their hyperosmolar nature imposes their administration through central venous

catheters. Home chronic TPN is possible through hyperspecialized care units.

- Intestinal replacement: Short gut function can be improved by various surgical techniques aimed at artificially lengthening the endogenous intestine (duplication of intestinal loops) or slowing down transit (inverted intestinal loop). Transplantation of a new intestine from a donor is now possible. However, the small bowel is still the most complex human organ transplant procedure, due to the exceptional immune reaction (graft versus host) caused by the immunological nature of the small intestine, and that requires to use ultrapowerful antirejection drugs.

3.9.8 Congenital Diarrhea

Congenital diarrhea is rare and usually requires highly specialized intervention. Conceptually, however, it does reveal and explains the importance of various absorption-secretion mechanisms discussed elsewhere in this chapter.

Sucrase-isomaltase deficiency is an autosomal recessive condition occurring in 1/5000 children, with a mutation of the sucrase-isomaltase enzyme complex of the brush border resulting in an inability to degrade disaccharides sucrose and maltose into monosaccharides, leading therefore to secondary osmotic diarrhea.

The child is asymptomatic during the first months of life when fed exclusively with milk, and clinical manifestations occur when sucrose and starch-containing foods are introduced to the diet.

The diagnosis is obtained by intestinal biopsy showing an almost total sucrase deficiency in the presence of normal intestinal histology.

Treatment consists of a diet low in sucrose and starch. Pharmacological treatment with artificial sucrase is also available. Some improvement may occur with age.

Malabsorption of glucose-galactose is a rare autosomal recessive disease caused by a mutation in the SLC5A1 gene encoding the SGLT-1 sodium-glucose intestinal cotransporter.

Patients present in the neonatal period with extremely important osmotic diarrhea resulting in severe dehydration.

The treatment consists of a glucose and galactose-free diet. The only sugar tolerated is fructose. The condition improves with age.

Enterokinase deficiency leads to non-activation of pancreatic enzymes (normally activated by brush border enterokinases) and malabsorption mimicking pancreatic insufficiency.

Congenital lactase deficiency is an extremely rare recessive disease resulting in severe osmotic diarrhea in early neonatal infancy.

Enzyme assays on intestinal biopsies show an absence of lactase in the presence of a normal histology.

Chylomicron retention disease (Anderson's disease) is an inherited recessive disease linked to a mutation of the SAR1B gene affecting the expulsion (among others, via the B48 protein) of chylomicrons (loaded with triglycerides, cholesterol, lipoproteins, fat-soluble vitamins) from the enterocyte into the lymphatics.

Patients have steatorrhea with malabsorption of fats and fat-soluble vitamins, low cholesterol in the presence of normal triglycerides, and low vitamin E. Duodenal biopsies reveal fat-loaded enterocytes.

Treatment consists of a diet low in long-chain fatty acids and supplements of vitamin A, D, and E.

Abetalipoproteinemia is a recessive disease caused by a mutation in the MTTP (microsomal triglyceride transfer protein) gene affecting the transport of lipids in the enterocyte and allowing the synthesis of apolipoprotein B.

Affected children show failure to thrive, diarrhea with steatorrhea, hepatic steatosis, ataxia, and retinitis pigmentosa. There is a marked decrease in triglycerides, apolipoprotein B, vitamins A and E, as well as an acanthocytosis (abnormal crenated red blood cells due to excess cholesterol membrane accumulation).

Treatment consists of lipid restriction and massive doses of vitamin E.

Congenital chloride diarrhea is an autosomal recessive disease due to a mutation in the gene coding for the protein SLC26A3 (solute carrier, family 26, member 3), also known as CLD (chloride anion exchanger), involved in the Cl^- reabsorption in the intestine.

Diarrhea has an prenatal onset and manifests as polyhydramnios. In the postnatal period, the child presents with diarrhea and dehydration.

Treatment is symptomatic and aims to replace chlorine and potassium losses as well as fluid losses.

Congenital sodium diarrhea is a recessive disease caused by a mutation of the SPINT2 gene and characterized by an abnormality of the NHE-3 transporter (also called SCL 9) at the enterocyte level.

Diarrhea, which starts prenatally, results in polyhydramnios. At birth, the child presents with severe diarrhea and metabolic acidosis.

Treatment is aimed at replacing fluid and sodium losses. Diarrhea tends to improve with age.

Microvillous inclusion disease is an autosomal recessive disease due to a mutation in the MYO5B gene encoding myosin 5b.

Extremely severe secretory diarrhea in neonatal onset leads to profound dehydration. Intestinal biopsy shows in electron microscopy an interruption of microvilli at the apical wall of the enterocyte, and typical intra-enterocyte vacuoles with microvilli on their inner surface.

These children require intravenous hydroelectrolytic and caloric support to survive. Ultimately, only intestinal transplantation can correct the situation.

"Tufting enteropathy" is an autosomal recessive disorder, also called epithelial intestinal dysplasia, caused by a mutation in the EpCAM (epithelial cell adhesion molecule) gene.

Patients present with severe secretory diarrhea of neonatal onset. Histology reveals enterocyte disorganization with characteristic focal epithelial tufts (composed of closely packed enterocytes) and villous atrophy.

Treatment consists of parenteral nutritional and hydroelectrolytic support. As a last resort, intestinal transplantation is necessary.

Necrotizing enterocolitis affecting mainly premature infants under 1500 g usually occurs between the second and third week of life when enteral feeding has been started. The precise etiology remains unknown, but ischemia/reperfusion, immaturity of the mucosa, intestinal dysbiosis, and enteric infections have been implicated. The prophylactic value of breast milk and possibly of probiotics is recognized.

Symptoms range from a simple increase in apnea/bradycardia of the premature infant to intestinal ileus with vomiting, abdominal distension, rectorrhagia, erythema of the abdominal wall to septic shock with disseminated intravascular coagulation and death.

Abdominal X-ray typically shows dilation of intestinal loops, air in the portal vein, and intestinal pneumatosis which is the pathognomonic sign. Free air is a sign of intestinal perforation.

Initial treatment includes fasting and nasogastric drainage, IV fluids, as well as broad-spectrum antibiotic therapy. Fluid resuscitation, parenteral nutrition, inotrope agents, and mechanical ventilation may be required. Clinical follow-up by pediatric surgeons is indicated.

Necrotizing enteritis can be severe and lead to complications such as intestinal perforation, peritonitis, sepsis, and even death. Sometimes extensive bowel resections may be necessary. It is the main cause of short bowel syndrome in children. Intestinal stenosis can also occur in the long-term.

Autoimmune enteropathy usually begins after a normal neonatal period. The most common form is IPEX (immune polyendocrinopathy X-linked) which affects boys and is caused by an abnormality in the FOX P3 gene. Digestive damage consists of abundant, mucoid, (sometimes) bloody diarrhea, often with exudative enteropathy. Anti-enterocyte antibodies are present. Autoimmune extra-digestive disorders are frequent (diabetes, hypothyroidism, hemolytic anemia, thrombocytopenia, hepatitis, polyarthritis, nephropathy).

3.9.9 Diarrhea in Children

Diarrhea in children may have presentations that require specific considerations.

Toddler's diarrhea In small children, intestinal transit is faster than in adults. Toddler's diarrhea is characterized by frequent loose stools with no impairment of growth. It is often associated with a diet low in fat and high in carbohydrates, especially fruit juices. It improves with diet correction.

Infectious diarrhea A normal child can have up to four episodes of gastroenteritis per year, especially if he or she attends daycare. Rotavirus is a common virus. It is usually treated with oral rehydration solution but may sometimes require intravenous rehydration. The consequences of rotavirus infection are usually minimal in healthy children but can be serious in infants and malnourished children. An oral vaccine is available.

Post-infectious diarrhea After infectious gastroenteritis, frequent loose stools are often seen for a few weeks. This may be related to dietary changes initiated by the parents (restriction of milk which is replaced by fruit juice) or to a bacterial overgrowth. The problem usually improves by readjusting the diet or administering probiotics. If diarrhea persists, it is important to look for *Giardia lamblia* or an underlying celiac disease.

Food allergy Cow's milk protein allergy (CMPA) is the most common food allergy in children.

Type 1, or IgE-mediated allergy, is manifested by atopic dermatitis, hives, or more severe reactions with asthma and anaphylactic shock. In this type of allergy, skin tests will be positive.

In the case of type 4 allergy, clinical signs can be more subtle with diarrhea that will sometimes be mucoid or even bloody, vomiting, failure to thrive, or mental irritability. The diagnosis is made when symptoms improve following the complete removal of cow's milk protein from the diet (and ideally a return of symptoms when reintroduced). Manifestations of CMPA can be seen even in the breastfed child; exclusion of cow's milk protein from the mother's diet will then be necessary if breastfeeding is to be continued. CMPA usually disappears between 1 and 2 years of age. See ▶ Chap. 22.

Celiac disease typically appears between 12 and 18 months of age, with weight plateauing or weight loss, chronic diarrhea, abdominal bloating, and irritability. However, clinical signs may be more discrete such as isolated anemia, weight and/or statural growth retardation, or unexplained pubertal retardation. In about 10% of cases, constipation may occur.

Cystic fibrosis (of the pancreas) is a cause of chronic diarrhea in children. It is discussed in ► Chap. 5.

PS: For complementary lectures on the small bowel, see ► Chaps. 13, 14, 16, 22, 23, and 29.

The Colon

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4.1 Macroscopic Anatomy

4.1.1 Shape and Structure

The colon follows the small intestine. It is approximately 5- to 8-cm-wide and 80- to 150-cm-long and begins after the ileocecal valve and ends at the anus. Its different segments are shown in ◘ Fig. 4.1.

The *ileocecal valve* (or Bauhin's valve) separates the small bowel from the colon and opens into the pouch-like cecum in the right iliac fossa. In the cecal base, a few centimeters below the valve, the appendix, a finger-like thin tube (3- to 5-cm-wide, 5- to 10-cm-long) opens and extends toward the retrocecal region (2/3 of cases) or the pelvis.

The *ascending colon*, or right colon, rises along the right flank for 15–20 cm up to the hepatic flexure. The anterior and lateral surfaces of the ascending colon (like the descending colon) are positioned inside the peritoneal cavity; the posterior surface is retroperitoneal. The outer lateral surface of the colon is attached to the retroperitoneum by the Toldt's fascia which attaches to the lateral taenia.

The *transverse colon* extends 25–40 cm in the upper abdomen between the hepatic flexure at the right hypochondrium and the splenic flexure at the left hypochondrium. These two structures are fixed by the phrenocolic and splenocolic ligaments, respectively, whereas the transverse colon is mobile in the peritoneal cavity. The transverse colon is the point of attachment (along the anterior taenia) of the large omentum, a structure made by the fusion of the visceral and parietal peritonea, containing, among other things, visceral fat and plunging toward the pelvis to cover, like an apron, the abdominal viscera.

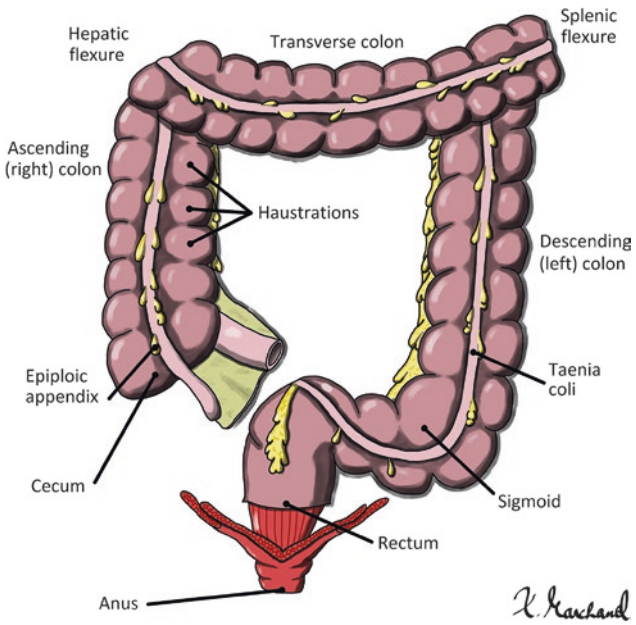
The *left colon*, or descending colon, runs along the left side of the abdomen for 15–20 cm proximal to the sigmoid. Like the right colon, its anterior surface is within the peritoneal cavity, while its posterior surface, attached by the Toldt's fascia to the retroperitoneum, is isolated behind the peritoneal cavity.

The *sigmoid* is an S-shaped colonic segment, often smaller in size and of variable length (15–50 cm). The mobility of the sigmoid in the abdominal cavity makes torsion (volvulus) possible.

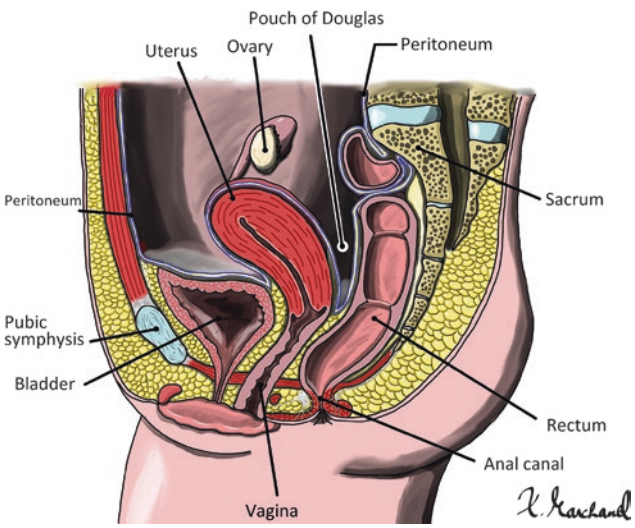
The *rectum* extends 12–15 cm from the anus to the rectosigmoid angle. The posterior rectum, with its mesorectum, rests against the sacrum, while the anterior wall faces the pelvic organs (bladder, uterus) (◘ Fig. 4.2). The rectum is located outside the peritoneum, except for its anterior part which is covered by visceral peritoneum up to 5–10 cm from the anus. This peritoneal recess between the anterior part of the rectum and the pelvic organs is called Douglas' cul-de-sac (or Pouch of Douglas) (where cancerous cells from intra-abdominal tumors can "fall" and form the "Blumer's shelf" that can be palpated on a digital rectal examination as a rigid or indurated area). Inside the rectum, three transverse folds are known as the valves of Houston (anatomical structures however without a decisive physiological role).

The *anal canal*, 2- to 3-cm-long, begins at the mucocutaneous junction where the colonic glandular mucosa meets the cutaneous squamous epithelium. The rectum and anus are described more extensively in the ▶ Chap. 7.

A colon that is distended more than 10–12 cm in width (usually in the transverse or ascending colon) is



◘ **Fig. 4.1** Anatomy of the human colon (anterior view)



◘ **Fig. 4.2** Rectum and pelvis – lateral view in woman: the rectum is extraperitoneal except for its anterior part which is partially covered by the peritoneum

known as a megacolon. An excessively long colon (usually at the expense of the sigmoid) is called a dolichocolon (dolicho: "long" in Greek). The colon appears as a tubular organ, with sacculations, or haustrations, made by contractions of the longitudinal muscles that shorten the colon like an accordion.

4.1.2 Vascular Supply

Arteries The right colon, from the cecum to the proximal transverse colon, is vascularized by branches of the superior mesenteric artery arising from the aorta at the level of the L1 vertebra just above the renal arteries. The left colon and sigmoid are vascularized by the inferior mesenteric artery arising from the aorta at L3 (above the aortoiliac bifurcation at L4) (Fig. 4.3). The transverse colon is vascularized by the Drummond's marginal artery an arcade connecting the superior and inferior mesenteric arteries and running along the mesenteric edge of the transverse colon. The splenic angle region is located in the middle section of this vascular arcade, at the very end of vascular territories from both feeding arteries, and constitutes a watershed zone, an area highly susceptible to ischemic damages in case of hypoperfusion (see Ischemic colitis).

The rectum is vascularized by five rectal arteries (also called hemorrhoidal arteries): the upper, middle (right and left), and lower (right and left). The superior rectal artery is the main one. Arising from the inferior mesenteric artery, it is divided into two branches for the posterior and anterior sides of the rectum. The middle and lower rectal arteries originate from the internal iliac arteries to supply the lower rectum and the genital area.

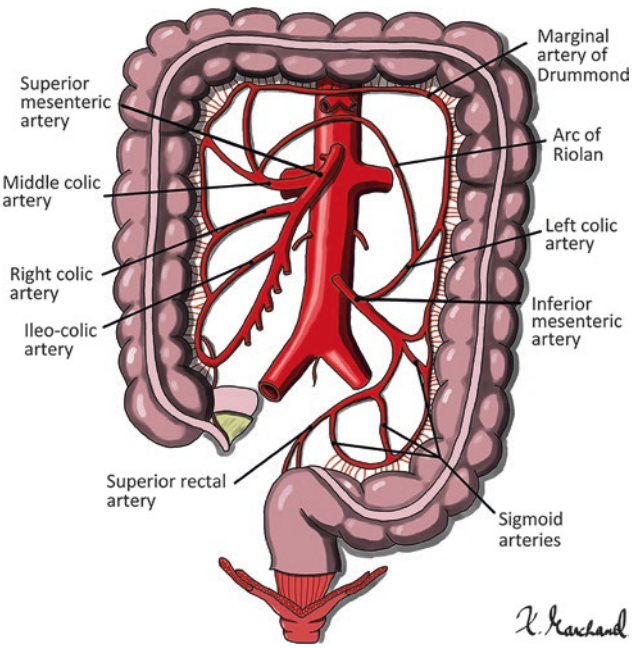


Fig. 4.3 Colon irrigating arteries

Veins Veins follow artery routing. The superior mesenteric vein and inferior mesenteric vein (via the splenic vein) drain into the portal vein toward the liver. For the middle and lower parts of the rectum, venous drainage is toward the internal iliac veins; the fact that the latter does not drain to the liver may explain the higher frequency of pulmonary metastases in rectal cancers compared to colon cancers (where metastases are mainly hepatic).

Lymphatics Lymphatics follow blood vessels. Abdominal lymphatics thus run through the mesentery to the large cistern and then, through the thorax, to the thoracic duct and the left subclavian vein. Lymphatics from the lower rectum and anus drain to lymph nodes in the iliac and inguinal regions.

4.1.3 Innervation

Extrinsic innervation of the digestive tract depends on parasympathetic and sympathetic fibers, efferent as well as afferent, often connected to the central nervous system, including the hypothalamus.

Parasympathetic Fibers Central parasympathetic fibers synapse with cells from the dorsal motor nucleus (and nodose ganglion for afferent fibers) on the floor of the fourth ventricle to give rise to the tenth cranial nerve, the pneumogastric or vagus nerve, which runs down along the esophagus to the abdomen. Parasympathetic fibers also descend into the spinal cord to synapse with sacral roots from S2 to S4.

Abdominal parasympathetic innervation is provided by the vagus nerve for the proximal colon and by pelvic parasympathetic fibers for the more distal colon, i.e., sigmoid and rectum. Pelvic parasympathetic fibers, both motor and sensory, play a decisive role in the evacuation function (see ▶ Chap. 7).

Sympathetic Fibers Sympathetic fibers pass through the spinal cord and the intervertebral nerve roots. The fibers issued from the spinal cord are called "preganglionic fibers" and all go to paravertebral nerve ganglia from where the so-called postganglionic fibers emerge to reach the digestive organs. There are five important neurological nodes (or plexuses) in the abdomen:

- The celiac node located between the aorta and the celiac trunk, from which fibers innervate the foregut organs (stomach, duodenum, etc.).

- The superior mesenteric ganglion located at the junction between the aorta and the superior mesenteric artery receives lower thoracic fibers (from T6 to T12) giving rise to postganglionic fibers innervating the midgut, i.e., small bowel and the proximal colon.
- The inferior mesenteric ganglion, at the aortic root of this artery, receives mainly lumbar fibers from L1 to L3 and innervate the left colon.
- The upper hypogastric plexus, located just in front of the aortic bifurcation, receives lower lumbar preganglionic fibers from L4 to L5 and gives postganglionic fibers innervating the sigmoid and the rectum.
- The pelvic plexus receives sacral fibers from S2 to S4 to innervate the anorectal region and pelvic organs such as the prostate, bladder, seminal vesicles, etc. Damage to these pelvic nerves during rectal dissection can lead to erectile or bladder dysfunction.

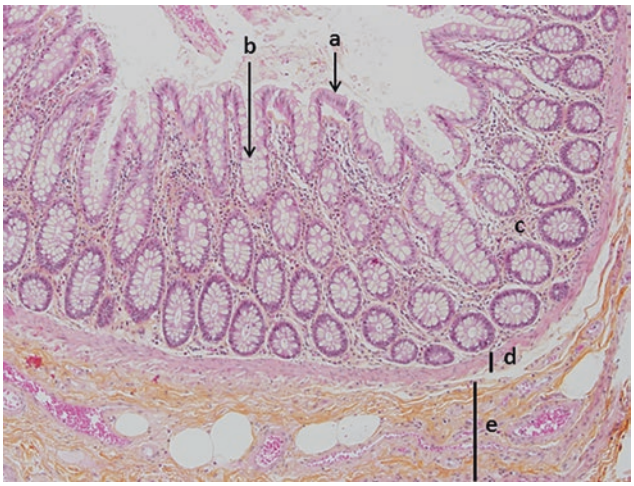
Postganglionic fibers are made of preganglionic nerves crossing the paravertebral ganglion without interruption, or that have merged with sympathetic fibers of different intervertebral nerves (e.g., fibers from the T6/T7 intervertebral space merging with fibers from T7/T8, T8/T9, etc.), or even have synapsed with parasympathetic fibers, resulting in overlapped zones and systems of influence on the innervated organs. The postganglionic fibers of the extrinsic nervous system reach the digestive organs by following the blood vessels that irrigate these organs. In the visceral wall, they usually synapse with nerves of the enteric nervous system (see ► Chap. 3) to influence motor or secretory functions of these organs. The afferent sympathetic fibers (running centrally to vagal nodose ganglion) play a major role in the perception of visceral pain.

4.2 Microscopic Anatomy

Like the other organs of the digestive tract, the wall of the colon is made up of different structural layers: the mucosa facing the intestinal lumen, the submucosa with mucosa feeding vessels and ENS-regulating nerves, the dual-component muscle layer with internal circular muscles and external longitudinal muscles, and the serosa (or adventitia, depending on its relationship to the peritoneum).

4.2.1 Mucosa

The *mucosa* of the colon (■ Fig. 4.4) is made up of crypts lined with a layer of various epithelial cells: the colonocyte, which plays an important role in colonic absorption; mucus cells (or goblet cells), which are numerous especially at the base of crypts; some endocrine cells, including enterochromaffin cells producing serotonin; and other endocrine cells producing GLP, PYY, and somatostatin. This monolayer of epithelial cells rests on a chorion and a muscularis mucosa.



■ **Fig. 4.4** Colon mucosa: (a) colonocyte, (b) goblet cell, (c) lamina propria (or chorion), (d) muscularis mucosae, (e) submucosa. (Photo by G. Soucy)

The *muscularis mucosa*, a thin muscle layer, separates the mucosa from the submucosa and supports the colonic epithelium and its chorion. It is the demarcating site between invasive and noninvasive neoplasia.

The *submucosa*, between the mucosa and the muscularis, is made of connective tissue, blood vessels, lymphatics, and neural fibers (Meissner submucosal plexus).

4.2.2 Muscularis

The colon wall, like the other organs of the GI tract, has two muscle layers working together to assure the motility process.

The *internal muscle layer* is made of circular fibers that generate phasic contractions to mix and propel the colonic content. Sustained and scattered contractions of these circular fibers can also generate prolonged annular contractions forming sacculations called haustrations.

The *external muscle layer* of the colon is peculiar in that it does not provide continuous coverage of the organ. The longitudinal muscle fibers are concentrated in three bands about 8-mm-wide and located at 120 degrees around the colonic circumference. These longitudinal bands, called taenia coli or colonic bands, start at the base of the appendix and are easily visible all along the colon. At the level of the upper rectum, they come together to cover diffusely the entire surface of the

rectal ampulla. These taeniae, by contracting in a sustained manner, shorten the colon like an accordion, thus participating in the formation of haustrations. The taeniae also serve as attachment points for the large omentum on the transverse colon (anterior taenia), as well as for Toldt's fascia on the left and right colon (medial lateral taenia).

The muscle layer is of variable thickness and tends to thicken from the proximal to the distal colon. The sigmoid colon contains a very thick muscle layer that can even become enlarged under certain conditions such as diverticular disease (see ► Sect. 4.9). The cecum, on the other hand, is a few millimeters thin, which explains the increased risk of perforation of this region when there is air distension of the colonic lumen (megacolon), or during endoscopic polypectomy for example.

4.2.3 Serosa

The outer layer of the colon is covered with visceral peritoneum except for the posterior portion of the ascending colon, the posterior portion of the descending colon, and a large part of the rectum. These segments are therefore extraperitoneal.

On the outer surface of the colon, there are small pouches of peritoneum filled with fat and called epiploic appendix. While these structures were thought to be of no pathological significance, it is now known that they can become inflamed to give a clinical picture that resembles diverticulitis or appendicitis and is recognized on a CT scan as epiploic appendagitis (see ► Sect. 4.9).

4.3 Embryology/Development

Embryological development of a large part of the colon is intimately linked to that of the small intestine (see ► Chap. 3). Errors in colonic development may give rise to malrotations most often without great clinical consequences. The development of the distal region is different and may be subject to serious abnormalities as discussed in ► Chap. 7.

By the fourth week of fetal life, the intestine is a tube (closed at both ends) divided into three parts: the foregut, the midgut, and the hindgut. The three parts of the gastrointestinal tract will then grow more or less isolated along their respective vascular axes, i.e., the celiac trunk for the foregut, the superior mesenteric artery for the midgut, and the inferior mesenteric artery for the hindgut. Development of the midgut will give rise to the colon. From the sixth week onward, the lower part of the primitive intestinal loop developing along the superior mesenteric artery will dilate to form the cecal bulge.

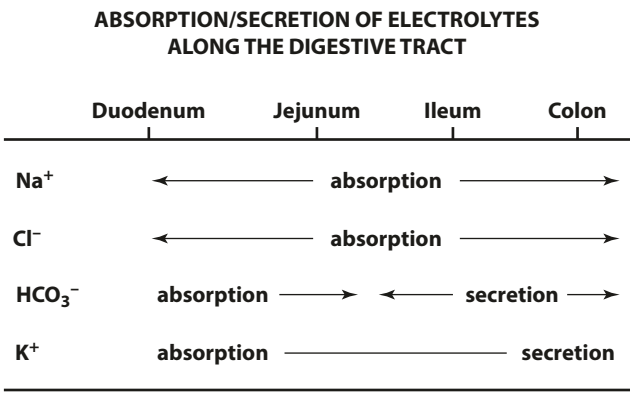
The intestine will then rotate on the axis of the superior mesenteric artery 270 degrees counterclockwise. This rotation is described in three phases of 90 degrees each: (1) the small intestine goes to the right and the colon to the left; (2) the colon is above and the small intestine below the axis of the superior mesenteric artery (the cecum is then at the level of the pyloric region); and (3) the small intestine returns to the left side of the abdomen and the cecum descends toward the right iliac fossa. As the appendix develops in the third phase, during the descent of the cecum, it may be in different positions along the migration path of the cecum: from subhepatic to pelvic position.

Once reintegration has been achieved, as in the case of the duodenum, peritoneal folds will form. The posterior face of the ascending and descending colons will merge with the posterior plane, forming, respectively, the right and left Toldt's fascia. As a result, these parts of the colon are fixed, while the whole of the small intestine, the transverse colon, and the sigmoid colon remain mobile. Defects in these attachments may increase segmental intestinal mobility leading to volvulus or internal hernias.

Abnormalities in the rotation process may occur at any developmental phase, and the intestinal rotation may be incomplete, reversed, etc., leading to various malrotations, many of which may remain without clinical consequence.

4.4 Absorption/Secretion

The colon receives from the small intestine 1–2 liters of chyme per day. This liquid contains water and electrolytes (fluxes of electrolytes along the digestive tract are summarized in ◘ Fig. 4.5), some amount of unabsorbed nutrients, as well as certain substances unabsorbable by the intestine (e.g., fibers). The colon absorbs



◘ **Fig. 4.5** Movements of ions from the proximal digestive tract to the distal colon

almost 90% of this liquid quantity since the fecal volume of water is 100–150 mL/day (in about 200 g of stool daily). Colonic absorption occurs mainly in the right colon and is promoted by the motor mixing and the back and forth movements present in this part of the colon.

4.4.1 Water Absorption

Water is absorbed via the ENaC channel (epithelial sodium channel) and will mainly follow sodium transport movements. The amount of water absorbed by the colon is normally 1–2 liters/day, but it can increase up to 5 liters per day under certain circumstances (e.g., to minimize fluid loss from small intestine diarrhea). Clinically, colectomy is usually well tolerated. In a subject with an ileostomy, gradual adaptation of the body usually reduces fecal fluid loss (normal ileal flow: 1–2 liters/day) to about 800 mL per day. However, the loss of the colonic reabsorption function makes a colectomized subject (with ileostomy or with ileo-rectal or ileoanal anastomosis) particularly susceptible to dehydration during diarrheal episodes.

Aldosterone, in response to circulating hypovolemia (secondary to exaggerated fecal losses for example), is an effective stimulus for ENaC and the absorption of H_2O (and Na^+) by the colon.

4.4.2 Sodium Absorption

Sodium absorption requires active transport mechanisms. The Na^+/K^+-ATPase pump of the basolateral membrane acts in the colonocyte as it did in the enterocyte: driving sodium out of the cell, the intracellular sodium hypoconcentration creates a favorable gradient for the entry of sodium from the intestinal lumen to the cell. Various apical transport mechanisms then allow the entry of sodium (discussed extensively in the chapter on the small bowel), such as a Na^+/H^+ exchanger (NHE2 and NHE3), an aldosterone-regulated sodium channel (ENaC), and an electrochemical gradient established by the HCO_3^-/Cl^- exchanger.

4.4.3 Potassium Movements

Potassium is secreted in the colon. The Na^+/K^+-ATPase pump of the basolateral membrane keeps the cell concentration of potassium high, facilitating its exit from the cell at the apical membrane via high conductance potassium channels.

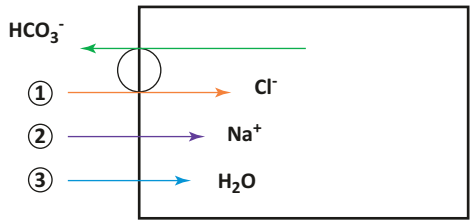


Fig. 4.6 Absorption of Cl^-: (**1**) via an HCO_3^-/Cl- exchanger, Cl^- enters the colonocyte; (**2**) by electrochemical gradient, Na^+ follows Cl^- into the cell; (**3**) H_2O, by osmotic gradient, follows Na^+ and Cl^- into the cell

4.4.4 Chloride Movements

An HCO_3^-/Cl^- exchanger ensures the exit of $HCO3^-$ and the entry of Cl^- into the colonocyte. The entry of Cl^- leads, by means of an electrochemical gradient, to the entry of Na^+, which consequently causes H_2O absorption (Fig. 4.6). A similar mechanism exists in the small intestine (see ▶ Chap. 3). This mechanism is physiologically very active since the congenital deficiency (very rare condition) of this $Cl^-/HCO3^-$ exchanger is a lethal condition where chlorinated diarrhea (high presence of Cl^- in the stool) and metabolic alkalosis (deficiency of HCO_3^- excretion by the intestine) are encountered.

4.4.5 Nutrient Uptake

A certain amount of ingested food is not absorbed by the small intestine and is found in the colon. Some substances, such as fibers, are not absorbable by the human small intestine and therefore reach the colon in large quantities. Other substances are more or less well absorbed in the small intestine; 0–5% of ingested lipids are poorly absorbed by the small intestine, while starch and dietary polysaccharides are poorly absorbed in a variable proportion of 1–20%. These substances that are not absorbed by the small intestine are found in the colon where they can be metabolized and/or utilized, mainly by intestinal microbiota.

Sugars Metabolism Malabsorbed sugars reaching the colon can be fermented by colonic bacteria into short-chain fatty acids (3–4 C atoms) such as butyric acid (or butanoic acid), acetic acid, or propionic acid (or propanoic acid) which can be absorbed by simple diffusion through the colonic cell membrane. Butyric acid is important for the colonocyte: (1) it has an essential trophic effect; (2) it can stimulate its absorption activity. It has been proposed that inhibition of fermentation (and of butyric acid formation) by antibiotics reduces absorption

of sodium and water by colonocytes, which explains diarrhea often encountered when taking antibiotics; (3) it can serve as a nutrient substrate. It is estimated that 10% of the daily caloric intake is due to these short-chain fatty acids absorbed by the colon. In case of malabsorption by the small intestine (e.g., short bowel syndrome), caloric absorption by the colon can increase significantly (up to 25% of the total caloric intake) and allow an important nutritional gain for the patient.

Malabsorption of sugars by the small intestine can be due to a "normal" malabsorption (e.g., sucrose and fructose often absorbed in a variable quantity) or to a "pathological" malabsorption which can be specific (e.g., lactase deficiency) or generalized (by small intestinal or pancreatic diseases). Some sugars are not absorbable by the small intestine, such as lactulose (used as a laxative), sorbitol (used as hypocaloric sugar substitute), raffinose or stachyose from beans, or fibers (cellulose, bran). Malabsorbed sugars are metabolized by colonic bacteria, which cause the formation of short-chain fatty acids (or volatile fats) and other gases such as CO_2, methane, and nitrogen, which explains increased flatulence in presence of malabsorption, as well as particularly malodorous H_2S.

Amino Acids Unabsorbed amino acids can be converted by colonic bacteria into various gases such as indole, mercaptan, etc., which contribute to the unpleasant odor of stools.

Dietary Fibers Dietary fiber is not digestible in humans, but some, including cellulose, can be broken down by colonic bacteria. We distinguish between insoluble fibers (such as lignin, cellulose) contained in bran or wheat cereals and soluble fibers (such as pectin) found in vegetables, psyllium, enriched cereals, etc.

4.4.6 Secretions

Colonic secretion comes mainly from goblet cells, which secrete mucus-containing glycoproteins, defensins, trefoil factor, etc. All these substances are intended to protect the colonic mucosa against, among other things, aggressive bacteria from the intestinal microbiota.

4.4.7 Intestinal Flora (Microbiota)

The human body is composed of 10^{14} cells but also contains 10^{15} microbial cells, mostly living in the digestive tract and especially in the colon. The digestive tract of the newborn is sterile, and its bacillary colonization occurs rapidly after birth when in contact with food and terrestrial environment.

The colon contains a large quantity of bacteria (10^{11} bacteria/mL) from multiple different species. This colonic flora is clearly predominant in anaerobic bacteria (*Bacteroides*, bifidobacteria, lactobacilli, etc.); aerobic bacteria are 100,000 times less frequent (*Escherichia coli*, enterococci, streptococci, *Klebsiella*, etc.). The genome of the intestinal microbiota human is now known. More than 30,000 bacterial species are present! They are classified in various phylogenetic classes: *Firmicutes* [(64% of gut microbiota), *Clostridium*, lactobacilli, enterococci, staphylococci, streptococci, etc.], *Bacteroidetes* [(23%), *Bacteroides*, flavobacteria, etc.], *Proteobacteria* [(8%), *Enterobacteriaceae*, *Escherichia coli*, *Pseudomonas*, etc.], *Actinobacteria* [(5%), corynebacteria, etc.], *Fusobacteria*, and *Verrucomicrobia*.

Intestinal bacteria tend to be considered as harmful, and in the clinical setting stool, cultures are used to identify bacterial pathogens responsible for diseases (*Campylobacter*, *Salmonella*, *Shigella*, etc.). The harmful action of bacteria cannot be denied, as evidenced, for example, by infectious enterocolitis and the syndrome of intestinal bacterial overgrowth in humans (see ▶ Chap. 3), or by inflammatory bowel diseases (e.g., Crohn's disease) that remain absent in germ-free animals (until bacterial colonization). However, the beneficial role of certain bacteria is now realized, as suggested by the development of *Clostridium difficile* colitis (see ▶ Sect. 4.6.1), which occurs almost exclusively with an alteration of intestinal flora by antibiotics, or the therapeutic action of probiotic bacteria in certain diseases (such as IBD), or the participation of the colonic flora in energy intake (discussed previously).

4.4.8 Intestinal Gas

The formation of gas is a normal phenomenon obtained by bacterial fermentation of nutrients arriving in the colon, unabsorbed by the small intestine. Part of this gas is reabsorbed, while the other part is evacuated through the anus. It has been estimated that approximately 1 liter of gas in total (volatile AG, CO_2, CH_4, N_2, etc.) is evacuated normally each day, on average 13 times a day. Exaggerated flatulence, intestinal meteorism (bloating), may constitute the clinical presentation of certain malabsorptions (e.g., lactose intolerance). Intestinal gases can cause visceral distension, which can be uncomfortable especially in people with visceral hypersensitivity (see IBS discussed in Function Diseases section).

4.4.9 Summary

The colon completes the absorption process done by the small intestine. In normal situations, it reabsorbs more than 1 liter of water (and electrolytes such as Na^+)/day and provides the final transformation (and absorption) of nutritive substances (such as carbohydrates) that have escaped small intestinal absorption. In pathological situations, the colon can increase its water absorption capacity by up to five times (e.g., during diarrhea caused by small bowel secretion), as well as its caloric absorption capacity up to 25% of daily requirements (e.g., during malabsorption by short bowel).

Stools (approx. 200 g/day) contain 75% H_2O and 25% nonabsorbable matter (fibers, bacteria, mineral salts, proteins, malabsorbed fats or sugars, etc.). The brown color is due to bilirubin (hence the pale stools in case of biliary obstruction). The foul-smelling odor comes from gases resulting from bacterial fermentation.

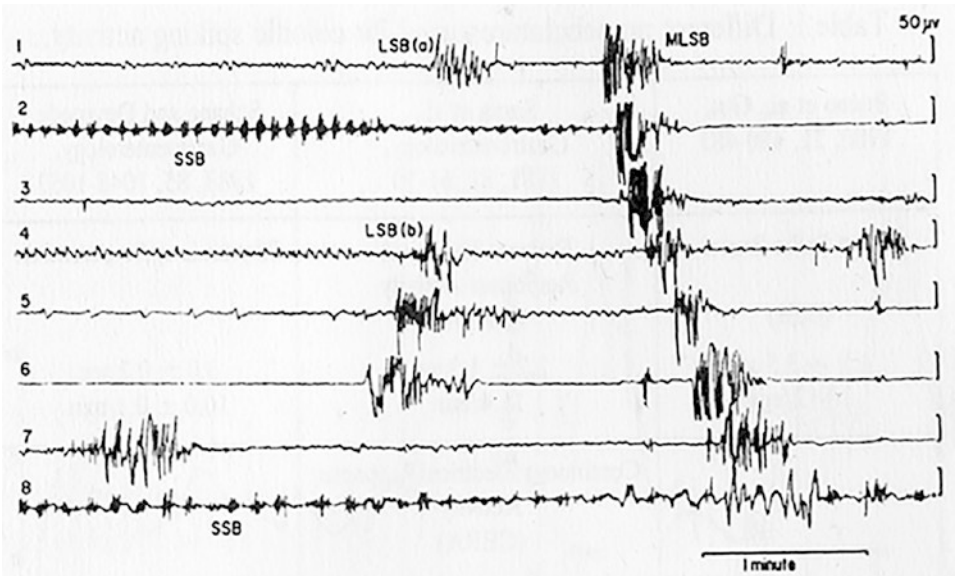
4.5 Motility/Sensitivity

4.5.1 Motility

Transit through the colon is much slower than through any other digestive organ, ingested substances normally taking 1–3 days to pass through the colon. Motility of the colon is complex and less characterized than that of the other digestive organs. Our limited knowledge of colonic motility explains why the nomenclature and characteristics of the patterns or types of colonic contractions remain controversial.

Colonic motility differs from other organs in several ways: (a) the external longitudinal muscle exists as in the other digestive organs, but rather than covering diffusely the entire surface of the organ, the longitudinal colonic fibers are grouped into three thin separated bands or taenias. These taenias seem to induce sustained colonic contractions, shortening the colon like an accordion and generating, with circular contractions, an irregular "sausage-shaped" appearance called haustrations. (b) The electrophysiological activity of the circular muscles is not constant throughout the colon and even seems to vary according to, among other things, the distension of the organ. (c) The electrical activity (pacemaker) of circular muscles does not come from interstitial cells of Cajal (ICC cells) located in the myenteric plexus as in small bowel but rather from ICC cells dispersed in the smooth muscles layer.

An example of a colonic motility profile is shown in ◘ Fig. 4.7. We use this sketch for a better understanding of colonic contractile activity, although we realize that it is questionable since the types of contractions are of different natures and designations according to researchers in the field. Generally speaking, the following can be summarized: (a) a nonmigratory contractile activity of low amplitude and prolonged duration (the result of electrical waves called SSBs in ◘ Fig. 4.7) exists, mainly in the right colon, probably to induce a mixing of luminal substances submitted to bacterial metabolism in this portion of the colon; (b) contractile waves with an



◘ **Fig. 4.7** Electromyographic recording of the colon using eight electrodes distributed along the organ (1, right colon; 2, ……; 8, distal sigmoid) and revealing what researchers (Frexinos, Fioramonti et al. from Toulouse) have identified as "short spike bursts" (SSB), "long spike bursts" (LSB) or "migrating long spike bursts" (MLSB)

anterograde or retrograde direction on short segments and of medium or high amplitude (result of LSBs) exist to ensure a stirring and back and forth movement promoting the absorption of the intestinal chyme and ensuring a slow transfer of the colonic content from proximal to distal, especially in the proximal colon; and (c) large amplitude contractions, starting in the transverse colon and migrating rapidly to the left colon, occur four to six times a day (mass contractions, result of MLSB), to push the fecal bolus to the rectum. This mass contraction activity often occurs after a meal and is part of the "gastrocolic reflex."

Contractile activity of the colon increases during the following events: (1) waking up, motor activity decreases during sleep and increases upon waking; (2) food in the stomach stimulates colonic motor activity, the gastrocolic reflex, probably of neurohormonal origin (CCK?), is responsible for the urge to defecate often felt after a meal and possibly increased in certain diseases such as IBS; (3) stress, via secretion, among others mediators, of corticotropin-releasing factor (CRF); (4) stimulation of cholinergic or NK receptors; and (5) local irritation by certain laxatives such as bisacodyl.

In the clinic, manometric (or electromyographic) analysis of colonic contractility (so useful for the identification of esophageal or anorectal diseases) is very rarely utilized. The speed of transit of the colon can be evaluated by following the progression of radiopaque or isotopic markers: in case of diarrhea, colonic transport, normally about 1–3 days, can be accelerated (to a few hours). In the case of constipation, it can be slowed down over several days. However, the measurement of colonic transit is only necessary in very selected cases.

4.5.2 Sensitivity

The colon, especially the rectum, is the digestive organ where visceral sensitivity has been most extensively studied.

Briefly, pain originating from the colon (or from any GI organ) relies on the following pathways: (1) afferent sensitive fibers detect pain signals in the intestinal wall; (2) the signal is transmitted to a second order neuron in the dorsal horn of the spinal cord and travels to the brain; (3) then central nuclei, responsible for pain sensation, are stimulated; (4) a compensatory mechanism (descending inhibition) is elicitated from the brain to reduce the pain signal coming from peripheral neurons.

Increased visceral sensitivity is found in many patients with irritable bowel syndrome (IBS). As discussed extensively in the Function Disorders section, increased pain sensation in IBS patients may involve dysregulation at any one of the four transmission steps described above.

4.6 Inflammation Disorders

The diagnosis of colitis is most often made clinically during endoscopy. Colonic mucosa is then granular, and/or friable, and/or erosive, and/or ulcerated. Inflammatory damage may be widespread or limited to certain areas. The endoscopic aspect will evoke some of the differential diagnoses mentioned below. Mucosal biopsies taken during endoscopy will be used to confirm and guide the diagnosis.

Colitis is suspected in patients presenting diarrhea, most often accompanied by cramp-like abdominal pain. Rectal bleeding, if not due to hemorrhoids, is a sign of a mucosal break (eruption, ulceration) by the inflammatory process. Bloody diarrhea is colitis until proven otherwise. Mucus may also be present (however, it can also be seen in irritable bowel syndrome, which is characterized by a macroscopically and microscopically normal colonic mucosa).

An inflamed colon may appear on radiological examinations with edematous thickened walls (◘ Fig. 4.8).

4.6.1 Infectious Colitis

Acute Bloody diarrhea or dysentery Acute bloody diarrhea or dysentery is most often caused by bacteria such as *Shigella*, *Campylobacter*, or *Salmonella* (see ▶ Chap. 3). Any infection leading to colonic mucosal breaks is likely to cause bloody diarrhea.

***E. coli* colitis.** Enterohemorrhagic *E. coli* colitis (EHEC) usually affects the transverse colon and often causes bloody diarrhea. It is due to *E. coli* bacteria that produce a Shiga toxin (named after its Japanese discoverer, professor Shiga, in 1897). *E. coli* 0157H7 is the best known bacterium, but other bacterial germs have now been identified (e.g., O104 H4 which was epidemic in Germany and Europe in 2011). The 0157H7 infection is classically contracted by eating undercooked contaminated beef (hence its name "hamburger colitis"). Meat contamination by fecal bacteria occurs during the animal slaughtering; bacteria are present on the outside of the meat and are easily destroyed when meat surfaces are adequately cooked. Undercooked ground meat is most often implicated as a causal factor. Epidemics by ingestion of contaminated water (e.g., Walkerton,

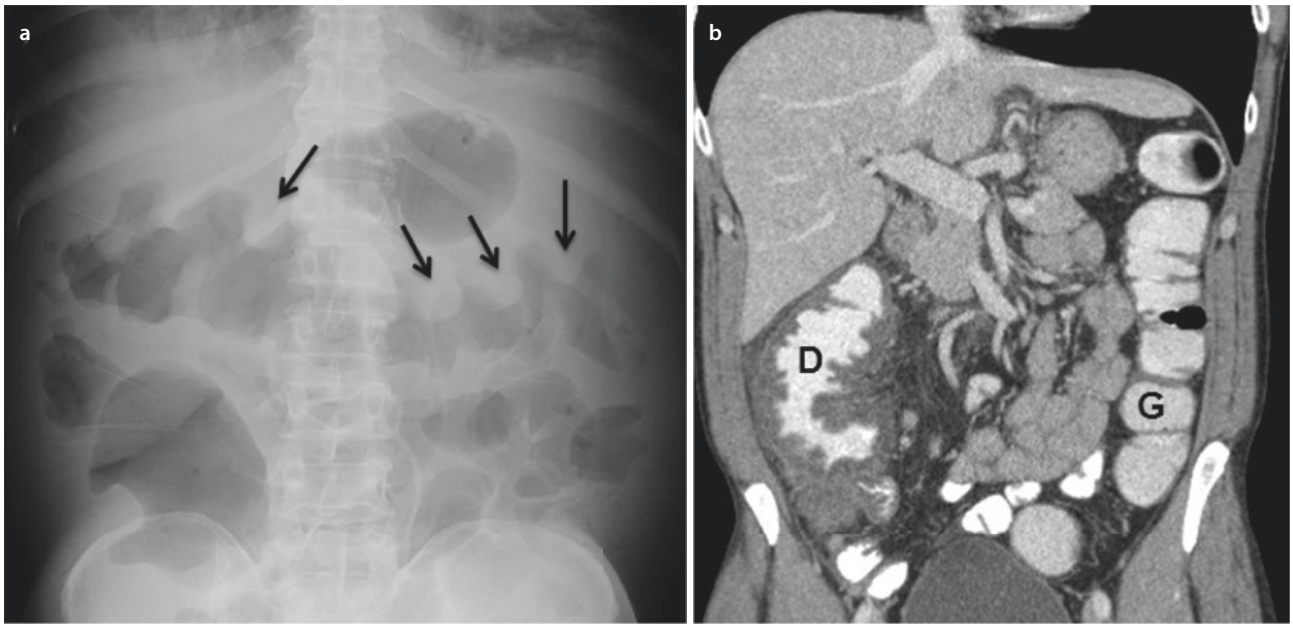


Fig. 4.8 Colitis images: **a** flat plate of the abdomen showing parietal edema of the transverse colon with thumbprint images (indicated by the arrows); **b** CT scan with significant wall thickening of the right colon (D), while the left colon (L) is normal. (Photos from R. Déry)

Ontario in 2001) or by ingestion of fruits or vegetables sprinkled with contaminated water (e.g., Texas spinach in 2005) have occurred.

EHEC colitis usually resolves spontaneously within a few days. Use of antibiotics has been associated with an increased release of bacterial toxins (thus worsening the clinical picture) and is discouraged. However, in the European epidemic of 2011, treatment with azithromycin appeared to have a safe and beneficial effect.

This infection may be complicated by a severe hemolytic process with vascular complications affecting mainly the kidneys (hemolytic uremic syndrome) or the brain (strokes); two-thirds of children with hemolytic uremic syndrome will require hemodialysis.

Yersinia enterocolitica can present with acute onset diarrhea often with ileitis or mimicking appendicitis (pseudoappendicitis). It can also give a subacute picture mimicking Crohn's disease of the ileum or colon.

Pseudomembranous or *Clostridioides difficile* colitis has been recognized since the 1980s. *Clostridioides difficile* (*C. diff* or *C. difficile*; preciously called *Clostridium difficile*) is a bacterium that can be carried asymptomatically and will proliferate during an antibiotic-induced imbalance of the colonic flora. Broad-spectrum antibiotics such as quinolones have been strongly incriminated, but all antibiotics are capable of triggering this problem. Additional contributing factors include hospitalization, immunodeficiencies, use of gastric hyposecretory agents such as PPIs, and advanced age.

C. diff. infection has become a major nosocomial infection in recent years. Its frequency increased seriously in our hospitals, and its severity has become a major problem, particularly with the emergence of new virulent strains of bacteria that lead to severe and possibly fatal colitis.

C. diff. is diagnosed by stool examination, which will reveal the presence of the bacteria itself and/or its toxin (A or B) responsible for colitis. Infection with *C. diff.* can, in 1/3 to 1/2 of the cases, give visible endoscopic signs, which may be nonspecific (erythema, etc.) or may have characteristic appearance with pseudomembranes (Fig. 4.9).

Treatment of *C. diff.* infection is summarized in Table 4.1. It includes its prevention through the judicious use of antibiotics and through hygienic measures designed to limit its transmission (especially in the hospital setting). Certain probiotics designed to maintain an "adequate" intestinal flora have been able to reduce post-antibiotic therapy infection rates. Curative treatment most often uses antibiotics such as metronidazole (250 mg qid or 500 mg tid for 10–15 days p.o. or i.v.), or vancomycin (125–500 mg qid p.o.; i.v. vancomycin does not penetrate the intestine and is therefore not effective), or fidaxomicin (200 mg bid p.o. × 10 days). However, relapses may occur when antibiotics are stopped (≈ 10–20% of cases) and require either prolonged re-retreatment or alternate antibiotic therapy (vancomycin instead of metronidazole, fidaxomicin

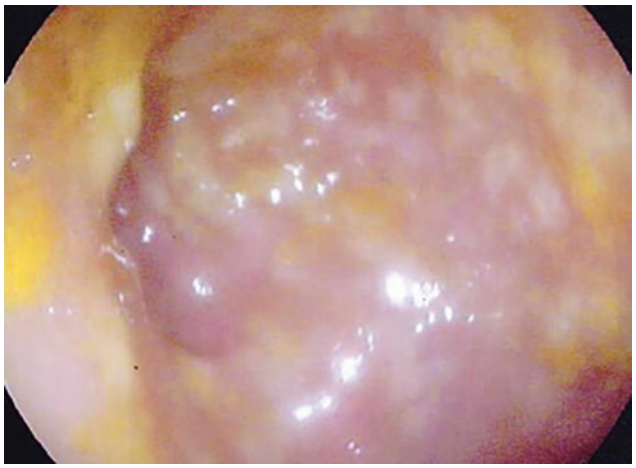


Fig. 4.9 Colonoscopy revealing flaky deposits of pseudomembranes typical of *Clostridioides difficile* colitis. (Photo by P. Poitras)

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Table 4.1 Management of *Clostridioides difficile* infection

Prevention

- Judicious use of antibiotics (especially quinolones)
- Judicious use of PPIs
- Hygiene measures (hand washing, etc.) to limit transmission
- Concomitant administration of probiotics (Bio K, *Saccharomyces boulardii*, etc.)

Treatment

1. Metronidazole po 250 mg qid or 500 mg tid × 2 weeks (or 500 i.v. q 8 hours if vomiting, etc.)
2. Vancomycin 125 mg po q 6 hours × 2 weeks
3. Fidaxomicin 200 mg po bid × 2 weeks
4. If severe: colectomy

Recurrence treatment

1. Change antibiotic (metronidazole → vanco, or, vanco → fidaxo) × 10–14 days
2. Prolonged antibiotic use (and progressive tapering): 7–14 days qid → bid → die
3. New antibiotic: fidaxomicin 200 mg bid × 2 weeks
4. Fecal transplantation

instead of vancomycin). For recurrent relapse fecal transplant has been shown to be curative. Cholestyramine (4.0 g tid) can be used to bind the toxin. In severe cases, especially if megacolon ensues, surgical colectomy may be necessary.

Colonization by *C. difficile* in normal infants ranges from 25% to 80% versus 2% to 15% in adults, with a peak at about 6 months of age. This high carrier rate has been attributed to intestinal immaturity and the lack of protective microbiota to prevent the growth of *C. diff.* The immaturity or lack of receptors for toxin A along the intestinal epithelium explains why there are far fewer *C. diff.* diseases in this age group. The bacterium is more often found in formula-fed babies or in babies born by caesarean section.

Viral colitis. Viral diarrhea is frequent and spontaneously resolves after short courses. Viral infections most typically cause enteritis rather than colitis. Cytomegalovirus (CMV) colitis may emerge in immunosuppressed patients and requires treatment with i.v. ganciclovir.

Parasites. Some parasites can cause colitis. Amoebic colitis must be suspected in any traveller or inhabitant of countries at risk for this infection (tropical countries). Diagnosis can be obtained by examination of stools or by colonic biopsies revealing the pathogen (*Entamœba histolytica* is pathogenic and must be treated; *Entamœba gingivalis*, *E. hartmanni*, *E. coli*, *E. dispar* are however considered nonpathogenic). Treatment will be provided with metronidazole 500–750 mg tid for 1–3 weeks. The infection may be complicated by an amoebic abscess of the liver (easily identifiable on ultrasound) which may be suspected in the presence of high fever, pain in the right hypochondrium, or abnormal liver function tests.

Dientamœba fragilis and *Blastocystis hominis* are other parasites that can affect the colon.

- Nail-cut ulcerations on the rectocolonic mucosa are indications of amoebiasis.
- Bilharziosis (schistosomiasis) is characterized by punctiform, whitish lesions on an erythematous mucous membrane. Mucosal biopsies reveal the parasites or their eggs.

4.6.2 Ischemic Colitis and Colonic Ischemia

Colonic Ischemia Ischemia of the colon, especially in the proximal colon, may be associated with ischemia of the small intestine due to arterial or venous occlusion of the superior mesenteric vessels. Acute intestinal ischemia is a life-threatening emergency that is often difficult to diagnose and treat and whose consequences are particularly severe in the small intestine (see ▶ Chap. 3). If vascular repermeabilization (pharmacologically with anticoagulants/thrombolytic agents or mechanically by radiological or surgical techniques) is impossible or ineffective, resection of the necrotic intestine is necessary.

Ischemia of the colon can be isolated (ischemic colitis described below) and most often affects the distal colon supplied by the inferior mesenteric artery.

Ischemic Colitis Ischemic colitis occurs as a result of a localized reduction in colonic arterial flow either during vascular occlusion (by atheromatosis, more rarely by arteritis, or by embolisms from atheromatous plaques of the abdominal vessels or from heart clots) or as a result of a decreased colonic perfusion flow due to hypovolemia, shock, dehydration, etc. Ischemic colitis is a condition whose frequency increases with age. In more than 3/4 of cases, no obvious cause is found. Colitis is most often attributed to a "low flow" condition and will then mostly involve the "watershed" regions at the distal limit of the arterial irrigation areas: the splenic flexure (at the rim of the territories supplied by the superior and inferior mesenteric arteries) or the rectosigmoid junction (at the junction of the vascularizations by the inferior mesenteric artery and the rectal arteries coming from the iliac vessels).

The *clinical presentation* of ischemic colitis involves acute abdominal pain often more or less localized to the diseased colon segment and accompanied by bloody stools.

The *diagnosis* is frequently suggested on abdominal CT scan (Fig. 4.10) showing segmental colitis (thickened walls due to edema) and which can also reveal obstructed abdominal arteries..

Colonoscopy shows colitis, extended over a more or less long segment, almost always sparing the rectum (irrigated by rectal arteries from iliac arteries), and with suggestive macroscopic features such as an erythemato-erosive mucosa on the antimesenteric edge of the colonic wall (Fig. 4.11) or a bluish or even blackish mucosa in severe cases. Biopsies reveal suggestive histological changes.

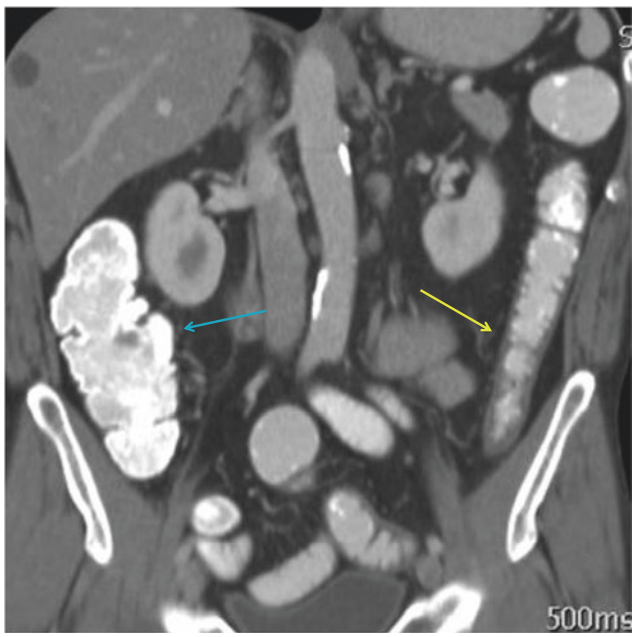


Fig. 4.10 Ischemic colitis seen on CT scan of the abdomen: thickened colon wall (arrows) suggesting colitis of the left colon (compared to the normal right colon), which here was ischemic in origin. (Photo from R. Déry)

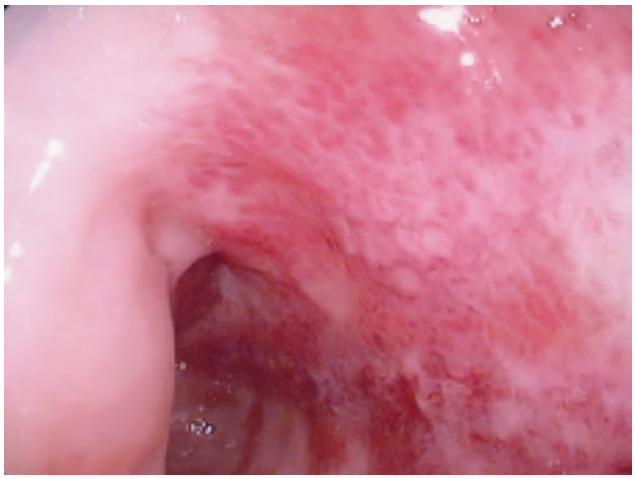


Fig. 4.11 Ischemic colitis as seen endoscopically: the antimesenteric side may be more affected. (Photo by P. Poitras)

Acute *treatment* of ischemic colitis is most often monitoring and supportive treatment (hydration, analgesia, etc.) since the phenomenon will usually regress spontaneously within a few days. In case of transmural involvement, a peritoneal reaction (abdominal rigidity, Blumberg's sign, paralytic ileus, etc.) is possible, but intestinal perforation remains a rare complication. Bleeding sometimes requires transfusion. Surgical treatment is rarely necessary except in cases of proven perforation or uncontrolled bleeding.

Ischemic colitis is usually an isolated, non-repetitive phenomenon that leads to uncomplicated and complete healing of the colonic mucosa; late complications from stenosis developing in the weeks or months following the acute episode are still possible.

Complementary examinations looking for potentially embolic lesions (electrocardiogram, cardiac echography, abdominal Doppler ultrasound, etc.) or for coagulation disorders (deficiency in protein C, S, antithrombin III, mutated factor V Leiden, polycythemia, etc.) are used to detect predisposing conditions in 10–30% of individuals and thus prevent a recurrence of the ischemic problem.

4.6.3 Microscopic Colitis

Microscopic colitis is characterized by a macroscopically normal appearance of the colon and histological abnormalities in the form of epithelial infiltration by lymphocytes (lymphocytic colitis) or a thickening of the submucosal collagen table (also called basal lamina) (collagen colitis). The two abnormalities often coexist.

It is manifested by chronic diarrhea which can be of variable importance, i.e., from mild to very severe (leading to dehydration, hypokalemia, etc.). The etiopathogenesis of this condition remains unknown. It may be associated with celiac disease, with autoimmune diseases (hypothyroidism, rheumatoid arthritis, etc.), and with certain medications (NSAIDs, PPIs).

The evolution may be benign with a moderately severe clinical picture, improving spontaneously or with recurrences. In some cases, however, the disease may be very severe and require aggressive therapy.

The diagnosis requires colonic biopsies.

Basic treatment is loperamide to slow intestinal transit. Bismuth (Pepto-Bismol® 2 tablets qid), 5-ASA (mesalamine 3–4 g/day), cholestyramine (4–12 g die) or various antibiotics may be useful. In more severe cases, "local" corticosteroid therapy (budesonide) or even systemic corticosteroid therapy (prednisone) may be used. Some severe or refractory cases will respond to immunosuppressants (azathioprine or 6-mercaptopurine), anti-TNF infliximab, or anti-integrin vedolizumab. Rarely, severe cases require surgery (total colectomy).

4.6.4 Radiation Colitis

During *acute radiotherapy treatment*, colorectal mucosa may suffer from "mucositis" (as elsewhere in the digestive tract) causing soft, mucoid, hemorrhagic stools that rapidly regress when treatment is stopped.

Long-term complications of radiotherapy are due to small vessels vasculitis, which is a progressive and self-deteriorating condition overtime, and can manifest even years after the irradiation treatment. Proctitis or ischemic-type colitis with mucosal bleeding and parietal fibrosis (with obstructive stenoses and/or rigid wall infiltration) are common. Radiation colitis is mainly localized in the lower rectum in cases of irradiation for prostatic or anorectal neoplasia; it may extend more proximally, especially at the sigmoid level, in cases of irradiation for pelvic diseases (uterus, ovaries).

4.6.5 Colitis in Oncology

Neutropenic colitis (or typhlitis, from the Greek cecum): it occurs in patients with febrile neutropenia under cytotoxic chemotherapy. Affecting mainly the right colon (and the cecum), it can be very severe (mortality rate of 20–60%) and often leads to translocation septicemia.

Its precise cause is unknown, but polymicrobial infection (*Pseudomonas*, E coli, *Bacteroides*, *Candida*) is common. The diagnosis is evoked by CT scan, and colonoscopy is not desirable, given the high risk of perforation.

Supportive treatment, in addition to GM-CSF (granulocyte macrophage colony-stimulating factor), includes broad-spectrum antibiotics (piperacillin-tazobactam, imipenem) and antifungals (amphotericin B).

Colitis on cancer immunotherapy. Patients on checkpoint inhibitors immunotherapy (such as ipilimumab but also nivolumab or pembrolizumab) may develop immune colitis mimicking ulcerative colitis or Crohn's colitis. Corticosteroids and anti-TNFs may be required to control the disease.

4.6.6 Inflammatory Bowel Diseases (IBD): Ulcerative Colitis and Crohn's Disease

Inflammatory bowel disease (IBD) includes two related diseases: ulcerative colitis (UC) and Crohn's disease (CD). Briefly, ulcerative colitis refers to an inflammation limited to the colonic mucosa that begins in the rectum and may extend continuously in the proximal regions of the colon (right, transverse, left colon). Crohn's disease (so named from Dr. Burrill Bernard Crohn (see Fig. 4.12) who identified the condition) is a granulomatous inflammation that can involve all layers of the intestinal wall and affect, often discontinuously, the colon and/or the small intestine (or any other region of the digestive tract). The two colonic diseases can sometimes be difficult to differentiate, and the colitis is then referred to as an "unclassified (or undetermined) coli-

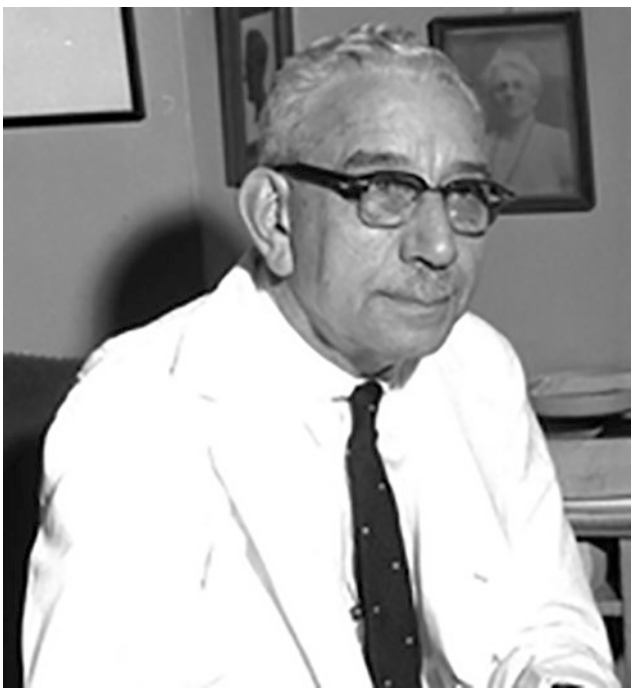


Fig. 4.12 Burrill Bernard Crohn (photo), with colleagues L. Ginzburg and G.D. Oppenheimer of Mount Sinai Hospital in New York, described "regional enteritis" in 1932

tis." Both are as yet of unknown causes and use a relatively similar treatment regimen. Both diseases are chronic (due to our inability to provide curative treatment). They are a most common and serious intestinal ailment seen by the gastroenterologist.

(a) Epidemiology of IBD

IBDs affect up to 500 persons per 100,000 population in Canada. While UC was once considered more common, an increasing frequency of CD is now observed (prevalence per 1000: CU 1.94; Crohn's 2.34). IBD affects both men and women, often with peaks incidence at ages 15–30 and 50–80 years. The incidence appears higher in Jews than in non-Jews, and lower in Blacks or Asians. The incidence also appears elevated in Western countries of the Northern Hemisphere. Canada is one of the countries where IBDs are most common. In the past 30 years, the incidence has been raising in the developing world.

(b) Etiology of IBD

Etiology of IBDs is unknown, but several factors are suspected:

Genetic factors: A family history of IBD in first-degree relatives is found in 10–25% of patients. Studies of twins revealed a concordance of the disease in 6% of heterozygous twins but in 58% of homozygous twins, clearly suggesting a genetic incidence in the development of IBD. Having a parent with inflammatory disease increases the risk of IBD (1/250 people in Canada) by 3–20 times in their children (4% of children). If both parents have inflammatory disease, children have a 20–30% risk of also having IBD. The location of the disease (i.e., small vs. large bowel) and the type of disease (e.g., perforating vs. stenosing disease) are consistent in 50–80% of cases of familial disease.

Many genes have been statistically associated with IBD. The most important mutation was discovered in 2001: mutations in the NOD2 gene located on chromosome 16 appear to predispose to ileal Crohn's disease. Genes abnormalities are related to either a facilitating (e.g., NOD2) or a protective (e.g., IL-10 gene) influence for IBD. The multiplicity of genes involved demonstrates the very likely polygenic nature of these diseases and makes it difficult to apply these discoveries in clinical practice. In 2020, more than 200 genetic abnormalities genetic have been associated with CD and UC.

Immune factors: The autoimmune character of IBD is supported by its association with various autoimmune diseases such as ankylosing spondylitis, arthritis, uveitis, etc.

Environmental factors: the elevated prevalence of IBD in the Nordic countries and Canada may suggest the existence of environmental factors involved in their genesis. However, no dietary, toxic, or other factors are currently identified. Smoking doubles the risk of developing CD and is associated with adverse disease outcomes. Curiously, however, smoking seems to decrease the risk of developing UC and even seems capable of reducing its clinical severity.

Infectious factors: The granulomatous nature of CD is reminiscent of mycobacterial diseases that can affect humans (e.g., tuberculosis) or animals (e.g., bovine ileitis, or Johne's disease, caused by mycobacterium avium paratuberculosis). Spousal transmission of the disease has been reported anecdotally. However, multiple attempts to identify infectious agents or to eradicate the disease with various combinations of antibiotics have not yielded any positive results. An imbalance of the intestinal microbiota (dysbiosis) is also considered as a potential factor inducing inflammation.

«Unicist» theory: A theory that would bring all these hypotheses together would be that (1) in individuals predisposed by genetic mutations (single or multiple, protective or favoring), (2) exposure to (or aggression by) certain "environmental" (or infectious) products triggers IBD (it is interesting to note that in an experimental model mimicking CD, the IL-10 deficient-mutant mouse does not exhibit intestinal inflammation as long as it remains in its germ-free environment) (3) and induces inflammation with lymphocytes and neutrophils producing cytokines, interleukins, TNF, etc.

(c) Clinical Presentation of IBD

UC and CD have characteristic manifestations of each disease (extensively discussed later, see Table 4.3), but it is not uncommon to have difficulty in determining whether a colitis is due to CD or UC (and is then referred to as colitis type, unclassified) or to see a colitis initially diagnosed as UC later manifests itself as CD (for instance, when a person with UC presents a fistula or small bowel disease the diagnosis is changed to CD).

1. ***Ulcerative Colitis:*** UC is a Chronic disease characterized by inflammation of the colonic mucosa that typically begins in the rectum (proctitis) and may extend continuously to more proximal colonic segments such as the left colon (left or distal colitis), or beyond the splenic flexure (extended colitis), or into the cecum (pancolitis). Inflammation in UC, as opposed to CD, is limited to the mucosa and to the colon.

Symptoms of UC. Frequent stools with bleeding and mucus are the cardinal signs of UC. Rectal involvement (proctitis) often results in an increased defecatory rate but without real diarrhea, with urges for bowel movements and/or frequent (but unproductive) need to pass stools (tenesmus). Defecation is frequent, even compelling, with blood and mucus, but each time with only a small amount of stools, which may in fact have normal or even hard consistency. More extensive inflammation compromises normal colonic functions and leads to diarrhea with frequent, soft, or watery stools. Friability

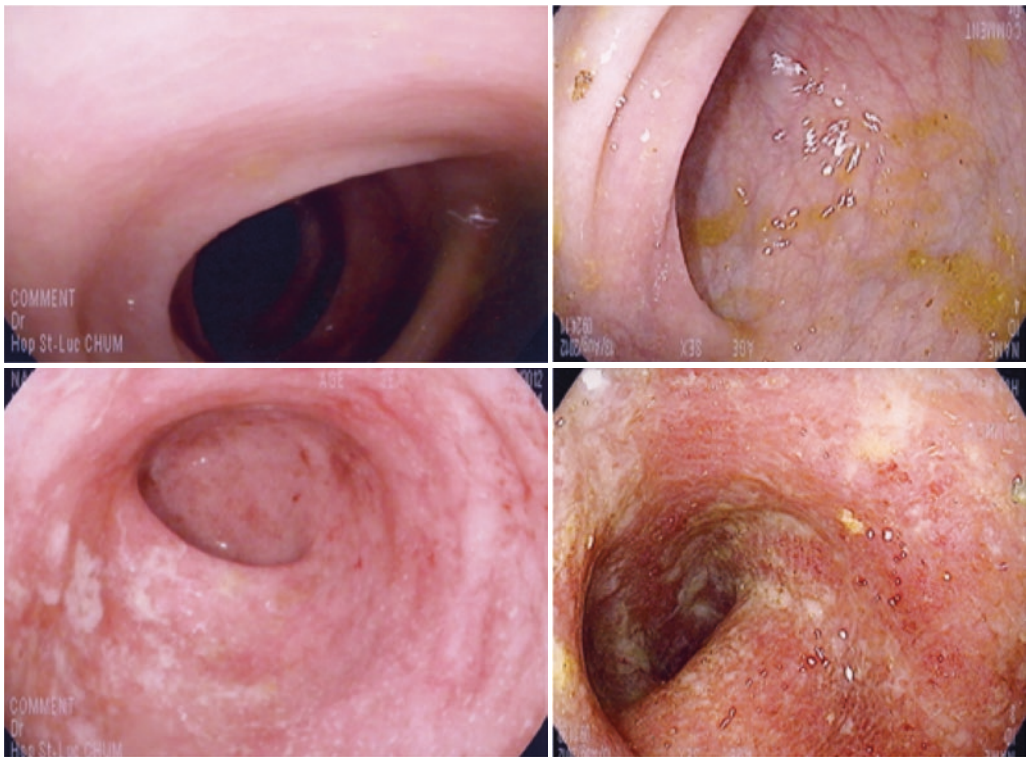


Fig. 4.13 Colonoscopy images of two patients (patient 1, left; patient 2, right) with distal ulcerative colitis showing an abnormal mucosa in the rectosigmoid (bottom images) that is diffusely erythematous, friable, micro-ulcerated, while the upper images show the smooth, shiny mucosa of the normal left colon. (Photos by P. Poitras)

of colonic mucosa is responsible for blood loss, as well as mucus.

At initial presentation, 1/3 of patients have proctitis, 1/3 have left colitis, and 1/3 have extensive colitis or pancolitis. Less than 10% of patients may initially suffer from severe or fulminant colitis, a potentially lethal condition with extensive and severe colon involvement resulting in debilitating symptoms such as severe diarrhea, painful abdominal cramps, blood loss (that may require transfusions), fever, weight loss, undernutrition, etc. Inflammation in these individuals with severe colitis not only can affect the colonic mucosa but can extend to deeper layers of the colonic wall, putting the patient at risk for megacolon (distension of the colon) and perforations.

Digestive complications of UC include:

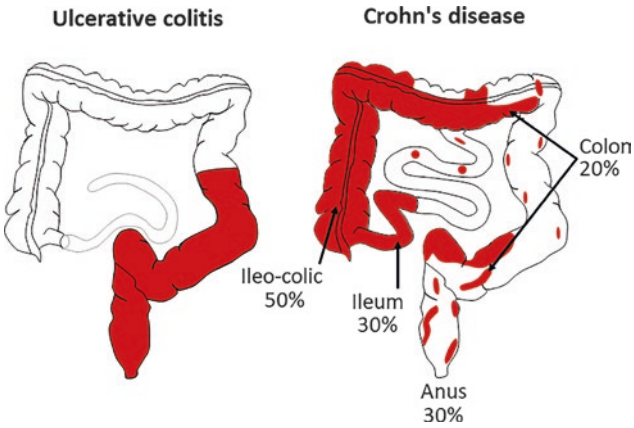
- Colonic hemorrhage is possible but rare. Loss of sufficient blood to cause anemia is common.
- Severe or fulminant colitis occurs in about 15% of patients. The severity of the symptoms (pain, diarrhea, dehydration, etc.), the general health status (undernutrition, etc.) of the patient, the risk of toxic megacolon, etc. then justify hospital treatment.
- Toxic megacolon (distension of the colon with severe colitis and signs of systemic toxicity) is an emergency due to the risk of perforation of the colon (which can lead to mortality in 50% of cases in presence of peritonitis). Failure to respond to intensive medical treatment within 48 hours usually requires an emergency surgical colectomy.
- Development of neoplasia: The probability of developing adenocarcinoma of the colon is increased in individuals with colitis. The risk factors are (1) the extent of the disease, extensive colitis is significantly more at risk than left-sided colitis; (2) the duration of the disease, the risk begins after 8 years and increases by approximately 1% per year (after 20 years, 10% of patients with UC would have developed colonic neoplasia, after 30 years, 20%, etc.); (3) the association with other diseases such as primary sclerosing cholangitis; and (4) probably the importance of the chronic inflammatory reaction (anti-inflammatory treatments with 5-ASA or immunosuppressants seem to have a protective effect). To detect early neoplastic transformation, surveillance colonoscopies (with biopsies) every 1–5 years (depending on risk factors) are recommended. Prophylactic colectomy is a treatment option.

Diagnosis of UC is made by colonoscopy, which shows inflammatory disease that almost invariably affects the rectum and may extend continuously to other colonic segments. The inflammation is characterized by an erythematous, often friable mucosa, possibly with erosions and often covered with muco-pus (Fig. 4.13). In peri-

ods of remission, the mucosa may return to a completely normal appearance. In severe forms, extensive and deep ulcers can be seen. In chronic forms, healed colonic walls (lead pipe colon on radiological exams) or inflammatory polyps (often called pseudopolyps) may be present.

Evolution of UC. In the course of evolution, the extent of the colitis diagnosed in the initial episode may progress more proximally in the colon. In patients with proctitis, the disease may extend proximally in 20–50% of cases. Over the years, the clinical course is most often made up of repeated acute attacks requiring treatments that are fortunately mostly effective. Surgery may be required for resistance to medical treatment or for cancer prophylaxis. It is rarely necessary in the distal forms of colitis and appears to be required in about 20–30% of individuals with more proximal and severe disease. Life expectancy is not significantly affected in patients with UC given the therapeutic modalities now available (discussed later).

2. ***Crohn's disease.*** Identified in 1932 in New York by Doctors B.B. Crohn, L. Ginzburg, and G.D. Oppenheimer, Crohn's disease is a granulomatous inflammation that can involve all layers of the intestinal wall and affect all digestive organs. Crohn's disease is localized to the ileocolic region in ≈50% of patients, or may be limited to the small intestine (more often to the terminal ileum) or to the colon in about 30% of affected patients (◘ Fig. 4.14). The anorectal region is frequently involved (≈30% of patients). The stomach and esophagus may be affected (≈5% of patients).



◘ **Fig. 4.14** Inflammatory sites in IBDs

The colon is thus affected in 2/3 of patients with Crohn's disease. Inflammation, sometimes, may be continuous and superficial as in ulcerative colitis but, more often, characteristically, is discontinuous, patchy, and mixed with skip area of normal mucosa. Mucosal breaks made of superficial erosions in UC may appear in CD as aphthous ulcerations surrounded by normal mucosa to deep penetrating ulcers in severely inflamed colonic walls (◘ Fig. 4.15).

The disease is often described as having an inflammatory, stenosing (1/3 of patients), or perforating (1/3 of patients) profile. Stenosing disease causes narrowing of the intestinal lumen with obstruction and blockage. Perforation of the intestinal wall may occur in the abdominal cavity resulting in peritonitis, abdominal abscesses, etc. or may produce communication(s) (fistula) to surrounding organs (enteroenteric, enterocolic, entero- or colo-vaginal fistula, etc.).

Clinical manifestations of Crohn's disease include:

- Abdominal pain is common in CD. It may be related to obstructive (often ileal) bowel involvement (with cramp-like periumbilical pain) or to trans-parietal inflammation (possibly with abdominal masses) of the intestine or colon. Severe acute pain is present during complications such as intestinal obstruction or during perforation and abscess formation.
- Diarrhea is common. Several pathophysiological factors may be involved: (a) reduced absorption capacity due to intestinal inflammation, surgical resection of the small intestine or colon, enteroenteric or enterocolic fistulas that exclude certain digestive segments from normal bowel function, etc.; (b) intestinal bacterial overgrowth due to stenoses inducing stagnation of bacteria or due to fistulas allowing the recirculation of colonic bacteria toward the proximal intestine; and (c) choleretic diarrhea due to the bile salt malabsorption in the terminal ileum which is affected by inflammation or absent following surgical resection.

Digestive complications of Crohn's disease:

- Digestive bleeding with acute hemorrhage (rare) or chronic blood loss from intestinal ulcers that lead to anemia may occur.
- Obstruction of the small intestine or colon by inflammatory stenoses (likely to respond to anti-inflammatory medical treatment) or by fibrous stenoses (resistant to anti-inflammatory treatment and which will require surgical treatment or endoscopic dilatation).

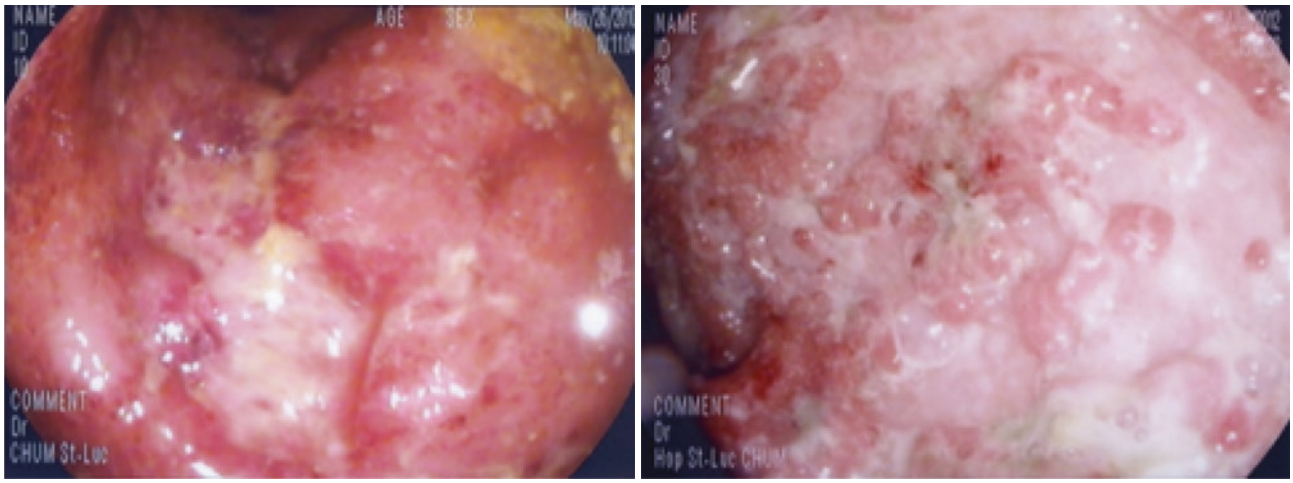


Fig. 4.15 Colonoscopy: in Crohn's disease, inflammatory areas may contain ulcers, either aphthous or ulcerous, often deep and penetrating (which may even rest on a healthy mucosa). Inflammatory areas can be irregularly distributed and mixed with areas of healthy normal mucosa. (Photos by P. Poitras)

4

- Perforation of ulcers with peritonitis or formation of abdominal abscesses.
- Fistulas (communication with a nearby organ due to perforation of a penetrating intestinal ulcer):
  - Enteroenteric or entero-colonic fistulas with short-circuiting of intestinal segments or with secondary bacterial overgrowth
  - Entero- or colo-vesical fistulas with pneumaturia or fecaluria, urinary infection (often with multiple germs of digestive origin), risk of pyelonephritis
  - Entero- or colo-vaginal fistulas with passage of air or stool through the vagina and secondary vaginitis
  - Entero-cutaneous fistulas
- Perianal involvement with complicated ulcers leading to pain, abscesses, risk of incontinence due to sphincter destruction, etc. The alteration in quality of life can be significant and may require treatments that are unfortunately radical and mutilating (proctectomy with ileostomy or colostomy).
- Oral injury due to aphthous ulcers.
- Proximal digestive damage with dysphagia or odynophagia in case of esophageal damage, or gastric outlet obstruction if gastric or duodenal damage.
- Increased risk of colon cancer is present (at sites of chronic colon inflammation) in both CD and UC.

Evolution of Crohn's disease. The course of CD is variable and unpredictable. A major Scandinavian study looked at the natural evolution of the disease after its discovery and treatment of the initial episode (Fig. 4.16); many patients (45% of the patients) had a favorable course, while others had acute recurrences repeatedly (32%) or chronic symptoms (19%).

Crohn's disease is often associated with a negative image. However, an administrative database study in the Canadian province of Manitoba revealed that, over a 1-year observation period, 50% of patients with a previous diagnosis of CD had not seen a physician and 60% did not use medication; another analysis showed that, by 5 years, half of this patient population was not using any IBD-related medication A Scandinavian study found that CD patients had lower rates of absenteeism from work than normal population and a higher socioeconomic status. Various observations suggest that 2/3 of the patients have a benign or favorable course with prolonged remissions or easily treatable recurrences, but that 1/3 of the patients will have an aggressive course requiring the use of complex therapeutic strategies. Our inability to predict the disease profile in a specific patient makes it difficult to manage and prevent the disease.

In cases of drug resistance (or certain cases of drug dependence), surgery may be necessary. It is recognized that surgery does not cure the disease and that inflammation may recur in remaining intestinal segments. It is estimated that approximately 50% of CD patients will require surgery.

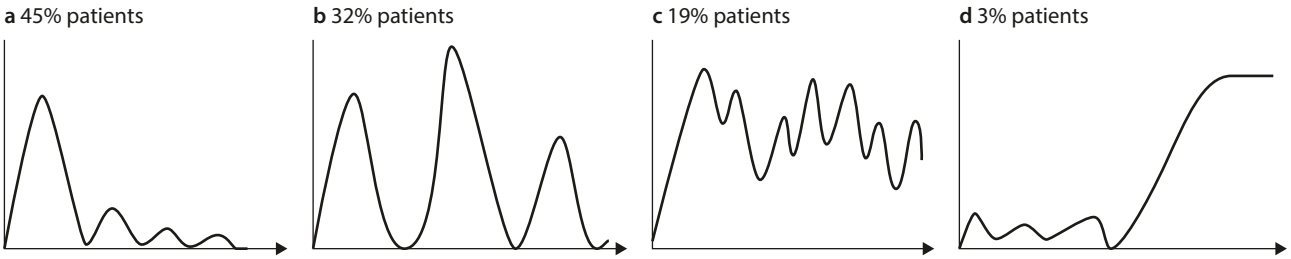


Fig. 4.16 Ten-year course of patients with Crohn's disease (schematic representation according to Solberg et al, 2007): **a** in 45% of patients, after the initial episode the symptoms severity decreased during the follow-up period; **b** 32% of patients had chronic recurrent relapses; **c** 19% had chronic persistent symptoms; **d** in few patients (3%), the disease severity increased during the 10-year follow-up period

(d) Extra GI Manifestations of IBD

IBDs may be associated with abnormalities of several non-digestive organs as summarized in Table 4.2. Some of these manifestations tend to parallel inflammatory bowel episodes (e.g., peripheral arthritis, erythema nodosum, uveitis), while others (e.g., primary sclerosing cholangitis, spondylarthritis) appear to evolve independently.

Table 4.2 Extraintestinal manifestations (20–40% of patients) of IBD

Musculo-skeletal	Peripheral arthritis (follows disease activity) (10–30% of patients)
	Central arthritis (sacroiliac/spondylarthritis) (2–8% of patients)
Cutaneous	Erythema nodosum (10–15% of patients)
	Pyoderma gangrenosum (1–5% of patients)
Ocular	Uveitis, episcleritis (1–5% patients)
Hepatic	Sclerosing cholangitis (3–7% patients) → liver transplantation
	Chronic autoimmune hepatitis
	Gallstones (Crohn's)

(e) Differences and Similarities of IBDs

Ulcerative colitis and Crohn's disease can be differentiated according to the characteristics listed in Table 4.3.

Identification of UC vs. CD is not always an easy task. In up to 20% of cases, it is not clear whether the patient has UC or CD; this is referred to as unclassified colitis. Some patients initially presenting with diffuse colonic involvement and diagnosed as UC can develop overtime CD traits (e.g., perianal or ileal lesions) and see their diagnosis change from UC to CD.

(f) Diagnosis of IBD

IBD will be diagnosed mainly by endoscopic (colonoscopy) or radiological (X-ray, ultrasound, CT scan, MRI) examinations. Serological tests are complementary to the evaluation of the patient but are of little diagnostic significance. Table 4.4 summarizes different options for a diagnostic approach.

Endoscopic examinations: When colitis is suspected, the examination of choice is colonoscopy. The macroscopic appearance will help to differentiate UC (diffuse and continuous inflammation extending from the rectum) from CD (aphthous or deep ulcers, geographic, skip areas of normal mucosa, etc.) or other diseases (ischemic colitis, infectious colitis, etc.). Biopsies can be obtained to clarify the diagnosis (e.g., immune granuloma, although rare, will confirm CD).

Radiological examinations: Barium enema is only exceptionally used nowadays in the management of IBD. Small bowel follow through (X-rays of the small intestine after oral ingestion of a barium solution), once the gold standard for intestinal exploration, is gradually abandoned (to be performant, this test, like other digestive tests such as the barium swallow, barium meal, or barium enema, requires time-consuming attentive assistance for fluoroscopy, and few radiologists maintained interest and expertise for it). Radiological investigation of the small bowel is now based mainly on cross-sectional imaging (CT or MR enterography). Transabdominal ultrasound (with Doppler) is increasingly used for intestinal exploration. MRI and US have the advantage of being performed without radiation and may differentiate inflammatory vs. fibrous nature of stenotic lesions.

Table 4.3 Ulcerative colitis and Crohn's disease can be identified by certain differences

	UC	Crohn
Clinic		
Bloody stools	≈ always	Possible
Mucus	Often	Possible
Diarrhea	≈ always	Common
Abdominal pain	Possible	Common
Abdominal mass	No	Common
Abdominal abscess	No	Possible
Toxic megacolon	Possible	Possible
Colon cancer	Increased risk	Increased risk
Gallstones	No	Possible
Radiology		
Small bowel injury	No	80% patients
Colon injury	Always	70%
Fistula	No	Possible
Stenosis	Rare	Possible
Endoscopy		
Rectal inflammation	≈ always	Possible
"Skip areas"	≈ never	Common
Ileitis	No	80%
Isolated proctitis	Possible	Possible
Pancolitis	Possible	Possible
Diffuse friability	Always	Possible
Aphthous ulcers	No	Common
Healthy/unhealthy mucosa	No	Common
Ulcer(s)	No (except severe colitis)	Common
Pathology		
Granulomas	No	25–40%
Transmural Inflammation	No (except severe)	Yes
Others		
Peripheral arthritis	Possible	Common (25%)
Central arthritis	Possible	Possible
Sclerosing cholangitis	Possible	Possible
P ANCA/ASCA	70%/0	50%(colitis)/30%
Tobacco effect	Protective	Deleterious

Table 4.4 Diagnostic tests for diagnosis and follow-up of IBD

Anomaly sought	« Gold standard »	Others
Inflammation	C-reactive protein	Anemia inflammatory type (iron↓, transferrin↓, ferritin N, platelets ↑)
	Fecal calprotectin	
Intestinal lumen damage	CT enterography	Small bowel follow through X-ray
	MR enterography	Duodeno-jejunoscopy (oral)
	Ileocolonoscopy	Enteroscopy per videocapsule
		Echography
Colon lumen damage	Colonoscopy	CT/MR enterography
		Barium enema (very rarely used)
Extra-luminal damage (abscess, fistula)	CT Scan	MRI (anorectal)

Extra-luminal damage (e.g., abscess, fistula) will be best characterized by axial tomography.

Blood and fecal tests can help monitor systemic inflammatory response and disease activity. Plasma elevation of C-reactive protein is the most commonly used marker, but is not found in all patients. Fecal calprotectin is a good marker of intestinal inflammation.

(g) Treatment of IBD

IBD treatment may be required (1) for the management of an acute episode (acute treatment for induction of remission), or (2) to maintain disease (otherwise active in absence of medication) in a quiescent (remission) state (chronic or maintenance treatment), or (3) to prevent recurrences (preventive or prophylactic treatment). UC and CD differ here in terms of preventive treatment. For UC, prophylaxy with 5-ASA is indicated for most patients since it is an effective and safe treatment. For CD, pharmacological prophylaxis needs to take into account the long-term safety and economic limitations on balance with potential clinical benefits. On the other hand, smoking cessation is an effective prophylactic regimen in CD and is recommended for all patients.

As seen below, IBD management involves several drugs of various therapeutic efficacy, side-effect profile and financial cost.

Corticosteroids: Corticosteroids are very potent drugs and have been used to control inflammatory disorders for decades. They constitute a classical treatment for acute phases of IBDs. Their beneficial effect is usually rapid, within a few days, and observed in most patients.

Corticosteroids are most often taken orally, in initially high doses and gradually reduced at a weekly interval. In the "american" approach, prednisone (5 mg/tablet) is given at 40 mg/day initially, followed by a weekly reduction of 5 mg (i.e., 40 mg/day, once-daily, in the first week; 35 mg/day in the second week; 30 mg in the third week, etc.); experience shows that 70% of patients are rapidly improved by this therapy. The "european" recipe often uses higher doses, i.e., 1 mg/kg of prednisolone (1 mg prednisolone = 1.2 mg prednisone) with a progressive weekly reduction over 12–15 weeks. A favorable response is obtained in approximately 90% of patients undergoing this therapy.

Corticosteroids may be given intravenously [methylprednisolone (Solu-Medrol®) 20 mg i.v. q 6–8 hours] when the patient cannot tolerate the oral route, or when maximum efficacy is sought. They may also be given by rectal administration as a suppository for rectal inflammation, as a foam (Cortifoam®) for rectosigmoid involvement, or as an enema (Betnesol®, Cortenema®, Entocort®, etc.) for disease extended up to the distal left colon.

Corticosteroids have well-known adverse effect on bones, and it is now advised for bone protection to administer calcium supplements (calcium 500+ vitamin D 400 bid) and possibly bisphosphonates [risedronate (Actonel®) 35 mg/week or alendronate (Fosamax®) 70 mg/week], during the course of corticosteroid therapy.

Corticosteroids are without any doubt highly effective in reducing intestinal inflammation and patient symptoms. However, as shown in Table 4.5, they are responsible for multiple side effects that limit their use. Even during the few weeks of corticosteroid therapy for the acute control of IBD, some patients can experience serious side effects (e.g., diabetes, hypertension, psychotic episodes, etc.), and most patients will suffer from cosmetic disorders (Cushingoid appearance, obesity, acne, etc.) as well as insomnia. Prolonged treatment with corticosteroids can have severe and permanent harmful consequences (osteoporosis, adrenal suppression, etc.) and should, by all means, be avoided. There is no evidence that corticosteroids are useful for maintenance of remission, so their role should be strictly reserved for induction of remission.

Table 4.5 Corticosteroids. Side effects

Possible with brief treatment

- Acne (30%)
- Bruises/petechiae (17%)
- Diabetes
- Edema (hydrosodic retention)
- Glaucoma
- Hirsutism (7%)
- Hypertension (20%)
- Moon face (57% of patients)
- Myopathy (7%)
- Obesity/hyperphagia
- Osteonecrosis (5% hip)
- Psychic agitation/depression
- Stretch marks (6%)

With prolonged treatment

- Adrenal suppression
- Delayed healing wounds/post-op anastomosis
- Infections/immunosuppression
- Osteoporosis (50%)

Fortunately, to avoid the side effects of corticosteroid therapy, other treatment options are available (see below; Fig. 4.17). Moreover, it is estimated that approximately 50% of IBD patients will not require corticosteroid treatment.

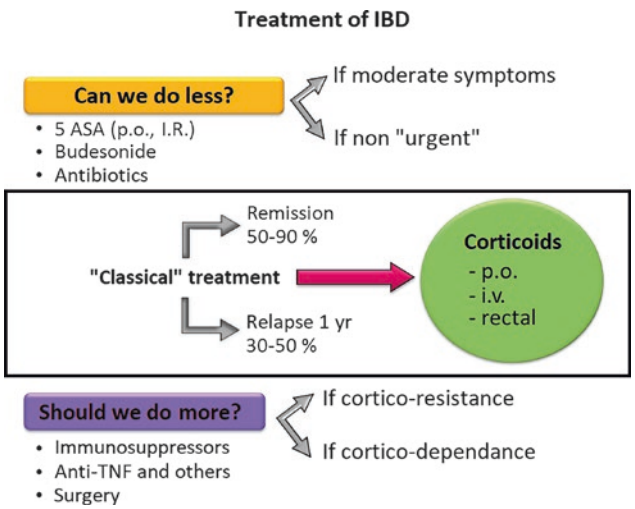


Fig. 4.17 Treatment of IBD

Can We Do Less Than Corticosteroids?

Alternative treatments do exist to avoid corticotherapy. However, they are often less effective than corticosteroids, often acting more slowly (1–3 weeks rather than 1–3 days) and having a beneficial effect in only 1/2 of the patients (rather than 3/4). For the patient whose disease is not too severe and who can afford a delayed clinical remission or risk a therapeutic failure, the following solutions can be considered:

- *5-ASA:* 5-ASA (mesalamine) are aminosalicylates that will have a local anti-inflammatory action on the intestinal mucosa. These drugs are active topically, and only about 20% of ingested doses are absorbed. To allow this topical contact, various pharmaceutical preparations exist to prevent orally ingested 5-ASA from being absorbed in the proximal intestine (and therefore of being ineffective, by not reaching the distal gut) and to allow its delivery to the distal intestine or colon (for a local anti-inflammatory action at the site of injury) (Fig. 4.18). By using 5-ASA that can be activated by colonic bacteria (Salazopyrin®, Dipentum®) or contained in pills dissolvable gradually over time (Pentasa®) or at higher pH (Asacol®, Salofalk®), the therapeutic agent can be released along the distal GI tract.

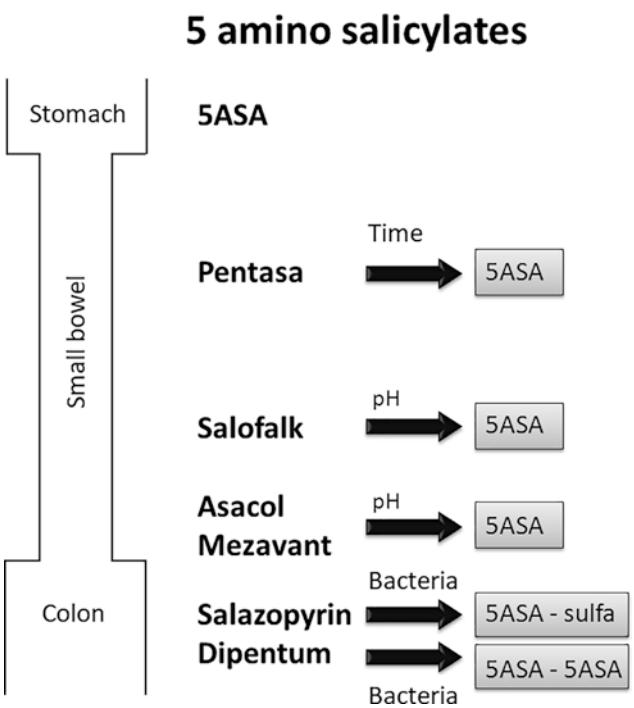


Fig. 4.18 Various preparations of 5-ASA exist for delayed delivery to the colon or small bowel. Pentasa® begins to release 5-ASA in the proximal intestine, and Salofalk® in the distal small intestine, while Asacol®, Mezavant®, Dipentum®, and Salazopyrin® have colonic delivery

For the acute treatment of IBD (more often UC than CD), oral 5-ASA can have a beneficial effect in 50–60% of patients but often with a delay of action of 1–3 weeks. Their low absorption and very limited side-effect profile make them safe pharmaceutical agents even for long-term use.

Sulfasalazine (5-ASA-sulfa) has been shown more than 30 years ago to prevent UC recurrence. New 5-ASA formulations without the sulfa moiety are better tolerated and more effective; they are used for long-term prophylaxis in all UC patients (especially since it has been associated with a decreased risk of colonic adenocarcinoma).

5-ASA can also be administered rectally using suppositories (Salofalk® 1 g or Pentasa® 1 g) which are highly effective in the treatment of proctitis (90% efficacy; more potent than corticosteroids), or by enema (Salofalk® 2–4 g or Pentasa® 4 g) for rectosigmoid inflammation.

- *Antibiotics* may also be useful in the management of IBD. Metronidazole (250 mg qid or 500 mg tid) has long been recognized for the treatment of anorectal CD, ileal CD (although less effective than prednisone), or pouchitis. The efficacy of ciprofloxacin (500 mg bid) has also been reported in several studies (albeit with a limited number of patients). In practice, the combination metronidazole/ciprofloxacin is often used for 2–4 weeks. The mechanism of action of this pharmacological approach remains unknown.
- *Nonsystemic corticosteroids*: budesonide is a potent corticosteroid (budesonide 1 mg = prednisone 5 mg) catabolized as it passes through the liver. Entocort® is a budesonide pill preparation allowing delivery of the corticosteroid in the ileocolonic lumen for a local therapeutic action before it is absorbed into the mesenteric circulation and reaches the liver where it is destroyed. Side effects of budesonide corticosteroid therapy are detectable in only one in four patients. However, its therapeutic efficacy is inferior to prednisone; its onset of action (1–3 weeks) and limited activity (50% of patients) are comparable to 5-ASAs. Cortiment® allows the delivery of budesonide into the colon lumen.

Should We Do More Than Corticosteroids?

In case of corticosteroid resistance or corticosteroid dependence, various therapeutic options are available:

- *Immunosuppressants:* Chronic corticotherapy should never be a viable option for IBD management. Immunosuppressive drugs, although not a panacea, are, since 40 years, part of the therapeutic arsenal for patients with cortico-dependence, as well for those, less common, with cortico-resistance:

- Thiopurines: 6-mercartopurine (Purinethol® 1.5 mg/kg day), or its equivalent azathioprine (Imuran® 2.5 mg/kg day), is classically used in cases of cortico-dependence. They may also be useful in cortico-resistant patients. However, it should be noted that their therapeutic efficacy is often delayed, being apparent after 3–6 months. The main side effect of thiopurines is bone marrow suppression including neutropenia. Measuring TPMT (thiopurine methyltransferase enzyme responsible for thiopurine catabolism) prior to treatment allows detection of enzyme deficits that would expose the patient to toxic levels of the drug; when therapy is initiated, a blood count should be checked every 2 weeks to detect iatrogenic leukopenia or thrombocytopenia. Other side effects of thiopurines include allergic pancreatitis (1–3% of patients) and drug fever. In the long term, an increased risk of lymphoma is recognized. Thiopurines are, however, effective and mostly well tolerated without the disastrous side effects of corticosteroids in most patients.
- Methotrexate may also be used (25 mg/week as a loading dose for 12 weeks and 15 mg/week as a maintenance dose thereafter). Methotrexate appears to be useful in patients with both corticosteroid dependence and corticosteroid resistance. Methotrexate induces its therapeutic effect within 1–3 months. Short-term side effects include myelosuppression (regular monitoring of white blood cells is therefore required) while in the medium- or long-term interstitial pneumonitis or hepatotoxicity are feared. Methotrexate can be administered orally, but for optimal results, intramuscular or subcutaneous administration is preferred.

- *Biological agents (and other new drugs)*: Since the 2000s, biological agents (i.e., pharmaceutical agents consisting of monoclonal antibodies developed in animals, usually mice) to neutralize various pro-inflammatory agents have appeared.
  - Anti-TNFs (antibodies against tumor necrosis factor alpha) are remarkably effective in IBD. Two main preparations are currently available: infliximab (Remicade®, Inflectra® administered intravenously at 5 mg/kg as a loading dose at 0, 2, and 6 weeks prior to maintenance treatment every 8 weeks) and adalimumab (Humira® given subcutaneously in doses of 160 mg at 0, 80 mg at 2 weeks, and 40 mg every 2 weeks thereafter). Other anti-TNF agents (certolizumab, adalimumab) are also available.

    Anti-TNFs alter immune defenses and may promote the development of certain diseases such as tuberculosis and hepatitis B (anti-TNF treatment is contraindicated in the case of untreated abscesses and should not be started until active tuberculosis and viral hepatitis have been ruled out). They are not recommended in patients with recent neoplasia, especially hematological malignancies, or with multiple sclerosis.
  - Anti-integrin vedolizumab prevents lymphocytes from adhering to the intestinal inflammatory site. Entyvio®, given i.v. every 8 weeks, has a targeted action on the intestine with little systemic effect. VARSITY study showed superior improvement with vedolizumab vs. anti-TNF adalimumab in UC patients.
  - Anti-interleukins 12 and 23 ustekinumab known for its beneficial effect against psoriasis is also very useful for the treatment of IBD. Stelara® is administered initially i.v. and then sc every 8 weeks. Other anti-IL-23 drugs are currently under development.
  - An inhibitor of JAK 1 and 3, tofacitinib (a chemically synthesized, nonbiological agent and given orally), initially developed for the treatment of rheumatoid arthritis, is also used for the treatment of ulcerative colitis. Other anti-JAK 1 agents are expected in the near future.

Biologic agents that provide targeted therapy for a factor of the IBD inflammatory cascade (still poorly understood) have revolutionized the management of these diseases. They are highly potent in IBD, and their side-effect profile appears very reassuring. Many physicians believe that they should be used much more often (instead of corticosteroids and immunosuppressants) and much earlier (to influence the course of the disease and prevent complications). However, their cost is currently the limiting factor to a widespread use since the price of an annual therapy (which will be perpetual) is 15,OOO–25,000 $CDN for a single-dose treatment (double or even quadruple doses are common!).

Given the multitude of new therapeutic options currently available (and more are on the way), choosing a specific therapeutic agent (e.g., should one start treatment with an anti-TNF or with an anti-integrin?) can be difficult. It can very rarely be guided by scientific data (comparative studies, efficacy based on patient's phenotype, etc.), and is often left to the physician's judgment and the patient's preference.

Summary

No treatment exists to cure IBD, but numerous medications are available to manage the disease and provide a satisfactory quality of life to IBD patients. Treatment was classically initiated with safest and cheapest drugs before, according to patient response, stepping up to more complex and expensive medications. This

traditional step-up approach (sequence of 5-ASA-corticosteroids-immunosuppressants-biologics) has been recently challenged (since biologics arrival) by the top-down strategy where patients are initially treated with the best medication (biologics) to induce a rapid and perfect recovery before switching to maintenance therapy (possibly) with other drugs and hoping to reduce long-term complications. Most medication insurance plans (private or governmental), for budget reasons, try to limit biologics use to patients refractory to other drugs and, therefore, are indirectly supporting the traditional step-up strategy.

Surgical Treatment of IBD

Surgery, once the only treatment for cortico-resistance or cortico-dependence, was, despite its mutilating effects (ileostomy if proctocolectomy, short bowel syndrome following extensive small bowel resections, etc.), a major actor in IBD management. Its role has been modified by new medical treatments (immunosuppressants in the 1980s and, more recently, biologics). Long-term risk of surgery now appears 25–50% lower in patients diagnosed with IBD in the twenty-first century than in those seen earlier. Surgical treatment is still necessary in medically resistant IBDs (often emergency surgery in acute complicated situations) and can be considered in various selected patients with UC or CD (Table 4.6).

In UC, the only desirable surgery is total excision of the colon, since partial resections are known for a high disease recurrence rate. Total colectomy with proctectomy now includes reconstruction surgery with an ileoanal pouch reservoir and eliminates the need for permanent ileostomy in most patients. Proctocolectomy has a clear benefit as it is the only known treatment to cure UC. It is used in patients resistant to medical treatment (often acute fulminant colitis), and it can be offered in selected cases of medical dependence or as prophylaxis for prevention of adenocarcinoma.

Table 4.6 Surgery in IBD

Crohn's	Ulcerative colitis
25–45% pts. operated in 3 years (prebiologics data) 25–40% of these pts. have a second surgery 30% of these pts. have a third surgery	Proctocolectomy cures the disease
Segmental limited resections if medico-resistance Short resections in medico-dependence?	Proctocolectomy Ileoanal reservoir (pouch) Illeostomy (rare)

Historical series revealed that 15% of CD patients required surgery within 1 year and 50% within 10 years after diagnosis; approximately 25% of these operated patients required a second surgery, and 30% of these twice operated patients may require a third surgery. Crohn's disease can benefit from surgery, which however cannot be curative since the disease will almost invariably reappear (most often in the gastrointestinal tract prior to the resection site). The surgical approach is therefore conservative and aims at limited colonic or intestinal resections, most often in patients resistant to medical treatment. In some cases of drug dependence (e.g., short ileal disease), surgery may be considered. Ileostomy or colostomy are now less commonly done but can still be required, especially in cases of severe anorectal disease.

(h) IBD and Women

IBD is highly prevalent in young women, where it could have specific consequences.

Fertility may be reduced in young women with IBD. Inflammation of intestinal loops in the pelvic area can affect the adjacent fallopian tubes. Surgeries involving pelvic structures (e.g., proctectomy with ileoanal pouch) can induce tubal damage in women (as well as neurological damage and erectile dysfunction in men). The systemic inflammatory state associated with IBD can cause hormonal dysfunction with amenorrhea as well as spontaneous abortion.

Pregnancy is not contraindicated in IBD. Pregnancy has no standardized effect on IBD: during pregnancy, 1/3 of women experience improvement in IBD symptoms, 1/3 feel deterioration, and 1/3 remain in a stable condition. Women who enter pregnancy in remission are most likely to remain in remission. Women using biologics (or thiopurines) are generally maintained right through pregnancy on these agents. Follow-up in a high-risk pregnancy clinic is often desired. Ileostomy and colostomy are not contraindications to pregnancy.

Delivery. Women with an active perineal CD should undergo Cesarean section.

Medication. The majority of therapeutic agents required for IBD can be used safely during pregnancy. 5-ASA and corticosteroids have long been proven safe. Immunosuppressants, as well as more recent biological agents do not pose significant risks to the mother or the fetus. The only prohibited drug is methotrexate because of its well-established teratogenic effects. Ciprofloxacin should also be avoided in the first semester.

On the other hand, birth control pills are not contraindicated in IBD patients.

Breastfeeding. The majority of treatments used in IBD are acceptable while breastfeeding. For most oral medications, a delay of 2–3 hours after taking the medication is suggested before breastfeeding.

Children born from an IBD parent have 4% risk of suffering from IBD; if both parents are affected, the risk increase to 20–30%.

(i) IBD in Children

About 25% of all IBD cases is diagnosed before the age of 18 years, and of this group about 20% will be diagnosed before the age of 10. In pediatrics, 60–70% of IBD is CD. Before the age of 15, CD is more common in boys than girls (1.5/1), while UC is equally prevalent in both sexes. A positive family history of IBD is found in 10–15% of first-generation members. In the early form of IBD, diagnosed before the age of 8 years, immunodeficiency must be ruled out (e.g., chromic septic granulomatosis, IL-10 deficiency); early onset IBD tends to have a less favorable course.

Some diseases such as Turner syndrome are associated with an increased frequency of CD. Growth and pubertal delay are often associated with IBD (CD > UC); and a decrease in growth velocity precedes the onset of digestive symptoms in about half of patients [in fact, Pediatric Crohn's Disease Activity Index (PCDAI) includes growth velocity]. Obesity does not exclude IBD.

Nutritional therapy (with polymeric formulations or others) has been shown as effective as prednisone in inducing remission in children and is often favored for the initial treatment of CD. Immunosuppressive agents, methotrexate or thiopurines, are rapidly introduced in the treatment of IBD in pediatrics. Methotrexate is now more popular than thiopurines since the reports of thiopurine-associated hepatosplenic T-cell lymphoma. Prior to prescribing thiopurines, an assay of the thiopurine-metabolizing enzyme TMPT should be obtained. Levels of thiopurine metabolites can be monitored. Anti-TNF therapy in pediatrics improves growth failure. Three years after a diagnosis of pediatric IBD, more than 10% of patients with UC or CD will have undergone surgery.

4.7 Tumor Disorders

4.7.1 Benign Neoplasms: Polyps

A polyp is an abnormal growth of tissue protruding from the mucosa in the intestinal lumen. Most polyps measure less than 2 centimeters.

Macroscopically, a polyp may be *pedunculated*, i.e., located at the end of a stalk forming like a mushroom, or it may be *sessile*, i.e., stalkless and flattened on the mucosa (Fig. 4.19).

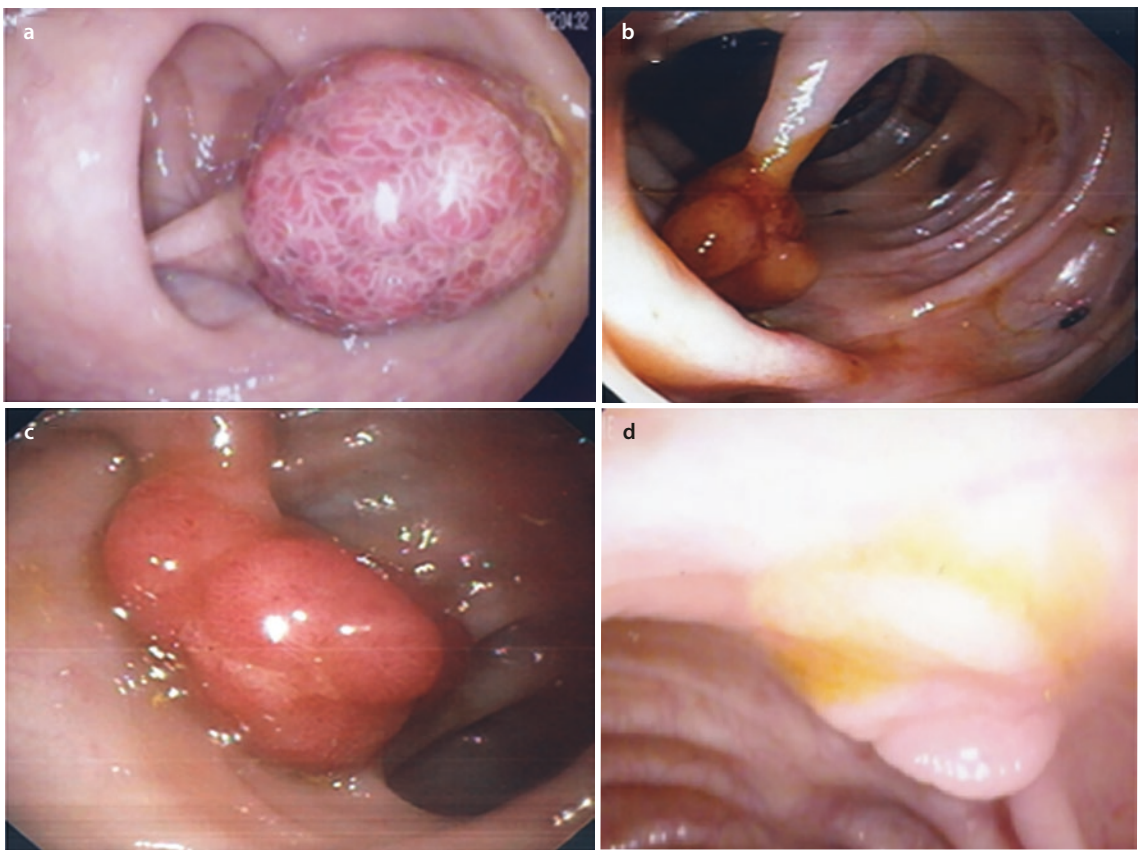


Fig. 4.19 Polyps seen on colonoscopy: **a**–**c** pedunculated; **d** sessile. (Photos by P. Poitras)

(a) Types of Polyps Microscopically, various types of polyps exist:

1. *Adenomatous polyp* constitutes an outgrowth of dysplastic glandular epithelium and is therefore at risk of a malignant transformation. Their exaggerated glandular architecture is presented in three subtypes: *tubulous* in 80% of cases, *tubulovillous*, or *villous* (Fig. 4.20). The adenomatous polyp is the most frequent and most important colon polyps since it is the precursor of colon cancer. Risk of malignant transformation increases with the size of the polyp (<1 cm, <1%; >2 cm, >10%) and its villous character (tubulovillous, 3–5%; villous, 10–40%).
2. *Serrated polyps* represent a family of epithelial polyps characterized by microscopic crypt serration with sawtooth, lace, or garland appearance of the lumen of their epithelial crypts (Fig. 4.20d). Serrated polyps include the following three subtypes:
   - The *hyperplastic polyp* (HP) is an outgrowth of normal colonic epithelium. These polyps are usually small in volume (5–6 mm), most often present in the distal colon, and without malignant potential. This is the most common (60%) of serrated polyps.
   - The *sessile serrated lesion* (SSL) is supported by the muscularis mucosae. It resembles a hyperplastic polyp but with deep dilated crypts with irregular shapes (boat anchor, inverted boot). It is most often located in the right colon and is capable of a malignant transformation. The SSL is often difficult to recognize by fecal or imaging examinations since it is flat, not very elevated on the mucosa, and does not cause major macroscopic mucosal changes; it probably partly explains the unexpected occurrence of colonic cancer in subjects who had negative screening tests a few years earlier (that SSL had been missed on previous endoscopic examinations). SSL and SSL with dysplasia (SSLD) constitute respectively 30% and 5% of serrated polyps.
   - The *traditional serrated adenoma* (TSA, formerly identified as mixed polyp or serrated adenoma) also has a serrated appearance, but unlike the SSL, it has elongated and dysplastic nuclei as the adenomatous polyp, and therefore, in the clinic, it should be treated and monitored as an adenomatous polyp.
3. The *hamartomatous* (or juvenile) polyp is made up of a stroma with hyperabundant lamina propria and

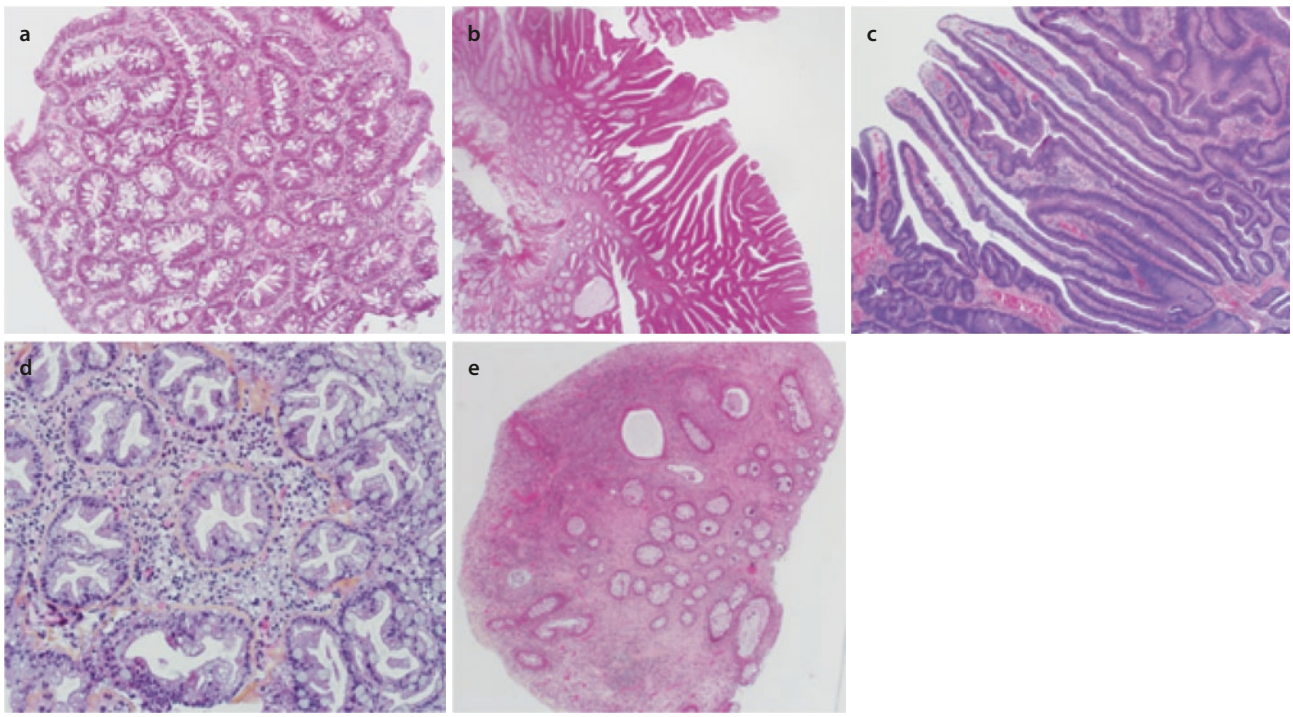


Fig. 4.20 Histology of polyps: **a** tubulous adenoma (note the tubular appearance of the glands); **b** tubulovillous adenoma; **c** villous adenoma (villous extensions are evident here); **d** hyperplastic/serrated polyp (with the sawtooth or lace-like appearance of the crypts); **e** inflammatory polyp. (Photos by G. Soucy)

cystic glands. It is most often unique and is found mostly in children or in certain forms of polyposis.

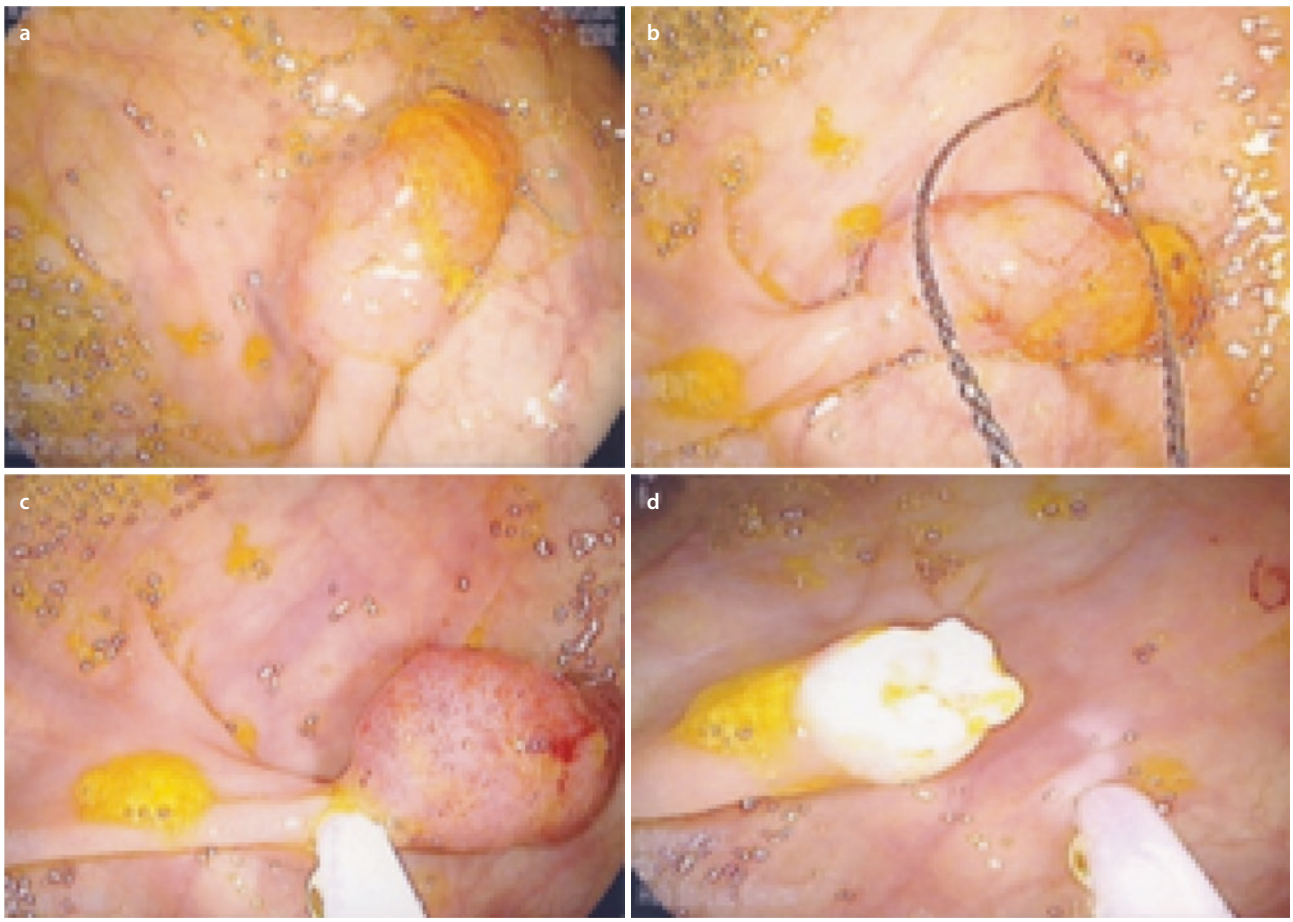
4. The *inflammatory* polyp, or mucosal polyp (or, wrongly, pseudopolyp), consists of either normal or inflamed mucosa and proliferates in inflammatory conditions such as inflammatory bowel diseases like ulcerative colitis or Crohn's disease (◘ Fig. 4.20e).

Polyps are common. Screening colonoscopies in subjects aged 50 years and over identify polyps in 1/4 to 1/3 of individuals. Prevalence of polyps seems to increase with age, since autopsy examinations reveal polyps in about 50% of cases.

(b) Clinical Colonic polyps are mostly asymptomatic. Sometimes, especially with large polyps (>1 cm), their mucosal membrane may be ulcerated or friable and may be the cause of bloody stools (polyps of the left colon) or of silent chronic blood loss (especially if in the right colon). Due to the large diameter of the colonic lumen, colonic polyps can very rarely be large enough to cause blockages. The importance of the polyps lies in their potential for malignant transformations.

Most of the time, polyps are unique or in small numbers and without obvious cause or predisposition. They may also be part of genetic syndromes promoting their development at a young age and in large numbers and are then referred to as polyposis such as familial adenomatous polyposis, Peutz-Jeghers syndrome, etc. (discussed later).

(c) Treatment of Polyps Because of their potential for malignancy, polyps are excised during the colonoscopy examination. A lasso coupled with a coagulation current is used to cut the base or stalk attaching them to the colonic wall (◘ Fig. 4.21). The polyp is then recovered for histological analysis to detect neoplastic cells.



◘ **Fig. 4.21** Colonoscopic polypectomy: the polyp **a** is surrounded by a metal loop **b** clamping the stalk like a lasso **c** and sectioning the stalk **d**. (Photos by P. Poitras)

4.7.2 Malignant Neoplasm: Adenocarcinoma

Colorectal cancer is very common. It affects 5% of the population. Colon cancer unfortunately has a poor prognosis, with nearly 40% of those affected not living beyond 5 years (Table 4.7). It is the second most lethal cancer (after lung cancer); it kills annually more people than breast and prostate cancers taken together.

The prevalence of colorectal cancer increases with age (90% of those affected are over 50 years of age). Men are affected more often than women (RR 1.2), as are blacks more often than whites (RR 1.2) or patients with acromegaly or diabetes. Colorectal cancer is associated with epidemiological factors such as obesity, smoking, and consumption of alcohol and of red or barbecued meat, while physical activity, high-fiber diet, and calcium supplements appear as protective factors against this cancer.

The majority (80–85%) of colon cancers are sporadic. A familial predisposition is suspected (given a seemingly high familial prevalence) in 10–15% of cases but most often without specific gene identification. A familial genetic incidence is well established in 5% of patients (below). The most popular theory proposes that adenocarcinoma of the colon develops from an adenoma.

Table 4.7 Diagnosed cancers (Statistics Canada 2017)

Cancer	%cancers (rank)	Survival 5 years
Lung	13.9% (1)	17% patients
Colon/rectum	13.0% (2)	64%
Breast	12.8% (3)	87%
Prostate	10.3% (4)	95%
Pancreas	2.7% (12)	8%
Stomach	1.7% (14)	25%
Liver	1.4% (18)	19%
Esophagus	1.1% (19)	14%

(a) Risk Factors for Colonic Neoplasia

1. ***Familial genetic syndromes.*** Polyposis syndromes are defined as genetic conditions that lead to the development of a large number of polyps (often more than 100 polyps). Polyposis may be made of adenomatous, hamartomatous, or hyperplastic polyps.

Adenomatous Polyposis

- Familial adenomatous polyposis (FAP) occurs in both men and women, in about 1/5000 individuals. These subjects have more than 100 colonic adenomas that develop even in childhood. The neoplastic transformation process in FAP polyp is not different than in sporadic polyp, but the high number of polyps and their early onset make the development of cancer almost inevitable by the age of 40. This condition is linked to an autosomal dominant transmission of a mutation in APC gene (adenomatosis polyposis colon) located on chromosome 5. FAP may include extracolonic manifestations such as osteomas, desmoid tumors (Gardner syndrome), or intracranial tumors (Turcot syndrome). Extracolonic polyps, mainly in the small bowel (especially in the duodenal region), are known to develop into adenocarcinoma (often at an older age). Attenuated FAP is a more benign form, with affected individuals having a smaller number of polyps (often <100) and a later evolution (around the age of 55) to colonic neoplasia. Screening in childhood of FAP candidates and prophylactic colectomy (at diagnosis) are suggested.
- Hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome, is the most common of the familial genetic abnormalities of colon cancer. As the name suggests, it is not a polyposis syndrome per se (since there are no multiple polyps). MLH-1, MSH-2, MSH-6, and PMS-2 genes normally involved in the repair process of gene abnormalities are most often the cause of HNPCC. In short, a disorder of these repair genes will not allow the correction or the normally planned repair of gene abnormalities that may occur spontaneously in life or may be induced by various factors (environmental or other), and the transformation of a colonic polyp into cancer is thus accelerated (without increasing the occurrence of polyps). The pathophysiology of HNPCC is therefore different from that of FAP, where the risk of neoplastic transformation is increased due to the low age of appearance of the polyps (evolution from 30 to 40 years of age!) and their large number (out of more than 100 polyps, it is plausible to think that some will evolve unfavorably).

Lynch syndrome is strongly suspected when a family meets the Amsterdam criteria: *one* cancer before age 50 (colorectal, endometrial, small bowel, or ureter), *two* successively affected generations, and *three* people with cancer who are first-degree relatives.

In histopathology, the presence of "microsatellite instability" in resected tumors is suggestive of HNPCC and is often the starting point of a familial genetic investigation to identify individuals with genetic abnormalities (mutations in MLH-1, MSH-2 genes, etc.) and at risk of cancer. Neoplastic damage may be exclusive to the colon (Lynch type 1) or affect other organs including the small intestine, uterus, and urinary tract (Lynch type 2).

Suspicion of HNPCC syndrome or its confirmation by gene screening requires a strategy of close colonoscopic screening every 2–3 years given the rapid progression of neoplasia in these indications, as well as monitoring of the endometrium and urinary tract. Prophylactic therapies by colectomy or preventive hysterectomy are justified but are difficult to plan because of the non-absolute and unpredictable nature of neoplastic development in these individuals with HNPCC.

Hamartomatous Polyposis

- Peutz-Jeghers syndrome is characterized by hamartomatous polyps located mainly in the small intestine and by brownish stains on the oral mucosa. Mutations in STK11/LKB1 gene on chromosome 19 are identified in several families. Small intestinal polyps are mainly responsible for intestinal blockage, either because of their size or because of the intussusception they may cause. An increased risk of neoplasia is found in these individuals (90% patients have cancer at 40–50 years of age); colon cancer seems independent of hamartomas, and neoplasia can also occur in the stomach, pancreas (40% pts), breast (50%), or ovary (10–20%).
- Juvenile familial polyposis is a rare syndrome of hamartomatous polyps found mostly in the colon. Despite their hamartomatous nature, an increased incidence of neoplasia is recognized.
- Cowden syndrome is characterized primarily by multiple hamartomas on various parts of the body including the colon as well as pathognomonic skin lesions (benign tumors of the hair follicle, mouth papules). Most cases are caused by mutations in the ► PTEN gene (tumor suppressor gene) of chromosome 10 and are inherited in an autosomal dominant manner. People who have Cowden syndrome are at an increased risk of developing cancer of the breast (85% patients), ► thyroid, uterus, as well as colon cancer.
- Cronkhite-Canada syndrome is characterized by hamartomatous polyps of the GI tract (colon, small bowel, stomach), diarrhea with malabsorption, and cutaneous signs (dystrophic nails, alopecia, darkening skin). Its cause is unknown and it is not a familial disease.

Hyperplastic Polyposis

- Hyperplastic polyposis is a newly described familial polypoid syndrome characterized by multiple (>5 polyps) large (>1 cm) serrated polyps located in the proximal colon.

2. ***Inflammatory bowel diseases***, such as ulcerative colitis and Crohn's disease, are risk factors for the development of colonic neoplasia. The risk is increased according to (1) the extent of the colitis (pancolitis is significantly more at risk than left colitis), (2) the duration of the colitis (the risk increases by about 1%/year after 8 years of evolution, (3) the presence of uncontrolled inflammation (hence the protective role of 5-ASA, etc.), and (4) the association with liver disease (such as primary sclerosing cholangitis). Colon cancers under these conditions are often aggressive in their evolution and can be at multiple sites. They can be predicted by the presence of dysplastic changes in the colonic mucosa (hence the screening strategy of chromoendoscopy and multiple colonic biopsies for dysplasia).
3. ***A positive family history*** is an important risk factor for colonic neoplasia. The majority of colonic cancers are sporadic, while a positive family history is found in 20% of individuals. The minority (5%) is associated with well-identified gene conditions (familial polyposis, HNPCC as discussed above); in the remaining subjects (about 15%), the gene factors involved are not yet known. The risk of developing colorectal cancer is doubled in the presence of colorectal cancer in a first-degree relative.
4. ***Polyps.*** It has long been known that the risk of neoplastic transformation of an adenomatous polyp increases with the size of the polyp (if less than 1 cm = risk less than 1%; if more than 2 cm = risk >10%) and the histological type (villous polyp = 10–40% cancer, tubulous polyp = 3–5%). The most accepted theory at present is that adenocarcinoma is derived from an adenoma. If it is estimated that colon cancer affects 1/20 people and that polyps are present in 5–10/20 people, it can be deduced that 10–20% of the adenomatous polyps would develop into malignant neoplasia over time.

(b) Pathophysiology of the Development of an Adenocarcinoma

Tumor evolution from adenoma to carcinoma is thought to be due to progressive accumulation over time of mutations affecting several genes that regulate normal cell growth (either by limiting their growth or by promoting it) in body organs (Fig. 4.22). Mutations can be inherited (germline) or acquired (somatic).

- APC (adenomatosis polyposis colon) gene normally involved in cell migration and adhesion is mutated in 60–80% of sporadic cancers in the early stages of carcinogenesis. Germline mutations are key factors in FAP.
- P53 gene on chromosome 17, normally an apoptosis inducer and cell growth limiter, is mutated in advanced cancers.
- Mutations in DNA repair genes are known. About ten repair genes (such as MLH-1, MSH-2, etc.) are normally involved in nucleic acid transcriptional repair during DNA replication. If uncorrected, such errors in the sequence of these cell growth regulatory genes (such as TGF-B) can promote tumor growth. Germline mutations of MLH-1, MSH-2, MSH-6, or PMS-2 are detected in a large number of patients with HNPCC. Short portions of DNA, called microsatellites, are particularly susceptible to these replication errors leading to the loss or gain of various nucleic acids; these "microsatellite" areas can be identified as abnormal (or unstable) by various immunochemical methods used clinically to detect the existence of an abnormality in the DNA repair process.
- MYH is one of the excision repair genes for oxidative damage to DNA. Germline abnormalities of MYH (inducing genomic instability affecting APC or KRas genes) are identified in some cases of polyposis.

Schematically, from colonic mucosa an adenoma is initially formed (probably linked to mutations in the APC gene) and then progress to an adenocarcinoma when several genes regulating cell growth are victims of mutations stimulating their pro-carcinogenic role or preventing their anticarcinogenic action. Multiple genetic abnormalities (e.g., MSH, KRas, P53, etc.) are required for the explosion of malignant cells. Somatic abnormalities may accumulate progressively (and probably in a variable order) over the years (under the impulse of triggers yet to be identified such as "toxic" food, environmental, etc.). Germline abnormalities in these same genes enhance the risk of a neoplastic transformation.

The sequence adenoma → adenocarcinoma is probably true in the vast majority of colonic neoplasia encountered in the Western world. As this process of deterioration and acquisition of pro-cancerous abnormalities evolves over several years, strategies for screening and treatment of polyps are feasible to reduce colorectal cancer deaths.

Non-adenomatous serrated polyps can also lead to colon cancer. Different cellular mechanisms (including a mutation in the BRAF gene) are involved in the malignant transformation of serrated polyps into adenocarcinoma. Rarer and more difficult to detect (since small, flat, and weakly protruding on the mucosa) than adenomatous polyp, serrated polyp probably explains some of the rare colonic adenocarcinomas that appear to be not linked to an adenomatous polyp.

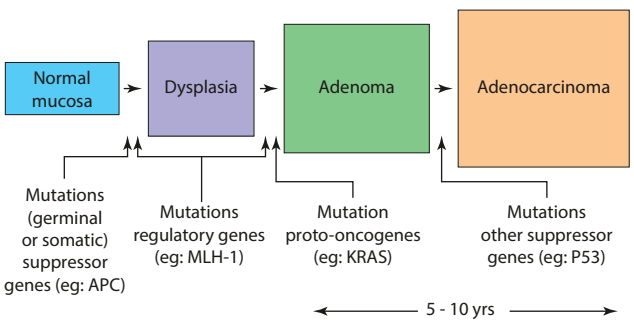


Fig. 4.22 Inherited and acquired germinal and somatic abnormalities involved in the genesis of adenomatous polyps and colon cancer according to the Vogelstein model

(c) Clinical Presentation of Colorectal Cancer

While traditionally common in the distal colon, colon cancer is now recognized to also affect the proximal colon. Cancers of the distal colon can manifest themselves by rectal bleeding, stools of reduced caliber, abdominal pain (of an obstruction type), constipation, or diarrhea (reflex to an obstacle). Cancer of the proximal colon is mainly manifested by iron deficiency anemia caused by occult blood loss (Table 4.8).

Physical examination may reveal an abdominal mass or metastatic hepatomegaly in advanced cases.

Table 4.8 Colorectal cancer: clinical presentation

Proximal colon	Distal colon canceref
Anemia/occult bleeding	Rectal bleeding
Abdominal mass	Change stools caliber
	Change stools frequency constipation/ diarrhea
	Abdominal pain
	Intestinal obstruction
	Abdominal mass

A digital rectal exam is essential to diagnose cancers of the lower rectum.

(d) Classification of Colon Cancer

As for many neoplasms, colorectal cancers are classified according to their degree of invasion to lymph nodes or distant organs. Such classification is essential for the management of the patient and the selection of the therapeutic options. It can often be complete only after surgery and pathological analysis of the removed specimen.

TNM classification (Table 4.9) is now widely used and has replaced the classic Dukes classification. Neoplastic cells are thus derived from the mucosa (T0 in situ according to the TNM classification) and may invade the submucosa (T1), the muscularis (T2), the subserosa (T3), and the serosa (T4a) or, by crossing the wall, reach nearby organs (T4b). Lymphatic invasion results in metastatic nodes in the mesentery (N1 or N2, i.e., < or >3 affected nodes). Venous invasion leads to metastases (M1), mainly hepatic, or pulmonary (mainly in the case of rectal neoplasia).

(e) Diagnosis of Colorectal Cancer

The diagnosis of colonic adenocarcinoma is made by different imaging techniques. The most sensitive method is colonoscopy (Fig. 4.23), which also allows tumor biopsies for histological confirmation of neoplastic disease. Radiological imaging includes barium enema, axial tomography, or virtual colonoscopy (CT scan with 3D reconstruction of the images).

(f) Treatment of Colorectal Cancer

The treatment will be carried out according to the stages of neoplastic invasion (Fig. 4.24).

Surgery: Invasive cancer requires segmental surgical resection including lymphatic drainage territories. Superficial cancer can be adequately treated by endoscopic polypectomy.

Chemotherapy has clear advantages against stage III cancer, i.e., with lymph node involvement. The benefit of chemotherapy is questionable in stage II and is not required in stage I. In stage IV, it can offer palliation.

Chemotherapy typically uses 5FU (thymidylate synthase inhibitor blocking DNA synthesis) in combina-

Table 4.9 Staging and prognosis at 5 years in colorectal neoplasia

TNM classification					*Dukes classification*
Stage	**Tumor**	**Nodes**	**Metastasis**	**Survival 5 years**	
0	Tis (in situ): mucosa	N0 (0)	M0(absent)		
I	T1: submucosa	N0	M0	97%	*A*
I	T2: muscularis	N0	M0	90	
IIa	T3: subserosa	N0	M0	*85*	*B*
IIb	T4: serosa-proximal organs	N0	M0	70	
IIIa	T1–2	N1(1–3)	M0	80	*C*
IIIb	T3–4	N1(1–3)	M0	60	
IIIc	T1–4	N2(>4)	M0	40	
IV	T1–4	N2	M1(present)	10–30	*D*

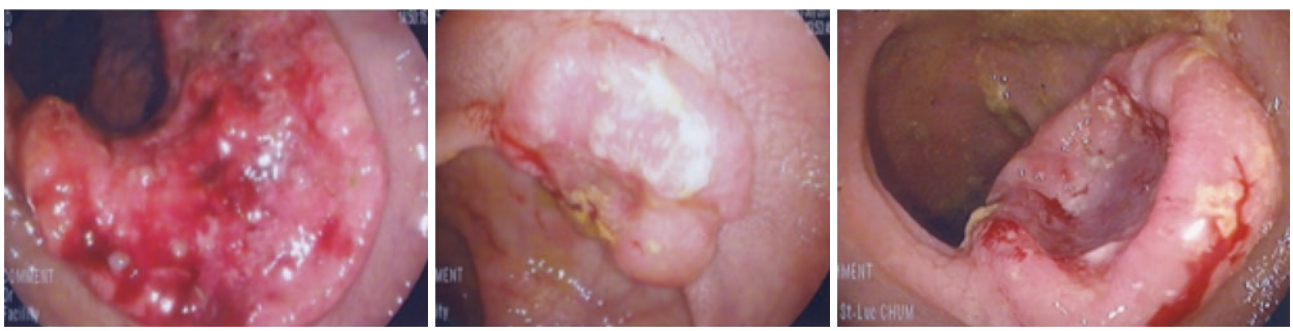


Fig. 4.23 Colon cancer seen on colonoscopy: ulcerated sessile masses. (Photos by P. Poitras)

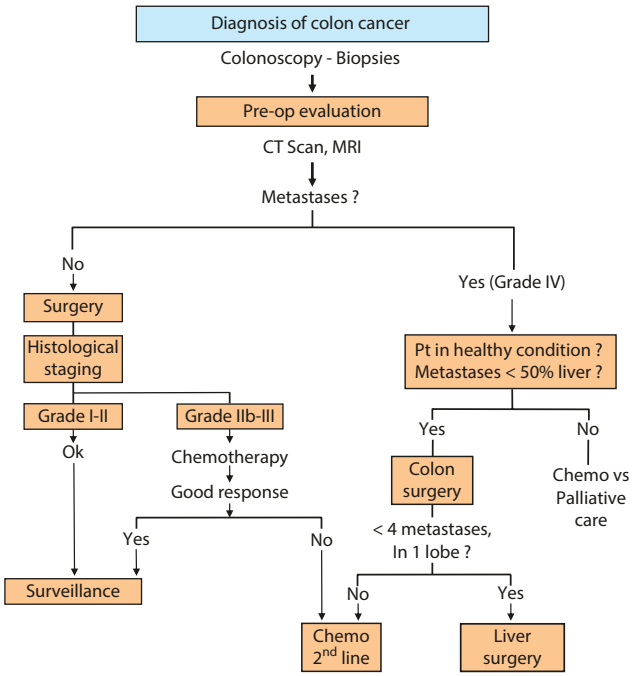


Fig. 4.24 Colon cancer management, based on the cancer staging (TNM stages I–IV) and health status (good condition) of the patient

tion with leucovorin (modulator of 5FU activity). 5FU requires intravenous administration and can be replaced by capecitabine (precursor of 5FU and taken orally). Second-line (and even third or fourth lines) chemotherapy is now common. Agents such as oxaliplatin (apoptosis inducer) or irinotecan (topoisomerase 1 inhibitor) are frequently used (called the FOLFOX or FOLFIRI regimen, respectively). Monoclonal antibodies against VEGF (vascular endothelial growth factor) such as bevacizumab or against EGF (epidermal growth factor) receptors such as cetuximab or panitumumab are also part of the oncological therapeutic arsenal.

Radiotherapy: Preoperative radiotherapy is almost always used in rectal cancer.

Liver metastases: At the time of diagnosis, 18% of patients already have liver metastases and therefore unfortunately have a limited survival of 5–10 months. However, modern chemotherapy allows median survival of about 2 years. Solitary or unilobar liver metastases can be brought to surgical resection with a 5-year survival up to 25–50%.

Neoplastic recurrence after initial treatment is detected in the liver (33% of cases), lungs (20%), or locally at the resection site (20%).

Post-diagnosis follow-up. A colonoscopy is undertaken 1 year post-colon cancer resection and then every 3–5 years. If stage II or higher, CT scans of the abdomen, pelvis, and thorax are obtained every 6–12 months, as well as CEA (carcinoembryogenic antigen) determination for 5 years.

(g) Prevention of Colorectal Cancer

Sreening strategy for prevention of colorectal cancer by early detection is possible due to the development sequence from a polyp to an adenocarcinoma progressing over an extended period of 5–10 years. Colorectal cancer screening strategies have been shown effective in reducing colorectal cancer mortality.

Who to screen? The high incidence of colorectal cancer (5% of population) justifies a screening strategy for everyone.

When to screen? Given the increase in polyps and cancer with age, it is suggested that screening should generally begin at 45–50 years of age. If there is a family history of colonic neoplasia, screening should begin 5–10 years before the age of cancer onset in the family.

How to screen: Colonoscopy will surely be the tool of choice since it is the most effective in detecting colonic lesions and allows immediate treatment of polypoid precancerous lesions. During screening colonoscopies in asymptomatic individuals, polyps are detected in approximately 25–40% of the population. Considering a prevalence of colon adenocarcinoma of 5%, it can be estimated that 1/5 of polyps seen endoscopically would develop into cancer if not resected.

However, colonoscopy has the disadvantage of being an invasive examination, most often performed under sedation, carrying certain risks (colon perforation: 1/1–2000, post-polypectomy bleeding, 1/100; sedation complications, 1/300, etc.) and requiring technical expertise (of limited availability). Other strategies are therefore used, as described in Table 4.10.

At the other end of the spectrum, fecal occult blood test (FOBT) provides a mass screening tool that has been shown effective in many studies; the presence of blood in the stool then warrants further investigation by colonoscopy. This strategy aims to reduce the socioeconomic and medical impact of colonoscopy, as well as to facilitate prevention programs for people uncomfortable with colonoscopy. The classical FOBTs such as Guaiac or Hemoccult methods are of low sensitivity (detecting about 50% of colorectal cancers)/low specificity and should be abandoned. New immunochemical tests (FIT test/fecal immunochemical test using antihuman hemoglobin antibodies) provide better results [detecting >90% of cancer lesions and 50–60% of advanced adenomas (precursors of cancer); 5% of the screening tests are positive (6–8% of them reveal cancer, 35% show significant polyp]. Other diagnostic tools, based among others on the recognition DNA abnormalities, seem promising and could be available in a near future. However, the

Table 4.10 Colorectal cancer prevention: screening methods

Test	Sensitivity	Risks	Disadvantages	If neg.	If positive
Colonoscopy	95–100%	Perforation (1/1000)	Laxative preparation, Sedation (accompanying person)	10 years	Rx made (polypectomy)
Virtual colonoscopy	Polyp 1 cm: 90% >0.6 cm: 80%	X-rays (scan)	Laxative preparation	5 years	Colonoscopy for Dx and Rx
Barium enema	Cancer: 80% Polyp >1 cm: 50%	X-rays	Laxative preparation	5 years	Colonoscopy
Fecal blood (FIT)	Cancer: 90% Advanced adenoma: 50%	0	Stool manipulation	2 years	Colonoscopy
Endoscopic capsule	Polyp >0.6 cm: 80%.	0	Laxative preparation	?	Colonoscopy

Legend: *Dx* diagnosis, *Rx* treatment, *if neg.* if negative: time before next exam

success of these methods of prevention by identifying cancer markers in the stool will still depend on the willingness of subjects to repeat the tests at frequent intervals (a test every 1–2 years is required).

In specific cases, prevention strategies can be adjusted:

- Subjects with familial polyposis (FAP) are subjected to prophylactic colectomy, even at a young age, given the inevitable development of colonic neoplasia before the age of 40 in these individuals. In the presence of a family history of polyposis, screening begins as early as possible at 10–12 years of age.
- Subjects with HNPCC syndrome may undergo colonoscopies every 2 years or even a prophylactic colectomy. Screening usually begins at ≈ 20 years of age.
- Subjects with inflammatory bowel diseases affecting the entire colon and with more than 8 years of evolution are submitted to colonoscopy every 1–5 years with multiple biopsy samples to look for premonitory dysplasia with neoplastic transformation.

Prophylaxis of colorectal cancer:

- Lifestyle: considering the epidemiological associations of colorectal cancer, general measures aimed at normal weight, healthy diet (rich in fiber and vegetables, restricted in deli meats and barbecued meats), physical exercise, and nonsmoking are recommended.
- Chemoprophylaxis with NSAIDs (sulindac) or COX-2 inhibitors (celecoxib) is effective in reducing the development of polyps in individuals at risk such as polyposis. ASA and calcium supplements have been associated with a reduced polyp transformation. However, the benefit of generalized and systematic chemoprophylaxis in colon cancer remains to be demonstrated.

4.7.3 Other Colon Tumors

Apart from polyps and adenocarcinomas, which constitute the vast majority of colon tumors, other tumors, benign or malignant, can be found sometimes in the colon, including lipomas, stromal tumors (GIST), endocrine tumors (NET), lymphomas, etc.

4.7.4 Tropical Specificity

Ameboma is an inflammatory tumor of parasite origin (*Entamoeba histolytica* inflammatory pseudotumor). Clinically, endoscopically or radiologically, it mimics colorectal cancer and is located in the cecum or sigmoid. The diagnosis is made by histology. The tumor melts under amebicide treatment.

4.8 Function Disorders

4.8.1 Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is a term often used by both the public and the medical profession to refer to a variety of functional GI disorders (FGID) in general, for example, a patient suffering from gastric disorders

and functional dyspepsia may be labeled as IBS! Personally, we prefer that FGIDs be clearly identified as proposed by Rome Classification (Table 4.11).

In the medical world in general, the word «functional» is often associated with a "pejorative" meaning, suggesting symptoms not due to organ damage, but rather attributed to psychogenic conditions such as anxiety, somatization, or even purely imaginary. The Rome group of international experts prefers to see functional digestive disorders as digestive symptoms unexplained by lesions (inflammatory or others, that would then be detectable by endoscopic, radiological, histological examinations well available to the medical team) and attributable to disorders in the function of digestive organs (often difficult to show on «standard» medical tests). The misunderstanding comes from the fact that the traditional medical diagnostic approach is quite appropriate to identify lesions by tests such as endoscopy, radiology, histology, etc. but less so to study functions such as motility, sensitivity, etc. In this textbook of gastroenterology, we have used the term "functional" to refer to the function of organs as suggested by the Rome group.

(a) Definition of IBS IBS is characterized by abdominal pain associated with abnormal bowel movements, in the absence of a lesion on diagnostics tests. IBS is the most common and most typical disease of FGIDs.

IBS can be defined as a chronic condition, consisting of symptoms of abdominal pain or discomfort associated with abnormal bowel movements in the form of diarrhea (IBS-D), or constipation (IBS-C), or mixed bowel movements (IBS-M, alternating with days of constipation followed by days of diarrhea; this pattern is near pathognomonic for IBS). It is often associated with gastrointestinal, somatic, or psychological comorbidity. Positive and systematic identification of IBS can be facilitated by diagnostic criteria proposed by Rome IV in 2016 or by Manning in 1978 (Table 4.12).

Table 4.11 Functional GI disorders: Rome Classification IV (2016)

A. Esophageal disorders 1. Functional chest pain 2. Functional heartburn 3. Hypersensitivity to reflux 4. Globus 5. Functional dysphagia	**B. Gastroduodenal disorders** 1. Functional dyspepsia Postprandial distress syndrome (PDS) Epigastric pain syndrome (EPS) 2. Belching disorders Excessive supra-gastric belching Excessive gastric belching 3. Nausea/vomiting disorders Chronic N-V syndrome Cyclic vomiting syndrome Cannabinoid hyperemesis 4. Rumination syndrome	**C. Bowel disorders** 1. Irritable bowel syndrome With constipation With diarrhea With mixed bowel habits Unclassified 2. Functional constipation 3. Functional diarrhea 4. Functional bloating/distension 5. Nonspecific disorder 6. Opioid-induced constipation
D. Centrally mediated GI pain disorders 1. Centrally mediated abdominal pain 2. Narcotic bowel syndrome/opiate hyperalgesia	**E. Gallbladder and Oddi disorders** 1. Biliary pain Functional gallbladder disorder Functional biliary Oddi dysfunction 2. Functional pancreatic Oddi disorder	**F. Anorectal disorders** 1. Functional incontinence 2. Functional anorectal pain Levator ani syndrome Unspecified anorectal pain Proctalgia fugax 3. Defecation disorders Inadequate defecatory propulsion Dyssynergic defecation

Table 4.12 IBS diagnostic criteria

Rome IV criteria	Manning's criteria
Abdominal pain that has progressed for >6 months, recurs at least 1 day/week in the last 3 months, and is associated with two or more of the following: – Related to defecation – Associated with a change in frequency of stool – Associated with change in form (appearance) of stool	Abdominal pain plus 2 of the following: – Pain decreasing after defecation – Pain accompanied by soft stools – Pain accompanied by frequent stools – Abdominal bloating/distension – Feeling of incomplete evacuation – Mucus in the stools

IBS is found in all countries of the world with a prevalence of about 15% of population. In Western world, it mainly affects women (1 man/3 women).

(b) Causes and Pathophysiology of IBS

Genetic factors: A family history of FGID is often present in patients with IBS. Two studies in twins from Australia and the USA found that the diagnosis of IBS was significantly more common in monozygotic than in dizygotic twins (33% vs. 13% and 17% vs. 8%), confirming the genetic hypothesis. However, the US study also found that the existence of IBS in the mother of the twins, whether dizygotic or monozygotic, was an even more important factor for the presence of IBS in the child, thus giving way to not only a genetic but also an "environmental" influence in the onset of the disease.

Childhood trauma is reported in a large number of subjects with IBS. Studies in the USA, France or Australia reported a prevalence of 30–50% childhood sexual abuse in IBS patients. The precise link between these events and IBS has yet to be established, but experimental animal studies confirm that stress in early childhood can have a significant impact on the functioning of the digestive tract in adulthood.

Inflammation is frequently cited as a causal factor for IBS. An increased contingent of inflammatory cells in the GI tract of IBS patients has been detected by some authors (but could not be confirmed by others). Postinfection IBS is a recognized entity; there is a history of enteric infection that appears to initiate the onset of IBS disease in 5–15% of IBS patients, and prospective studies have shown that 5–20% of patients with bacterial gastroenteritis may develop IBS. The inflammatory hypothesis is also supported by the existence of intestinal bacterial overgrowth in some patients, or by the beneficial effect of antibiotic therapy (rifaximin) reported in some publications, or by the suspected efficacy of probiotics in many studies.

Motor theory: IBS intestinal transit perturbations obviously suggest an alteration in digestive motility. Pain, often cramp-like, could be due to high amplitude

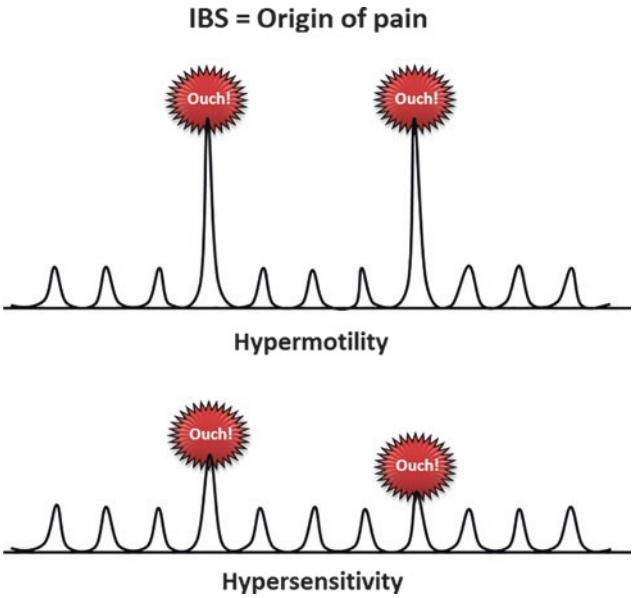


Fig. 4.25 Origin of abdominal pain in IBS. Top, motor theory – high amplitude contractions generate abdominal pain. Bottom, sensitivity theory – lower amplitude contractions can generate pain in a hypersensitive patient

intestinal contractions. So-called antispasmodic drugs (anticholinergics, anticalcics, etc.) are used clinically to reduce intestinal contractions and abdominal pain. However, motor abnormalities of the colon or small intestine have been detected in only 10–20% of IBS patients, and the motor dysfunction theory seems to explain IBS in only a minority of patients.

Hypersensitivity theory: If abdominal pain cannot be explained by contractions of exaggerated amplitude, hypersensitivity could explain why contractions of slightly increased (or even normal) amplitude may cause pain in hypersensitive patients (Fig. 4.25).

Studies of colonic sensitivity (usually done by rectum distension of with an inflatable balloon) revealed that IBS patients (1) were hypersensitive to distension (as compared to normal subjects), (2) were sensitized by repeated distensions (in opposition to normal subjects

who become more tolerant), and (3) had aberrant pain irradiation (i.e., exceeding the pain irradiation usually experienced in normal subjects). Hypersensitivity is detectable in 50–90% of patients according to various authors. In some patients, hypersensitivity is organ-specific (colon in IBS, stomach in dyspepsia), while in others it is diffused throughout the GI tract; in many cases, it can affect not only visceral but also somatic sensitivity. Brain imaging studies using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) have shown that intestinal distension evoked an exaggerated pain signal in the brain of IBS patients. As shown in Fig. 4.26, this exaggerated pain signal could originate from (a) a hypersensitive bowel sending an increased neurological signal to the brain, (b) a normal bowel having its sensory signal amplified as it passes through the spinal cord, (c) a normal peripheral signal amplified centrally, or (d) a normal ascending sensory signal not compensated for by normal descending inhibition mechanisms (Fig. 4.26).

Given the hypersensitivity, mild discomfort may become disabling pain (hyperalgesia), just as a normally imperceptible phenomenon may become source of discomfort or pain (allodynia). Hypersensitivity acts as a sensory amplifier.

Hypersensitivity may account for the fact that food and stress, both normal stimulants of the digestive tract, are triggers of pain or motor symptoms in IBS patients. Hypersensitivity will lead any dietary or psychological

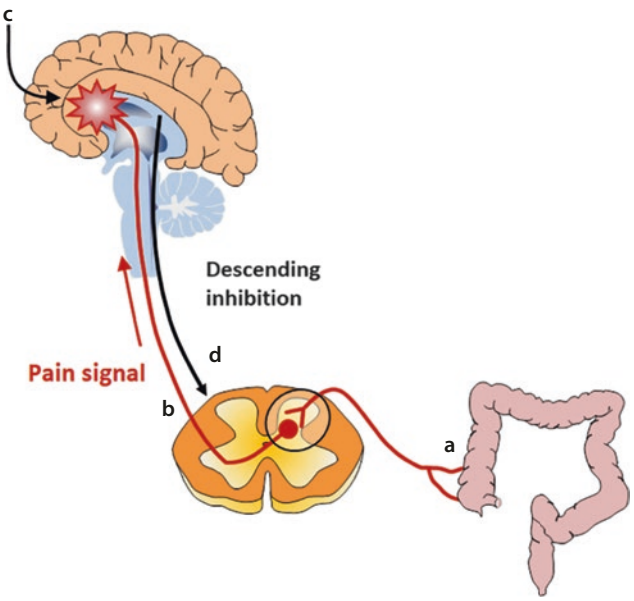


Fig. 4.26 Pain perception: intestinal stimulation is perceived at the central level. Exaggerated perception in IBS may result from an intestinal signal (a) increased from an abnormal intestine, or (b) amplified as it travels through the spinal cord, or (c) amplified as it reaches the brain, or (d) not compensated for by descending inhibition

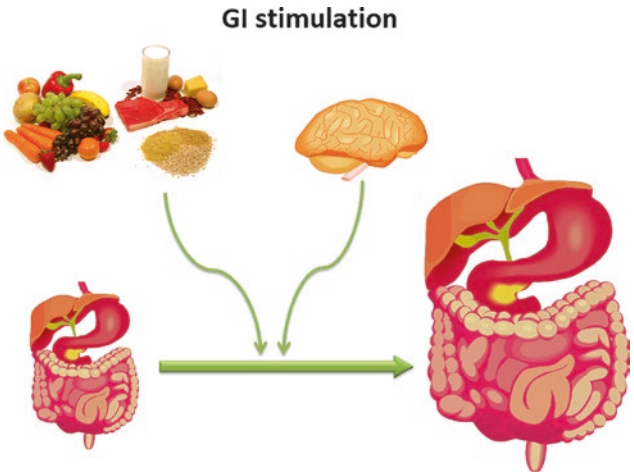


Fig. 4.27 Diet and stress are two normal stimuli of digestive motor function. The so-generated signal is over-perceived in IBS

stimuli to exaggerate the perceived digestive response in these patients (Fig. 4.27).

(c) Diagnosis of IBS

The diagnosis of IBS is not a diagnosis of exclusion, i.e., it is not made exclusively after elimination of lesions. The diagnosis of IBS is based on a positive approach and is based on three points (Table 4.13): (1) a history of symptoms according to type and duration, (2) a normal physical examination, and (3), if necessary, biological examinations without lesions.

1. ***Clinical Symptoms.*** The main dominant symptom as well as accompanying symptoms must be collected and analyzed in a differential diagnosis approach.

Table 4.13 IBS = positive diagnosis

1. **Clinical Symptoms**
   - Main symptom = pain + abnormal stools (Rome/Manning)
   - Accompanying symptoms
     - Digestive comorbidity (functional dyspepsia, proctalgia fugax, etc.)
     - Somatic comorbidity (migraine, fibromyalgia, interstitial cystitis, etc.)
     - Psychogenic comorbidity (anxiety, depression, sleep disorder, etc.)
   - Differential diagnosis
     - Diarrhea
     - Constipation
     - Pain
2. **Clinical examination:** normal
3. **Biological (exclusion) tests:** normal
   - If necessary
   - Taking into account the differential diagnosis

- *Main Symptom.* The goal of the clinical approach is to establish a positive diagnosis based on the main symptom as identified by Rome or Manning criteria [which can be summarized as chronic abdominal pain or discomfort, with abnormal stools in the form of either diarrhea, constipation (or both), and often accompanied by abdominal bloating, mucus in the stool or a feeling of incomplete evacuation].
- *Accompanying symptoms* involving digestive organs other than the colon, non-digestive organs, or psychological health are common in IBS patients.
  - Digestive comorbidity is often present. In addition to the main symptom suggestive of colonic disease, IBS patients frequently complain of other functional digestive symptoms affecting, for example, the stomach (ulcer-like functional dyspepsia or motor dyspepsia), the esophagus (functional dysphagia, globus, etc.), the anorectal region (proctalgia fugax, etc.), etc. These extracolonic digestive symptoms may be present concomitantly with the IBS symptoms, or may have existed in the past, or may appear in the future.
  - Somatic comorbidities (or extra-GI manifestations) are very frequently encountered in patients with IBS (as with other FGIDs): low back pain, headache, fatigue, cardiovascular abnormalities (palpitations, dizziness, etc.), musculoskeletal pain (fibromyalgia), urinary disorders (irritable bladder, interstitial cystitis), reactive hypoglycemia, etc. It is estimated, for example, that 1/3 to 1/2 of patients with IBS have fibromyalgia, just as 1/3 to 1/2 of fibromyalgia patients have IBS.
  - Psychological comorbidities are identified in many patients (anxiety, depression or depressive features, unstable mood, sleep disturbances, etc.).
- *Differential diagnosis* of functional GI symptoms includes lesional abnormalities. Thus, depending on the main symptom (pain with diarrhea or constipation), the differential diagnosis will include different causes of diarrhea (e.g., inflammatory bowel disease, celiac disease, enteric infections, etc.) or of constipation (obstruction by stenotic lesion, motor dysregulation, etc.). Moreover, GI symptoms may be present in psychogenic disorders (such as depression, panic disorders, somatization disorders, etc.), and these conditions must be considered in the differential diagnosis (Fig. 4.28).

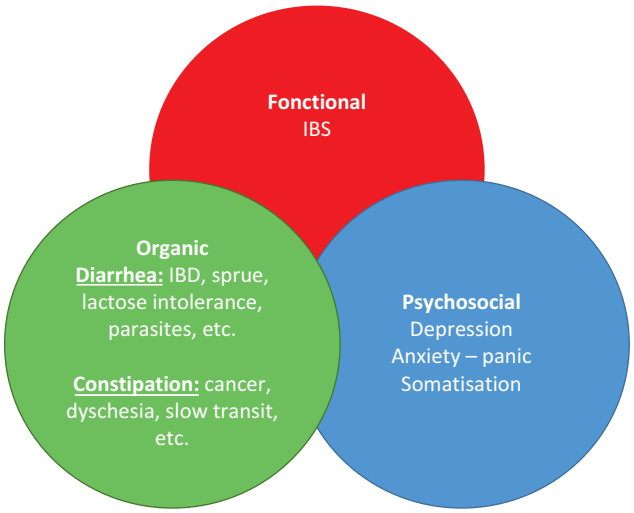


Fig. 4.28 The differential diagnosis of gastrointestinal symptoms includes functional disorders, lesional abnormalities, and psychosocial disorders

2. ***Physical examination.*** A complete physical examination is essential. It is always normal.

3. ***Biological examinations.*** There is no biological test that affirms the diagnosis of IBS (or other FGIDs). Laboratory tests or examinations are used to rule out other digestive pathologies that may be suspected. The differential diagnostic approach (above) is essential to guide the nature of the biological investigation. For example, in the case of diarrhea, an inflammatory bowel disease, gluten enteropathy, intestinal parasitosis, etc. may be considered, just as in the case of constipation, an obstructive lesion of the colon may be considered.

Biological examinations are not always required. Often, the symptoms and the subsequent physical examination will allow to establish the diagnosis. Extensive investigation with blood tests, stool cultures, X-rays, endoscopy, etc. may be warranted in patients with atypical symptoms history and/or physical examination, or with warning signs (red flags) (Fig. 4.29).

(d) Treatment of IBS

The management of IBS is based on a positive diagnosis (following careful questionnaire and physical examination), and a therapeutic trial (Fig. 4.30) is recommended. It has been well established that this approach has a low risk of error and allows a safe and effective management of IBS. Some patients, especially those seen in tertiary settings, will undergo extensive exclusion testing before a diagnosis of IBS is made. The art and science of the physician are often used here to determine how far the investigation should go.

IBS: ALARM SIGNS

HISTORY	EXAM
- Weight loss	- Anemia
- Rectal bleeding	- Abdominal mass
- Nocturnal symptoms	- Signsof intestinal obstruction
- Fever	- Signs of malabsorption
- > 50 yrs	
- Recent onset	
- Family history of cancer, IBD, etc.	

Fig. 4.29 The following symptoms and signs are not typical of IBS and should be considered along with other diagnoses such as neoplasia, inflammation, etc.

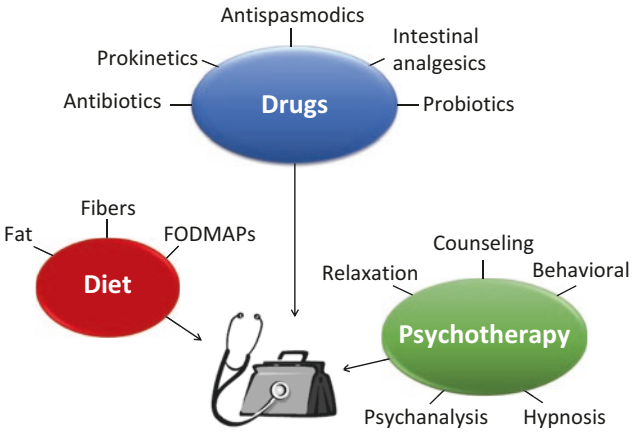


Fig. 4.31 For the treatment of IBS, the physician may use a variety of treatment options

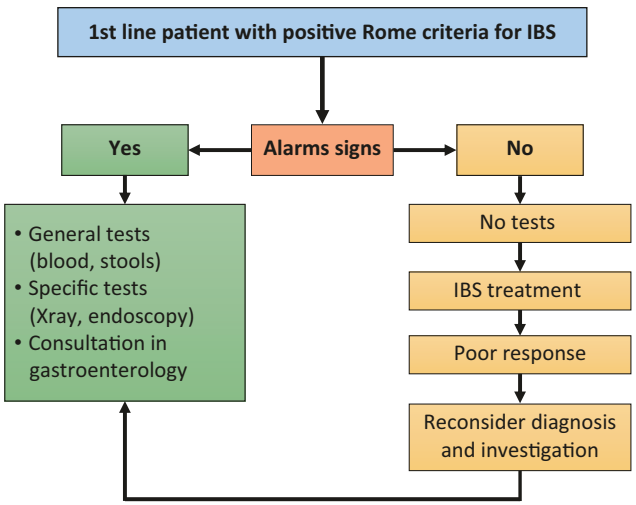


Fig. 4.30 Management of an IBS patient as proposed by N.J. Talley. (Gastroenterological Disorders, 2003)

The treatment of IBS uses a comprehensive approach that includes (1) reassurance and patient education, (2) dietary counseling, (3) pharmacotherapy, and (4) psychotherapy (Fig. 4.31).

1. ***Reassurance and patient information.*** Several studies have shown that the accumulation of negative tests did not have the expected beneficial effect on IBS patients. The "you have nothing because your tests are normal" approach (classical medical strategy used for decades) may sometimes be useful but appears unsatisfactory in most patients. Information to patients is now easier to provide given our knowledge of the motor, sensory, or inflammatory dysfunctions involved in these patients. Popular education material, patients group, etc. are useful tools.
2. ***Nutritional counseling.*** IBS patients often try to relate their digestive symptoms to their food profile. Many may benefit from a consultation with a nutrition professional. Dietary advice is based on findings obtained more through observation and experience than through scientific experimentation. The regimen excluding "FODMAP" [fermentable oligosaccharides, disaccharides (lactose), monosaccharides (fructose), and polyols (sorbitol, xylitol)] has recently been validated. Fiber may be useful in constipated patients, but beware of fiber-induced bloating. Fermentable foods should be ingested with caution in many patients, as should fatty foods (Table 4.14).

Table 4.14 IBS management: general dietary guidance

To consume (with moderation):
- Insoluble fibers
  - Bran
  - Whole-grain cereals
  - Seeds, nuts
- Soluble fibers
  - Pectin: fruits (apple, citrus fruits), vegetables (cabbage, corn)
  - Psyllium
  - Flax seeds

To avoid:
- Fermentable foods
  - Fibers
  - Legumes (chickpeas, lentils, beans)
  - Vegetables (cabbage, broccoli, onion)
  - Dried/candied fruits
- Fats
  - Fried food
  - Sauces (cream)

3. ***Pharmacotherapy.*** The general approach for the treatment of IBS is to identify the main dominant symptom (diarrhea, constipation, or pain) and to focus treatment measures toward this abnormality (■ Table 4.15, ► Chaps. 13 and 15). For example, in the diarrhea patient, medication will be prescribed to slow GI transit (loperamide, etc.), in the constipated patient laxatives or prokinetics will be used and in the predominantly painful patient treatment will include antispasmodic or intestinal "analgesics."

   Probiotics (live microorganisms that, when administered in adequate amounts, produce a host health benefit) are probably useful in the treatment of IBS according to various studies. However, the dose and type of probiotic to be used remain to be clarified. The therapeutic effect of altering the intestinal microbiota is also supported by the beneficial action of the antibiotic rifaximin on IBS symptoms.
4. ***Psychotherapy.*** The importance of stress or other psychogenic conditions in the genesis or manifestation of IBS should be considered. Stress is a normal stimulant of the human digestive system, and intestinal hypersensitivity explains why IBS patients cannot tolerate so-called normal stresses or feel exaggerated pain in face of stress. Several psychotherapy techniques have been satisfactory used in the management of these patients. Hypnosis and behavioral therapy techniques have been studied in particular, but benefits can also be observed with humanistic approaches such as interpersonal therapy, counseling, etc. Patient preference and therapist availability need to be considered. The psychotherapeutic approach has the advantage of offering a prolonged and lasting result compared to pharmacotherapeutic approaches that require chronic medication to avoid a recurrence of symptoms when therapy is stopped.

■ Table 4.15 IBS Pharmacotherapy: by main symptom

Diarrhea	Constipation	Pain
Opiates and derivatives Loperamide 1–8 co die Diphenoxylate 1–6 co die Codeine (po, sc) 15–30 mg qid Eluxadoline 75–100 mg bid *Cholestyramine* 4–8 g die *Tricyclics:* amitriptyline 10–30 mg hs *Antibiotics:* rifaximin *5HT-3 antagonists:* alosetron	*Bulk agents* Dietary fibers Bran Psyllium *"Lubricants"* Mineral oil Lansoyl Docusate *Osmotics* Lactulose PEG Mg^+ Sulfates *"Stimulants"* Bisacodyl Sennosides *Secretors Cl^-* Lubiprostone Linaclotide, plecanatide Misoprostol (?) *"Prokinetics"* 5-HT4 agonists: prucalopride Colchicine (?) *NHK antagonist* Tenapanor	*Antispasmodics* Anticholinergics: dicyclomine, hyoscine Anticalcics: pinaverium Mu opiates: trimebutine Peppermint oil *Tricyclics:* amitriptyline *SSRIs* Fluoxetine Paroxetine Citalopram Venlafaxine *Others* Pregabalin? Linaclotide?

(e) IBS: Summary

IBS is a chronic, nonlethal condition that does not progress to other gastrointestinal conditions (such as inflammatory or neoplastic diseases) but can seriously affect the quality of life of those who suffer from it.

IBS is a common condition (1/6 people!). It is therefore not surprising that IBS is found in patients also suffering from other digestive diseases such as celiac disease, lactose intolerance, IBD, etc. These diseases have symptoms that are often very similar to IBS and can be complex to identify and treat.

The name IBS refers to a heterogeneous group of patients. Past discoveries have taught us that some so-called IBS patients in fact were suffering from lactose intolerance, microscopic colitis, gluten enteropathy, etc. Current research tells us that the symptom pathophysiology is not the same in everyone (some have a condition that responds to antibiotics, others are hypersensitive, etc.). It is therefore illusory to think of a universal treatment. Management of IBS requires a strategy tailored to the individual patient.

Management of IBS requires a combination of science and skill from the physician. How far should the patient be investigated? Which treatment approach should be chosen? These are questions that should be adapted to each patient.

4.8.2 Colon Transit Disorders

Colonic transit usually lasts 1–3 days. *Rapid colon transit* reduces contact time of the chyme with the colonocytes, thus compromising absorption and promoting diarrhea by increasing fecal volume and the number of defecations. A *slow colon transit*, on the contrary, promotes hyperabsorption of colonic fluid generating constipation with a reduction in fecal volume and in defecation frequency.

Fecal transit can be assessed by different methods. The most accurate method uses nuclear medicine scintigraphy to detect progression of ingested isotope ligands marking the fecal chyme; it is used almost exclusively in research. The easiest clinical method is to follow the progression of radiopaque markers on daily X-ray images of the abdomen (1–3 days are normally sufficient to clear the markers). Since colon transit is usually the major component of total digestive transit (esophagus, 5–6 seconds; stomach, 1–4 hours; small bowel, 2–6 hours; colon, 1–3 days), colonic transit can also be assessed by measuring the evacuation time of an orally ingested "colored" marker (e.g., carmine red or activated charcoal), or a telemetric capsule (Smart Pill®). In practice, however, colon transit is only measured in very selected cases.

The causes of colonic transit disturbance are listed in Tables 4.16 and 4.17.

The diagnostic and therapeutic approach to diarrhea and constipation is discussed in the section Digestive Symptoms of this manual.

Table 4.16 Rapid colon transit: causes

Hormone stimulation
- ↑ T4 (hyperthyroidism)
- ↑ Serotonin (carcinoid tumor/syndrome)
- ↑ Thyrocalcitonin (medullary thyroid cancer)

Neuromuscular dysfunction
- Post-vagotomy
- Diabetic neuropathy
- Dysautonomia

Colon mucosa abnormalities
- (↓ absorption, ↑ secretion → ↑ motility)
- Infectious or inflammatory colitis

Exaggerated ileal flux
- Malabsorption/maldiges tion
  - Generalized (celiac disease, pancreatic insufficiency)
  - Specific (lactose intolerance)
- Small intestinal hypersecretion
  - Infections (virus, bacteria, etc.)
  - Metabolic (VIP, etc.)
  - Bile salts

Drugs
- Laxatives
  - Osmolar (Mg, PEG, lactulose, etc.)
  - Stimulants (senna, etc.)
- Prostaglandins (misoprostol, lubiprostone)
- 5-HT4 agonists (cisapride, prucalopride)
- Chemotherapy agents (mucosal cytotoxicity)
- Others with ± identified mechanism: colchicine, quinidine, metformin, olsalazine, lithium, PPIs, ticlopidine, etc.)

Reflex hypermotility
(overflow past an obstructing « lesion »)
- Fecaloma
- Stricture (neoplastic or inflammatory)

« Idiopathic » hypermotility
- Irritable bowel syndrome

4.8.3 Bile Acid Diarrhea

Bile acid diarrhea (BAD) is due to colonic secretion caused by bile acids reaching the colon in excessive quantities since malabsorbed at the distal ileum (as discussed in the ▶ Chap. 3). The colon is completely normal in appearance, and the response to treatment with bile salts binding resins (cholestyramine, etc.) confirms the diagnosis.

BAD occurs under the following conditions: (a) after ileal resection or with ileal diseases (most often Crohn's ileitis) where bile acids are malabsorbed from the ileum and reach the colon in excess quantity; (b) post-cholecystectomy (10% of cases) in which the loss of gallbladder reservoir function results in bile acids delivery to

Table 4.17 Slow colon transit: causes

Obstruction: lesion
- Distal colon: stricture (tumoral or inflammatory)
- Anorectum: stricture, rectocele

Obstruction: functional
- Hirschsprung's disease (rectal aganglionosis)
- Anorectal dyssynergy
- Dyschezia (rectocele, prolapse)

Neuromuscular diseases
- Neural: Parkinson's, multiple s sclerosis, diabetes, intestinal pseudo-obstruction syndrome
- Muscular: scleroderma – Steinert's disease, etc.

Systemic diseases
- Hypothyroidism
- Metabolic disturbances (K^+, Ca^+)

Drugs
- Opiates
- Anticholinergics (including tricyclics, SSRIs)
- Anticalcic agents (verapamil, etc.)
- Anti 5-HT3 (alosetron, etc.)
- Iron/calcium/aluminum supplements

Others
- Colonic inertia (↓ neurological plexus, ICC)
- Dolichocolon?
- Irritable bowel syndrome
- Postoperative Ileus
  - Generalized
  - Colon (Ogilvie's syndrome)

the intestine (and colon) which is no longer synchronized with meals; and (c) in idiopathic (or so-called primary) BAD (often erroneously attributed to IBS-D). Recent work has shown a deficit in FGF19 secretion (inhibitor of bile salts hepatocyte synthesis) by the enterocyte which leads to the overproduction of bile salts by the liver.

4.9 Miscellaneous

4.9.1 Diverticular Disease

A colon diverticulum is made by herniation of colonic mucosa and submucosa through the muscles of the colonic wall (Fig. 4.32). The herniation occurs at the sites of penetration of the vessels passing through the muscularis to irrigate the inner layers of the intestinal wall.

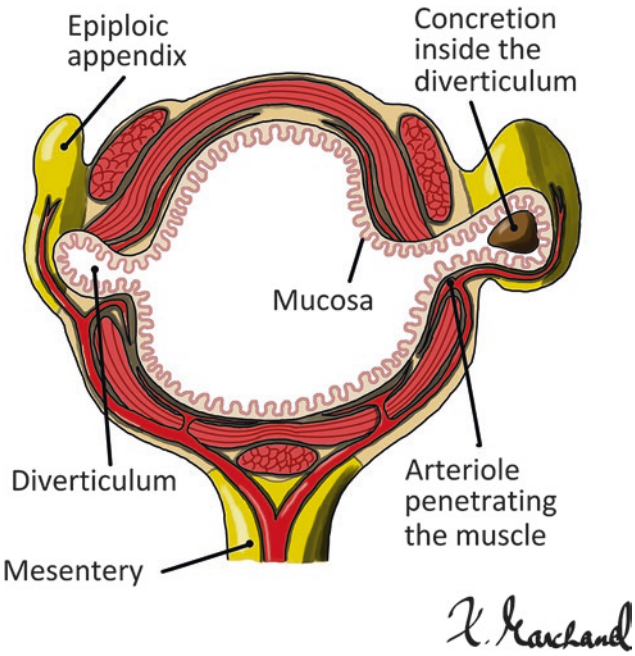


Fig. 4.32 Diagram of a diverticulum: the entry points of the vessels (from deep muscularis to superficial mucosa) are areas of weakness through the circumferential muscle layer where the mucosa (with submucosa) can protrude

Diverticulosis indicates the condition of being a carrier of diverticula. Diverticulitis is inflammation of a diverticulum.

(a) Incidence

Colon diverticula are common. They increase with age. In Western industrialized countries, their prevalence is roughly comparable to age, i.e., at age 50, about 50% of individuals would be affected, at age 70, 70%, etc.

(b) Identification

Diverticula appear as small pockets of 1 to 2 cm projecting outside the colonic wall. They are easily recognizable during a barium enema, CT scan, or colonoscopy (Fig. 4.33). They are located mainly at the sigmoid but may be found throughout the colon.

(c) Etiology

Epidemiological studies have linked colon diverticulosis to low dietary fiber intake by comparing the prevalence of diverticula in industrialized or developing countries where the diet is usually higher in fiber content. It has been suggested that low fiber intake reduces fecal mass and forces the colon to contract more strongly, thus generating muscle hypertrophy (myochosis as described on X-rays) and promoting herniation of the mucosa and

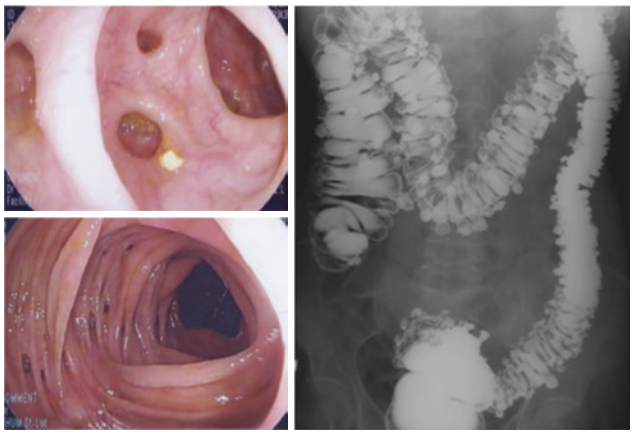


Fig. 4.33 Colon diverticula. Left image, diverticular openings of the colon wall seen in colonoscopy; right image, diverticular sacculations projecting out of the colonic lumen seen here in white contrast during barium enema X-ray. (Photos by P. Poitras)

submucosa internal layers through "weak areas" of the muscle layer. However, the questionable benefit of high-fiber diet in the treatment of diverticular disease raises doubt about the clinical validity of this epidemiologically based hypothesis.

(d) Clinic

Colonic diverticulosis, whatever popular culture may think, is asymptomatic in most cases (except perhaps in some extreme circumstances of muscle hypertrophy, according to our personal opinion). Abdominal pain reported by patients with uncomplicated colonic diverticulosis is most often due to irritable bowel syndrome. Colonic diverticulosis does not require treatment; the once classic high-fiber diet prescribed to hopefully reduce the development of additional diverticula and the occurrence of future diverticulitis is now being questioned.

The clinical importance of colonic diverticulitis lies in the complications that may arise. Colon diverticula can be complicated by bleeding or inflammation (diverticulitis). One popular theory attributes these complications to "abrasive" fecal content stagnating in the diverticular pouch. It is indeed tempting to think that erosion of a blood vessel or perforation of the diverticular wall is due to trauma by hard and/or sharp objects, such as fruit pits, peanuts, etc. stagnating in the diverticular pouch. However, no dietetic or other gesture is known in practice to prevent or avoid diverticular complications.

Diverticulitis is the inflammation of a diverticulum with a peridiverticular inflammatory reaction that classically manifests itself as the triad of (1) pain (most often localized to the left iliac fossa), (2) fever, and (3) leukocytosis.

Diverticulitis is caused by a perforation (most often a micro-perforation) in the thin, fragile wall of the diverticulum. The perforation results in an inflammatory reaction that either (1) is local (parietal edema and inflammation of the pericolic fat) which often seals the micro-perforation, limiting the extent and severity of the damage, or (2) can spread and become complicated with a localized abscess around the colon, or (3) may be accompanied by diffuse fecal spilling into the abdominal cavity resulting in purulent or stercoral peritonitis, or (4) may create a fistula with surrounding organs (most often the bladder).

Diagnosis of acute diverticulitis: (a) Clinical presentation is mainly made by acute abdominal pain (lasting few hours or few days) at the site of diverticulitis, most often the left iliac fossa. (b) Physical examination reveals local sensitivity or localized to diffuse peritoneal signs depending on the severity and extent of the inflammation. Typically, the triad of pain in left iliac fossa, fever, and elevated circulating white blood cells is found. (c) Diagnosis is usually confirmed on abdominal CT scan (Fig. 4.34) which reveals an edematous colon loop (most often the sigmoid) with inflamed pericolic fat; complications (abscess, etc.) may be identified. CT scan, now almost routine exam for abdominal pain assessed in the emergency room, has led to the realization that diverticulitis may present without its classic manifestations of fever and leukocytosis and is much more common than previously thought.

Management of diverticulitis: it relies classically on medical treatment with broad-spectrum antibiotics with gram-negative and anaerobic coverage effective against colonic flora (Table 4.18). Recent studies suggested that in cases of uncomplicated diverticulitis (without severe inflammation, abscess, or sepsis) in immunocompetent patients, symptomatic treatment (analgesics, without antibiotics) may be used. If the patient is able to eat, clear liquid diet is recommended during the acute phase of diverticulitis, and oral antibiotics may be used. Abscess usually requires drainage (if >3 cm), which can be done transcutaneously (radiological approach) in preference to the surgical approach. Severe cases of abscess or peritonitis may require surgery, which will most often involve temporary colostomy, colon resection, and subsequent reanastomosis (so-called two- or three-step surgery). Early diagnosis by CT scan and treatment with antibiotics and percutaneous drainage have revolutionized the management of severe diverticulitis, which previously relied exclusively on surgery and was much more morbid.

Recurrence of diverticulitis occurs in approximately 30% of patients (8% at 1 year, 20% at 10 years. after a first episode; risk increases after recurrences). Recurrence of diverticulitis was a few years ago considered a surgical indication for resection of the colon seg-

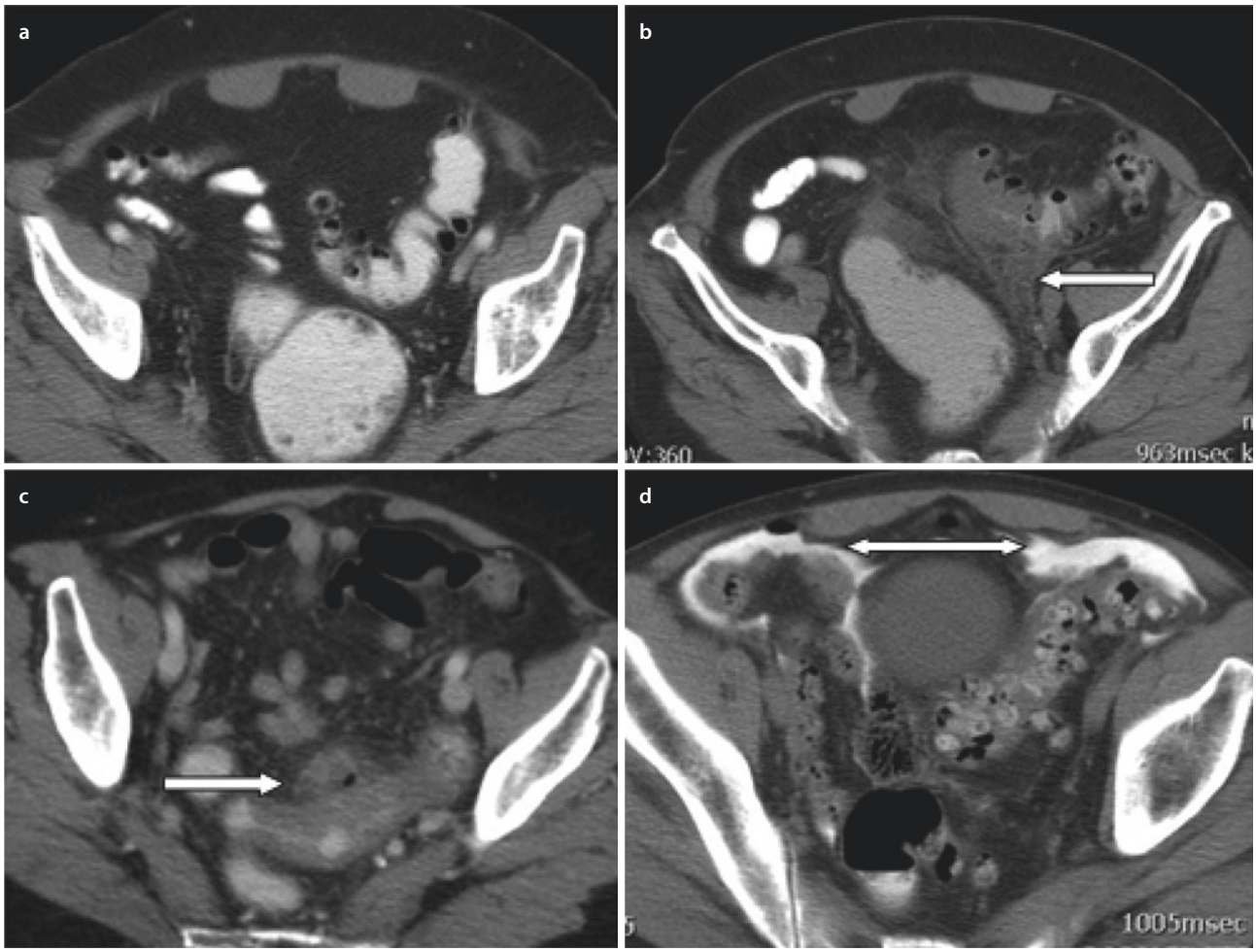


Fig. 4.34 CT scan of the abdomen: **a** uncomplicated diverticulosis (white contrast dye in the colon lumen and small black formations outside the lumen); **b** sigmoid diverticulitis with pericolic (grayish) fat infiltrated by inflammation; **c** acute diverticulitis with wall abscess; **d** perforated diverticulitis with contrast fluid that has fused into the abdominal cavity. (Photos from R. Déry)

ment affected by diverticula. However, given the often benign evolution of the disease (in fact, risk of severe complicated diverticulitis is highest with the first presentation and decreases with recurrences) and the good response to medical treatment, elective "prophylactic" surgery is now limited to immunosuppressed subjects or to some patients with severe complications. It was often recommended to consume fiber supplements in order to reduce the development of new diverticula that may become complicated and to limit fruits seeds and nuts to avoid hurting a fragile diverticular mucosa by these so-called abrasive foods; but none of these recommendations has been shown to effective in altering the course of diverticular disease. Decreased risk of incident diverticulitis has been associated, in «epidemiological» analysis, with «high-quality diet» (high in fiber from fruits, vegetables, and legumes and low in red meat and sweets), physical activity, and weight loss as well as to avoidance of smoking or regular use of NSAIDs.

Diverticular bleeding: A vessel within a diverticulum may erode, resulting in acute digestive bleeding with hematochezia. Diverticular bleeding is the most common cause of lower GI bleeding (see ► Chap. 21). The severity of the bleeding is variable; it may stop spontaneously within a few hours or may be intense and long enough to require transfusions or even therapeutic measures up to surgical resection of the hemorrhagic diverticular segment. Diverticular bleeding, in the majority of cases, is an isolated and nonrecurrent accident (recurrence ≈25% in 5 years).

Table 4.18 Medical treatment of diverticulitis

Diet: clear liquid diet may be used during acute phase

Support treatment (analgesics, no antibiotics) can be used in immunocompetent patients with uncomplicated diverticulitis.

Antibiotics oral treatment (preferred if the patient can eat):

- Ciprofloxacin 500 mg bid + metronidazole 500 mg tid or
- Amoxicillin/clavulinic acid 875/125 bid

Antibiotics intravenous treatment (if the patient cannot take oral medication):

- Ciprofloxacin 400 q 12 h + metronidazole 500 q 8 h or
- Piperacillin/tazobactam 3.375 g q 6 h or
- Ampicillin 2 g q 6 h + gentamicin 1.5 mg/kg q 8 h + metronidazole 500 mg q 8 h or
- Ticarcillin/clavulinic acid 3.1 g q 6 h or
- Meropenem 1 g q 8 h or
- Ertapenem 1 g id

4.9.2 Acute Appendicitis

Acute appendicitis is the most common cause of urgent abdominal surgery. Most often affecting young adults, it can also affect children as well as the elderly. It is due to an inflammation of the appendix, which distends in response to an obstruction of its lumen (normally 3–4 mm), most often by fecal impaction. If not treated promptly, excessive distension can lead to rupture of the appendix and infected peritonitis, which can result in death.

The initial peri-appendicular inflammation perceived by the sensory C fibers (see ▶ Chap. 16) is most often felt in the umbilical region as a dull, vague pain. Progression (after 8–24 hours) of the inflammation toward the peritoneum activates sensory fibers A/Delta, allowing the pain to be felt more precisely in the right iliac fossa.

It is important to diagnose acute appendicitis as early as possible in order to intervene before its perforation. Physical examination, which is not very specific at the beginning of the attack, will later reveal pain with abdominal guarding located in the right lower quadrant and maximal at the McBurney point (point of contact of the appendix tip with the anterior abdominal wall and located 1/2–2/3 the distance connecting on an imaginary line the umbilicus to the anterior superior iliac spine). In cases where the appendix projects toward the retrocecal or pelvic region, psoas or obturator sign (pain in right lower quadrant, respectively, on extension or rotation of the right hip) may be detected.

Appendicitis used to be a clinical condition relying on the clinician's ability to diagnose it and to perform an appendectomy before appendicular rupture occurred. Nowadays, ultrasound or CT scan of the abdomen confirm the diagnosis early (leading to prompt surgical treatment), reveal possible confounding conditions (e.g., tubo-ovarian lesions in women, diverticulitis of the right colon, ileitis, etc.), and avoid unnecessary laparotomies (where a normal abdomen was found despite positive clinical signs).

Acute appendicitis is an urgent condition treated by a usually simple surgical procedure. Treatment with antibiotics may also be done.

4.9.3 Colonic Bleeding

Colon lesions are the most common sources of lower GI bleeding (LGIB). They are manifested by hematochezia, i.e., passage of bright red blood through the anus, but darker (burgundy) blood can be seen with proximal lesions (over time, hemoglobin is altered by intestinal enzymes and bacteria, and the color of blood darkens (red → burgundy → black); the darker the color of blood, the more proximal the bleeding lesion is likely to be).

LGIB is caused by a variety of conditions, the frequency of which varies between series (◘ Table 4.19). However, diverticular hemorrhage is the main cause in all reported series.

The origin of the bleeding will be established at colonoscopy (◘ Fig. 4.35). The diagnosis of diverticular bleeding is most often based on the exclusion of other pathologies (colitis, cancer, etc.) that may cause bleeding, as it is rare that the bleeding from the causal vessel can be visualized during colonoscopy.

Management of LGIB is summarized in ◘ Table 4.20. Lower GI bleeding is discussed extensively in ▶ Chap. 21.

◘ Table 4.19 Causes of lower GI bleeding in various series of literature

Colon diverticulum	10–40% of cases
Colitis	
Ischemic	5–20%
Infectious	3–30%
Inflammatory	2–4%
Radiation	1–3%
Neoplasia or polyps	3–10%
Vascular lesions/angiodysplasias	3–30%
Anorectal lesions (hemorrhoid, fissure, etc.)	5–15%

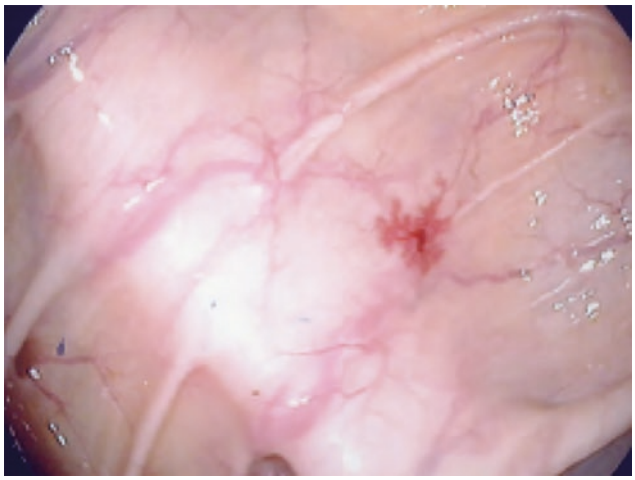


Fig. 4.35 Angiectasis seen on colonoscopy. Possible source of digestive bleeding. (Photo by P. Poitras)

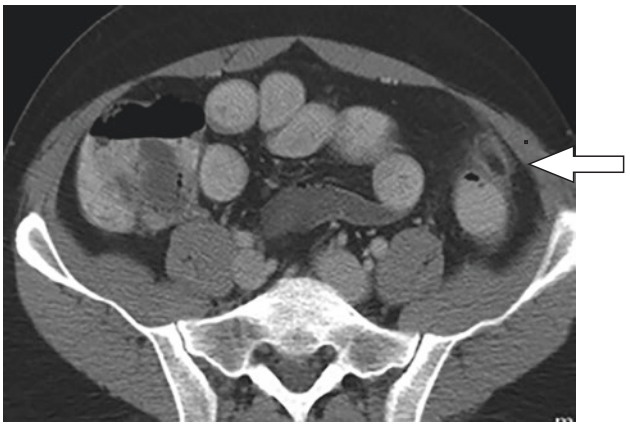


Fig. 4.36 Scan of abdomen showing appendagitis (or epiploic appendicitis): inflammation (infiltrated fat) around an extra-colic round structure differentiable from a diverticulum (with black stained air) by its fat content (more greyish coloration like abdominal fat). (Photo from R. Déry)

Table 4.20 Management of lower GI bleeding

Hemodynamic stabilization
- Iso-osmolar solute (NaCl 0.9 or Ringer's lactate)
- Blood transfusions prn

Identification of the site and cause of bleeding
- Colonoscopy (usually performed 24 hours after patient admission due to the need for colonic lavage preparation)
- Angiography or angioscan (if active bleeding)
- Scintigraphy with labelled red blood cells

Treatment of hemorrhagic lesion
- According to the hemorrhagic cause:
  - Endoscopy with polypectomy, vessel sclerosis, etc.
  - Angiography with arterial embolization
  - Surgery with suture or resection of the causal lesion

4.9.4 Epiploic Appendix/Appendagitis

On the outer surface of the colon, there are small fatty sacs called epiploic appendages. Inflammation of one of these structures (by twisting?) can lead to a clinical picture highly suggestive of diverticulitis. The diagnosis is often a "surprise" revealed on CT scan by a characteristic image (Fig. 4.36). Anti-inflammatory drugs (NSAIDs) help the painful condition to regress within a few days.

4.9.5 Volvulus

Volvulus refers to a twisting of the intestine around its mesenteric pedicle resulting in occlusion of the intestinal lumen and compromising blood supply to the affected organ. Volvulus of the sigmoid is the most common. A long sigmoid (dolichocolon), age (more frequent around 70–80 years), and chronic constipation (secondary to dolichocolon?) are contributing factors.

The patient presents with acute (or subacute) abdominal pain and intestinal obstruction (cessation of materials and gas, vomiting, etc.). The abdomen is distended and tympanic. Signs of visceral suffering (rebound tenderness, etc.) may exist in case of ischemia.

Radiography of the abdomen (flat plate) is often diagnostic by revealing a very distended sigmoid loop (Fig. 4.37a). Barium enema shows the classic "bird's beak" image caused by torsion of the organ. On CT scan, torsion of the mesentery may be visible (Fig. 4.37b).

The sigmoid must be rapidly decompressed, either by means of a rectal tube introduced through the sigmoid torsion or, more often, by colonoscopy. Given an expected recurrence in 50% of patients, surgical correction may be required at a later stage.

Volvulus of the cecum is more rare. Involving torsion of the right ileocolic region, it most often requires urgent surgical treatment.

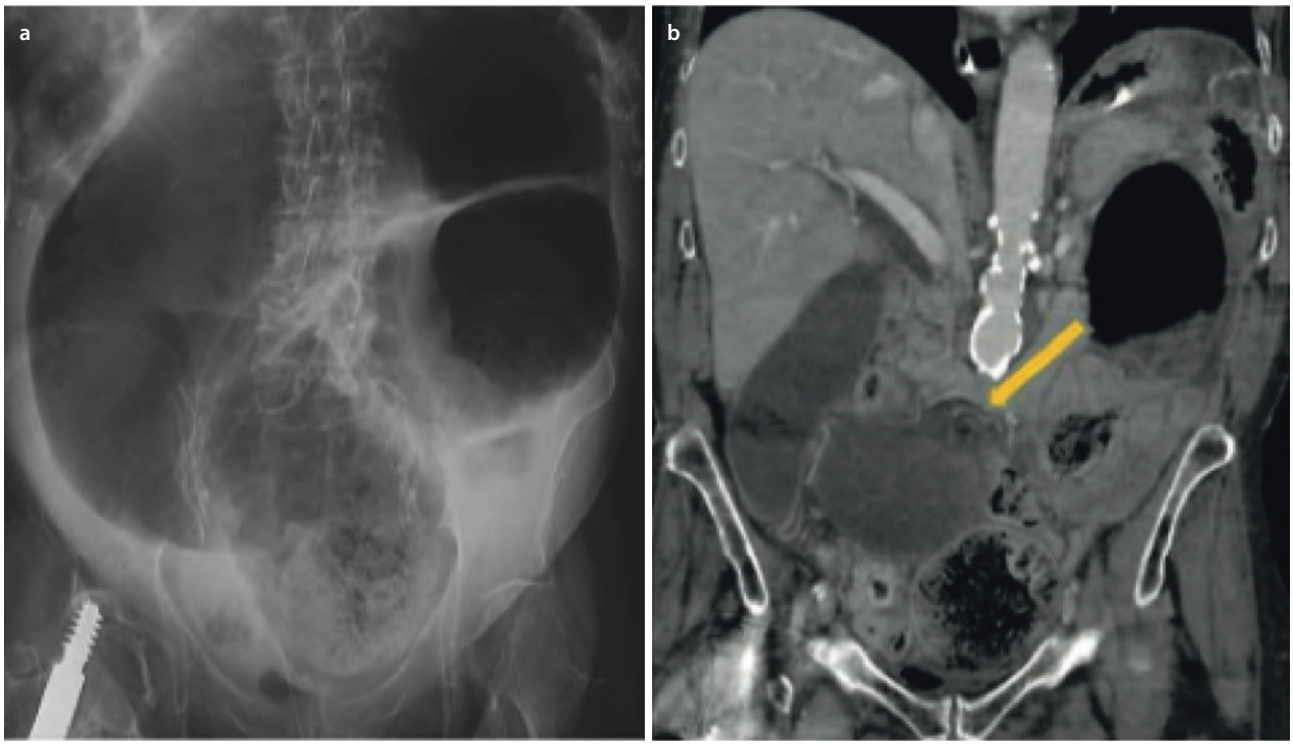


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Fig. 4.37 Volvulus of the sigmoid: **a** on flat plate, the sigmoid is highly distended in a typical "coffee bean" loop; **b** on CT scan, colonic distension is clearly visible and a "swirl" of the mesenteric vessels twisted by the sigmoid rolling is detected (indicated by the arrow). (Photos from R. Déry)

4.9.6 Melanosis Coli

This is a blackish coloration of the colon, giving the appearance of snakeskin (Fig. 4.38), due to the deposition in the mucosa of a dark pigment in constipated patients who make extensive use of anthracene laxatives (senna, etc.).

Melanosis coli was previously considered a risk factor for colonic dysmotility and even for colonic cancer, but it appears now to be only a spectacular harmless marker of intensive laxative use.

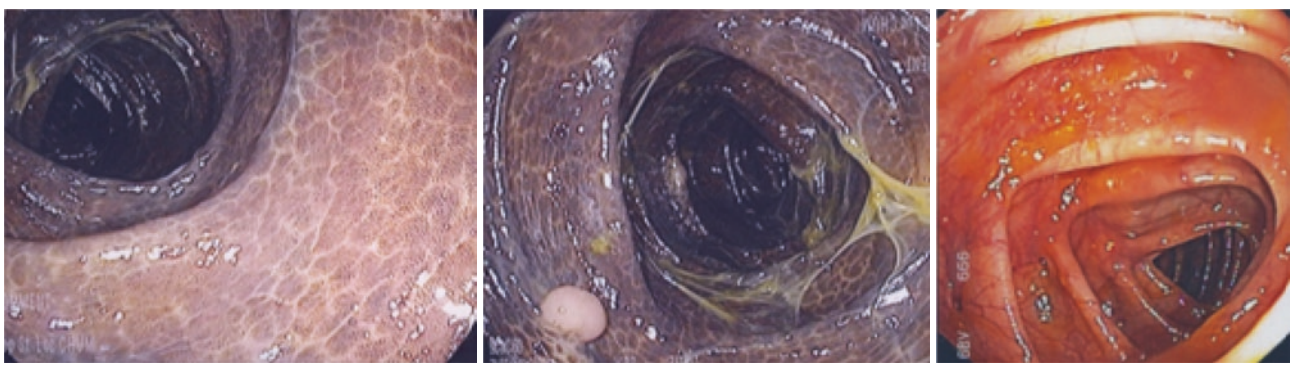
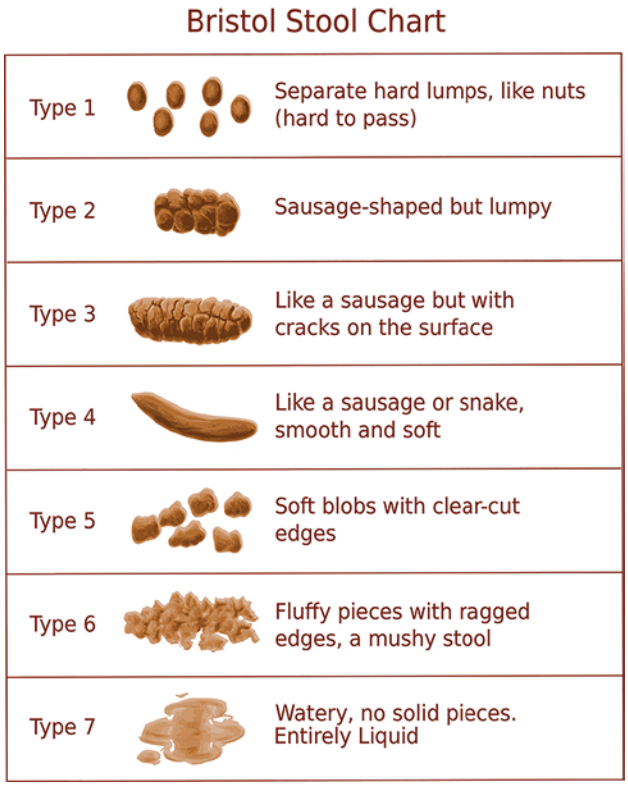


Fig. 4.38 Colonic mucosa seen under colonoscopy showing melanosis coli (quite different from a normal bright pink mucosa shown on the right). (Photos by P. Poitras)

4.9.7 Bristol Stool Chart

Bristol stool chart (or scale), shown on ◘ Fig. 4.39, was used by researchers to quantify stool appearance and obtain a quantitative analysis to statistically compare stool appearance under various conditions (drug treatment, symptoms of diarrhea vs. constipation, etc.). It is sometimes used as a clinical tool by physicians, as well as by patients to report on their stools (« today, instead my usual Bristol 1 or 2, I had a Bristol 4»).

PS: For complementary readings on the colon, see ► Chaps. 13, 14, 15, 16, 21, 22, 25, and 29.



◘ **Fig. 4.39** Bristol stool chart. Types 3 and 4 are considered normal. Types 1 and 2 are seen in constipation, while types 5, 6, and 7 refer to diarrhea

The Pancreas

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Contents

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The pancreas is a mixed gland with an exocrine (secretion of digestive enzymes) and endocrine (release of insulin and glucagon for blood glucose control) functions. In this book, we will focus on the digestive function of the pancreas.

5.1 Macroscopic Anatomy

5.1.1 Shape and Structure

Pancreatic regions The pancreas is a retroperitoneal organ that can be divided into four anatomical regions:

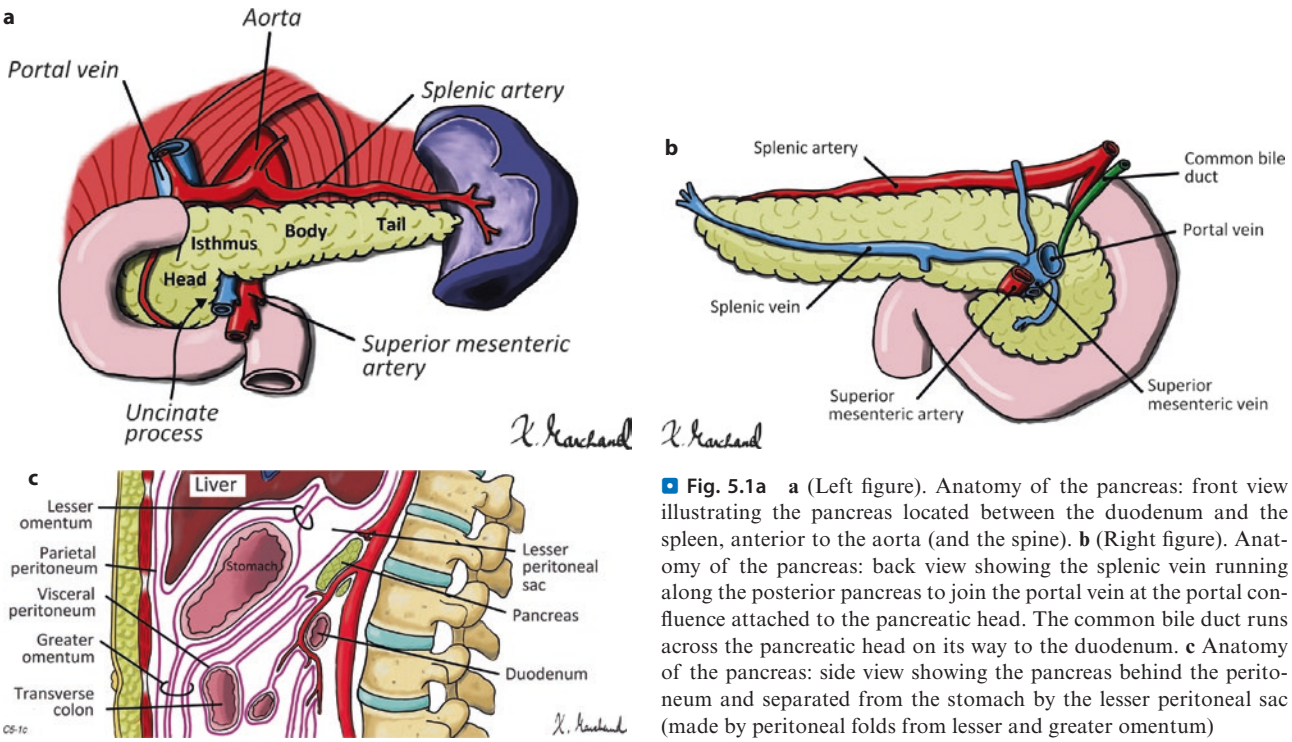
The *head*, including the uncinate process, is located in a vertical position to the right of the aorta and the spine; it intimately abuts the duodenal wall (surgical resection of the pancreatic head will therefore involve resection of the duodenum during the Whipple procedure) and is close to the superior mesenteric vein and artery (common sites of neoplastic invasion in pancreatic head cancers) (◘ Fig. 5.1a, b).

The *isthmus, body, and tail* of the pancreas are in a horizontal position and extend from in front of the spine (at the level of D12–L1) and the abdominal aorta to the spleen. This position in front of the spine makes the pancreas vulnerable to abdominal trauma by anterior compression (e.g., car accident with blunt impact on the steering wheel).

The anterior portion of the pancreas is covered by posterior peritoneum and is separated from the posterior wall of the stomach by the lesser peritoneal sac (or omental bursa) formed by peritoneum folds from lesser and greater omentum (◘ Fig. 5.1c). The retroperitoneal position of the pancreas explains why pain tends to radiate to the back when it is caused by pancreatic lesions. The anterior surface of the pancreatic neck is intimately attached to the duodenal bulb; a peptic ulcer from the bulb of the duodenum can penetrate to the pancreas (known as a boring ulcer) and lead to abdominal pain radiating to the back as well as pancreatitis.

Pancreatic ducts The pancreas is a solid organ containing the main and accessory pancreatic ducts, as well as the common bile duct.

The *main (or major) pancreatic duct (also known as the duct of Wirsung)* drains secretions from the exocrine pancreas to the duodenum. The duct traverses from the



◘ **Fig. 5.1a** **a** (Left figure). Anatomy of the pancreas: front view illustrating the pancreas located between the duodenum and the spleen, anterior to the aorta (and the spine). **b** (Right figure). Anatomy of the pancreas: back view showing the splenic vein running along the posterior pancreas to join the portal vein at the portal confluence attached to the pancreatic head. The common bile duct runs across the pancreatic head on its way to the duodenum. **c** Anatomy of the pancreas: side view showing the pancreas behind the peritoneum and separated from the stomach by the lesser peritoneal sac (made by peritoneal folds from lesser and greater omentum)

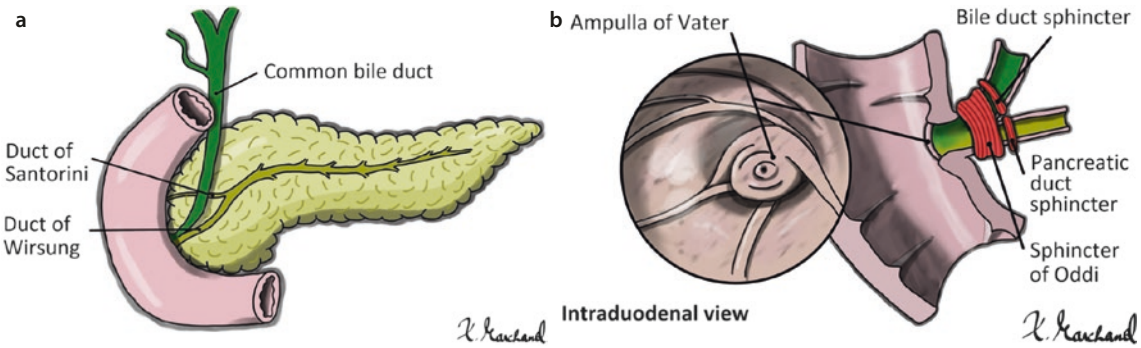
tail to the head of the pancreas, meeting with the distal bile duct at the level of the major papilla (also known as the ampulla of Vater) within the middle of the second portion of the duodenum. A smaller *accessory duct (duct of Santorini*: embryological remnant and atrophic in 30% of normal adults) connects the middle portion of the duct of Wirsung to the upper duodenum via the minor papilla (◘ Fig. 5.2a).

The *ampulla of Vater*, where end up pancreatic secretions drained by the main pancreatic duct and biliary secretions from the common bile duct, includes a sphincter, the *sphincter of Oddi (S0)*, to regulate the delivery of these secretions into the duodenum. The SO is comprised of three sphincter rings: a pancreatic sphincter specific to the pancreatic duct, a biliary sphincter dedicated to the bile duct, and a distal sphincter common to both ducts (. Fig. 5.2b). A sphincterotomy can be performed during interventional endoscopy to facilitate biliary interventions such as the extraction of stones from the common bile duct.

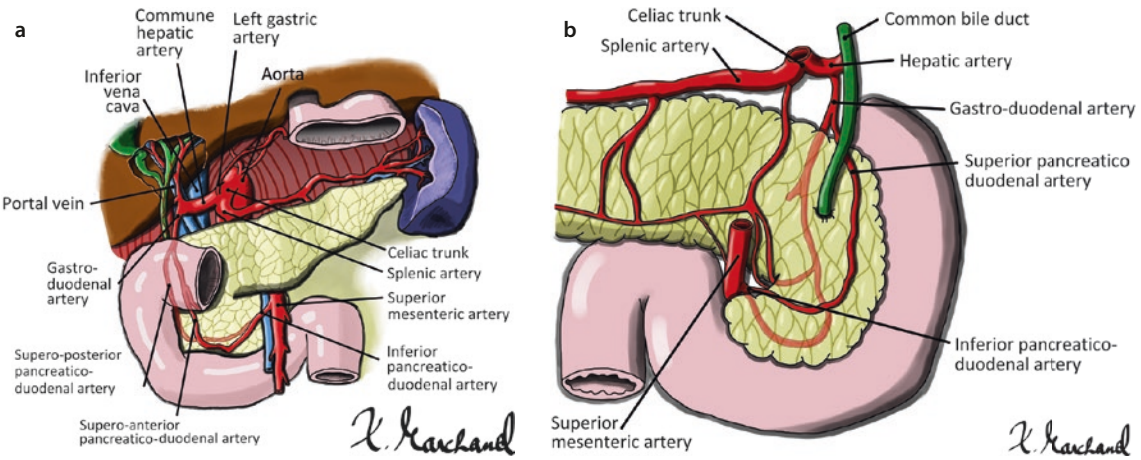
The *common bile duct* runs vertically through the pancreatic head, carrying bile from the liver to the duodenum; an inflammatory or tumoral lesion of the pancreatic head can obstruct the bile duct and impair bile evacuation, leading to jaundice.

5.1.2 Vascular Supply

Arteries Blood supply to the pancreas comes from two major arteries emerging from the aorta: the celiac trunk (CT) and the superior mesenteric artery (SMA). These vessels arise from the aorta at the height of vertebrae T12 and L1, respectively) (◘ Fig. 5.3).



◘ **Fig. 5.2** **a** (Left figure): Pancreatic ducts. **b** (Right figure): Ampulla of Vater and sphincter of Oddi



◘ **Fig. 5.3** Arterial supply to the pancreas. On the left figure, the anterior view shows the celiac trunk emerging from the aorta and its three branches: (1) the left gastric artery (going to the stomach), (2) the splenic artery which, on its way to the spleen, gives arteries to the corporeo-caudal pancreas, (3) the common hepatic artery dividing into (**a**) the proper hepatic artery (going to the liver and gallbladder) and (**b**) the gastroduodenal artery, from which originates the superior pancreaticoduodenal artery irrigating the cephalic pancreas. On the right figure, the posterior view shows the superior mesenteric artery which, in the direction of the small intestine, gives rise to the inferior pancreatico-duodenal artery to also supply the cephalic pancreas

The pancreatic gland to the right of the aorta is supplied by a vast anastomotic network that links the celiac and mesenteric circulations. This dual supply ensures continuous vascularization of the pancreas and reduces the risk of ischemic damage to the pancreas. The common hepatic artery (also called hepatic artery, one major branch of the CT) gives birth to the gastroduodenal artery (GDA) which is at the origin of the superior pancreaticoduodenal artery that links with the inferior pancreaticoduodenal artery (first branch of the SMA) to vascularize the pancreatic head and the uncinate process.

The pancreatic gland located on the left side of the aorta receives its vascular supply via the splenic artery (one of the three branches of CT) which runs along the body and tail of the pancreas and divides into smaller pancreatic arteries all along this route.

Veins Venous blood from pancreatic tail and body drains into the splenic vein. At the pancreatic head, veins run along the branches of superior and inferior pancreaticoduodenal arteries and drain into the superior mesenteric vein. The junction of the superior mesenteric vein to the splenic vein (known as the portal confluence), forming the portal vein, is done behind the head of the pancreas.

Lymphatics Lymphatic drainage of the pancreas follows the main arterial vessels. Lymphatic vessels from body and tail of the pancreas drain to lymph nodes located along the splenic vein. Lymphatics from cephalic pancreas drain to lymph nodes of the hepatic hilum.

5.1.3 Innervation

The pancreas is innervated by the parasympathetic (via the vagus nerve) and sympathetic (through splanchnic nerves) systems. Vagal efferent nerves terminate, within the pancreatic tissue, at parasympathetic nodes whose postganglionic fibers innervate acini, islets of Langerhans, and pancreatic ducts. Sympathetic axons from neural bodies of the thoracic spinal cord synapse with neurons of abdominal plexus (e.g., celiac node) whose postganglionic fibers run along the arterial vessels to reach the pancreas.

Little is known about pancreatic afferent nerves. They probably travel through splanchnic nerves, crossing the main plexus ganglions to reach the spinal cord, and then the brain. Celiac node infiltration (done during ultrasound endoscopy) with a local anesthetic agent (such as xylocaine) is used to reduce pain from pancreatic cancer.

5.2 Microscopic Anatomy

Most pancreatic tissue is devoted to exocrine functions, with acinar cells and ducts comprising more than 85% of the pancreatic tissue. This exocrine activity aims to synthesize and secrete enzymes, water, and bicarbonates that are transported through the pancreatic ducts to the duodenum to participate in the digestion of the ingested nutrients. The endocrine function of the pancreas relies on the islets of Langerhans, which represent only 2% of pancreatic parenchyma, to ensure the synthesis and secretion of the hormones insulin and glucagon released into the bloodstream to regulate carbohydrates metabolism.

The histological appearance of the pancreas can be seen in ◘ Fig. 5.4.

5.2.1 Acini

The cells responsible for synthesis and secretion of pancreatic enzymes are grouped together in a spherical anatomical unit called an acinus. The acinar cell has a pyramidal shape, with a wide and basophilic (bluish coloration on hematoxylin and eosin stain) basal portion, and a narrow and acidophilic (pinkish coloration due to the presence of many zymogen grains that store pancreatic proenzymes waiting to be secreted in the duodenum) apical portion. The basal portion of the acinar cell is in contact with the blood vessels and nerves regulating pancreatic function, while the apical portion opens onto a duct through where enzymes can be released.

Each acinar cell has a general function and synthesizes all pancreatic enzymes (amylase, lipase, etc.). The morphology of the acinar cell varies with meals. After food ingestion, the membrane of the zymogen grains fuses with the apical membrane of the acinar cell to allow exocytosis of pancreatic enzymes from the cell to the duct lumen. This massive release produces a depletion of zymogen grains which is followed by an increase in the synthesis activity by the acinar cells to replace enzymatic stocks that have been secreted.

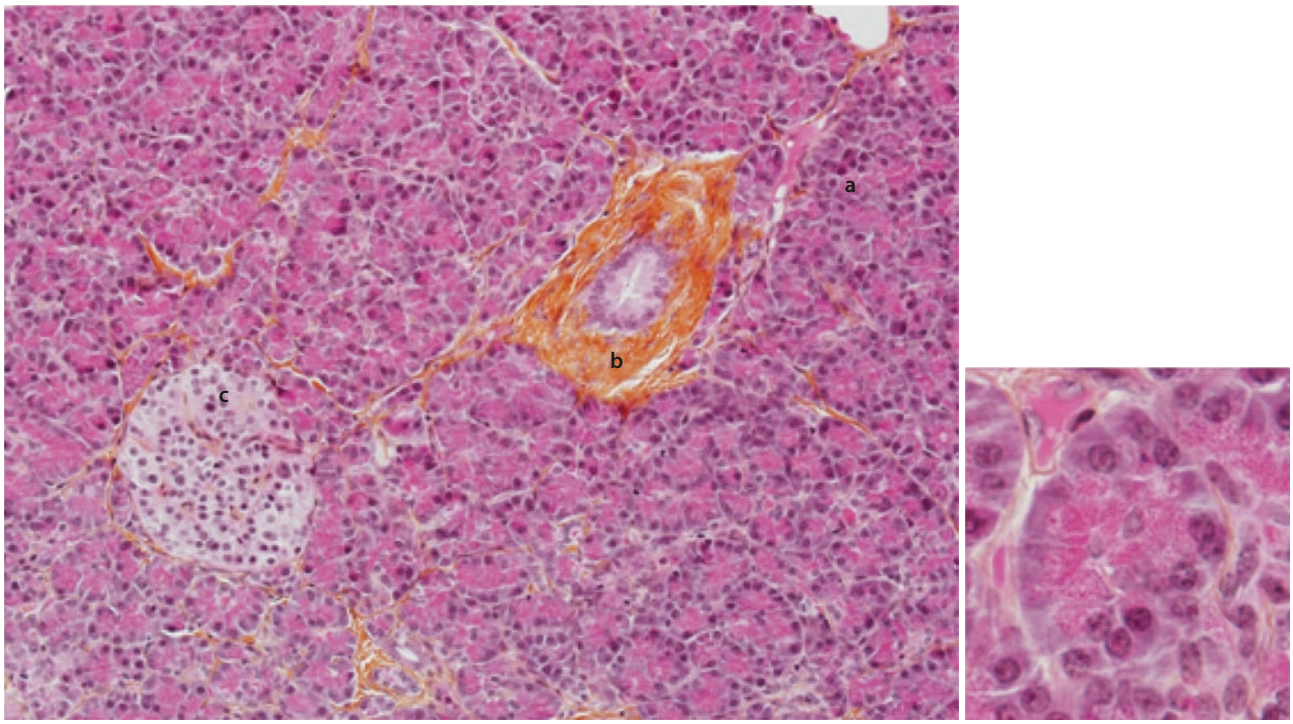


Fig. 5.4 **Left**: histological appearance (on H&E stain) of a normal pancreas with acini **(A)**, pancreatic ducts **(B)** and islets of Langerhans **(C)**. **Right**: at higher magnification, pancreatic cells with their acidophilic secretory granules are grouped in an acinus around a central canaliculus where enzymes will be secreted

5.2.2 Ducts

Acinar cells are grouped in circle around a central opening receiving their secreted enzymes and forming a canaliculus where enzymes will flow to peripheral canaliculi draining into larger ducts leading to the central main pancreatic duct (duct of Wirsung). Pancreatic enzymes will then travel to the duodenum lumen where they will be activated to participate in nutrients digestion.

The canaliculi are lined by cylindrical cells duct cells that secrete H_2O and HCO_3^- in the duct lumen.

5.2.3 Islets of Langerhans

There are about 1 million islets of Langerhans in the human pancreas (2% of pancreatic mass). Each one measures approximately 0.2 mm in diameter and is therefore larger than an acinus. The islets are surrounded by a connective tissue sheath but communicate with the systemic circulation where hormones are released. Each islet is made up of four major types of endocrine cells: beta cells are the most numerous (50–80%) and secrete insulin, alpha cells (5–20%) secrete glucagon, PP cells (10–35%) the pancreatic polypeptide, and D cells (5%) somatostatin. In contrast to the acinar cell which has a general activity and synthesizes all pancreatic enzymes, each endocrine islet cell has a specific function and produces only one type of hormone.

5.3 Embryology

5.3.1 Normal Development

The fetal pancreas begins to develop around the fourth week of gestation when the embryo measures only 4 mm. Initially, from the endoderm of the primitive duodenum, two buds are formed in an antero-posterior axis, one ventral and one dorsal. The dorsal (or posterior) bud will form the body and tail of the pancreas, while the anterior ventral bud will form the head of the pancreas and the uncinate process (as well as the bile ducts and liver) (Fig. 5.5a). At about the sixth week, begins a process of rotation along the vertical axis of the digestive tract, bringing the ventral bud to the right (pulled by the hepatic bud that will develop in the right hypochondrium), while the dorsal bud will move to the left (Fig. 5.5b). The proximal potion of the ventral bud passes from behind to be positioned under the dorsal bud. Toward the seventh week, the ventral and dorsal buds merge together. The distal portion of the dorsal

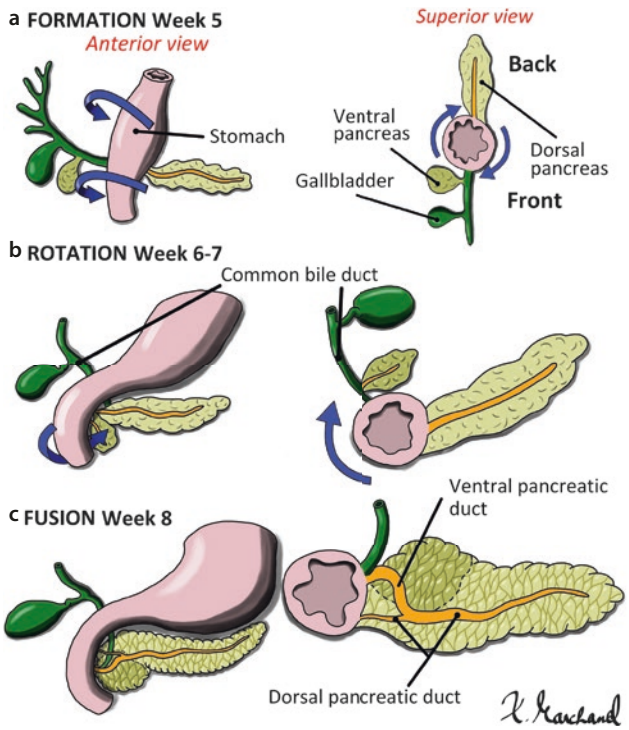


Fig. 5.5 Pancreas development in the embryo: **a** from the endoderm of the primitive duodenum, two buds are formed in an anterior-posterior axis, one ventral and one dorsal; **b** a rotation, along the vertical axis of the digestive tract, brings the ventral bud to the right (pulled by the hepatic bud which will develop in the right hypochondrium) and the dorsal bud will move to the left. The proximal portion the ventral bud passes from behind to be situated beneath the dorsal bud; **c** at around the seventh week of gestation, a merger occurs between the two buds, ventral and dorsal, as well as between their ducts that will form the main pancreatic duct (Wirsung's duct)

duct will connect to the ventral duct to form the main pancreatic duct (of Wirsung) (Fig. 5.5c). The remainder of the proximal dorsal duct will form the accessory duct (of Santorini; atrophic in 30% adults) which drains into the duodenum via the minor papilla.

5.3.2 Developmental Abnormalities

Several abnormalities in the development of the pancreas may occur (Fig. 5.6).

Pancreas divisum (Fig. 5.6a) is the result of a lack of union between the ducts of the ventral and dorsal pancreas during the fusion of the two embryonic buds. The pancreatic head (born from the ventral pancreas) drains its secretions toward the duodenum via the.

Wirsung's duct and the Vater's ampulla, while the corporeo-caudal pancreas (issued from the dorsal pancreas) will drain its secretions via the Santorini's duct and the minor ampulla. This congenital anomaly is found in 5–10% of autopsies or pancreatography examinations (ERCP, MRI). Most individuals with pancreas divisum are asymptomatic and have normal pancreatic exocrine function. Some authors have proposed that pancreas divisum can cause some forms of pancreatitis. They hypothesized that the minor ampulla is too small to allow an easy flow of secretions from corporeo-caudal pancreas, leading to an excess pressure within the duct and secondary pancreatitis; they proposed sphincterotomy of the minor ampulla as a form of treatment for this anomaly. The association between pancreas divisum and risk of pancreatitis remains controversial. More recently, it has been suggested that pancreas divisum is a risk factor for pancreatitis when it is combined to other risk factor, such as the hyperviscosity of the pancreatic juice seen in cystic fibrosis.

Annular pancreas (Fig. 5.6b) is an uncommon variant (1 in 20,000 births) where pancreatic tissue persists around the duodenum from the rotation that has brought the ventral bud into its final position. This pancreatic tissue surrounding the second portion of the duodenum (at the level of the major ampulla) may cause

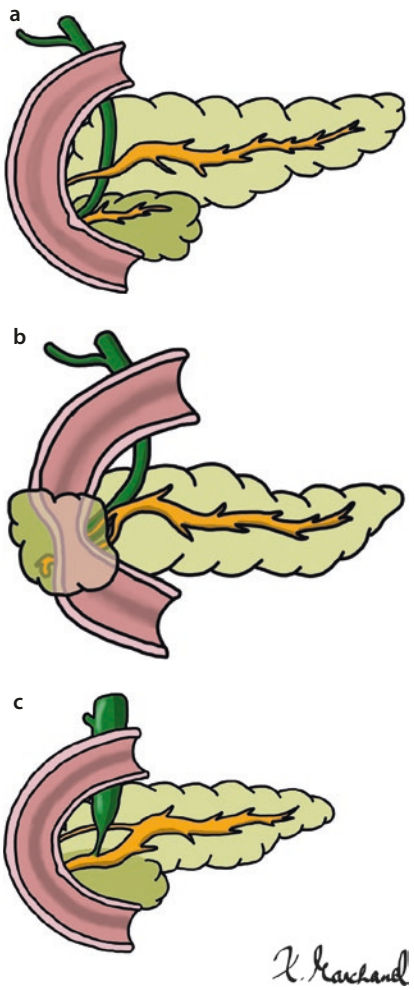


Fig. 5.6 Developmental abnormalities: **a** pancreas divisum; **b** annular pancreas; **c** abnormally implanted bile duct

partial or complete obstruction of the duodenum. Annular pancreas can be associated with other congenital anomalies (such as Down's syndrome, duodenal atresia, tracheoesophageal fistula, cardiac abnormalities, etc.). In symptomatic cases, treatment is provided by bypass surgery (e.g., gastrojejunostomy) to allow food to avoid duodenal obstruction and come out of the stomach into the intestine. The annular pancreas may occasionally be revealed in an adult who experiences obstructive symptoms (pain, nausea, vomiting, bloating) during episodes of pancreatitis produced by the inflammatory swollen pancreatic ring.

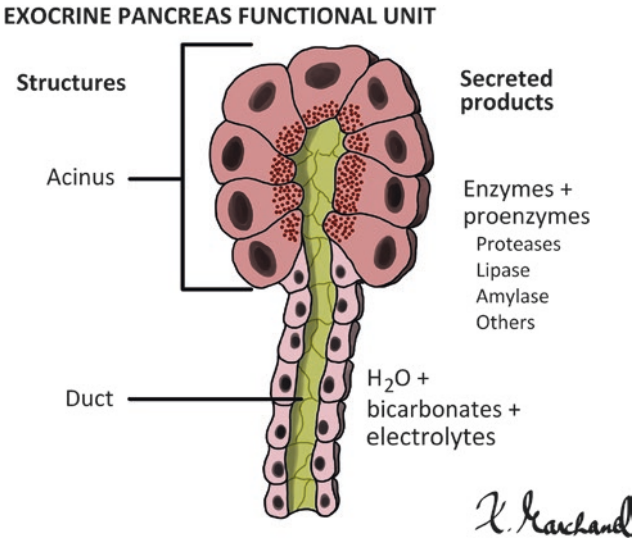
Ectopic pancreas (also known as heterotopic or accessory or aberrant pancreas) refers to the presence of pancreatic tissue outside of its normal location, in various sites of the digestive tract (mostly in submucosal surfaces of the stomach, duodenum, or jejunum). Present in up to 10% of autopsies, the ectopic pancreas is usually asymptomatic and is identified incidentally during digestive endoscopy (showing a small submucosal lesion with a central umbilication) or on imaging studies. Clinical manifestations of the ectopic pancreas include cystic dystrophy of the duodenal wall (CDDW, also known as groove pancreatitis or paraduodenal pancreatitis) where pancreatic secretions, unable to drain from their acini due to the absence of functional excretory ducts in the ectopic pancreas, accumulate to form walled-off fluid collections within the duodenopancreatic region that can result in duodenal obstruction, jaundice, or pancreatitis.

Complete pancreatic agenesis is a rare phenomenon that may be associated with other developmental abnormalities and which usually results in death in utero or at birth. Incomplete and segmental agenesis can occur and is usually asymptomatic (incidental finding in MRI or CT abdominal imaging).

Congenital cysts of the pancreas are relatively rare. They may be solitary or multiple and may occasionally be associated with other development abnormalities or certain genetic diseases (polycystic kidney disease, etc.). Unlike pancreatic pseudocysts (consequence of inflammatory fluid accumulation during pancreatitis), congenital cysts have an epithelial lining capable of fluid secretion. Congenital cysts can be found in the newborn, child, or adult. Large cysts can cause symptoms by compressing adjacent digestive or biliary structures and can then require surgical treatment.

5.4 Secretion

The pancreatic exocrine secretory apparatus is made up of two functional units: the acinus and the ductule (◘ Fig. 5.7). The acinus is a spherical grouping of acinar cells secreting enzymes for the intestinal digestion of



◘ **Fig. 5.7** Functional units of the exocrine secretory pancreas: acinus and duct

carbohydrates (amylase), lipids (lipase), and proteins (trypsin, elastase, etc.) of the diet. The ducts are lined with an epithelium of cells that secrete large quantities of bicarbonate (to neutralize gastric acid arriving in the duodenum) and water (to transport enzymes from the acinus to the duodenum). Every day, 1.5–2 liters of pancreatic juice is released into the duodenum.

5.4.1 Acinar Cell

The acinar cell synthesizes and secretes pancreatic enzymes involved in the digestion of food (glycolytic, lipolytic, proteolytic enzymes), as well as other proteins which have various roles in pancreatic homeostasis. This cell, therefore, is very rich in organelles involved in protein synthesis, such as rough endoplasmic reticulum (RER), Golgi apparatus, condensation vacuoles, and zymogen granules.

Like all exocrine proteins, pancreatic enzymes, after nucleic acid transcription from DNA to RNA in the cell nucleus, are synthesized in the cytoplasm: messenger RNAs, helped by ribosomal and transfer RNAs, enter the reticulum endoplasmic (RER) where nucleic acids will be translated into amino acids; posttranslational modifications that occur in RER and Golgi apparatus allow newly made proteins to acquire their final tertiary and quaternary structures; once their synthesis is completed, the pancreatic enzymes are stored in very dense zymogen granules that accumulate at the apex of the cell, waiting for secretion out of the cell. See ◘ Fig. 5.8.

Stimulation of the acinar cell (through mechanisms to be discussed shortly) leads to migration of zymogen granules to the apical membrane of the cell where the membranes of the cell and granules will fuse to deliver,

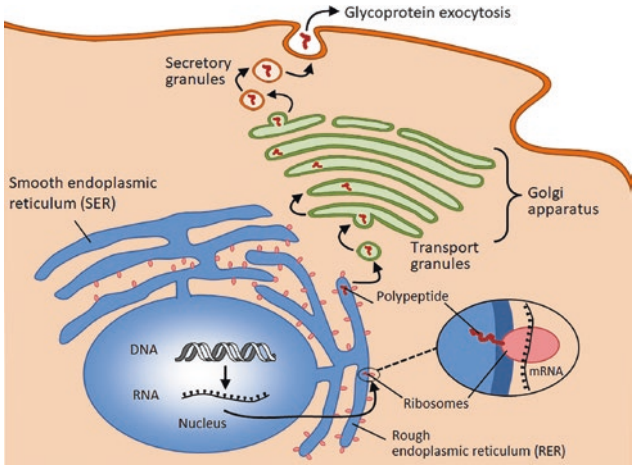


Fig. 5.8 Protein synthesis in the acinar cell. After transcription in the nucleus of DNA into RNA, translation of nucleic acids into amino acids (3 nucleic acids = 1 amino acid) occurs in the endoplasmic reticulum to form a polypeptide protein sequence that will be submitted to subsequent transformations during its maturation through the Golgi apparatus toward its storage in secretion vesicles (zymogen granules) while waiting for exocytosis to be transported outside of the cell

Table 5.1 Products of the acinar cell

Proenzymes	Enzymes	Nonenzyme products
Chymotrypsinogens (A, B)	Amylase	Bradykinin
Kallikreinogen	Sterol esterase	Ions: Na+, Cl^-, Ca^{2+}
Procarboxypeptidases (A, B)	Lipase	Glycoprotein 2 (GP2)
Phospholipases (l, ll)	DNase	Lithostatin
Proelastase	RNase	Monitor peptide
Mesotrypsin	Lysosomal enzymes	Pancreatitis-associated protein (PAS)
Trypsinogens (1, 2, 3)	Unknown	Trypsin inhibitor

via a secretion process called exocytosis, the granule content into the lumen of the acinus, and then pancreatic ductules.

The acinar cell indiscriminately synthesizes all digestive enzymes. However, the relative concentration of enzymes can vary according to the ingested diet (e.g., increase in lipase content if high-fat diet). The main proteins synthesized and secreted by acinar cells are listed in Table 5.1. In humans, proteases account for 90% of the total enzymatic content (amylase 7%, lipase 2.5%, nuclease <1%). The predominance of proteolytic enzymes is probably an adaptation to the carnivorous nature of man since its origin. Pancreatic secretion therefore includes: (a) proteolytic enzymes of two main types, (1) endopeptidases (which cleave proteins at specific peptide bonds within the polypeptide) such as chymotrypsin, trypsin, kallikrein, and elastase and (2) exopeptidases (which cleaves peptide bonds at the carboxyterminal end of the polypeptide) such as carboxypeptidases A and B; (b) a glycolytic enzyme, amylase, to hydrolyze starch and complex carbohydrates; (c) lipolytic enzymes such as lipase, esterases, and phospholipases; (d) enzymes involved in hydrolysis of nucleic acids, DNase and RNase; and (e) nonenzymatic products, such as trypsin inhibitor, procolipase, etc.

If proteolytic and lipolytic enzymes were synthesized in an active form, they would constitute a great threat to the pancreas (and to any human tissue since we are largely made up of proteins and lipids). These enzymes are therefore synthesized and secreted as inactive proenzymes that remain harmless as long as they have not been activated (see ▶ Sect. 5.4.4). Activation of proenzymes into active enzymes occurs in the duodenum by trypsin (itself secreted as inactive trypsinogen). In case of premature activation of trypsin within the pancreas, an additional protection mechanism involving a trypsin-inhibiting protein can intervene to avoid pancreatic acinar cell damage.

5.4.2 Ductal Cell

Cuboidal cells make up the epithelium of the ductules that originate at the acinus border (see Fig. 5.7) and will merge and grow until they reach the main pancreatic duct of Wirsung.

The main functions of ductal cells and the ducts they form are (1) to ensure an anatomical route to transport pancreatic enzymes to the duodenum, (2) to provide water facilitating movements of pancreatic secretions in ducts lumen, and (3) to secrete bicarbonates to neutralize acidic gastric chyme poured into the duodenum. The ductal cell (Fig. 5.9) is equipped with secretory mechanisms that ensure high concentrations and high flow rates of electrolytes:

- HCO_3^- is secreted at the apical membrane via an ion channel and a Cl^-/HCO_3^- pump. Intracellular availability of HCO_3^- is provided by cytoplasmatic carbonic anhydrase (transforming CO_2 and H_2O to HCO_3^-), as well as by an HCO_3^-/Na^+ carrier located on the basolateral membrane (promoting the entry of HCO_3^- into the cell).
- Cl^- is secreted out of the cell by a CFTR channel (cystic fibrosis transmembrane regulator) (hence the

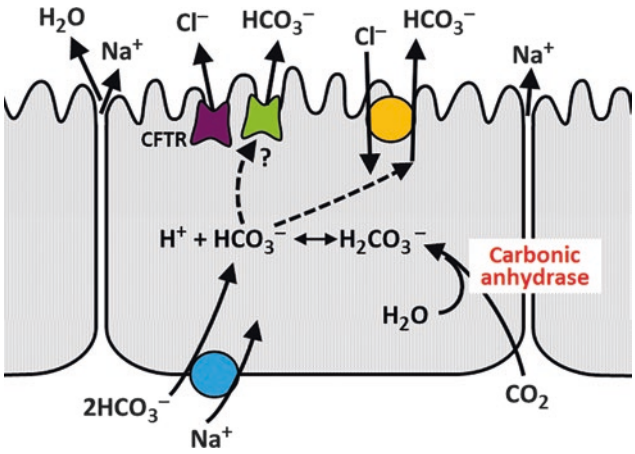


Fig. 5.9 Duct cell secretion. HCO_3^- is secreted at the apex of the cell by various mechanisms (channels, pumps). Secreted HCO_3^- is manufactured inside the cell (carbonic anhydrase) or is transported there (Na^+/HCO_3^- carrier on basal membrane). Cl^- is secreted through a CFTR channel. Na^+ diffuses, with H_2O, through paracellular spaces toward the pancreatic duct

pancreatic damage in cystic fibrosis discussed in the ▶ Sect. 5.9 of this chapter).

- Na^+ and H_2O pass into the canaliculus passively, following electrochemical and/or concentration gradients, by diffusion through intercellular junctions.

Circulating secretin and neuronal acetylcholine are the main stimuli for duct cell secretion.

5.4.3 Regulation of Pancreatic Secretion

Pancreatic secretion is essential for assimilation of food: pancreatic enzymes (lipase, amylase, etc.) are essential for chemical digestion of nutrients; bicarbonates are necessary for neutralization of acidic gastric chyme to optimize enzymatic digestion, micellar formation, etc. (as described in ▶ Chap. 3).

Pancreatic secretion is regulated by neurohormonal mechanisms. Parasympathetic control mechanisms are provided by the vagus nerve, secondary intrapancreatic neurons, and pancreatic reflexes. The sympathetic system may influence blood circulation to the pancreas and otherwise has a limited role in the regulation of pancreatic secretion. The hormones cholecystokinin (CCK) and secretin are essential for pancreatic postprandial stimulation (◘ Fig. 5.10).

Pancreatic secretion is activated by meal. Three phases of secretion can be distinguished:

1. The cephalic phase of pancreatic secretion occurs before meal ingestion and when seeing and smelling food stimulates vagal efferences synapsing with intrapancreatic secondary neurons to induce cells secretion through various neurotransmitters including acetylcholine, VIP (vasoactive intestinal polypeptide), and GRP (gastrin releasing peptide).
2. The gastric phase of pancreatic secretion results from distension of the stomach by meal. Gastric distension activates acinar cells by vago-vagal reflexes, and this effect is abolished by vagotomy. It can be reproduced experimentally with distension by a balloon and is therefore independent of chemical stimuli such as gastric acid or meal contents.
3. The intestinal phase of pancreatic secretion is the most important. It is triggered when the gastric chyme reaches the duodenum to induce the release of hormones secretin and CCK into the blood (as shown in ◘ Fig. 5.11).

- *Secretin:* Acidity of the gastric chyme stimulates S-cells located in duodenal mucosa. These endocrine cells, responsible for synthesis and secretion of secretin, are activated by H^+ ions contained in duodenal luminal fluids and release their hormone into the blood circulating to the pancreas. Secretin acts mainly on pancreatic duct cells to activate the secretin receptor located on the basal membrane and its intracellular second messenger cyclic AMP (◘ Fig. 5.10 left). Secretin also acts on the acinar cell to potentiate the effect of CCK on enzyme secretion (◘ Fig. 5.10 right).
- *CCK:* Fatty acids and amino acids from the meal induce the release into circulation of CCK from I-cells of the duodenal mucosa. Activation of the I-cell is due to a direct cell stimulation by the nutrients, to a paracrine action of CCK-RP (CCK-releasing peptide) secreted by endocrine cells of the duodenal mucosa, and by "monitor peptide," a stimulatory agent contained in pancreatic secretions (◘ Fig. 5.12).

Serum CCK acts on specific CCK receptors (CCK-R2) to activate acinar cell secretion of pancreatic enzymes (via the second messenger intracellular Ca^{2+}). Although CCK receptors on the acinar cell basal membrane are well demonstrated in many experimental animal models, they are hardly identifiable in humans where CCK is probably acting on vagal afferent branches to stimulate acinar cells through intermediary neurotransmitters such as acetylcholine, VIP, and GRP (◘ Fig. 5.10). CCK effect on enzyme secretion is potentiated by secretin.

During the intestinal phase, inhibitory mechanisms of pancreatic secretion are also elicited. When trypsin no longer has food substrate to digest, it breaks down

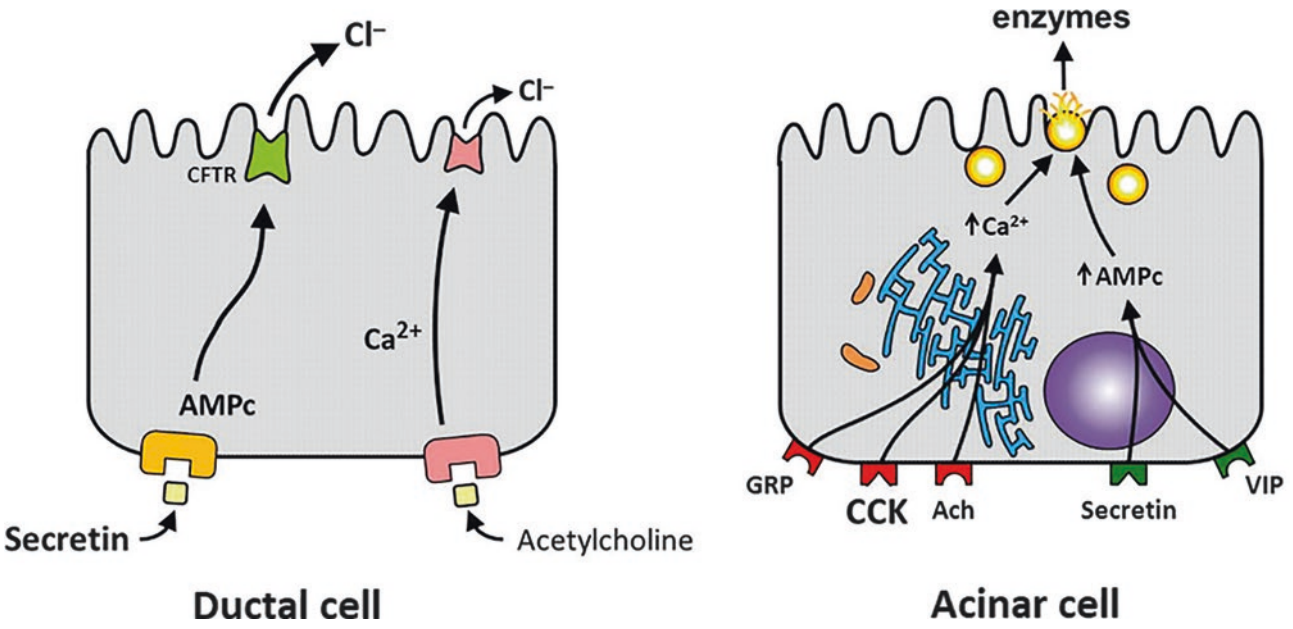


Fig. 5.10 Stimulation of ductal and acinar cells. On the left, the duct cell is stimulated by circulating secretin and neuronal acetylcholine to secrete bicarbonates and ions. On the right, enzymatic secretion of the acinar cell is stimulated by circulating CCK and cholinergic neurotransmitters; CCK stimulation is potentiated by secretin

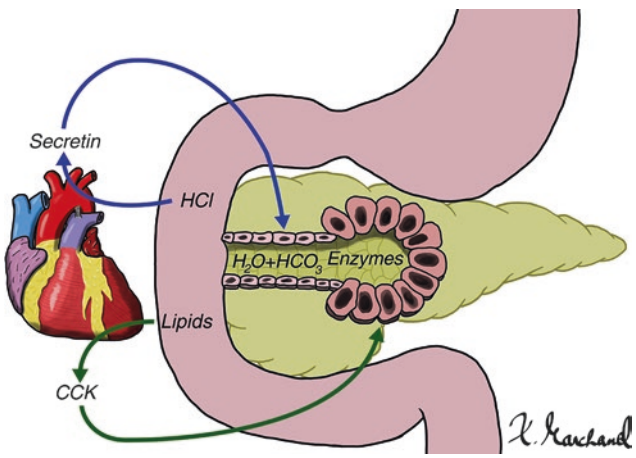


Fig. 5.11 Pancreatic secretion is activated by duodenal hormones secretin and CCK released into the circulation by the gastric chyme reaching the duodenum

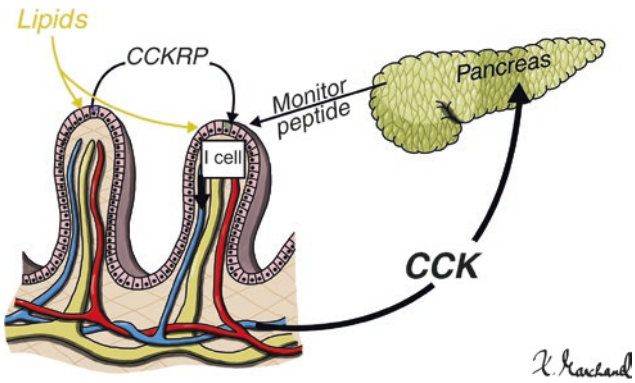


Fig. 5.12 Postprandial release of CCK from I-cell is due to (1) a direct action of diet lipids on the I-cell, (2) CCK-releasing peptide issued from duodenal mucosa, and (3) "monitor peptide" contained in pancreatic secretions

CCK-RP as well as monitor peptide, so that they can no longer stimulate the release of CCK.

5.4.4 Activation of Pancreatic Proenzymes

Pancreatic proteolytic enzymes necessary for digestion of food proteins are secreted in the pancreas in the form of inactive proenzymes to prevent self-digestion of the pancreas. Inactive proenzymes are transformed to active enzymes (chymotrypsinogen/chymotrypsin, trypsinogen/trypsin, proelastase/elastase, etc.) after cleavage, by trypsin, of their inactivation peptide situated at the NH_2 terminal end of the molecule. This activation of pancreatic proenzymes by trypsin takes place in the duodenum after inactive pancreatic trypsinogen has been transformed into active trypsin by the enzyme enterokinase produced by intestinal mucosa (Fig. 5.13).

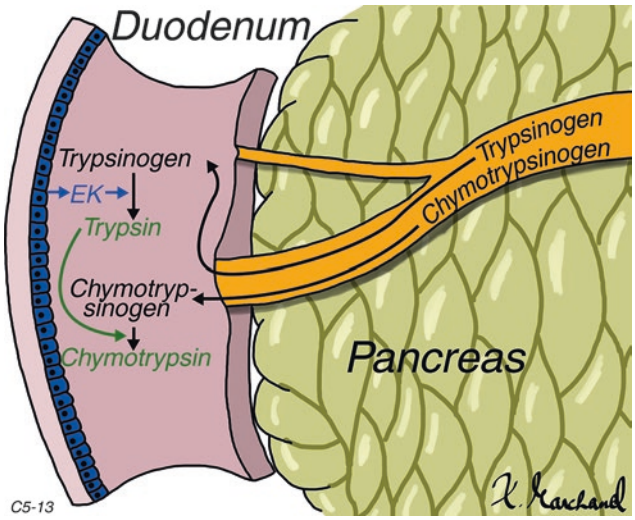


Fig. 5.13 Pancreatic proteolytic enzymes are secreted as inactive proenzymes. Enterokinase (EK) contained in the intestinal brush border transform inactive trypsinogen into active trypsin which will then transform inactive pancreatic proenzymes into activated enzymes

Activation of pancreatic enzymes (and hence pancreatic digestion of nutrients) can therefore be affected in case of enterokinase deficiency (e.g., villous atrophy with celiac disease; see ► Chap. 3).

5.5 Motility/Sensitivity

The sphincter of Oddi (SO) relaxes to allow the passage of the pancreatic (and biliary) secretions into the duodenum. CCK, while stimulating pancreatic secretion and gallbladder contraction, relaxes SO.

Impaired SO relaxation can increase pancreatic duct pressure and lead to pancreatic pain. Impaired relaxation may be due to a fibrous ampulla (for instance, after passage of a biliary stone) or to a neurological dysfunction equivalent to esophageal achalasia ("achalasia of Oddi," which remains however a much debated clinical entity). Rome IV classification (see ► Chap. 4) of functional GI disorders includes SO dysfunction affecting the pancreas or the bile ducts (see ► Chap. 6).

The pancreatic gland seems sensitive to increased intraductal pressure. Pancreatic pain sensation is transmitted mainly by sympathetic afferences traveling through abdominal nodes to the medulla and the brain. Infiltration of the celiac node by pharmacological agents such as lidocaine can, in some cases, relieve pancreatic pain.

5.6 Inflammation Disorders

5.6.1 Acute Pancreatitis

(a) Definition and Generalities

Acute pancreatitis is a common condition, with an incidence up to 38 cases per 100,000 population. It is defined as an acute inflammation, of variable intensity, of the pancreas. In most cases, it is a benign self-limited condition with edema and inflammation of the pancreas (manifested as a severe abdominal pain) that will heal without any anatomical or functional sequelae. In 10–20% of cases, acute pancreatitis is severe and leads to local complications (intra-abdominal fluid collections, abscesses, etc.) Systemic consequences (sepsis, end-organ failure with renal, respiratory insufficiency, etc.) are associated with up to 30% mortality. Severe pancreatitis is associated with important necrosis of the pancreatic parenchyma and can leave, after healing, functional sequelae such as exocrine and endocrine pancreatic insufficiency.

(b) Etiology of Acute Pancreatitis

Causes of acute pancreatitis are summarized in Table 5.2. Biliary pancreatitis and alcoholic pancreatitis account for more than 80% of cases of acute pancreatitis.

- ***Biliary pancreatitis or gallstone pancreatitis*** (40–60% of acute pancreatitis) occurs when a gallstone migrated through the cystic duct to the common bile duct becomes trapped (often transiently) within the ampulla of Vater causing obstruction of the Wirsung pancreatic duct. It is more frequent when the gallbladder contains small stones (>5 mm stones are more likely too large to enter the cystic duct) or biliary sludge (which contains micro-stones likely to migrate across the cystic duct to the common bile duct).
- ***Ethyl alcohol abuse*** is the second most common cause of acute pancreatitis (25–35% of cases). Patients, most often, have a history of chronic alcohol overuse and are more likely to demonstrate clinical and imaging features of chronic pancreatitis when they present with an acute episode of pancreatitis. The mechanism by which alcohol induces damage to the pancreas remains uncertain. It has been proposed that alcohol increases the concentration of pancreatic juice to cause protein plugs obstructing small pancreatic ducts. Alcohol has also been linked to early activation of trypsinogen, which can lead to pancreatic acini autodigestion. Direct toxicity of alcohol or one of its metabolites on pancreatic cells is also possible.

Table 5.2 Causes of acute pancreatitis

Obstructive	***Metabolic***	***Trauma***
Gallstones	Hypertriglyceridemia	
Neoplasia	Hypercalcemia	***Autoimmune***
Parasites		IgG4-mediated
Duodenal diverticulum	***Infectious***	Non IgG4-mediated
Annular pancreas	Viruses	
Choledocele	Bacteria	***Iatrogenic***
Others	Fungi	Post-ERCP
	Parasites	Postoperative
Toxic		
Ethyl alcohol	***Vascular***	***Controversial causes***
Methyl alcohol	Vasculitis	Pancreas divisum
Scorpion venom	Embolic	Dyskinesia of Oddi sphincter
Organophosphorus insecticides	Hypotension	
Medication		***Idiopathic***

5

Other causes of pancreatitis are more rare:

- ***Obstructive pancreatitis*** is due to a blockage of the pancreatic duct leading to increased intraductal pressure and pancreatitis upstream of the obstacle. Intraductal papillary mucinous neoplasm of the pancreas (IPMN) is the most common lesion. In these cases, the acute nature of pancreatitis is probably related to a sudden episode of obstruction caused by a mucin plug trapped within the pancreatic duct; pancreatitis secondary to slow duct obstruction by pancreas adenocarcinoma or ampullary tumor is more rare. In countries where parasitic infections such *Ascaris* or *Clonorchis* are endemic, these parasites can obstruct the pancreatic duct and induce acute pancreatitis.
- ***Drug-induced pancreatitis*** can usually be diagnosed after ruling out more common causes of pancreatitis and establishing an exposure to a drug known to be associated with pancreatitis [the causal association being more or less solid according to the number of cases reported and (but rarely available) to the documentation of recurrence of pancreatitis after reintroduction of the drug]. The most common drugs associated with acute pancreatitis are listed in Table 5.3. Pathological mechanisms are multiple: immunological (e.g., 6-mercaptopurine/azathioprine, 5-ASA), direct drug toxicity (thiazide diuretics), indirect toxicity from metabolites (e.g., valproic acid, DDI), ischemic (diuretics), and thrombotic (estrogens). Delay between exposure to medication and occurrence of pancreatitis is variable, 24 hours (e.g., acetaminophen, codeine, propofol) to more than 30 days (e.g., valproic acid, tamoxifen, hydrochlorothiazide, estrogens, DDI). Drug-induced pancreatitis is seldom severe and usually regresses when the responsible drug is discontinued.
- ***Metabolic*** causes of acute pancreatitis are recognized:

Table 5.3 Drugs classically associated with pancreatitis (alphabetical order)

Azathioprine	Mesalamine (5-ASA)
6-mercaptopurine	Metronidazole
Codeine	Pentamidine
Dapsone	Pravastatin
DDI (didanosine)	Procainamide
Enalapril	Sulfas
Estrogens	Sulindac
Furosemide	Tamoxifen
Hydrochlorothiazide	Tetracycline
INH (isoniazid)	Trimethoprim
Losartan	Valproic acid

  - *Hypertriglyceridemia* can cause pancreatitis when triglyceride serum level exceeds 10 mmol/L as it can be seen in hereditary hyperlipidemia types 1, 2, and 5 or during certain conditions that may increase lipids serum level (alcohol abuse, pregnancy, use of estrogens, tamoxifen, glucocorticoids, etc.). Reducing serum triglycerides levels below 5 mmol/L helps to prevent the recurrence of pancreatitis. The physiopathological mechanism of hypertriglyceridemic pancreatitis is not completely understood. Chylomicrons (triglyceride-rich lipoprotein particles) present in the blood stream in cases of hypertriglyceridemia could occlude pancreatic capillaries leading to ischemia; in animal experimentation, it is possible to induce pancreatitis by perfusing the pancreas with high concentrations of free fatty acids (producing pro-inflammatory mediators?).
  - *Hypercalcemia* (more than 3 mmol/L) is a (rare) cause of acute pancreatitis. The pathophysiological mechanism is unknown (premature activation of trypsinogen and calcium deposition within pancreatic ducts?). Underlying conditions include hyperparathyroidism, hypercalcemia associated to bone metastases, etc.
- ***Infectious agents*** that can cause pancreatitis including viruses (mumps, Coxsackie, hepatitis A or B, *Cytomegalovirus*, herpes zoster, Epstein-Barr, etc.), bacteria (*Mycoplasma*, *Legionella*, *Leptospira*, *Salmonella*), fungi (*Aspergillus*, *Candida albicans*), parasites (*Toxoplasma*, *Cryptosporidium*, *Ascaris*, *Clonorchis sinensis*).
- ***Ischemia-induced pancreatitis*** is usually of mild severity but sometimes can be severe. Causes include vasculitis (lupus, polyarteritis nodosa, etc.), atherosclerosis (thrombotic or embolic), or systemic hypoperfusion (hypovolemia secondary to hemorrhagic shock, intraoperative hypotension, sepsis, etc.).
- ***Iatrogenic pancreatitis*** is most often associated with retrograde cholangiopancreatography (ERCP). Hyperamylasemia (biochemical pancreatitis) can be found in more than 35% of patients after undergoing this endoscopic intervention, and clinical pancreatitis can be diagnosed in up to 5% of cases.
- ***Traumatic pancreatitis*** can be from penetrating (e.g., gunshot, stab wounds) or blunt where the pancreas is compressed against the spine (e.g., punch to the epigastrium, steering wheel impact during car accident, fall on bicycle handlebar).
- ***Acute pancreatitis in children***

  The most common causes of acute pancreatitis in children are, in descending order of frequency, abdominal trauma, idiopathic cases, genetic conditions involving the pancreas, infections, medications, and lithiasis.

  Diagnosis and treatment of pancreatitis in children follow the same cardinal rules as in adults.

(c) Physiopathology of Acute Pancreatitis

Acute pancreatitis results from self-digestion of the pancreatic gland by its proteolytic enzymes. This occurs during inappropriate intrapancreatic activation of trypsinogen in trypsin which surpasses the endogenous protection mechanisms of the acinar cell. Trypsin then activates other proenzymes co-located in the acinar cell, thereby inducing digestion of acinar cells and pancreatic tissue.

Necrosis of pancreatic tissue leads to an inflammatory reaction, locally at the pancreas as well as systemically via the release of pro-inflammatory (TNF; IL-1, IL-6, and IL-8; PAF; etc.) and anti-inflammatory cytokines (IL-2, IL-10, IL-11, etc.).

The local inflammatory reaction first manifests as edema of the pancreas and surrounding tissues (retroperitoneal pancreatic area, lesser peritoneal sac). In more severe cases, pancreatic necrosis with peripancreatic, retroperitoneal, or abdominal fluid collections can develop. When necrosis affects large vessels, hemorrhagic pancreatitis may occur, associated with hematomas in the pancreatic compartment or in the retroperitoneum.

The release of pro-inflammatory cytokines may be important enough to induce systemic complications such as acute respiratory distress syndrome (ARDS), renal failure, heart failure, shock, metabolic complications (e.g., hyper or hypoglycemia, metabolic acidosis, hypocalcemia, hypomagnesemia), etc.

Septic complications can occur later, generally after the second week of evolution of severe pancreatitis (fever in the early period of pancreatitis is rarely due to infection but rather to the inflammatory process). They result from infection of the necrotic pancreatic tissue, either by blood contamination or by translocation of intestinal bacteria (this explains the importance to administer enteral nutrition early in the course of pancreatitis, as it has been shown to maintain intestinal barrier integrity and decrease bacterial translocations and the risk of secondary pancreatic infections).

(d) Clinical Manifestations of Acute Pancreatitis

Abdominal pain, present in more than 90% of cases, has a fast onset, reaching its peak in the first hour, is constant, and can be very severe. It often lasts more than 24 hours and can extend over several days. Pain is perceived mainly in the epigastric area with transfixing radiation to the back; it frequently diffuses to the upper hemi-abdomen and can extend into the lower abdomen

if inflammatory collections are present in para-colonic gutters. Nausea and vomiting are common.

Findings on physical examination vary according to the severity of pancreatitis. In patients with benign acute pancreatitis, the clinical signs may be limited to epigastric tenderness only. In more severe pancreatitis, tachycardia, tachypnea, hypotension, and other signs of shock may be seen. Fever (37.5–39 °C) is frequent; it is related to the important inflammatory reaction prevailing during the first week of presentation and is uncommonly associated with an infection (which occurs later in the evolution of the pancreatitis). The abdomen may be distended because of paralytic ileus and its associated intestinal dilatation. Intestinal sounds are reduced. Palpation of the abdomen accentuates pain, especially in the epigastric region; abdominal rigidity and rebound tenderness (Blumberg's sign) are suggestive of peritoneal irritation.

In rare cases (1%), one may observe ecchymotic staining of one or both flanks (Grey-Turner's sign) or in the umbilical region (Cullen's sign) and witness of a necrotico-hemorrhagic pancreatitis which carries a poor prognosis. Subcutaneous nodules, red and tender, from 0.5 to 2 cm in diameter can be seen (often on the extremities but also on the trunk, scalp, or buttocks), corresponding to subcutaneous fat necrosis due to fat digestion by large circulating quantities of lipolytic enzymes.

The differential diagnosis of epigastric pain seen in pancreatitis include, among others, biliary colic, cholecystitis, perforated duodenal ulcer, mesenteric ischemia, intestinal obstruction, lower myocardial infarction, aortic dissection, etc.

(e) Diagnostic Evaluation of Acute Pancreatitis

***Blood tests*:** Amylase or lipase levels more than three times the upper normal limits are characteristic of acute pancreatitis. The level of both enzymes rises in parallel during the first 12 hours of pancreatitis and remains high from a few hours to a few days. The sensitivity of these two assays for the diagnosis of acute pancreatitis is similar (85–100%). There is no direct relationship between the rate of elevation of these enzymes and the severity of pancreatitis. Serum amylase has a shorter half-life and therefore decreases sooner after a pancreatitis episode compared to lipase. Hyperamylasemia is also not specific to the pancreas and can be encountered in several non-pancreatic conditions (such as parotitis, cholecystitis, intestinal perforation, mesenteric ischemia, renal failure, ectopic pregnancy, ovarian tumor, etc.). Given its low specificity, some laboratories have discontinued serum amylase dosage as a diagnostic test for pancreatitis and replace it with serum lipase due to its greater specificity (though not 100%) for pancreatitis.

Several other blood markers can be abnormal, without being specific for acute pancreatitis. Hyperleukocytosis is common. Elevated hemoglobin and hematocrit levels are indicative of hypovolemia in the vascular space at the expense of a "third-spacing" or fluid loss into the retroperitoneum; they can also decrease quickly in cases of hemorrhagic pancreatitis. Bilirubin, AST, ALT, and alkaline phosphatase may rise, especially in cases of biliary pancreatitis. Loss of circulating volume can lead to renal impairment with increased creatinine levels as well as electrolytes abnormalities. Some blood analyses can guide the etiological diagnosis (e.g., hypertriglyceridemia, hypercalcemia, high blood alcohol levels, etc.).

***Imaging*:** Multiple imaging modalities can be effective for the evaluation of acute pancreatitis and the techniques can often be complementary:

- *Abdominal X-ray* (flat plate) often appears normal in acute benign edematous pancreatitis. In a more severe pancreatitis, intestinal ileus characterized as a localized sentinel intestinal loop dilatation in the pancreas region or more diffuse intestinal distension is common; more rarely, intestinal or colonic wall edema and organ displacements (from inflammatory fluid accumulation) can be seen. Calcified gallstones can suggest a biliary etiology, while pancreatic calcifications sign an underlying chronic pancreatitis. Flat plate abdominal X-ray can be used to rule out visceral perforation (with free air in the abdomen) as a cause of the abdominal pain.
- *Chest X-ray*: atelectasis in the inferior segments of the lungs, pleural effusions, may occur. Pulmonary infiltrates, pericardial effusion, signs of heart failure, and ARDS are less common and usually associated with severe forms of acute pancreatitis.
- *Abdominal ultrasound* is the test of choice for asserting the presence of gallstone(s) when biliary pancreatitis is suspected; dilatation of the common bile duct (although found in only a minority of cases of biliary pancreatitis) is highly suggestive of an obstructing stone (sometimes, the stone can be seen). Ultrasound can also confirm inflammation of the pancreas and examine for pancreatic fluid collections; however, it is less sensitive for the identification of these finding compared to CT scan.
- *Scanner* (CT scan or computed tomography of the abdomen): CT scan is the imaging modality of choice for acute pancreatitis (see ◘ Fig. 5.14). It allows evidence (1) to make the diagnosis of pancreatitis, (2) to rule out other conditions with a similar clinical picture (e.g., perforation of a hollow viscus, mesenteric ischemia, etc.), (3) to assess the severity of pancreatitis (Balthazar's criteria), and (4) to identify complications (pseudocysts, abscesses, intestinal or biliary obstruction, etc.).

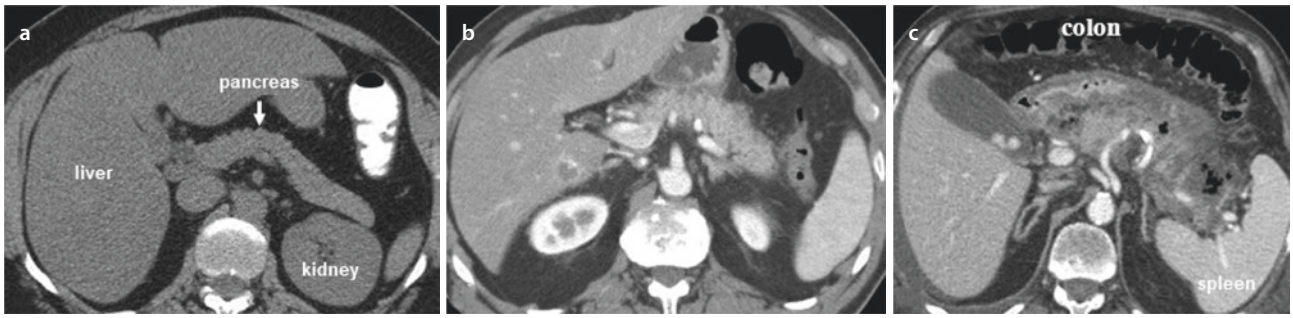


Fig. 5.14 CT scan of the abdomen and pancreatitis. **a** Normal pancreas. **b** Mild pancreatitis: edema of the gland and surrounding tissues; the pancreas is well perfused by the intravenous dye administered. **c** Severe pancreatitis: the pancreas is very edematous and necrotic with perfusion defects and air bubbles indicating abscesses

In benign self-resolving pancreatitis, CT scan performed within the first 48 hours of presentation is seldom useful, and it should not be prescribed routinely. Obtaining a CT scan in the first hours of pancreatitis should be limited to cases where the diagnosis is uncertain (e.g., to rule out perforated duodenal ulcer, aortic aneurysm, etc.).

In more severe pancreatitis, CT examination can be performed after 48–72 hours of evolution to evaluate the presence of pancreatic necrosis and other relevant complications. Edematous pancreatitis, recognizable by the good coloration of the gland, is always evolving favorably. Tissue digestion with significant necrosis of the pancreatic gland is characterized on CT scan by the lack of perfusion to necrotic tissue; clinical severity of acute pancreatitis is directly related to the extent of tissue necrosis.

- *Magnetic resonance imaging* (MRI): MRI is highly sensitive to detect choledocholithiasis. It is the only advantage of MRI (over CT scan) when used in the evaluation of acute pancreatitis.
- *Echo-endoscopy (EUS)* is highly sensitive for the evaluation of choledocholithiasis. It is seldomly used for this purpose in cases of acute pancreatitis as it is more invasive than MRI.
- *Endoscopic retrograde cholangiopancreatography (ERCP):* this endoscopic technique allows to visualize the bile duct or the pancreatic duct, but its complication rate (pancreatitis, infection, etc.) prohibits its general use in acute pancreatitis. It is the treatment of choice for choledocholithiasis, but its role in acute biliary pancreatitis is very limited. Stones trapped in the ampullary region, causing obstruction of the pancreatic duct and pancreatitis, will in a large majority (80–85%) of cases spontaneously pass into the duodenum within the first 24–48 hours of illness. The indication for ERCP (for biliary sphincterotomy and evacuation of gallstones) in acute biliary pancreatitis is limited to the case where persistent bile duct obstruction, especially with cholangitis, is suspected or confirmed.

(f) Assessment of Severity and Prognosis of Acute Pancreatitis

Early assessment of the severity of acute pancreatitis contributes to optimize treatment and prevent local and systemic complications.

Different clinical scoring systems have been developed to predict the severity of acute pancreatitis. The Ranson score is certainly the most popular (although more rarely used in nonspecialized units). It includes 11 variables that are collected during the first 48 hours of illness (Table 5.4). Mortality risk from acute pancreatitis increases significantly with the number of criteria present (Fig. 5.15). The APACHE-II and BISAP scores have also been suggested in the same context but are less commonly used due to their greater complexity. Other authors have suggested that simple markers, such as a CRP >150 mg/L at 48 hours after presentation, could help to predict the adverse evolution of a pancreatitis (and justify more aggressive therapies). In common practice, the importance of these predictive scores is however debated. In more than 80% of cases, pancreatitis resolves in less than 1 week.

Table 5.4 Ranson score (11 criteria) for acute pancreatitis

Criteria at arrival	Criteria after 48 hours
Age >55 years old if ROH, or >70 years if biliary cause	Ht decrease >10%
Leukocytes >16,000 × 10^6/L	Urea >2 mmol/L (in spite of liquids)
Blood glucose >11 mmol/L	Ca^+ < 2 mmol/L
LDH > 350 u/L	pO_2 < 60 mmHg
AST > 250 u/L	HCO_3^- deficit >4 mmol/L
	Liquid sequestration >6 L

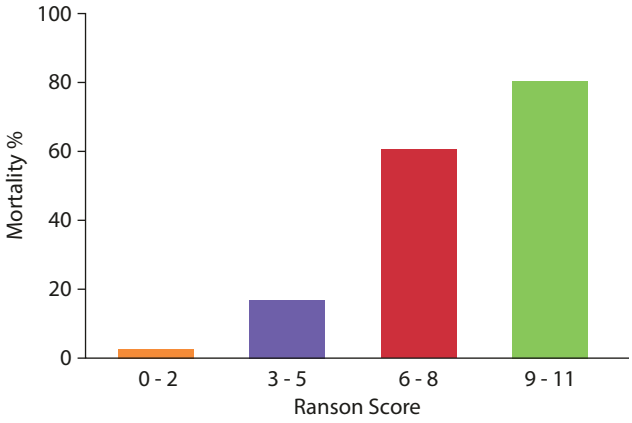


Fig. 5.15 Ranson score and mortality associated with acute pancreatitis. The majority of patients with severe pancreatitis have three to six criteria

Derived from CT scan findings, Balthazar radiological criteria also predict the severity of acute pancreatitis: severity of pancreatic/peripancreatic inflammation + pancreatic necrosis (areas with perfusion defects) in <30%, 30–50%, or >50% of the pancreatic gland = mortality rates of 3, 6, or 17% respectively.

(g) Complications of Acute Pancreatitis

Acute pancreatitis can be associated with local or systemic complications (Table 5.5).

- ***Fluid collections***, pancreatic as well as peripancreatic, are common. After 4 weeks, they can mature to become pseudocysts or encapsulated necrosis zones.
- ***Pseudocyst of the pancreas*** begins with an effusion of inflammatory fluid around the pancreas, especially in pancreatic retroperitoneum and at times extends to reach the para-colonic or pararenal gutters. These amylase (and lipase)-rich fluid collections may persist, and, after at least 6 weeks of evolution, become encapsulated by a fibro-inflammatory wall (hence the name pseudocyst, by comparison with a real cyst whose walls are lined with epithelial cells). The presence of pseudocysts is suspected when pain and/or elevated serum pancreatic enzymes persist following an acute episode of pancreatitis. Ultrasound or abdominal CT scan confirms the existence of pseudocyst(s).

Asymptomatic pseudocysts, regardless of their size, do not require treatment. Drainage is indicated when cysts are responsible for persistent pain, symptomatic compression of the digestive tract (such as biliary compression with jaundice or duodenal compression with gastric outlet obstruction and vomiting), or if the cyst becomes infected. Therapeutic intervention will also be required in presence of rare complications, such as intracystic hemorrhage (from arterial pseudoaneurysm) or pseudocyst rupture leading to pancreatic ascites with a very high amylase content.

Various interventions are available to drain a pseudocyst: percutaneous drainage is carried out under radiological imaging (US or CT scan); endoscopic drainage is done via the transgastric or transduodenal route; and surgical drainage evacuates the cystic content in the stomach (cystogastrostomy), or the duodenum (duodeno-cystostomy), or the intestine (on a Roux-en-Y intestinal loop).

- ***Sterile* vs *infected necrosis***. Necrosis of pancreatic tissue occurs early in the evolution of pancreatitis and is a determinant of pancreatitis severity. Pancreatitis is said to be necrotizing if more than 30% of the pancreatic tissue is not perfused on the CT scan of the abdomen realized with contrast dye. Necrotizing pancreatitis is generally more severe and is associated with more complications than edematous pancreatitis.

Pancreatic necrosis can be sterile or infected. It is rare for necrotic tissue to become infected before the second week of evolution of an acute pancreatitis. Leukocytosis or fever after 10 days of evolution must raise the suspicion of infected pancreatic necrosis. Diagnostic puncture, under radiological guidance or other, of the necrotic zone must be done with the aspirated liquid subjected to microbial study with gram staining and culture to determine the bacteria involved and tailor antibiotic therapy. Until recently, infected necrosis was treated by surgical debridement (often very morbid). We now prefer, in a stable patient without systemic failures, medical treatment with broad-spectrum antibiotics; if there is a suboptimal response or clinical deterioration of the patient's condition, minimally invasive debridement, by a surgical or endoscopic approach, is performed.

Table 5.5 Complications of acute pancreatitis

Local complications	Systemic complications
Fluid collection	Respiratory failure
Pseudocyst	Renal failure
Sterile necrosis	Shock
Infected necrosis	Hyperglycemia
Abscess	Hypocalcemia
Vascular	Intravascular coagulation
Thrombotic	Adipose necrosis
Hemorrhagic	

- ***Vascular complications.*** The splenic vein, running along the body of the pancreas, and the portal vein, being intimately connected to the pancreatic head, may be sites of reactive thrombosis related to peripancreatic inflammation. Thrombosis in these areas can lead to portal hypertension [central (portal vein thrombosis) or segmental (splenic vein thrombosis)] and, in some cases, result in esophageal or gastric varices which can be source of important GI bleedings (see ▶ Chap. 8). Prophylactic anticoagulation is a component of severe acute pancreatitis treatment in order to prevent thrombotic events.

  Rupture of vascular structures can cause bleeding in the abdomen (hemorrhagic pancreatitis), via the pancreatic duct (with "wirsungorrhagia"), or in a pseudocyst. These complications can be urgent and life-threatening. They are usually treated by radiological intervention (vascular embolization) or by (often morbid) surgery.
- ***Systemic complications.*** *V*arious organs can be affected in severe acute pancreatitis.

  Renal (prerenal) failure is common due to hypovolemia generated by severe vomiting or by loss if fluids to the "third space" in the pancreatic compartment. Shock, secondary to volume deficit, bleeding, sepsis, etc., may be lead to acute tubular necrosis requiring dialysis.

  Respiratory failure is a frequent complication in severe pancreatitis: atelectasis, pleural effusion, pneumonia, and acute respiratory distress syndrome (ARDS) are contributory. Increased oxygen supply, thoracocentesis, antibiotic therapy, and even ventilation may be necessary for treatment.

  Hyperglycemia, caused, among other things, by impaired insulin production due to islet cell necrosis, is possible. Hypocalcemia can occur as a result of calcium precipitation following fat saponification (chelation of calcium salts by free fatty acids, released due excess concentrations of lipase in circulation) which occurs mainly in the abdominal cavity (with the formation of yellowish droplets classically called "candle stains").

(h) Treatment of Acute Pancreatitis

No pharmacological treatment is recognized as effective for the treatment of pancreatic inflammation. The key principles for the treatment of patients with acute pancreatitis are early aggressive IV fluid resuscitation, analgesia, close monitoring, early identification and treatment of organ failure, and thrombosis prophylaxis.

(1) Early Days (Day 0–3)

- "*Pancreatic rest*" has always been the basic treatment (although empirical) for acute pancreatitis. Since the pancreas is active mainly during the postprandial period to secrete digestive enzymes, abstaining from oral food was proposed as the best way to minimize the production of pancreatic enzymes responsible for the autodigestion of pancreatic tissue.

  Recently, numerous studies focused on the risks of prolonged fasting and the benefit of early realimentation in patients with acute pancreatitis, and the strict and prolonged NPO diet is no longer recommended. Patients can often start within 24 hours of presentation with a clear fluid diet and progress to regular diet within 72 hours.
- *Intravenous fluid* replacement is necessary to compensate for a reduced oral intake as well as for losses resulting from vomiting or creation of a third space in the abdominal cavity (intra-abdominal or retroperitoneal). Hypovolemia is recognized as an unfavorable prognostic factor, and its aggressive treatment is essential. IV administration of several liters of fluid (lactate Ringer's) will be necessary on a daily basis, aiming to correct (1) hypotension, (2) plasma hematocrit, and (3) serum urea, and (4) maintain urine outcome greater than 0.5 mL/kg/h.
- *Analgesia* is often essential with opiates such as meperidine 50–75 mg i.m. q 3 h, hydromorphone 1–4 mg s.c. q 2–3 h, morphine 5–15 mg s.c. q 3–4 h, etc.
- *Thrombosis prophylaxis* is recommended.
- *Biological parameters* must be monitored to correct kidney failure, electrolytes disorders (serum urea, creatinine, sodium, potassium, bicarbonates), hypo- or hyperglycemia, as well as hypocalcemia.
- A *nasogastric tube* may be useful to relieve symptomatic nausea or vomiting (but is not essential or useful to improve pancreatitis outcome).

(2) Middays (Day 4–14)

- *Replacement feeding* is necessary after 3–5 days of fasting (for details, see ▶ Chap. 23). Enteral tube feeding, nasogastric or nasojejunal (more complex but possibly better tolerated), is preferred. If enteral feeding is not tolerated, parenteral nutrition will be required (but a small oral intake should be given to maintain intestinal mucosal integrity and prevent translocation of intestinal bacteria causing infection of necrotic tissues).
- *Fever* in the first 10–15 days of an acute pancreatitis episode is most often due to the inflammatory process and not infection.
- *Specific and particular considerations:*
  - With patients suffering from acute pancreatitis due to alcohol abuse, alcohol withdrawal syndrome may develop during the first days of hospitalization. Long-term management can be

facilitated with the support of specialty services such as addiction counselling, social work, psychiatry, etc.

- In biliary pancreatitis, the biliary stone responsible for the pancreatitis passes spontaneously in 80–85% of patients as the pancreatitis rapidly resolves. If pancreatitis persists, the possibility of a residual stone obstructing the pancreatic ampulla must be considered; MRI cholangiography or endosonography (EUS) may be useful before proceeding to an ERCP with sphincterotomy and stone extraction. The risk of gallstone pancreatitis recurrence is 20% in 1 month and 60% in 6 months; therefore, a cholecystectomy is required soon after the pancreatitis episode.
- In acute pancreatitis due to hypertriglyceridemia, lipid levels may decrease rapidly during the reduced oral intake period and fenofibrate treatment. In severe or persistent cases, plasmapheresis can be used to lower serum lipids levels and improve outcomes.
- Pancreatitis can be severe in 10–20% of cases. Close monitoring in a hospital setting or intensive care unit is warranted to prevent metabolic and respiratory complications.

(3) Late Days (Week 2–6)

Fever or clinical deterioration of the patient may be signs of infection of the necrotic tissues. Blood cultures and puncture of pancreatic or abdominal collections for culture of the collected liquids are essential. Medical treatment with antibiotics can be effective, but debridement with endoscopic, laparoscopic, or open surgical procedures may be required.

(4) Very Late Days (>6 Weeks)

Fluid collections are now encapsulated (pseudocysts), and, if symptomatic (compression of adjacent organs, pain, etc.), are amenable to drainage treatment.

The management of acute pancreatitis is summarized in Fig. 5.16.

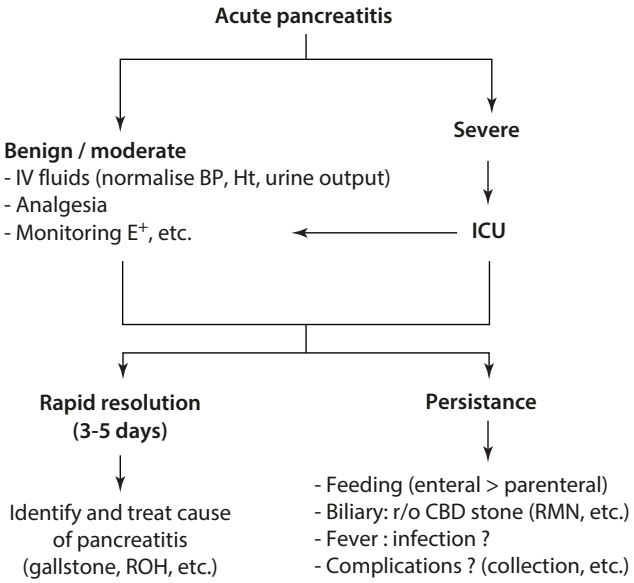


Fig. 5.16 Acute pancreatitis: initial treatment

5.6.2 Chronic Pancreatitis

(a) Definition and Generalities

Chronic pancreatitis is a chronic inflammatory disease of the pancreas that results in definitive structural and functional damage to the gland. This leads to a decline in exocrine and endocrine pancreatic secretory functions that become increasingly important over the course of disease progression and is often associated with chronic epigastric pain.

Stigmata of chronic pancreatitis are found in 5% of autopsies. The annual incidence of chronic pancreatitis is relatively low (3–9/100,000 population), and its prevalence is around 25/100,000 (and varies by the rate of chronic alcoholism in the population being studied). Chronic pancreatitis is a frequent cause of repeated hospitalizations, reduced quality of life, and death. Mortality and morbidity in subjects with chronic pancreatitis is related to various factors including complications from alcoholism, smoking, pancreatic cancer, or surgery.

(b) Pathology and Pathophysiology of Chronic Pancreatitis

On histology, chronic pancreatitis is characterized by fibrosis, dilated ducts, and protein precipitates in ducts lumen. Chronic inflammatory infiltration, with lymphocytes, plasma cells, and macrophages, often coexists with areas of acute pancreatitis characterized by edema, acute inflammation, and acinar cell necrosis. Histological damage is at first lobulated and heterogenous but will involve more and more pancreatic parenchyma over the progressive evolution of the disease. Calcifications develop from protein plugs formed within the ducts. Progressive replacement of acini, and later of the islets of Langerhans, by fibrosis explains the development of exocrine pancreatic insufficiency followed by diabetes.

In the obstructive forms of chronic pancreatitis, histological anomalies occur upstream of the obstruction and are more diffuse and homogenous. Ductal protein plugs, characteristic of others forms of chronic pancreatitis, are not present. Pancreatic tissue downstream of the obstructive lesion is spared.

The pathophysiological mechanism of chronic pancreatitis is unclear. Three main models are retained to date: (a) the work of J. C. Sarles suggested that the chronic ingestion of alcohol produces pancreatic secretions of reduced volume, rich in proteins and low in bicarbonate, which promotes the formation of protein plugs in the excretory ducts with progressive obstruction of the pancreatic ducts, leading to the atrophy and fibrosis of exocrine tissue found upstream of the obstruction. (b) A second model suggests a toxic effect of alcohol, or its derivatives, on exocrine pancreatic tissue and stellate cells is responsible for the fibrosis found in the pancreas. (c) The third model (necrosis-fibrosis) argues that repeated (clinical or subclinical) episodes of acute pancreatitis produce cellular necrosis that results in the disappearance of the pancreatic tissue and its replacement by fibrosis.

None of these models fully explains the development of chronic pancreatitis and, in particular, the fact that only a small proportion (about 5%) of alcoholics develops chronic pancreatitis. Other factors including exogenous (environmental) or endogenous (genetic predisposition) also probably contribute to the pathogenesis of the disease. It is now recognized that smoking is a very important cofactor in the development of alcoholic chronic pancreatitis. Certain genetic mutations, in particular SPINK 1 (see section on hereditary pancreatitis), have been associated with alcoholic or tropical chronic pancreatitis. A recent American-European study (Whitcomb, D. C., 2012) using GWAS technology (Genome Wide Association Study) which allows for the evaluation of the entire genome revealed an important association between chronic alcoholic pancreatitis and the gene encoding claudin 2 (CLDN2), a protein of acinar cells intercellular junctions. This gene is carried by the chromosome X, which could explain the strong preponderance of males in alcoholic chronic pancreatitis.

Table 5.6 Chronic pancreatitis: various causes are often identifiable by the presence or absence of calcifications (evaluated on imaging examinations)

With calcifications	Without calcification
Alcoholic	Metabolic
Tropical	Hypertriglyceridemia?
Genetic	Obstructive
Mutations PRSS1, CFTR, SPINK 1	Autoimmune
Metabolic	Postnecrotic
Hypercalcemia	Asymptomatic pancreatic fibrosis
Idiopathic	Chronic alcool
	Age
	Chronic kidney failure
	Diabetes
	Radiotherapy
	Idiopathic

(c) Etiology of Chronic Pancreatitis

Chronic pancreatitis may present in calcifying or non-calcifying forms (detectable in imaging examinations) and is each has been linked to several causes (Table 5.6).

Alcohol Alcohol abuse is responsible for 60–70% cases of chronic pancreatitis. The risk of developing the disease increases with amount of alcohol consumed. Although there is no lower risk threshold, in the majority of the cases, the consumption exceeded 150 g/day for a period of 5–10 years. However, only a small proportion (3–15%) of excess alcohol consumers will develop chronic pancreatitis. Smoking is now recognized as a major cofactor in the pathogenesis of alcoholic pancreatitis (and pancreatic cancer), and other factors were also mentioned such as genetic predisposition, diet rich in protein or fat, and antioxidant deficiency. Although the majority of heavy alcohol consumers do not develop clinical features of pancreatitis, autopsy and endosonography studies show morphological abnormalities of chronic pancreatitis in many of these individuals.

First clinical manifestation of alcoholic pancreatitis is often repetitive episodes of «acute» pancreatitis, on a background of morphological changes of chronic disease. Pancreatic calcifications are seen in about 60% of cases, and pancreatic insufficiency, exocrine and endocrine, occurs in 50% of patients after many years of evolution. In a small percentage of cases, the disease manifests with pancreatic insufficiency, calcified pancreas on imaging, and no abdominal pain. The prognosis for alcoholic-related chronic pancreatitis is poor, as these patients have reduced survival and poor quality of life. Stopping alcohol consumption can reduce disease progression and morbidity.

Tropical Calcifying chronic pancreatitis is common in tropical regions, particularly in the province of Kerala in southwest India. The cause is unknown, but genetic abnormalities have now been identified, and environmental factors (nutritional deficits, infections) have been mentioned. The disease is revealed clinically in most cases before the age of 40 years by abdominal pain associated with pancreatic insufficiency and severe malnutrition.

Hereditary/Genetic Chronic pancreatitis and recurrent pancreatitis have now been associated with various gene mutations including those encoding cationic pancreatic trypsinogen (PRSS1), trypsin inhibitor (SPINK 1), and membrane protein CFTR. The latter two are predisposing factors for pancreatitis, but are not sufficient alone to induce the disease.

- Cationic trypsinogen (encoded by the PRSS1 gene) is the major form of trypsinogen in the pancreas [the two other forms, anionic trypsinogen (PRSS2) and mesotrypsin (PRSS3) representing only 35%]. More than 20 PRSS1 mutations have been described. A single mutation is sufficient to produce the disease with autosomal dominant transmission. These mutations are responsible for hereditary pancreatitis by inactivating the trypsin self-degradation site.
- Trypsin inhibitor (encoded by the SPINK1 gene) is a 56-amino acid protein that specifically inhibits trypsin by binding to its active site. It is thus an internal defense system against inappropriate activation of trypsin in the acinar cell. Among the identified mutations of SPINK1, the two most common, N34S and P55S, are found in about 2% of the general population and are not able on their own to cause pancreatitis. On the other hand, the high frequency of these mutations (approximately 25%) in patient populations suffering from chronic idiopathic pancreatitis supports their association with pancreatic disease.
- CFTR (cystic fibrosis transmembrane conductance regulator) is a transmembrane protein of 1480 amino acids expressed in several epithelial cells of the respiratory tract, digestive tract, bile ducts, and pancreatic ducts to control ions exchange (in particular the secretion of chloride and bicarbonate). More than 1600 mutations in the CFTR encoding gene are known to modify to various degrees the synthesis or activity of the protein; they have been classified according to the resulting clinical phenotype as severe, moderate, or mild mutations. The association of two severe mutations abolishes the biological function of CFTR, and leads to cystic fibrosis of the pancreas (discussed in the ▶ Sect. 5.9).

  On the other hand, the association of a severe and a mild mutation leads to an atypical disease phenotype and has been found in cases of chronic or recurring pancreatitis of undetermined etiology. Heterozygote mutations and CFTR polymorphisms are common in European and American populations without necessarily leading to a clinical phenotype of chronic or recurrent pancreatitis; it is likely that other factors, environmental or genetic, must be combined with CFTR mutations to produce the clinical picture.

Identification of genetic abnormalities related to pancreatic disease is very contributive in the understanding of the disease physiopathology. Genetic variants associated to chronic pancreatitis can be classified into mechanistic pathways explaining their pathogenic effects: trypsin-dependent pathway (including PRSS1, PRSS2, SPINK1, CTRC genes) appears most important in pancreatitis physiopathology; misfolding of pancreatic enzymes (mutations in CPA1, CEL genes) is an apparent but rare mechanism; abnormal ductal secretion (CFTR, claudin 2, TPRV6 genes) is more and more confirmed as an important pathway in the genesis of chronic pancreatitis.

Metabolic Hypercalcemia is associated with the activation of trypsinogen and calcium deposition in the pancreatic ducts. The association between familial hyperparathyroidism and chronic pancreatitis is well recognized.

Hypertriglyceridemia is a classic cause of recurrent acute attacks of pancreatitis, but its relationship with chronic pancreatitis remains controversial.

Obstructive Chronic obstructive pancreatitis corresponds to a diffuse and homogenous atrophy of the exocrine pancreas upstream of a pancreatic duct blockage and associated with inter- and intralobular fibrosis. Various lesions may be responsible for ductal obstruction including neoplastic stenosis, inflammatory scar, pancreatic stone, papillary stenosis, etc. In some cases, correcting the blockage can restore the pancreatic function.

Obstructive pancreatitis caused by pancreas divisum? Pancreas divisum is an anatomical variant found in 4–11% of the population (see ▶ Sect. 5.3) and which has no clinical consequence in the majority of cases. The debate as to whether it is associated with a pancreatic pathology (acute recurrent pancreatitis or chronic pancreatitis) is still unresolved. In certain cases of pancreas divisum where the dorsal duct (of Santorini) is dilated upstream of the minor papilla, ductal hyperpressure leading to obstructive pancreatitis may probably be considered.

Autoimmune Pancreatitis (AIP) This inflammatory chronic pancreatitis occurs mainly in men (2:1) after the age of 50. Two types are recognized: AIP type 1 (which could be called IgG4 disease) is often associated with elevated serum IgG4. The pancreas is infiltrated with lymphocytes and plasma cells expressing IgG4. This form of pancreatic disease represents 5–6% cases of chronic pancreatitis. The disease may be limited to the pancreas or affect other organs, especially the bile ducts, salivary glands, and retroperitoneum. AIP type 2 has normal IgG4 levels, is restricted to the pancreas, and is associated

with chronic inflammatory bowel disease, Crohn's disease or ulcerative colitis.

Autoimmune pancreatitis can manifest as painful attacks of acute pancreatitis or by a painless obstructive jaundice due to an inflammatory mass in the head of the pancreas compressing the intrapancreatic portion of the bile duct. In this type of presentation, it is important to assess for the presence of a neoplastic lesion of the pancreas. Jaundice can also come from a biliary tract stenosis appearing like sclerosing cholangitis or a cholangiocarcinoma.

Imaging evidence of AIP includes a tumor-like mass (as discussed above) or a diffusely enlarged pancreas (typically having a "sausage" appearance). Serum hypergammaglobulinemia is present in 50–60% of cases, with elevated IgG4 levels (with a diagnostic sensitivity of 75–90% in AIP type 1).

A major diagnostic criterion for autoimmune pancreatitis is its rapid clinical and radiological response to corticosteroid treatment. Despite a complete response to corticosteroid therapy, 30–40% of patients will have a recurrence more or less later. This can be managed again with steroids or in some cases requires maintenance treatment with small doses of steroids or with thiopurine.

Chronic pancreatitis in children:

- Hereditary pancreatitis must be considered in any child with recurring episodes of unexplained pancreatitis or from the outset at the first episode if there is a family history of pancreatitis. PRSS1 gene, which codes for cationic trypsinogen, is most frequently involved.
- Between 30% and 70% of chronic pancreatitis case in children remains unexplained and is called idiopathic.
- Autoimmune pancreatitis, especially type 2 associated with inflammatory bowel disease, can occur in pediatric age.

(d) Clinical Presentation of Chronic Pancreatitis

The three clinical challenges associated with chronic pancreatitis are (1) *abdominal pain* from the sick pancreas, (2) *exocrine pancreatic insufficiency* due to the inability of the destroyed pancreas to produce digestive enzymes (amylases, lipases, etc.) in sufficient quantities to ensure digestion of ingested food, and (3) *endocrine insufficiency* by destruction of the islets of Langerhans and insufficient production of insulin to allow blood glucose homeostasis.

- ***Pain*** is the cardinal symptom of pancreatitis and the main reason for hospitalization and surgery in this population of patients. Chronic pain is present in 50–90% of subjects with chronic pancreatitis and is often a major impediment to their quality of life. It is felt in the epigastric area, throbbing, radiating to the back, and aggravated by meals.

  The natural history of this painful syndrome is variable. Pain can occur early or late in the evolution of the disease. It can present as intense but transient flare-ups which resorb completely or partially and leaving the patient asymptomatic between episodes or either with more or less intense chronic pain. In some cases, pain diminishes over time in parallel with the progressive destruction of the pancreatic parenchyma and appearance of exocrine pancreatic insufficiency.

  Pathophysiology of pain syndrome is not completely understood, but two main mechanisms seem to be at work: (1) increased pressure in pancreatic tissues and ducts (interventions, endoscopic or surgical, used to decompress and drain the pancreatic ducts may help in relieving pancreatic pain) and (2) perineural inflammation of sensory afferent fibers of the pancreas.
- ***Exocrine pancreatic insufficiency*** is revealed by steatorrhea (fatty stools). It is seen rather late in the evolution of the disease since pancreatic functional reserve is large and destruction of more than 90% of acinar cells is required before significant deficit in secreted enzymes occurs and results in maldigestion of dietary lipids and steatorrhea. Protein and carbohydrate maldigestion may be seen in advanced forms of the disease. Maldigestion of lipids occurs sooner because it is not only related to a reduction of lipase and colipase pancreatic input but also to a reduction in the secretion of bicarbonate, leading to acidification of duodenal pH and inactivation of bile salts and residual lipase.

  Maldigestion is revealed by frequent evacuation of oily stools that are pale and malodorous (steatorrhea), weight loss, and malnutrition. Proteolytic pancreatic enzymes are also necessary for digestion the R factor that binds dietary vitamin B12 (see ▶ Chap. 3), and thus vitamin B12 deficiency can sometimes occur.
- ***Endocrine pancreatic insufficiency***, through damage to the beta cells of the islets of Langerhans, is characterized by deficient insulin production. Diabetes is a late manifestation of chronic pancreatitis found in 40–80% of patients (half of them will need insulin). Glycemic control with insulin therapy is often difficult for these patients because of frequent hypoglycemic reactions (induced by insulin therapy) related to the concomitant damage to islets alpha cells that limits the production of serum glucagon (a pancreatic hormone which plays a compensatory role in glycemic equilibrium by increasing, if necessary, glucose blood levels lowered by insulin).

Congenital pancreatic insufficiency in children:

Isolated enzyme deficits mainly involving (intestinal) enterokinase or (pancreatic) lipase have been reported (but are very rare).

Lipomatosis with accumulation of adipocytes replacing the exocrine pancreatic tissue is known. Two entities can be distinguished: the syndrome of Shwachman-Diamond where a mutation of the SBDS gene on chromosome 7 induces exocrine secretory insufficiency is associated to hematological damage of central origin. The Johanson-Blizzard syndrome is characterized by exocrine pancreatic insufficiency associated with various malformations (aplasia of nose wings, deafness, skin aplasia, hypothyroidism, anal imperforation, etc.).

Pearson's syndrome, due to mitochondrial cytopathy secondary to a deletion of the mitochondrial genome, is associated with refractory sideroblastic anemia, exocrine pancreatic insufficiency, and deficient oxidative phosphorylation (resulting in metabolic crises with lactic acidosis).

(e) Diagnosis of Chronic Pancreatitis

The diagnosis is, in practice, most often made by an imaging evidence of anatomical changes suggestive of the disease or, more rarely, by a measure of pancreatic exocrine function.

Imaging Tests

- *Abdominal X-ray* is sometimes diagnostic in advanced forms of the disease since the typical pathognomonic pancreatic calcifications are common at this stage (Fig. 5.17).
- *Abdominal axial tomography (CT scan)* can detect pancreatic calcifications at an early stage of the disease, as it can reveal dilation of pancreatic ducts, inflammatory masses, or pseudocysts associated with the disease.
- *Cholangiopancreatography by resonance (MRCP or MRI)* may reveal more discreet morphological features.
- *Endoscopic retrograde pancreatography (ERCP)* has good sensitivity, but it is not used nowadays for diagnostic purposes given the invasiveness and risk of complications (post-ERCP pancreatitis, pseudocyst infection, etc.) of the procedure and the now established reliability and security of other diagnostic modalities.
- *Endosonography (endoscopic ultrasound, EUS)* is the most sensitive imaging test for detection of ductal or parenchyma abnormalities in the pancreas. However, the endoscopic procedure is invasive (usually performed under heavy sedation), requires a highly specialized technical expertise, and is less accessible compared to CT or MRI. In addition, chronic ingestion of alcohol is frequently associated with morphological changes of the pancreatic tissue that are asymptomatic and often difficult to differentiate from mild chronic pancreatitis.

Function Tests

- *Secretion tests.* The secretory function of the pancreas can be directly and precisely evaluated by using a tube positioned in the duodenum (or even in the pancreatic duct) to collect pancreatic secretions (obtained during various stimulations) to be ana-

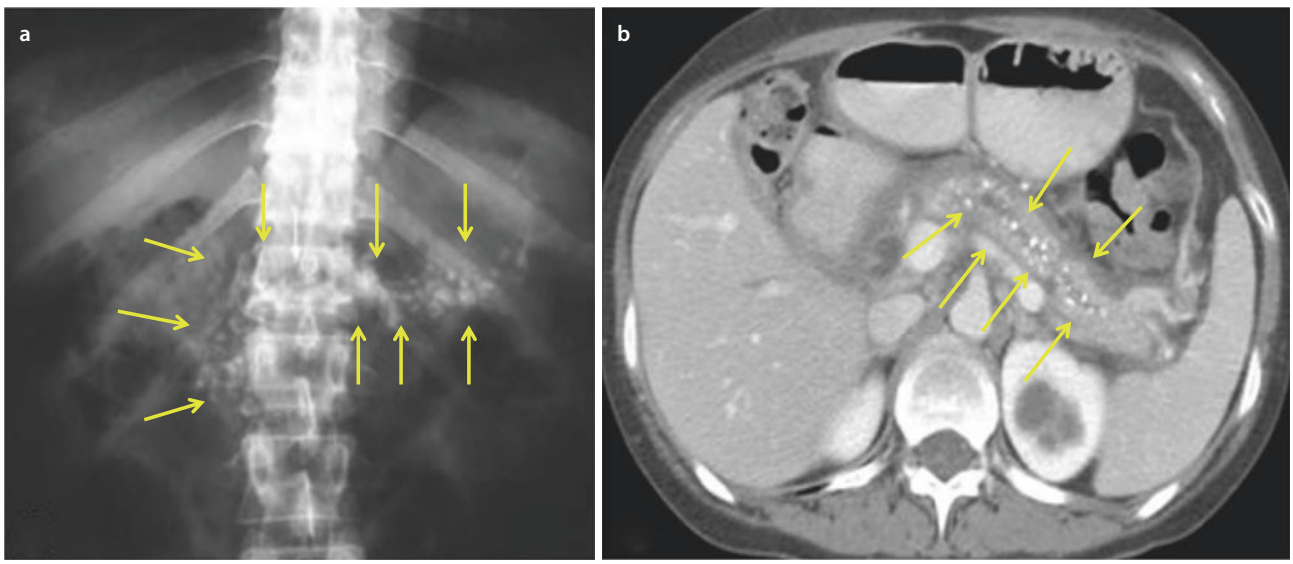


Fig. 5.17 Pancreatic calcifications seen in chronic pancreatitis on abdominal X-ray **a**, on abdominal CT scan **b**

lyzed for their ionic or enzymatic content. In presence of pancreatic insufficiency, the pancreatic secretion of bicarbonate in response to secretin injection is lowered, as is the secretion of pancreatic enzymes (trypsin, lipase, etc.) in response to CCK injection (or to a test meal ingestion).

Although considered as gold-standard procedures for the diagnosis of pancreatic insufficiency, these tubing tests for the measurement of the pancreatic function are invasive, relatively complex, tedious, and now usually replaced by imaging tests (although unable to assess pancreatic insufficiency, but they can confirm pancreatic disease).

- *Fecal fat* measurement [stool collection during 48–72 hours while the patient is consuming a high-fat (100 g per day) diet] confirms steatorrhea, but does not establish its origin (maldigestion due to pancreatic insufficiency or malabsorption by damage to the small intestine?).
- *Fecal elastase* or chymotrypsin dosage in the stool may in severe cases reveal low concentrations of these pancreatic enzymes and confirm pancreatic exocrine insufficiency.
- *Serum trypsinogen* levels (as well as serum lipase, although less specific) are often very low in severe pancreatic insufficiency.

(f) Treatment of Chronic Pancreatitis

It involves treatment of the causative or aggravating phenomenon and management of pain. Pancreatic insufficiency will be treated by replacement of the deficient secretion with enzyme supplements and insulin as needed. Treatment of chronic pancreatitis is summarized in Table 5.7.

Table 5.7 Chronic pancreatitis: manifestations/diagnosis/treatment

Manifestation	Diagnosis	Treatment
Abdominal pain	Imaging (confirms CP)	Stop ROH/smoking
		Pancreatic enzymes/ antioxidants
		Analgesics: • Acetaminophen-NSAIDs • Pregabalin-amitriptyline • Opiates
		Wirsung decompression: • Endoscopy • Surgery
		Celiac block
		Surgical resection
Exocrine insufficiency (steatorrhea)	Imaging (confirms CP)	Pancreatic enzymes: • Enterocoated/enteric release • Natural enzymes + PPIs
Endocrine insufficiency (diabetes)	Blood glucose	• Oral hypoglycemics • Insulin

Treatment of aggravating or causal phenomenon In alcoholic pancreatitis, total and definitive cessation of alcohol consumption is imperative. Even though chronic pancreatitis is an irreversible disease, stopping alcohol can not only improve the pain but can also slow disease progression toward pancreatic insufficiency. Multidisciplinary and specialized (medical, social, psychiatric, etc.) care for alcohol dependency is often essential for these patients.

Smoking, a recognized cofactor in the development of chronic pancreatitis, should be discouraged.

Pain management *Simple analgesics* such as acetaminophen, alone or in combination with nonsteroidal anti-inflammatory drugs, can be tried first

Opiate analgesics (codeine, oxycodone, hydromorphone, morphine, etc., in repeated oral doses or in oral sustained-release preparation or in skin patch) will often be necessary in face of an inadequate response to simple analgesics. The risk of narcotics addiction is obviously present since it is a chronic pain and a long-term treatment.

Antioxidants [vitamins, selenium (e.g., Stresstab Plus®)] may sometimes be effective and are a simple measure to try.

Calcium channels inhibitors (pregabalin, gabapentin) for the treatment of pancreatic pain (neuropathic?) can sometimes be useful.

P*ancreatic enzymes* administration for the reduction of pancreatic pain has physiological merit and is theoretically a logical therapeutic avenue (reducing pancreatic stimulation by providing an exogenous source of digestive enzymes). Although effective in animal experiments, it rarely seems a worthy solution in human practice; some literature suggests that the benefit would be better with natural enzymes than with enterocoated preparations (see below).

E*ndoscopic or surgical treatment* may be considered (see below) in cases where medical treatment of pain proves insufficient.

Treatment of exocrine pancreatic insufficiency Oral preparations of pancreatic enzymes (obtained from pig pancreas, freeze-dried and encapsulated) are available. To reduce steatorrhea, at least 30,000 IU (90,000 USP) of lipase should be administered with every meal, taken in divided doses at the beginning, middle, and near the end of the meal, to ensure better distribution of enzymes. Two formulations of pancreatic enzymes are available: the "natural" form, whose capsule is dissolved in the stomach (Viokase®), and the coated form with microgranules dissolving in the duodenum at noacidic pH (Creon®, Pancrease®). Since lipase is irreversibly inactivated by acid, natural unprotected enzymes preparations should be administered with a gastric acid inhibitor (PPI) to prevent enzyme inactivation by gastric acid. Preparations of enteric-release microgranules optimize the amount of enzymes available for nutrient digestion in the intestine and do not need to be protected from acid. However, they may dissolve distally in the small intestine and be unable to elicit duodenal feedback to inhibit postprandial pancreatic activity and reduce pancreatic pain (as discussed earlier).

Treatment of endocrine pancreatic insufficiency Diabetes associated with chronic pancreatitis can be difficult to manage since the concomitant glucagon deficiency can predispose persons to hypoglycemia. Some patients can respond to oral hypoglycemic medications, but the majority will require insulin therapy. Since pancreatic diabetes is associated with health complications, such as retinopathy, nephropathy, neuropathy, etc., appropriate glycemic monitoring is required for all patients.

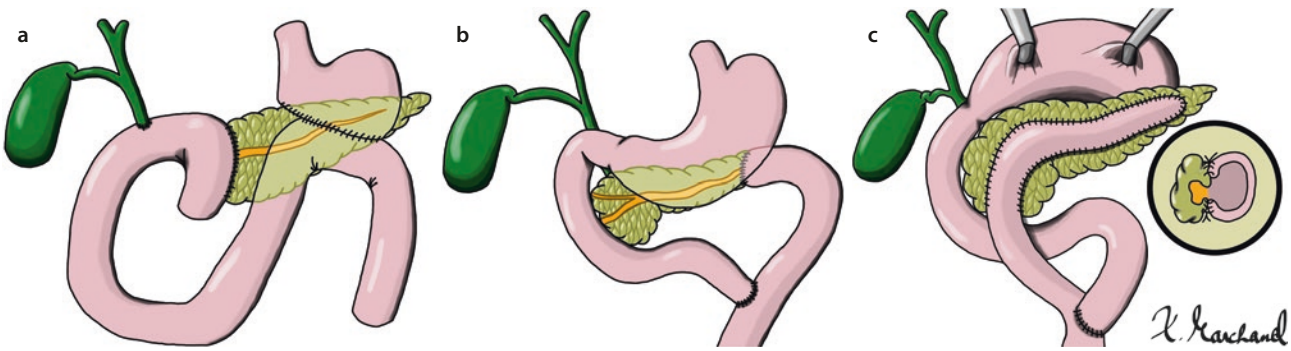
Endoscopic/surgical treatment of chronic pancreatitis In some cases, management of pancreatitis may benefit from endoscopic procedures or surgical procedures. The indication, as well as the execution of these techniques, which are often difficult and potentially highly morbid, must be entrusted to experts.

Endoscopic dilatation of pancreatic duct stenoses and/or extraction of pancreatic stones (with or without extracorporeal lithotripsy) can be done to improve function and/or pain. Endoscopy-guided drainage of pseudocysts, also a major cause of chronic pain, can be an effective treatment in selected cases. Celiac plexus blockade or neurolysis by injection, under endoscopic endosonographic vision, of corrosive alcohol or anesthetizing xylocaine solutions into the celiac plexus innervating the pancreas can also relieve pain, but the effect is unfortunately ephemeral.

Surgical treatment of chronic pancreatic pain can be done by resection of inflammatory masses or pseudocysts and/or by decompression of the pancreatic ducts and tissues. In the case of a dilated (hypertensive) pancreatic duct, it is possible to decompress the pancreatic gland via a lateral pancreaticojejunostomy (Puestow's procedure, or variants such as Frey's or Berger's procedures) which allows for a large surface drainage from the pancreatic duct opening along its entire length into an anastomosed intestinal loop. If the disease involves mainly the cephalic pancreas, a Whipple's duodenopancreatectomy may be necessary (this is one of the most complex interventions of modern surgery). In the case of a left-sided lesion, resection of the caudal pancreas (possibly with distal drainage of the remaining pancreas into an anastomosed intestinal loop according to Duval's procedure) may be done (see ◘ Fig. 5.18).

5.7 Tumor Disorders

Pancreatic tumors may be benign or malignant as shown in ◘ Table 5.8



◘ **Fig. 5.18** Surgical procedures for pancreatitis: **a** Whipple surgery involves resection of the pancreatic head and attached duodenum (and often includes the adjacent gastric antrum) and reconstruction using an intestinal loop to drain secretions from the remaining pancreas, from the bile duct, and to evacuate gastric contents; **b** in Duval operation (rarely performed now), the pancreatic tail is resected, and the remaining pancreas is anastomosed to an intestinal loop draining pancreatic secretions; **c** Puestow procedure is performed by opening the dilated pancreatic duct along its longitudinal axis and anastomosing it with an intestinal loop. This allows for secretions to be drained to the intestine and to decompress the pancreatic gland

5.7.1 Pancreatic Cancer/Adenocarcinoma

(a) General

Pancreatic adenocarcinoma is the second most common cancer of the digestive system. The prognosis is poor, with an average survival, all stages combined, of 25% at 1 year and 8% at 5 years. Its incidence is 9 per 100,000 population, with a slight predominance for males (1.3:1). It is uncommon before the age of 45, but risk gradually increases with age afterward; the average age at diagnosis is 71 years.

Environmental (lifestyle) factors associated with an increased risk of pancreatic cancer include alcoholism (via chronic pancreatitis; see Table 5.9), smoking, as well as excessive consumption of meat and fatty foods. The influence of tobacco smoking seems particularly harmful since the risk of developing pancreas adenocarcinoma by 70 years of age among persons with hereditary chronic pancreatitis is respectively of 40% or 20% in the presence or absence of smoking.

Genetic predispositions to pancreatic cancer are now recognized (Table 5.10). Recommendations for screening in these genetic forms of pancreatic cancer however do not yet make consensus. Some associations recommend screening from age 35 onward in patients with hereditary chronic pancreatitis and at 10 years less the age of the youngest afflicted member in the case of a subject where familial pancreatic cancer (defined as the occurrence of pancreatic cancer in two first-degree parents or in three parents) is suspected. Examination of the pancreas by magnetic resonance imaging (MRI) or endosonography can be used for screening.

Although ductal tissue only accounts for only 10–15% of the total pancreatic tissue (acinar 80%, endocrine 1–2%), 85–90% of pancreatic cancers are adenocarcinomas from duct origin. The majority of these tumors are found in the head of the pancreas (60–70%), 5–10% in the body, and 10–15% in the tail of the pancreas. These lesions progress by locoregional extension (invading adjacent structures, the retroperitoneum) and disseminates as metastasis to lymph nodes (peripancreatic, hilar, celiac) and the liver. Early invasion of essen-

Table 5.8 Primary tumors of the exocrine pancreas according to the World Health Organization

Benign lesions
Serous cystadenoma
Mucinous cystadenoma
Intraductal papillary mucinous adenoma
Mature cystic teratoma
Intermediate lesions (uncertain malignant potential)
Mucinous cystadenoma with moderate dysplasia
Intraductal papillary mucinous adenoma with moderate dysplasia
Solid pseudopapillary tumor
Malignant lesions
Ductal adenocarcinoma
Giant cell osteoclastic tumor
Serous cystadenocarcinoma
Mucinous cystadenocarcinoma
Intraductal papillary mucinous carcinoma
Acinar cell adenocarcinoma
Pancreatoblastoma
Solid pseudopapillary carcinoma
Other carcinomas

Table 5.9 Pancreatic cancer: risks and favoring factors

Subject	Cancer risk at 70
Normal	0.5%
Family history of pancreatic cancer (number of 1st degree relatives)	
1 Parent	1%
2 Parents	10%
3 Parents	40%
Chronic pancreatitis	4%
Hereditary pancreatitis	40%

Table 5.10 Genetic predisposition to pancreatic cancer

Clinical history	Gene	Relative risk
None	None	1
Breast-ovarian cancer	BRCA 1 and 2	2–10
FAMMM	P16 (CDKN2A)	10–25
Familial pancreatic cancer n: 1, 2, 3	Unknown	2, 6, 32
Hereditary pancreatitis	PRSS1	50–80
Peutz-Jeghers syndrome	STK11/LKB1	100–130
HNPCC	MLH1, MSH2 + others	4–8

FAMMM familial atypical multiple mole melanoma syndrome, *HNPCC*, hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome)

tial nearby structures (such as the portal vein and the superior mesenteric vein) is such that the majority of tumors cannot be surgically resected at the time of their diagnosis.

Unfortunately, pancreatic cancer is often characterized by a rapid and painful evolution.

(b) Clinical Presentation of Pancreatic Cancer

Pancreatic cancer commonly manifests by jaundice (in >50% of cases; due to obstruction of the intrapancreatic portion of the common bile duct), pain (often epigastric and radiating to the back; due to tumor invasion of nerves or peripancreatic structures or to pancreatitis upstream from an obstructed duct), and/or weight loss (due to malabsorption, postprandial abdominal pain that interferes with eating, or anorexia). Diarrhea with steatorrhea (obstruction of the pancreatic duct limiting enzymes delivery), de novo diabetes (mechanism uncertain), and symptoms of depression (mechanism unknown) may also be the initial clinical symptoms of pancreatic cancer. Symptoms appear however unfortunately late in the progression of pancreatic cancer, so that few (less than 10%) pancreatic lesions are resectable when discovered.

Physical examination is often of little help to make a diagnosis of pancreatic cancer. Jaundice is often due to a tumor of the head obstructing the intrapancreatic bile duct but too small to be appreciable via abdominal palpation. Large tumors (especially in the tail where they can progress without causing jaundice) may be palpable. In some cases, it is possible to palpate a distended gallbladder (Courvoisier's gallbladder distended by biliary obstruction usually related to a progressive malignant process since acute blockade by a stone will lead to pain and cholangitis before gallbladder can distend), or a hard metastatic nodule at the level of the umbilicus (Sister Marie-Joseph's nodule). Hepatomegaly, as ascites, is suggestive of metastatic diffusion. Cachexia, from either caloric deficit or neoplastic catabolic process, is a poor prognostic factor.

(c) Diagnosis of Pancreatic Cancer

Blood tests: jaundice (obstructive) is cholestatic, with elevated serum levels of conjugated bilirubin, alkaline phosphatase, and GGT.

Both serum pancreatic amylase and lipase may be mildly elevated, but this is not diagnostic.

Tumor marker CA19-9 is associated with pancreatobiliary cancers (86% sensitivity and 87% specificity). On the other hand, its usefulness is limited in the presence of cholestatic jaundice that can increase CA19-9 levels to very high values even in the absence of malignancy.

Imaging tests:

- *Abdominal ultrasound* is minimally invasive and is often one of the first imaging tests done. It can reveal enlarged bile ducts and gallbladder and less often identify the source the obstruction of the common bile duct (such as an infiltrating pancreatic mass). Hepatic metastases and/or ascites can also be detected.
- *Abdominal CT scan* (Fig. 5.19) with contrast is the most commonly used test to identify and evaluate a pancreatic cancer lesion and its extension and, most importantly, to assess its potential surgical resection. This examination can evaluate for the presence of distant metastases (liver, peritoneum, lymph nodes), as well as malignant invasion of the main vessels (celiac trunk, superior mesenteric artery, portal vein, superior mesenteric vein); all these items being radiological criteria for non-resectability of the lesion (however, up to 50% of pancreatic lesions deemed resectable with CT scan will be declared non-resectable at the time of surgery).
- *Magnetic resonance pancreatography (MRI)* has the advantage of avoiding iodine injection in an allergic patient or with renal failure. MRI with gadolinium contrast may be more sensitive for the identification and staging of pancreatic tumors; however, CT scan may be more accurate for identifying vascular invasion. MRI is increasingly being used to further characterize liver lesions suspicious for metastatic disease on CT scan.
- *Endoscopic retrograde cholangiopancreatography (ERCP)* may reveal a stricture of the common bile duct or the main pancreatic duct. It is primarily used for therapeutic decompression in cases of malignant biliary obstruction. Brushing samples can provide a cytopathological diagnosis.

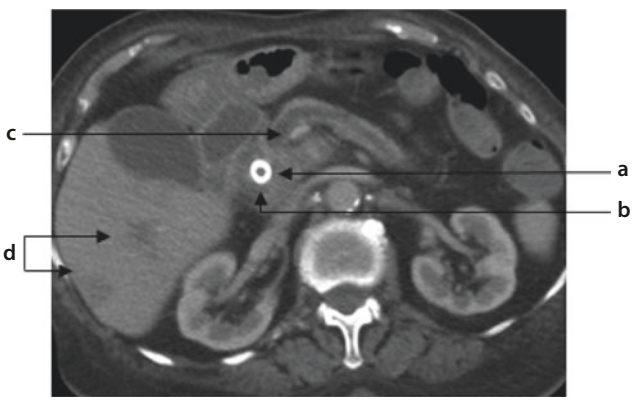


Fig. 5.19 Pancreatic adenocarcinoma on CT scan: **(a)** the pancreas head is replaced by a mass; **(b)** a plastic biliary stent (white plastic ring) for biliary decompression has been placed in the common bile duct; **(c)** the pancreatic duct is dilated on the obstacle; **(d)** metastases are present in the liver

- *Endosonography (endoscopic ultrasound, EUS)* is the most sensitive modality for the detection of tumors and evaluation for local extension to lymph nodes, vessels, adjacent organs, or ascites. Needle biopsy of the tumor can be performed to confirm the malignant nature of the lesion (useful in case of doubt or when precise histological diagnostic is needed to undertake treatment such as palliative chemotherapy). Moreover, a coeliac block (infiltration of xylocaine or alcohol) can be done to reduce abdominal pain.
- *Positron emission tomography (PET scan)* is of little use to reveal anatomical details and resectability of pancreatic lesions, but it may be of interest to demonstrate distant metastasis, to differentiate malignant from benign lesions, and to evaluate the response to neoadjuvant chemoradiotherapy.

Table 5.11 Treatment of pancreatic adenocarcinoma

Tumor	Frequency	Survival	Suggested treatment
Metastatic (liver)	60% of cases	6–12 months	Chemotherapy
Locally advanced (lymph nodes, vessels)	25%	9–12 months	Chemotherapy
Resectable	15%	15–55 months	Surgery + chemotherapy

(d) Treatment of Pancreatic Cancer

Curative treatment of pancreatic cancer requires complete surgical resection of the tumoral lesion and its lymph nodes. Unfortunately, curative surgery is possible in only 15–20% of patients at the time of diagnosis. Metastases or malignant infiltration of nearby structures are common contraindications to curative resection.

The type of surgical resection performed must be adapted to the site of the lesion. In case of a tumor in the head of the pancreas, Whipple's cephalic pancreatoduodenectomy, with or without pyloric preservation, is the procedure of choice but still remains a major and delicate surgical procedure (in expert centers, this can now be performed with reasonable morbidity and mortality rates). Survival at 5 years after surgery that was considered curative is limited historically to 10–20%; the role of adjuvant chemotherapy is now confirmed (median recurrence-free survival of 40% with FOLFORINOX).

Palliative treatment of cancer will unfortunately be the only possible therapeutic avenue for a large number of patients (see Table 5.11). Obstruction of the bile duct and/or duodenum can be managed by various surgical derivation procedures or, preferably, by a less morbid endoscopic approach allowing biliary and/or duodenal stenting.

Various palliative chemotherapy protocols have been studied (5-FU, gemcitabine, FOLFORINOX, Abraxane) in an attempt to improve patient survival. Gemcitabine since 1997 is a classical palliative treatment, recognized to provide a slight survival advantage at 1 year and above all a better quality of life with less pain and weight loss. FOLFORINOX (5-FU, irinotecan, oxaliplatin) appears more effective than gemcitabine, but its superior toxicity limits its use to patients in good general condition.

Pain is an important symptom in these patients. It can be managed by analgesic therapy with long-acting narcotics. Celiac ganglion neurolysis can be performed endoscopically (EUS; more rarely by surgical intervention or transcutaneously by X-ray guidance).

Since the obstruction of the pancreatic duct leads to impaired delivery of pancreatic enzymes and therefore to nutrient maldigestion, it is important to prescribe pancreatic enzyme preparations to these patients.

5.7.2 Cystic Tumors/Cysts

Cystic structures are found, often incidentally, in 3% of pancreatic imaging exams (CT scan, MRI, or ultrasound).

(a) Cysts and pseudocysts Nonneoplastic cysts of the pancreas include pseudocysts (extra-pancreatic liquid collections contained between various viscera and having fibro-inflammatory walls rather than epithelial walls like real cysts) or retention cysts [dilatation of a (secondary or primary) pancreatic duct by accumulation of pancreatic fluid upstream of a blockade] that may both occur in the context of pancreatitis (acute or chronic) and simple pancreatic cysts (congenital or acquired; usually of small size) most often discovered incidentally during an imaging exam.

(b) Cystic neoplasms Pancreatic cystic neoplasms account for only 10% of pancreatic neoplasms but for over 60% of cystic lesions of the pancreas identified during abdominal imaging. Of all lesions described in Table 5.12, serous cystadenoma, which accounts for about 30% of neoplastic cysts, is the only one with almost no malignant potential. All other lesions may transform into malignant lesions to variable degrees, so

Table 5.12 Cystic tumors of the pancreas

	Frequent (80%)	Rare (20%)
Benign	Serous cystadenoma	
Malignant potential	Mucinous cystadenoma	Pseudopapillary solid tumor
	IPMN	Cystic endocrine tumor
		Cystic duct adenocarcinoma
		Cystic acinar adenocarcinoma

that if there is any doubt about the nature of the lesion and its malignant potential, a surgical resection is indicated. Also, any symptomatic cystic lesion will have to be resected.

- ***Serous cystadenoma*** is a benign lesion found most often in women over 50 years of age. It is characteristically composed of multiple small honeycomb nests and can present a star shaped central calcification. When punctured, the aspirated cyst fluid is clear, serous, and nonviscous, contains no amylase and low CEA or CA 72-4, and is benign on cytopathology. The serous cystadenoma is common (30% of cystic pancreatic tumors), does not require follow-up, and should be resected only if >4 cm or symptomatic.
- ***Mucinous cystadenoma*** is the most common neoplastic cystic lesions of the pancreas. Surrounded by ovarian stroma, mucinous cystadenoma is found in women over 50 years of age, in the body or tail of the pancreas. On imaging, it presents a thick wall forming a single cyst containing some divisions by internal septa. When punctured (in EUS), the recovered liquid is clear, viscous, containing little amylase but high levels of CEA and CA 19-9. Surgical resection is clearly to be considered since in situ or invasive cancer is found in up to 17% of cases.
- ***Intraductal papillary mucinous neoplasm (IPMN)*** of the pancreas is most often found in the cephalic region and can be located either in the main pancreatic duct or in a side branch of it. This difference is important since IPMNs of the main duct have a much more malignant potential (15–40%) than those originating in collateral branches (10%).

Papillary tumors secrete significant amounts of mucin which can lead to obstruction and dilatation of the ducts upstream of the blockade. Duct dilatation is the major sign found by the different imaging methods that can highlight these lesions, either CT scan, MRI, or EUS.

IPMN incidence is equal in men and women and occurs at a median age of 65 years. It is symptomatic in 50–75% of cases, either by acute pancreatitis (by duct obstruction by mucin or the tumor) or epigastric abdominal pain associated with weight loss (caused by a lack of enzyme secretion due to duct obstruction).

Given the malignant potential of a main duct IPMN, the best treatment is complete surgical resection of the lesion (which can result in 5-year survivals up to 75%, if the lesion is not advanced at the time of resection). In the case of a collateral branch lesion (often of benign nature), it is agreed to perform surgical resection if the lesion is symptomatic, if it measures more than 3 cm, if it contains masses or nodules, or if it is associated with a main duct dilatation; otherwise, an imaging follow-up is recommended.

5.7.3 Neuroendocrine Tumors (NETs)

(a) General

NETs account for 1–10% of pancreatic tumors. They are histologically identifiable by their small round cells, and the German term *Karzinoide* (carcinoid-like) was first used to describe an intestinal tumor with the unique feature of behaving like a benign tumor clinically while having a malignant appearance microscopically. Carcinoid tumor of the intestine (which secretes serotonin leading to the carcinoid syndrome discussed in ▶ Chap. 3) was for long the prototype of these tumors containing secretory granules with neuroendocrine markers (chromogranin A, synaptophysin, etc.) and now identified as NETs. NETs can be found mainly in the pancreas (pNET) or intestine (iNET). Their granules contain various substances (serotonin, gastrin, insulin, etc. that can be released into circulation without regulation and induce typical clinical manifestations) which can be identified using electron microscopy (thanks to the size and density of the secretory granules) or by immunohistochemical staining markers (specific to each substance such as anti-gastrin or anti-insulin antibodies).

NETs can be nonsecretory (30–50% cases) or release into circulation large quantities of "hormonal" substances (such as insulin or gastrin) which leads to a clinical phenotype specific to this hormonal hypersecretion

(for instance, hypoglycemia if hyperinsulinemia or peptic ulcers if hypergastrinemia, etc.). The most common pNETs are insulinoma and gastrinoma; VIPoma and glucagonoma are less frequent, and somatostatinoma is rare.

NETs may be sporadic (80% cases) or associated with hereditary diseases such as the MEN-1 syndrome [multiple endocrine neoplasia type 1 with parathyroid, pituitary (often prolactinoma), and pancreatic tumors] or the rare phakomatoses (von Hippel-Lindau disease, Bourneville's tuberous sclerosis, von Recklinghausen neurofibromatosis).

NETs arise from neuroendocrine cells that are located throughout the body; however, NETs tend to occur mainly in the gastrointestinal tract, lungs, and pancreas (Table 5.13). All these lesions have a potential for malignancy and can therefore become metastatic (although it is rare in the case of insulinoma). Tumor evolution of NET is often less aggressive compared to adenocarcinoma, and patients survival may be prolonged for several years, even in the case of metastatic tumors.

(b) Phenotype and Clinical Presentation of NETs

Nonsecreting NETs (although this term may be inappropriate since the vast majority will secrete into circulation pancreatic polypeptide and/or chromogranin A, these substances do not have identifiable biological effects) may present, similarly to other pancreatic tumors with a pancreatic lesion, liver metastases, abdominal pain, impairment of general condition, etc.

Table 5.13 Neuroendocrine tumors

NET	Location	Secretions	Manifestations
"Carcinoid"	Ileum (30%)	Serotonin	Diarrhea
	Lung (25%)	Histamine	Bronchospasm
	Appendix (20%)	Kinins	Flushing
	Rectum (10%)	TGF-B	Fibrosis
Gastrinoma	Pancreas (50%) Duodenum (50%)	Gastrin	Ulcers Diarrhea Malabsorption
Insulinoma	Pancreas	Insulin	Hypoglycemia
VIPoma (WDHA, pancreatic cholera)	Pancreas	Vasoactive Intestinal Peptide	Diarrhea Achlorhydria Hypokalemia
Glucagonoma	Pancreas	Glucagon	Diabetes Rash Anemia
Somatostatinoma	Pancreas	Somatostatin	Steatorrhea Gallstones Diabetes
PPoma	Pancreas	Pancreatic polypeptide	None
ACTHoma	Adrenal gland Pancreas (10%)	ACTH	Cushing's syndrome
GRFoma	Lung (50%) Pancreas (30%)	Growth hormone releasing factor	Acromegaly
ECLoma	Stomach	Histamine	None

Secreting NETs are identified by the substance produced by the tumor and released into circulation:

- *Insulinoma* results in very high serum levels of insulin and manifests itself as hypoglycemic episodes. The tumor is usually pancreatic, unique, benign, and often easily resectable by enucleation.
- *Gastrinoma*, or Zollinger-Ellison syndrome (ZES), is due to tumoral gastrin hypersecretion resulting in an excessive secretion of HCl by gastric parietal cells causing a severe acido-peptic disease, often diarrhea (secretory volume exceeding the reabsorption capacities of the gut), and possibly malabsorption (lipase and bile salts inactivation by acid) (as discussed in ► Chaps. 2 and 3). Treatment of ZES aims to reduce the secretion of gastric HCl by PPIs (proton pump inhibitors usually needed at very high doses) to avoid the severe complications (even lethal) of this extraordinary hyperchlorhydria. The tumor is most often localized in the head of the pancreas (50% of the time) or in the duodenal wall (which thus requires a Whipple's cephalic pancreatoduodenectomy). In MEN type 1 (20% of cases), the tumors are often multiple and distributed throughout the pancreatic gland (prohibiting then surgical resection). Nodes and/or liver metastases are frequent.
- *VIPoma* [known as WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome, or pancreatic cholera, or Verner-Morrison syndrome before VIP was identified as the causal agent] is due to an exaggerated secretion of vasointestinal polypeptide which activates adenylate-cyclase of the enterocyte, thus inducing an intestinal secretion of electrolytes and H_2O that can be very severe. Watery stools, hypokalemia, and dehydration can make diarrhea look like cholera. VIP also inhibits the secretion of gastric HCl (achlorhydria of WDHA). The medical treatment of VIPoma relies on somatostatin analogues (e.g., octreotide) suppressing VIP release by the tumor, as well as inhibiting of the action of VIP on enterocytes to stop the severe (often lethal) diarrhea. Surgical resection of the tumoral lesion, if feasible, is indicated.
- *Glucagonoma* (presenting with diabetes, skin lesions, anemia, and sometimes constipation) and *somatostatinoma* (diarrhea/malabsorption, gallstones, diabetes) are more rare.

(c) Diagnosis of NET

Diagnosis of secretory NETs is achieved by confirming circulating excess "hormone" produced by the tumor. Measurement of plasma insulin or gastrin levels is readily available in most hospital laboratories; measurement of somatostatin or VIP is however limited to specialized laboratories.

Imaging for tumor localization uses the same tools as for adenocarcinoma, i.e., CT scan, MRI, endosonography, etc. Endocrine tumors usually contain somatostatin receptors, which allows imaging by nuclear scintigraphy (Octreoscan with isotopically labelled somatostatin analogue In^{111}octreotide) or by positron scintigraphy (PET scan with octreotide analogue dotatate labeled with Gallium ^{68}).

(d) Treatment of NET

Symptomatic treatment includes:

- Suppression of the biological action of the hypersecreted hormone (e.g., inhibition of gastric acid secretion with PPIs).
- Pharmacological suppression of the hypersecreted hormone (with somatostatin analogues such as octreotide).
- Suppression of "hormonal" hypersecretion through complete (if possible) or partial (debulking) surgical resection of the tumor.

Tumor progression of NET is usually much slower than that of other tumors, and the oncological prognosis is more favorable (survival of 10–20 years are observed, even in metastatic forms). Oncological treatment is provided by:

- Surgical resection of the primary tumor and its metastasis
- Control of tumor growth with somatostatin analogues
- Chemotherapy with classical streptozotocin (or temozolomide), or with new agents acting on tyrosine kinase (sunitinib) or on mTOR pathway (everolimus)

5.8 Function Disorders

The only pancreatic pathology that could be considered of functional origin is SO dyskinesia with secondary obstructive pancreatitis. Impaired relaxation of the sphincter of Oddi ("achalasia" of Oddi) in absence of a fibrous ampulla is however a much debated entity not recognized by all.

5.9 Miscellaneous

5.9.1 Cystic Fibrosis

Cystic fibrosis is an inherited condition that implies hyperviscosity of glandular and mucus secretions in various organs. Lung disease is usually the most serious complication of this disease which also affects the pancreas as well as other digestive organs such as the bile ducts and the small intestine.

(a) Etiopathogeny Cystic fibrosis is a genetic disease with autosomal recessive transmission and most frequently identified in Caucasians (1/2500 births). It is due to mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator) on chromosome 7, which alter the CFTR protein, an ion channel for the secretion of chloride through cell membranes (the efflux of Cl^- generates H_2O movement out of the cell). In respiratory and digestive tracts, the impaired secretion of Cl^- and, secondarily, H_20 leads to viscous and thick secretions.

(b) Physiopathology Mucus hyperviscosity leads to obstructive blockages in different organs:

- In the lungs, increased viscosity of pulmonary secretions leads to clogging of the airways by mucus plugs favoring pulmonary superinfection by different bacteria and progressive (and lethal) destruction of the lungs.
- In the pancreas, hyperviscosity of pancreatic juice leads to protein plugs preventing the flow of exocrine pancreatic secretions. This can cause recurrent acute pancreatitis as well as nutrients malabsorption via exocrine pancreatic insufficiency.
- In the small bowel, thick intestinal secretions may cause intestinal obstruction by meconium in the newborn. Dry stools that are difficult to externalize and require defecation efforts can cause rectal prolapse in infant. In adult, intestinal or colonic impactions by dry "stools" can occur.
- In the bile ducts, hyperviscosity of the bile can lead to obstructions in the hepatic ducts and an evolution toward secondary biliary cirrhosis.

(c) Diagnosis The diagnosis of cystic fibrosis is usually made in children using the sweat test which confirms high concentrations of sodium and chloride in skin sweat secretions. Several mutations of the CFTR gene are known, and prenatal genetic screening is available, as well as screening for individuals at risk of carrying a transmissible gene.

(d) Treatment of cystic fibrosis Life expectancy of patients with cystic fibrosis was previously very much reduced by pulmonary complications; in the absence of treatment, the average survival was 3–5 years. Over the last 50 years, life expectancy increased to 40–50 years. Even though there is no cure for cystic fibrosis, multidisciplinary management aiming to treat respiratory complications by pulmonary rehabilitation and antibiotics, preventing pancreatic and digestive tract conditions by enzyme supplements etc., improves quality of life and life expectancy of these patients. Lung transplantation is now possible for many patients, as well as pancreatic or liver transplantation if needed. Genetic therapies to correct the biochemical abnormalities responsible for this disease are still awaited.

PS: For complementary lectures on the pancreas, see ► Chaps. 16, 25, and 29.

The Biliary Tree

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Contents

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6.1 Macroscopic Anatomy

6.1.1 Shape and Structure

The biliary tree includes the bile ducts and the gallbladder.

Bile ducts allow bile secreted by the liver to reach the duodenum (where it will play a decisive role in lipid absorption).

They begin intrahepatically with canaliculi located between two hepatocytes and emptying into channels that progressively flow into larger and larger ducts to reach the right and left hepatic bile ducts exiting the liver.

The extrahepatic bile ducts are made up of the right and left hepatic ducts, the common hepatic duct and common bile duct (CBD). The gallbladder joins the CBD by way of the cystic duct, whose position defines the demarcation between the common hepatic duct (upstream) and the common bile duct (downstream) (◘ Fig. 6.1).

The CBD has a diameter of about 6 mm. Its upper 2/3rds travels in the hepato-duodenal ligament, while its distal (lower) portion passes through the posterior part of the cephalic pancreas to join the main pancreatic duct of Wirsung's at the ampulla of Vater (containing the sphincter of Oddi) that opens into the duodenum.

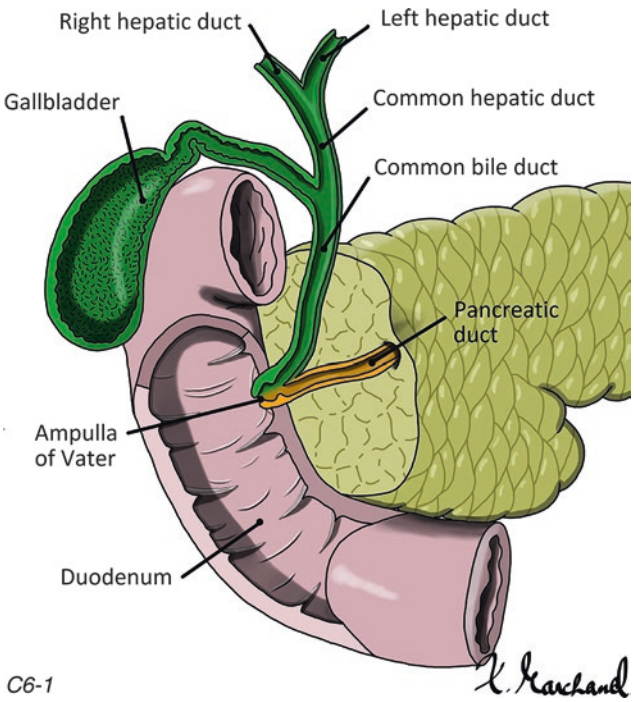
Anatomical variations in the bile ducts anatomy are frequent and numerous.

Gallbladder stores and concentrates bile between meals. The volume of the gallbladder averages 40–70 ml. It is 8- to 10-cm-long and 3- to 4-cm-wide. It consists of a fundus, a body, and a neck that extend through the cystic duct to the common bile duct. The neck of the gallbladder (or infundibulum) is angulated, folded on itself, forming a bulge called Hartmann's pouch. The cystic duct is on average 3-cm-long, often displaying anatomical variations. Its lumen has a diameter of 2–4 mm; it contains folds of mucosa and muscle fibers called Heister's valves whose actual function is not well understood.

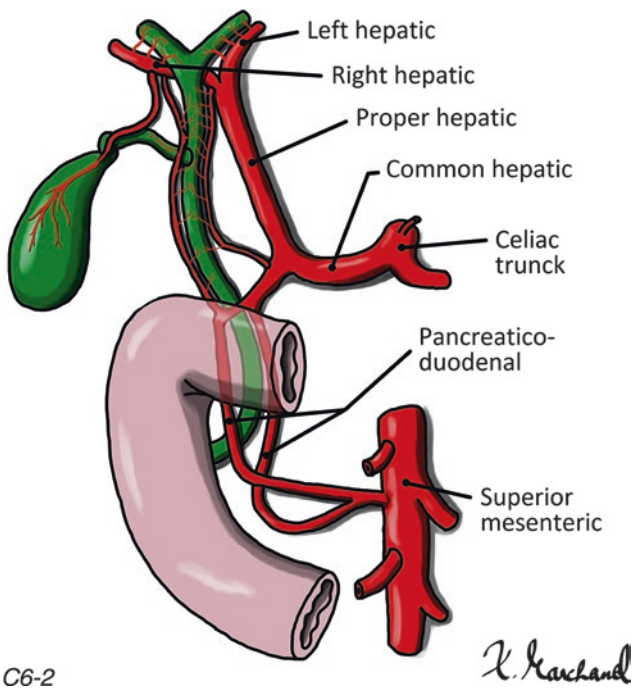
6.1.2 Vascular Supply

Arteries The common bile duct, like the intrahepatic bile ducts, is supplied in its proximal portion by the hepatic artery (common hepatic artery and hepatic artery proper). Its distal segment is irrigated by the pancreaticoduodenal arteries (anterior and inferior) giving rise to two arteries traveling longitudinally along right and left walls of the CBD. The right hepatic artery gives rise to the cystic artery (an important structure to recognize during cholecystectomy) which supplies the gallbladder and cystic duct (◘ Fig. 6.2).

Veins of the gallbladder and extrahepatic bile ducts are numerous and small. There is no main vein corresponding to the cystic artery. These small veins flow into the portal vein, the right portal vein, the intrahepatic portal network, and the pancreaticoduodenal vein arch.



◘ **Fig. 6.1** Macroscopic anatomy of extrahepatic bile ducts



◘ **Fig. 6.2** Arteries of the bile ducts

Lymphatic vessels drain into lymph nodes of the hepatic pedicle, including the lymph node of Lund (a sentinel node enlarged in the presence of gallbladder infections and located in the Calot's triangle (delimited by the common hepatic duct, the cystic duct and the cystic artery)), the hiatus node, and the posterior pancreaticoduodenal lymph nodes.

6.1.3 Innervation

Like other digestive organs, extrinsic innervation provides parasympathetic regulation via the vagus nerve and sympathetic control via mainly the celiac ganglion.

Parasympathetic innervation The right branch of the vagus nerve innervates the extrahepatic bile ducts and the gallbladder regulating, among other, muscle function (parasympathetic cholinergic mediators stimulate gallbladder contraction).

For the surgical treatment of duodenal ulcer disease, selective and hyper-selective vagotomy techniques had been developed to abolish parasympathetic stomach stimulation while sparing biliary innervation in order to preserve gallbladder contractility and avoid gallbladder stasis that favors stone formation (discussed later).

Sympathetic innervation Sympathetic innervation originates from the spinal cord nerves from T5 to T10 (preganglionic sympathetic nerves), which merge into the celiac ganglion an then give rise to postganglionic fibers that innervate the extrahepatic bile ducts. Sympathetic mediators reduce muscle tone. Sympathetic nerves also include afferent fibers that carry information, painful or other, from the bile ducts to the brain.

6.2 Microscopic Anatomy

6.2.1 Bile Ducts

The bile canaliculi, where bile is secreted, are located between the cytoplasmic membranes of adjacent hepatocytes and therefore do not possess a proper wall structure. They form an intralobular network that carries bile to periportal canaliculi (canals of Hering whose wall is composed of a simple cuboidal epithelium resting on a basal lamina surrounded by a dense collagen network) and then onto bile ducts of the portal space. From the portal space, ducts gradually merge, becoming larger and larger in diameter. The epithelium that lines these ducts then changes from simple cuboidal to simple columnar. The connective tissue becomes thicker and contains elastic fibers. Muscle fibers forming incomplete longitudinal and oblique layers appear only in the common bile duct; at the distal end of the CBD, the muscle layer becomes more prominent and forms the biliary sphincter of Oddi (SO).

6.2.2 Gallbladder

The gallbladder wall is composed of four layers:

- A mucosa (whose surface area is increased by folds and microvilli) with an epithelium (consisting of a layer of columnar cells and mucus-secreting tubuloalveolar glands) and a lamina propria
- A muscularis
- Perimuscular connective tissue
- A serosa, except at the level of the "gallbladder bed" where the gallbladder is directly attached to the liver

6.3 Embryology

6.3.1 Normal Development

Around the 4th week of gestation, in the distal portion of the anterior intestine (the "foregut"), two buds develop, one anterior and one posterior. They are destined to become, respectively, the hepatobiliary system and the pancreas (the embryology of the pancreas is discussed in ► Chap. 5). These two buds will move laterally when attracted by a rotational movement of the digestive tract to the right. In the anterior mesentery, the hepatic bud grows rapidly and divides into a cephalic and a caudal part (◘ Fig. 6.3). The cephalic part will generate the liver and intrahepatic bile ducts and from the caudal part will arise gallbladder and cystic duct. The pedicle connecting the hepatic bud to the duodenum becomes the extrahepatic bile duct. The most proximal portion of the anterior bud also contains the ventral pancreas and the lower common bile duct which, pulled in by the clockwise rotation of the proximal duodenum, will pass posterior to the digestive tract to end up on its medial border and will join the dorsal bud giving rise to the pancreas.

6.3.2 Developmental Malformations

The extrahepatic bile ducts and the gallbladder are frequent sites of anatomical variations, most often without clinical consequences except for the surgeon who has to operate in this area. There are, for example, abnormali-

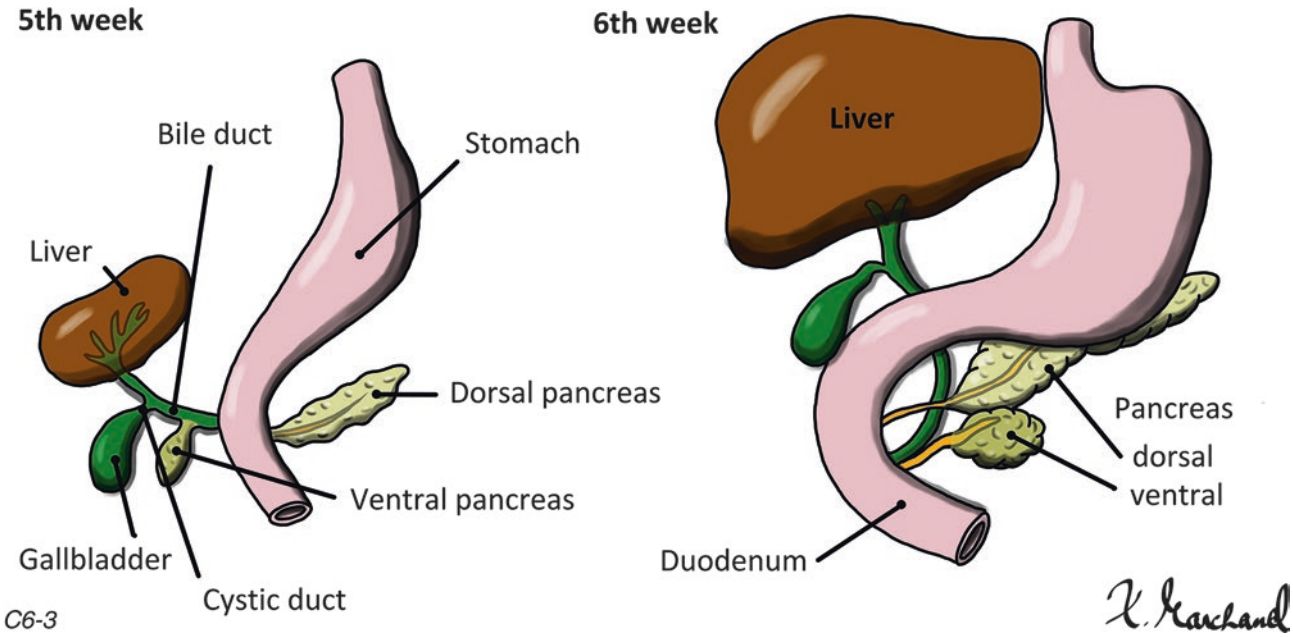


Fig. 6.3 Embryology of bile ducts: the hepatic bud is initially anterior and will move laterally to the right as the gastrointestinal tract rotates clockwise

ties in the fusion of bile and pancreatic ducts, "cystic" dilatations of the bile duct, duplication or agenesis of the gallbladder, etc.).

Biliary atresia (1/15,000 births) can affect extra or intrahepatic bile ducts. It causes jaundice in the first weeks of life and must be identified and treated promptly to avoid the fatal development of secondary biliary cirrhosis. Despite the fact that it occurs in the perinatal period, biliary atresia is not a developmental error but an acquired disease (in utero) with inflammatory necrosis affecting the bile ducts.

6.4 Secretion/Absorption

6.4.1 General Considerations

The gallbladder has a mucosal membrane that is capable of the greatest rates of water absorption in the human body. Absorption of water (active Na^+ transport coupled with passive H_2O absorption) by the gallbladder allows concentration of bile secretions by more than 80%. This phenomenon is of pathophysiological and clinical importance in the formation of gallbladder stones, since saturation of bile and formation of stones are much more important in the gallbladder (where secretions are concentrated) than in the bile ducts.

The gallbladder also secretes various substances, including H^+ ions and mucin, which are involved in bile lithogenicity.

Moreover, the biliary tree transports several important substances as we will see later.

6.4.2 Bile

Bile has always held an important place in the human psyche. Hippocrates hypothesized that the bile was part of the four body "humors" that determined our health and mood: blood, lymph, yellow bile, and black bile {which gave the term melancholy (με χ αϛ (melas), "black," and χολη (khōlé), "bile").

From a physiopathological medical point of view, bile plays an essential role in our body. Bile serves to transport secreted materials from the liver to the intestine. Some of these substances, including bile salts, are essential contributors to vital functions (such as nutrients absorption). Other substances in bile, such as bilirubin (degradation product of hemoglobin) or exogenous compounds (e.g., antibiotics such as metronidazole, aspirin, morphine), are harmful substances that will be expelled in feces to be removed from the body. The composition of bile is therefore of great importance.

The liver produces about 500–750 ml of bile per day. It consists of water (85%), bile acids/salts (10%), mucus and pigments (3%), lipids (1%), inorganic salts (0.7%), and cholesterol (0.3%). The ionic content of bile is close to that of plasma (Na^+ 140–160 mmol/l, K^+ 2.7–6.7 mmol/l, Cl^- 77–117 mmol/l). Bile is rich in HCO_3^- (12–55 mmol/l) and, in the case of external bile drainage,

used in management of bile duct obstruction; the alkaline loss may be great enough to require treatment with bicarbonate supplementation.

6.4.3 Bile Acids and Bile Salts

Bile acids are the most eloquent example of the contribution of bile and bile ducts to our homeostasis.

(a) Physiological importance

Bile acids make up 2/3 of all bile constituents (phospholipids, 22%; cholesterol, 4%; bilirubin, 0.3%).

Bile acids play an essential physiological role in the assimilation of nutrients: (1) they allow absorption of fatty acids and fat-soluble vitamins through the formation of micelles; (2) they facilitate protein digestion by denaturing dietary proteins to accelerate their cleavage by pancreatic proteases.

Bile acids and salts are complexed structures derived from cholesterol and exist under several forms (Fig. 6.4). They are synthesized in the liver, expelled into the bile ducts to reach the small bowel and participate then in nutrient absorption, before being reabsorbed and recirculated to the liver for further use (Fig. 6.5).

(b) Bile acids

They exist under various forms:

Primary bile acids. Bile acids are synthesized in the hepatocyte from cholesterol; 50% of circulating cholesterol uses this metabolic transformation pathway that is based on a complex phenomenon involving about 20 enzymes, including cholesterol 7α hydroxylase (whose synthesis activity is regulated by FGF 19 that is released by the enterocyte into the portal circulation (see below)). Primary acids thus formed include cholic acid and chenodeoxycholic acid, which make up 80% of all bile acids.

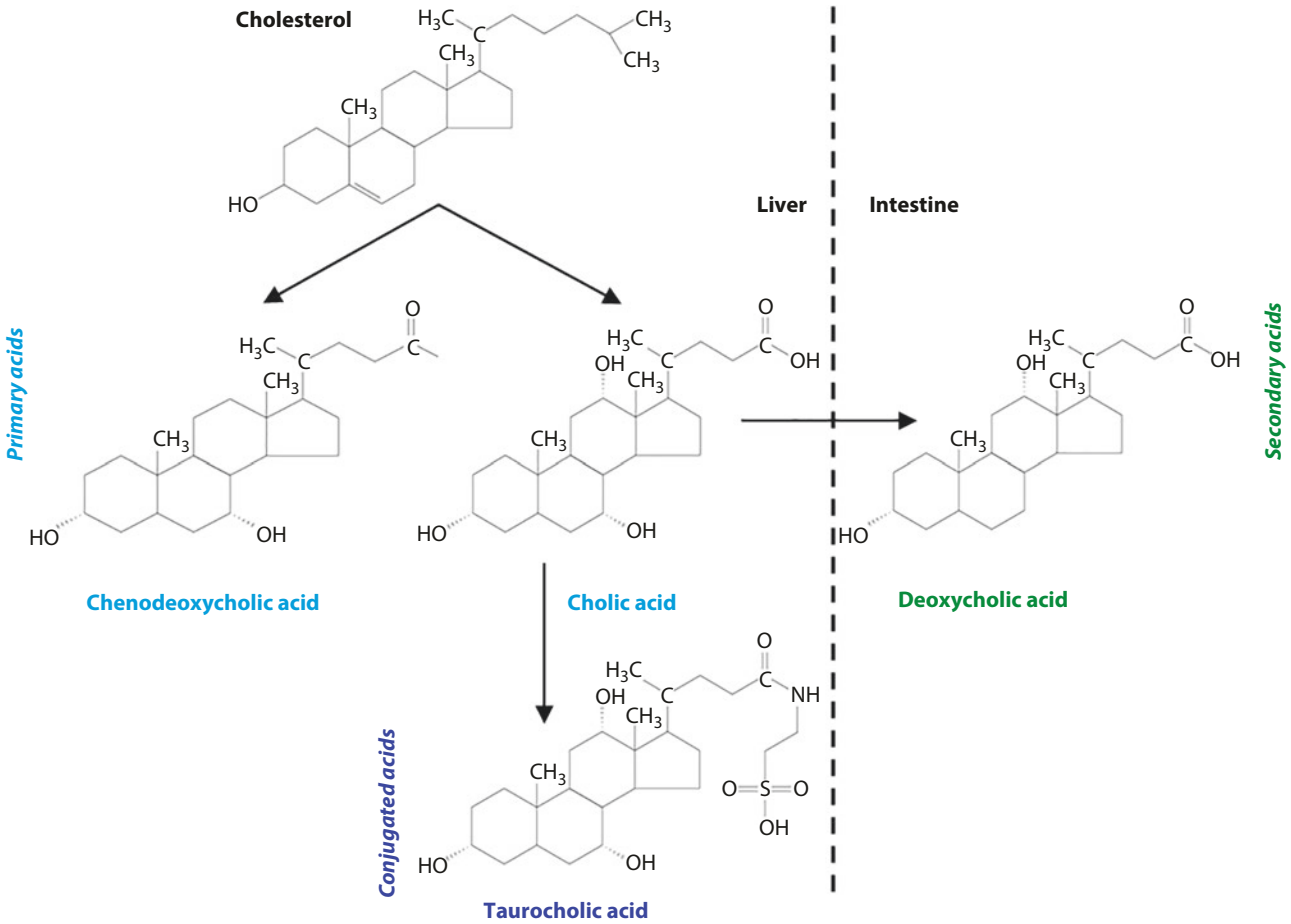


Fig. 6.4 Structures of major bile acids. Primary bile acids are synthesized in the liver, while secondary bile aids results from bacterial action in the intestine. In the liver, cholesterol is transformed into two primary bile acids, cholic acid, and chenodeoxycholic acid. These are then conjugated with glycine or taurine to form bile salts (e.g., taurocholic acid). In the distal small bowel, bacterial dehydroxylation (at the C7 position) of unabsorbed bile acids/salts to give rise to secondary bile acids/salts such as deoxycholic (from cholic acid) or lithocholic acid (derived from chenodeoxycholic acid)

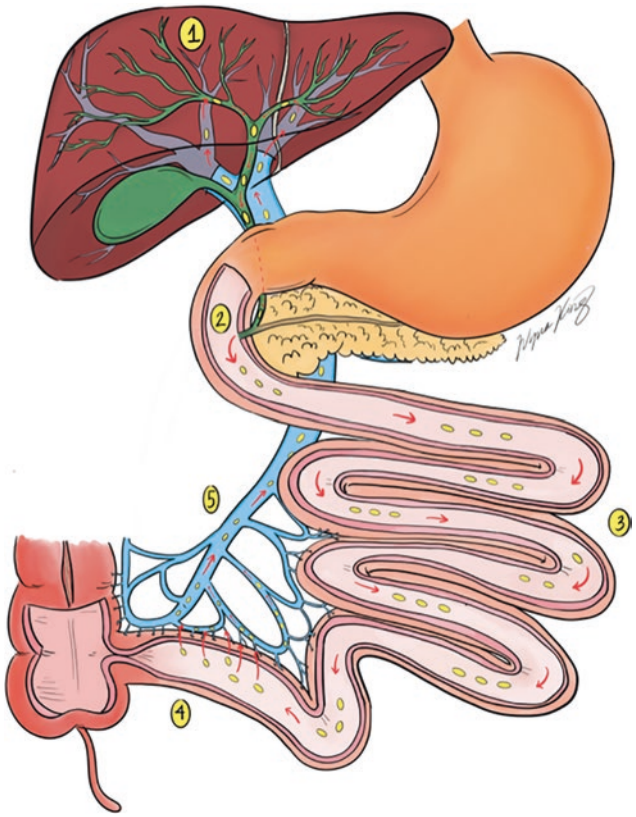


Fig. 6.5 Schematic journey of bile acids that are (**1**) synthesized in the liver, (**2**) excreted in the bile ducts, (**3**) then excreted in the small bowel, (**4**) absorbed in the distal ileum, and (**5**) recirculated via the portal vein to the liver

Secondary bile acids. Dehydroxylation of primary bile salts carried out by bacteria in the distal small intestine and/or colon can transform the primary bile acids cholic and chenodeoxycholic acid into so-called secondary bile acids, i.e., deoxycholic acid and lithocholic acid, respectively (which can be absorbed via the enterohepatic circulation to reintegrate the bile salts pool).

Conjugated bile acids (***or bile salts***). In the hepatocyte, primary or secondary bile acids are very effectively conjugated with amino acids taurine or glycine. The vast majority of bile acids are present in a conjugated form (and are known then as bile salts). Amino acid conjugation is essential for bile salt activity; it allows two things: (1) to limit the passive diffusion of unconjugated bile acids through the enterocytes and thus increase the concentration of bile salts available in the intestinal lumen for lipid absorption and (2) to render the bile acids much more water soluble, thus allowing the formation of micelles that are necessary for the solubilization of fatty acids and their subsequent absorption by the intestinal enterocyte (see ▶ Chap. 3).

Bile acids exist in approximately ten different forms (primary and secondary bile acids, conjugated or not with glycine or taurine, etc.), but the most important are cholic, chenodeoxycholic, and deoxycholic acids, which together represent more than 95% of all bile acid compounds (almost all present in a conjugated form). Ursodeoxycholic acid, formed as a result of bacterial modification of lithocholic acid, normally represents only 1–2% of total bile acids; however, its concentration can increase up to 40% when ursodeoxycholic acid is used as a pharmaceutical agent to alter the composition of bile salts (hoping, among other things, to dissolve gallstones).

(c) Enterohepatic Circulation of Bile Salts

Most bile acids present in the intestinal lumen are not excreted in the stools but rather are reabsorbed and processed through the enterohepatic circulation (Fig. 6.6). Bile acids present in the intestinal lumen (1) are absorbed at the apical membrane of the terminal ileum enterocyte by a specific apical sodium bile acid transporter (ASBT), (2) bind to the ileal bile acid-binding protein (IBABP), and (3) are exported by a

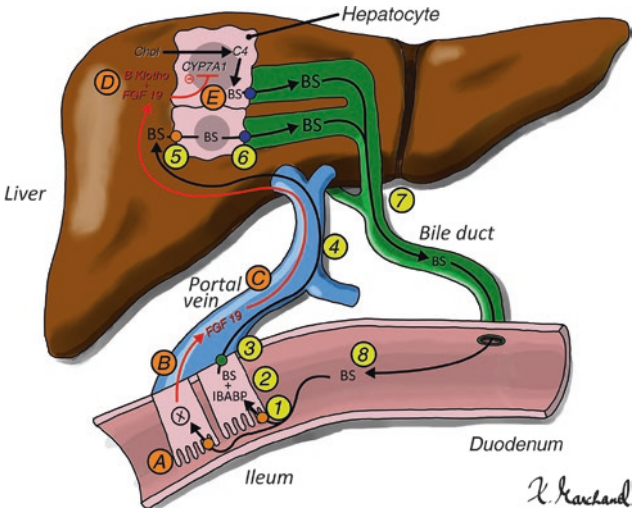


Fig. 6.6 **Recirculation of bile acids (BA)**: (**1**) the BA penetrates into the enterocyte via the apical sodium-dependent bile acid transporter (ASBT), (**2**) binds to the ileal bile acid-binding protein (IBABP), and (**3**) is then expelled from the enterocyte via the basolateral organic solute transporter (OST) to (**4**) the portal vein. (**5**) Once in the liver, BA enters the hepatocyte via an apical transporter called NTCP (Na^+- taurocholate cotransporting polypeptide) and (**6**) is then exported out of the hepatocyte by an ATP-dependent pump to (**7**) the bile duct (**8**) and ultimately reach the duodenum

Regulation of bile acid (BA) synthesis: BA absorbed from the intestine (**A**) stimulates the farnesoid X nuclear receptor (FXR) which (**B**) causes the enterocyte to secrete FGF 19, (**C**) which is then expelled into the portal vein. (**D**) At the hepatocyte, FGF19 and B Klotho protein bind together to the FGFr4 receptor, (**E**) to inhibit the transformation (by cytochrome CYP7A1 7a-hydroxylase) of serum cholesterol into 7a-hydroxy-4-cholesten-3-one (C4) and ultimately into BA (to be evacuated in the bile ducts en route to the duodenum)

basolateral enterocyte transporter (OST, organic solute transporter) out of the enterocyte (4) into the portal circulation. (5) Once at the liver, bile acids cross the hepatocyte apical membrane using a Na^+-dependent NTCP (Na^+- taurocholate cotransporting polypeptide) transporter, (6) to be conjugated with taurine or glycine, and (7) then secreted out of the hepatocyte into canaliculi using an ATP-dependent transporter, (8) to eventually join bile flowing down the common bile duct and (9) ultimately into the duodenum. Approximately 80–90% of the pool of bile acids used daily by our body is thus recycled through this enterohepatic circulation, which is repeated 4–12 times a day.

(d) Regulation of Bile Salt Synthesis

New bile acids (500 mg out of a global pool of 4 g) are synthesized daily from cholesterol to compensate for the fecal losses of bile salts. The synthesis of new bile acids by 7α hydroxylase is regulated by the global amount of bile acids/salts absorbed and generating the production of fibroblast growth factor (FGF) 19 by the enterocyte. As shown in ◘ Fig. 6.6, bile acids absorbed from the intestine (a) stimulate the farnesoid X nuclear receptor (FXR) which (b) cause the enterocyte to secrete FGF 19, (c) which is then expelled into the portal vein. (d) At the hepatocyte, FGF19 and B Klotho protein bind together to the FGFr4 receptor (e) to inhibit the transformation (by cytochrome CYP7A1 7a-hydroxylase) of serum cholesterol into 7a-hydroxy-4-cholesten-3-one (C4) and ultimately into bile acids (to be evacuated in the bile ducts en route to the duodenum). A lack of bile salts in the intestine therefore leads to a decrease in FGF 19 synthesized by the enterocyte into the portal vein, thus removing the inhibition of liver enzyme activity, and therefore resulting in the synthesis of new bile salts from serum cholesterol.

(e) Pathophysiological Implications of Bile Salts

Bile salts can be involved in different ways in various pathophysiological processes and diseases:

- Bile salts are essential constituents for a balance in bile solubility. Any quantitative or qualitative alteration of bile salts in bile (e.g., ileal resection interrupting the enterohepatic circulation) may therefore promote the formation of biliary stones, which will be discussed later.
- Deconjugation of bile salts by intestinal bacteria as noted with small intestinal bacterial overgrowth affects lipids absorption (as discussed in ► Chap. 3).
- Increased flux of bile salts into the colon, either as a result of ileal malabsorption due to ileal resection/disease or as seen with idiopathic bile acid diarrhea, promotes colonic secretion and diarrhea (see ► Chaps. 3 and 4).
- Liver toxicity from certain bile salts has been implicated in some diseases marked mainly by cholestasis such as in primary biliary cholangitis or sclerosing cholangitis (hence the use of ursodeoxycholic acid or obeticholic acid as therapeutic agents in these diseases).

In pediatrics, rare enzyme deficiencies are recognized that can affect synthesis, conjugation, or secretion of bile acids. Importantly, bile secretion is mature only after a few weeks of life; this state of immaturity is more pronounced in premature children. The uptake of bile acids on the hepatocyte membrane is also lower during the first month of life, increasing the "pool" of circulating bile acids, leading to the so-called physiological cholestasis.

6.4.4 Bilirubin/Icterus

Bilirubin is a typical example of the essential contribution of bile and bile ducts to the detoxification mechanisms necessary for our survival.

Bilirubin is a bile pigment that is also of primary clinical importance as it is the cause of jaundice (icterus) which occurs when bilirubin accumulates in the body as a result of lack of excretion through the liver or the bile ducts. Bilirubin (degradation product of hemoglobin) is produced before reaching the liver, transformed in the liver, and excreted through the bile ducts. The metabolism of bilirubin is described extensively in ► Chap. 8 and can be summarized as follows (◘ Fig. 6.7):

Prehepatic metabolism of bilirubin Bilirubin is a pigment produced during the degradation of heme in the reticuloendothelial system of the spleen and liver by two enzymes that convert hemoglobin to bilirubin (unconjugated).

Normal bilirubin plasma concentration is less than 20 µmol/l and is divided into two forms: an unconjugated form with a concentration not exceeding 15 µmol/l and a glucuronic acid-conjugated form with a concentration not exceeding 5 µmol/l in the absence of disease.

Unconjugated bilirubin is insoluble in water and is almost completely bound to albumin, which allows its transport in plasma. Unconjugated bilirubin is not present in urine since its binding to albumin prevents it from crossing renal glomerular membrane (hence the absence of dark urine in cases of icterus due to unconjugated hyperbilirubinemia).

Hepatic metabolism of bilirubin The passage of bilirubin from blood into bile through the hepatocyte consists of four steps:

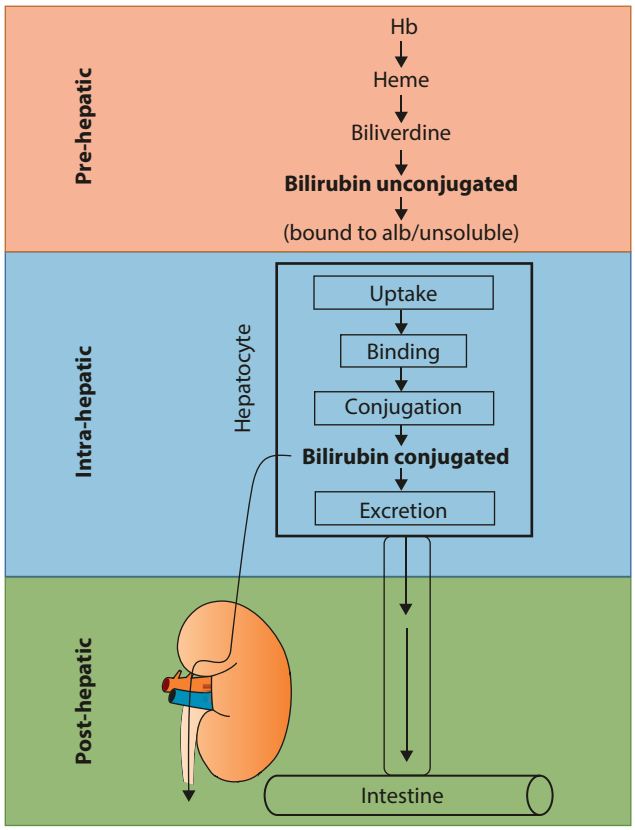


Fig. 6.7 Bilirubin metabolism: prehepatic, hepatic, posthepatic steps

- *Uptake:* unconjugated bilirubin transported by albumin is taken up at the sinusoidal pole of the hepatocytes via a transporter (not yet well identified).
- B*inding* of bilirubin in the hepatocyte cytoplasm to proteins belonging to the glutathione transferase family allows its migration to the endoplasmic reticulum.
- *Conjugation* is an obligatory step for an otherwise insoluble bilirubin to be excreted in the bile. This conjugation with glucuronic acid uses an enzyme located in the endoplasmic reticulum (bilirubin glucuronyl transferase, UGTIA1). Conjugated bilirubin is then transported to the biliary pole of the hepatocyte.
- *Excretion* of the conjugated bilirubin through the hepatocyte membrane into the bile canaliculus utilizes an active transporter (multidrug resistance-associated protein 2, MRP2).

Posthepatic metabolism of bilirubin Conjugated bilirubin is transported to the intestine via the bile ducts. It is not reabsorbed in the intestine. Following several steps, it is transformed by intestinal bacteria to urobilinogen (20%; colorless) and stercobilinogen (80%) which is further converted to stercobilin that is responsible for the brown color of the stools. Part of urobilinogen is reabsorbed and, following glomerular filtration, reaches the urine in the form of urobilin, giving it an amber color.

A hindrance to the flow of bile through the bile ducts (due to a mechanical obstacle such as a tumor, a stricture, a stone, etc.) leads to a backflow of bilirubin in the blood (jaundice), an increased urinary excretion of conjugated bilirubin in urine (dark urine) and an absence of bilirubin pigments in the stool (pale or acholic stools).

Diagnostic and therapeutic management of jaundice is described in ▶ Chap. 26.

6.4.5 Solubility of Bile Constituents/Biliary Stones

Bile constituents remain solubilized in bile owing to a physicochemical balance of these products. Disruption of this equilibrium may lead to the precipitation of certain components and formation of coarse concretions (called calculi) that can disturb biliary health by causing painful and/or functional blockages. An excess of cholesterol and/or a reduction in the solubilizing capacity of bile acids or phospholipids in the bile fluid may lead to precipitation of cholesterol and formation of cholesterol stones. An excess of bilirubin, e.g., as a result of hemolysis, leads to the formation of typical black pigment stones. Bacterial and mucin precipitates, formed especially in the presence of chronic biliary infections, serve as a matrix for the development of brown pigment stones. Stone disease is the most common clinical condition affecting bile ducts and gallbladder (see ▶ Sect. 6.6).

6.5 Motility/Sensitivity

The motor abilities of the biliary tree mainly affect the gallbladder and sphincter of Oddi (SO). They can be summarized as follows:

(a) Basal contraction of the SO prevents the reflux of intestinal contents into the bile ducts and promotes retrograde filling of the gallbladder with bile secreted from the liver.
(b) After a meal, the gallbladder contracts to empty its contents, and the SO relaxes, allowing the passage into of bile secretions needed for food digestion/absorption into the duodenum.

Contraction of the gallbladder and relaxation of Oddi sphincter are under neurohormonal regulation via the vagus nerve and the hormone cholecystokinin (CCK). CCK is synthesized and stored in endocrine I cells of the duodenal mucosa which, when stimulated by dietary lipids contained in duodenal chyme, will release the hormone into the bloodstream. The postprandial increase

in plasma CCK levels causes the gallbladder to contract, emptying its content in the common bile duct, while, at the same time, it relaxes and opens the SO, allowing the passage of the bile secretions into the duodenum.

Contraction/emptying of the gallbladder enables two events:

1. It synchronizes the arrival of bile salts in the small bowel at an optimal time when they are needed, i.e., during digestion/absorption of nutrients from a meal. However, loss of this postprandial synchronized activity, such as seen after gallbladder removal by cholecystectomy, does not seem to incur harmful consequences in the vast majority of patients.
2. It allows evacuation of precipitates of cholesterol, bilirubin, etc., which could form in the gallbladder and which are the basis for gallstone formation. Gallbladder hypomotility and stasis caused by fasting, octreotide, estrogen, etc. is a well-known risk factor for the development of gallstones.

6.6 Inflammation Disorders

6.6.1 Cholecystitis/Lithiasis

Cholecystitis is an inflammation of the gallbladder most often caused by obstruction of the cystic duct lumen from a stone formed in the gallbladder from bile secretions.

(a) Biliary Stone: Pathogenesis

A gallstone is a concretion formed from precipitation of certain components (calcium, cholesterol) of bile. (Another term describing a stone is "calculus," originating from when humans would count using pebbles).

Lithiasis is a general medical term characterized by the presence of stones or calculi in an organ or its excretion canal. In the case of a gallbladder stone (cholelithiasis), one or multiple calculi may be present.

There are three types of biliary stones (Table 6.1).

(a) Cholesterol stones contain more than 70% of their mass in cholesterol (hence, the name mixed stones, as pure cholesterol stones are rare). Small- and medium-sized stones are yellowish in color and contain cholesterol microcrystals, while larger stones often have a mixed composition with a center of cholesterol microcrystals and an outer layer of calcium salts.

(b) Black pigment stones are made up of a mixture of polymerized bilirubin and calcium salts. Hyperconcentration of bilirubin conjugates in bile appears to be a determining factor in the formation of these stones. They are found more frequently in Asia and in patients with hemolysis (42% of patients with sickle cell anemia) or with cirrhosis (30% of cirrhotic patients have gallbladder lithiasis).

(c) Brown pigment stones are found in the bile ducts where they form and are frequently associated with infection or obstruction. They are composed of an amorphous and brittle mixture of pigments, calcium salts, and glycoproteins. Accumulation of bacteria and mucus seems to play an initiating role in the formation of these stones.

Cholesterol stones make up about 85% of gallbladder stones in Western countries. Two main factors are implicated in the pathogenesis of cholesterol stones: (1) lithogenicity of bile (cholesterol saturation) and (2) gallbladder hypomotility.

(1) Bile lithogenicity

Cholesterol is insoluble in water and rendered soluble by insertion in a micelle structure formed with bile acids and phospholipids. The limits of cholesterol solubility in presence of bile acids and phospholipids were described in the 1960s using a diagram with triangular coordinates (Small's triangle, Fig. 6.8) to define the relative concentrations of the three main solid components from which bile becomes supersaturated with cholesterol (promoting stone formation). This supersaturation can be attributed to (1) hypersecretion of bile cholesterol, (2) hyposecretion of bile acids, (3) hyposecretion of lecithin, (4) or a combination of all three. The first mechanism is the most common; cholesterol secretion in bile increases with age, in obese people,

Table 6.1 Types of biliary stones

	Cholesterol	Black pigment	Brown pigment
Composition	Cholesterol	Bilirubin polymers	Calcium Bilirubinate
Formation site	Gallbladder	Gallbladder	Bile ducts
Radiopacity	15% of cases	50% of cases	No
Clinical association	Metabolic	Hemolysis/cirrhosis	Infection/inflammation

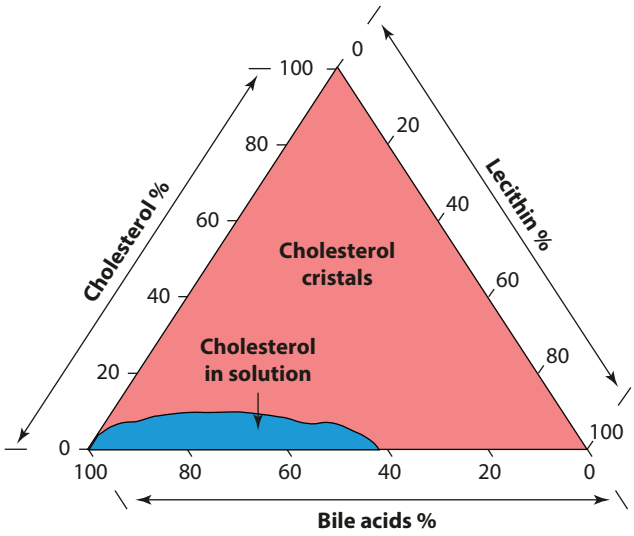


Fig. 6.8 Small's triangle shows that the formation of cholesterol biliary stones is promoted by high cholesterol concentrations (left scale), as well as by low concentrations of bile salts (base of the triangle) or lecithin (right) in bile

and in pregnant women, owing to increased estrogen. Bile acids are decreased in ileal diseases (e.g., Crohn's disease) or in liver diseases that alter the bile salt pool.

Cholesterol in high concentrations is non-soluble and gives rise to the formation of microcrystals (nucleation or crystallization) which with continued agglomeration lead to larger and larger stones.

(2) Gallbladder hypomotility

The gallbladder contribution to stone disease is emphasized by the observation of a much greater frequency of stones noted in the gallbladder than in bile ducts (where it is exceptional in the absence of factors promoting stasis such as strictures, malformation, etc.).

Gallbladder stasis is a risk factor for cholesterol gallstone formation. This is well demonstrated in patients treated with octreotide (a synthetic somatostatin that inhibits vesicular contraction); most patients treated long term with this drug (e.g., to reduce growth hormone levels in acromegaly) develop gallstones within 6 months that will become symptomatic and require cholecystectomy. Patients without oral feeding (and receiving parenteral nutrition) exhibit no gallbladder emptying (that is normally provoked by meals) and present, after only 3 weeks of fasting, with a thickened bile (biliary sludge) in the gallbladder (in which cholesterol crystals may precipitate and form stones putting the patient at risk for acute cholecystitis); this outcome can be prevented by periodically (once or twice a week) inducing gallbladder emptying using a prokinetic pharmacological agent such as CCK or erythromycin (a motilin agonist).

We can hypothesize two mechanisms promoting lithiasis in gallbladder hypomotility: (1) prolonged stasis of gallbladder fluids allows increased water reabsorption, therefore concentrating lithogenic factors ready to precipitate; (2) microcalculi formed in the gallbladder are not evacuated and can therefore grow to become true stones.

(b) Epidemiology and Risk Factors for Gallbladder Lithiasis

Gallbladder lithiasis is twice as common in women as in men. The prevalence of gallbladder lithiasis in white American women is 4–16% (increasing with age) and slightly lower in black individuals. Some Native American populations have a much higher prevalence, for example, among Pima Indians, 73.6% of women over 65 years of age have gallbladder disease, and nearly half have undergone a cholecystectomy for gallstones.

The classic "4F mnemonic" has been used for years to summarize increased risk factors for cholelithiasis: Female-Forty (years of age)-Fatty-Fertile.

The increased genetic incidence is obvious; first-degree relatives of patients with gallstones have four times the risk of developing gallstones.

The role of diet is less known, but certain observations seem to illustrate its importance. For example, in Japan, following World War II, adoption of a more Westernized diet was associated with an increased incidence of gallstones, with a shift from a prominence of pigmented to cholesterol stones. Diets rich in fiber, calcium, vitamin C, and coffee appear protective. Rapid weight loss, including bariatric surgery, is associated with biliary stone formation.

Hypercholesterolemia is not associated with an increased incidence of gallbladder lithiasis. However, hypertriglyceridemia, like diabetes, appear to be risk factors. Other factors are shown in Table 6.2

(c) Clinical Presentation of Biliary Lithiasis

Biliary stones most often cause symptoms by their presence in the gallbladder but may sometimes do so as a result of their migration from the gallbladder to the bile ducts. More rarely, stones form in the bile ducts – most often related to postsurgical or traumatic strictures, congenital abnormalities such as Caroli disease, or chronic infections.

Biliary stones are responsible for various clinical presentations by moving from the gallbladder to the cystic duct, the common bile duct or even the small intestine, as shown in Fig. 6.9.

(a) Asymptomatic (silent) gallstones Stones in the gallbladder may be discovered fortuitously in a patient without digestive symptoms having undergone a diagnostic

Table 6.2 Gallstones: promoting factors and physiopathological mechanisms

Factor	Bile cholesterol ↑	Bile acids ↓	Gallbladder motility ↓
Age	xx	x	
Female gender	xx		
Obesity	xx		
Weight loss	xx	x	
Pregnancy	xx	x	x
Estrogens (including contraceptives)	xx	x	
Clofibrate	xx	xx	
Ileal resection/disease		xx	
Fasting (prolonged)			xx
Octreotide/somatostatin			xx

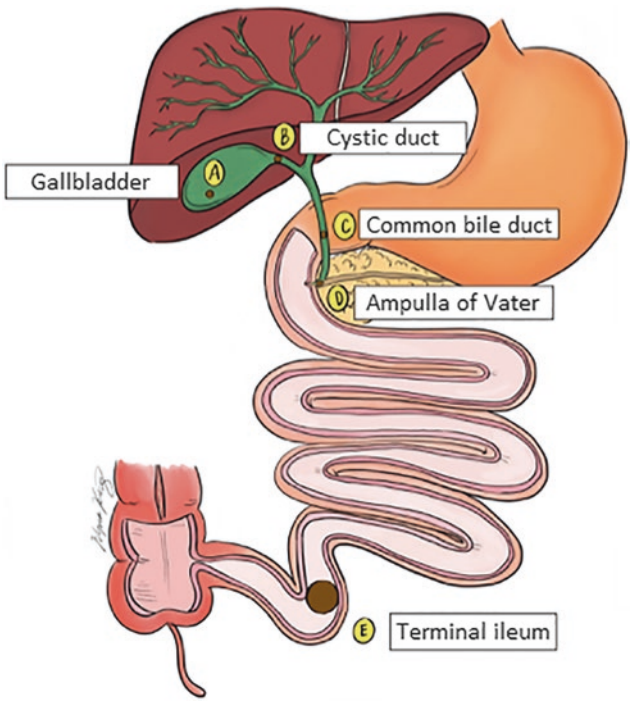


Fig. 6.9 Possible location of biliary stones and their associated clinical pictures. Stones (a) form in the gallbladder and are asymptomatic; (b) may obstruct the cystic duct, resulting in biliary colic, or, if obstruction persists for more than 4–6 h, in acute cholecystitis; (c) may migrate into the bile duct and cause migration syndrome with biliary colic, jaundice, and possibly cholangitis; (d) may obstruct the Wirsung duct and present with biliary pancreatitis; (e) may pass into the intestine to be expelled in the stools or, if large enough, get trapped at the ileocecal valve, causing intestinal obstruction (gallstone ileus)

examination (abdominal ultrasound, CT scan, etc.) for any other reason. Stones may also be detected in a patient with abdominal symptoms not attributable to a biliary origin (e.g., acidopeptic disease, dyspepsia, kidney stones, etc.); it is then up to the clinician to diagnose the correct cause of the abdominal pain.

In an asymptomatic person with gallstones, the risk of developing biliary pain (colic) is 1–4% per year, with a maximum risk of 20% after 20 years (NIH Consensus Statement (1992)). Therefore, there is usually no benefit in offering treatment to such an asymptomatic patient; there exist however special situations when treatment may be offered (Table 6.3).

Gallstones can be pushed by wall contractions to exit, with bile, the gallbladder; they can then obstruct the cystic duct, leading to biliary colic or acute cholecystitis:

(b1) Biliary colic is an acute abdominal pain due to rapid distension of the gallbladder (or bile duct), most of the time in relation with obstruction from a stone in the cystic

Table 6.3 Treatment of gallstone(s) disease

Acute cholecystitis

1. Cholecystectomy (urgent)
2. Antibiotics (if patient inoperable)

Biliary colic

1. Cholecystectomy (elective)
2. Urso (in selected cases)

Asymptomatic gallstone(s)

1. No treatment
2. Cholecystectomy in extraordinary conditions:
   - Suspicion or risk of malignancy
   - Gallbladder polyp >10 mm
   - Porcelain gallbladder
   - Stone(s) >30 mm
   - Gallstones associated with bile duct stone(s) (removed by endoscopic sphincterotomy)
   - Patients from ethnic groups with high incidence of gallbladder cancer (American Indians, etc.)
   - Post-liver transplant
   - Chronic hemolytic disease
3. Relative indications:
   - Patient with a long life expectancy
   - Diabetes
   - Patient with no easy access to medical resources
   - Cholecystectomy *en passant* during abdominal surgery for another reason

duct. It is felt in the epigastrium or right upper quadrant and is often severe enough to bring the patient to emergency room. It may be associated with nausea, vomiting, and/or with irradiation to the back (but this aspect is not part of the definition). Pain may occur after a meal but is often nocturnal. Biliary colic occurs when a stone is entrapped in the neck of the gallbladder or in the cystic duct (or in the main bile duct in the case of migrated stones), blocking luminal bile flow and causing upstream organ distension. Obstruction typically resolves itself by 4–6 h when the stone spontaneously dislodges; a more prolonged obstruction may lead to gallbladder inflammation (cholecystitis) which requires an emergency cholecystectomy (see below).

A diagnosis of gallbladder stones is made on abdominal ultrasonography (sensitivity >95%). Some stones (15%) are radiopaque and can be identified on a simple X-ray of the abdomen or at CT scan. Blood tests are usually normal during the attack (as in between attacks).

Treatment of symptomatic patients is recommended to avoid:

- Recurrences of unpleasant painful episodes
- Emergency room visits (2.5 visits per 100 patients per month)
- Acute cholecystitis (14% at 1 year)
- Acute pancreatitis (5% at 1 year)
- Obstructive jaundice (5% at 1 year)

The treatment of choice for symptomatic gallbladder stones is cholecystectomy. This is a surgical treatment in which both gallbladder and stones are removed. This treatment eliminates the risk of gallstone recurrence, which approximates 50% at 5 years when treatment only consists in emptying the gallbladder without removing it. Cholecystectomy can be done laparoscopically or by open surgery. The laparoscopic route is chosen in the majority of patients since hospital stay, postoperative pain, convalescence, and aesthetic damage are more favorable compared to the open route. The latter is used when a laparoscopic approach is impossible, or when a complication occurs during the operation, or when a tumor is suspected.

Complications of cholecystectomy are rare:

- Trauma to the biliary tract (<0.5%)
- Bile leak (<0.5%)
- Peritonitis and abscess (<0.3%)
- Postoperative hemorrhage (<0.5%)
- Perioperative death (<0.05% in patients <55 years of age)
- Post-cholecystectomy diarrhea (in up to 10% of subjects; responds well to treatment with bile salt-binding cholestyramine resin)

The surgical treatment of symptomatic gallbladder stones gives excellent results when patients are selected on the basis of typical symptoms. Other medical conditions, such as irritable bowel syndrome or peptic disease, may be present in patients with asymptomatic stones, and the patient will not benefit from gallbladder removal. Indications for cholecystectomy should therefore be carried out with care to effectively relieve patients with symptomatic lithiasis, avoiding unnecessary surgical risk and financial cost in subjects with asymptomatic lithiasis.

Nonsurgical treatments are available when the surgical risk is high due to medical comorbidity or when a patient refuses cholecystectomy. Gallbladder stones can be dissolved orally with ursodeoxycholic acid (10 mg/kg/day for 6–18 months); therapeutic efficacy increases when the stones are small, in limited number, not calcified and when the cystic duct is permeable. However, bile salt treatment does not correct the causal abnormality, and recurrence of lithiasis is common when the treatment is stopped. Nonsurgical treatment is more expensive than surgery except for elderly patients with small stones. Additional treatments are available in rare selected cases such as percutaneous or radiological gallstone extraction that can be performed in patients at high surgical risk.

(b2) Acute cholecystitis affects approximately 20% of patients with symptomatic gallbladder stones. It occurs when a stone blocks the outflow of bile from the gallbladder for a prolonged period of time. An inflammatory reaction may then develop. The gallbladder distends, and its wall thickens and becomes erythematous; an inflammatory exudate may spread to proximal surrounding organs. At the onset of the attack, the pain resembles biliary colic but gives way to sustained pain over time.

The patient usually presents to the emergency room. Physical examination reveals pain with signs of peritoneal irritation in the abdominal right upper quadrant. A Murphy's sign may be present (inspiratory arrest on deep inspiration with palpation of the right hypochondrium caused by contact of the inflamed gallbladder onto the examiner's fingers. The ultrasound Murphy's sign replaces finger palpation by an ultrasound probe that allows the radiologist to observe the contact of the gallbladder when the patient feels pain). There may be fever, leukocytosis, and a slight nonspecific increase in bilirubin or amylase.

Initially, the process is sterile, and inflammation explains the entire clinical picture. Bacterial superinfection occurs in up to 75% of patients. Antibiotic coverage is required but can be discontinued promptly postoperatively except for patients with severe sepsis or who are immunosuppressed.

For the vast majority of patients, an emergency cholecystectomy is indicated. Initial medical treatment (antibiotics ± percutaneous cholecystostomy) followed

Table 6.4 Severity of cholecystitis-cholangitis. Tokyo Classification, 2018

Acute cholecystitis	Cholangitis
Grade III	
One criterion required:	
Cardiovascular dysfunction requiring amines	
Altered state of consciousness	
Respiratory insufficiency	
Oliguria or creatinine >2X normal	
INR >1.5	
Platelets <100,000/mm^3	
Grade II	
Only one criterion required:	*2 criteria required:*
White blood cells >18,000/mm^3	White blood cells >18,000/mm^3
Palpable mass painful in the right hypochondrium	White blood cells <4000/mm^3
Pain >72 h	Temperature > 39°
Gangrenous cholecystitis	Age > 75 years old
Peri-gallbladder abscess	Bilirubin >5X normal
Liver abscess	Hypoalbuminemia
Biliary peritonitis	
Emphysematous cholecystitis	
Grade 1	
No criteria for grade II or III	

by cholecystectomy 6–8 weeks later may be appropriate in case of significant medical comorbidities (e.g., recent myocardial infarction or coronary stenting, clopidogrel use, etc.), a first or third semester pregnancy, or severe impairment (Table 6.4).

Gallstones (of relatively small volume) can pass through the cystic duct and reach the common bile duct:

(c1) Gallstone migration refers to the passage of stone(s) from the gallbladder into the bile duct. The clinical picture is similar to that of biliary colic. Blood tests done at the time of the attack may show cytolytic (increased AST, ALT) or cholestatic (increased bilirubin, alkaline phosphatase) disturbances in liver tests. Ultrasound of the abdomen, in most cases, shows gallstones (small stones in general, as large stones cannot pass through the cystic duct) and normal bile ducts (the stone(s) having migrated spontaneously into the duodenum or being nonobstructive in the bile duct while being undetected by US). If an MRI or endoscopic cholangiography (ERCP) is done early on, bile duct stones may be seen (usually, such examinations are not done when laboratory tests correct spontaneously). Cholecystectomy with intraoperative cholangiography is recommended in most patients.

(c2) Choledocholithiasis Stones in the common bile duct (CBD), most commonly, are due to gallstones having migrated from the gallbladder. Less than 10% of stones form de novo in the CBD; if so, in most cases, they are then related to ductal anomalies such as strictures.

Stones in the CBD may block bile flow, causing biliary pain, jaundice, cholangitis, pancreatitis, or, more rarely, secondary biliary cirrhosis. These stones may also be asymptomatic, discovered incidentally on an imaging exam done for another reason. Stones in the CBD should be treated even if they are not symptomatic due to possible complications.

Bile duct stones may be removed by surgical exploration of the bile duct during cholecystectomy or, most often, by endoscopic sphincterotomy with stone extraction. Endoscopic sphincterotomy is a simple procedure (in the hands of expert endoscopists) performed during ERCP (endoscopic retrograde cholangiopancreatography). During this examination, an endoscope introduced orally into the duodenum under brief conscious sedation allows to cannulate the papilla of Vater, to introduce dye opacifying the bile (or pancreatic) duct, and to cut and open the sphincter of Oddi in order to extract stones.

(c3) Cholangitis Migration of a gallstone into the CBD with obstruction of bile flow can be complicated by secondary bacterial biliary infection (ascending cholangitis) as discussed later.

Gallstones can migrate to the very distal portion of the CBD and obstruct the pancreatic duct:

(d) Acute pancreatitis Gallstones are the main cause of acute pancreatitis (discussed in ▶ Chap. 5).

Biliary pancreatitis is due to an obstruction of the main pancreatic duct (Wirsung, joining the common bile duct just above the papilla of Vater) by a stone that has migrated from the gallbladder to the CBD. The obstruction is usually transient, with the stone spontaneously disempacting or passing into the duodenum in most cases.

The role for an emergency ERCP in patients presenting with biliary pancreatitis is controversial since the obstruction usually resolves rapidly on its own. However, it is indicated if accompanied by persistent biliary obstruction or secondary cholangitis.

Following resolution of the pancreatitis, cholecystectomy during the same hospitalization is indicated considering the high risk of early recurrence (60% at 6 months).

Gallstones of small volume are evacuated from the biliary tree into the intestine without clinical consequences. Large volume gallstones can sometimes reach the intestine through fistulas created by an inflamed gallbladder.

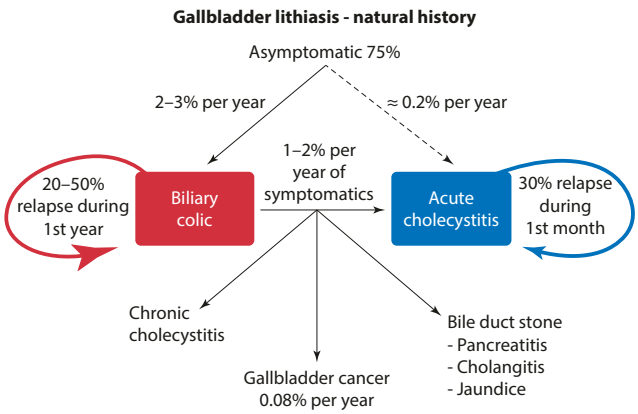
(e1) Bilio-biliary and bilio-enteric fistulas Fistulization of the gallbladder with the bile duct or with the digestive tract (most often with the duodenum, more rarely with the colon or the stomach) may occur during gallbladder inflammation.

The initial episode of cholecystitis that led to the gallbladder adhering to a nearby organ and forming a fistula may go unnoticed (fistulization probably leading to self-treatment of the cholecystitis by resulting drainage). Fistulas are often asymptomatic, unless bile acids cause choleretic diarrhea in the colon.

(e2) Gallstone ileus Gallstones migrating to the bile duct and reaching the duodenum are, most often, asymptomatically passed in the stools. However, a large stone (evacuated from the gallbladder via a biliary-enteric fistula) can block the intestinal lumen (most often at the ileocecal valve).

Classically, radiological examinations (abdominal X-ray or CT scan) reveal an intestinal ileus with mechanical blockage at the level of the terminal ileum (by the stone entrapped in the ileocecal valve), as well as the presence of air in the bile ducts (so-called pneumobilia, as a consequence the fistula between the biliary and digestive tracts). Surgical removal of the blocking stone may be necessary.

The natural evolution of gallstones is shown on ◘ Fig. 6.10.



◘ **Fig. 6.10** Gallbladder lithiasis: natural evolution

6.6.2 Cholangitis

Cholangitis (or ascending cholangitis, i.e., bile duct infection from bacteria ascending from the duodenum, in opposition to the more rare blood transmitted infections or to autoimmune cholangitis) is a bacterial infection of the biliary ducts manifested by the classical Charcot's triad: pain in the right hypochondrium, fever, and jaundice. This clinical presentation results from a partial or complete obstruction of the bile duct. Historically, the vast majority of cases were due to gallstones migrated from the gallbladder into the CBD. Today, many cases are related to malignant or benign bile duct obstructions operated or instrumented endoscopically or percutaneously (e.g., biliary stent decompression to relieve jaundice due to an obstructing neoplastic lesion).

Bacteria involved are mainly Gram-negative rods from the digestive tract such as *Escherichia coli* (50%), *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas*, *Proteus*, and *Enterobacter*; *Streptococcus* are possible, and anaerobes (*Bacteroides*, *Clostridium*) are found in 1/4 cases. These bacteria can translocate into the bloodstream, and half of the patients will have positive blood cultures.

Diagnosis Cholangitis is a serious and urgent condition, as it can quickly lead to septic shock. Abnormalities in hepatic blood tests (↑bilirubin, liver enzymes, alkaline phosphatase) usually confirm the diagnosis.

Treatment of these patients requires broad-spectrum antibiotic coverage for the intestinal flora (◘ Table 6.5). Approximately 90% of patients respond to this treatment and will subsequently be treated for the underlying obstruction (if a stone is involved, treatment is then carried out according to the principles outlined above in the section on stones of the CBD). However, for the 10% resistant to antibiotic treatment, urgent drainage of the bile duct must be obtained. Endoscopic approach (ERCP with sphincterotomy and stone extraction or stent insertion) is preferred. In cases where bile duct cannulation cannot be performed (due to prior surgical bypass or unfavorable anatomical conditions), transhepatic drainage will be performed. Definitive treatment of the underlying condition (most often gallstone with duct migration requiring cholecystectomy) is done once the patient's clinical condition has stabilized.

Table 6.5 Treatment of acute cholangitis

1. Antibiotics	
Cefotaxime	2 g i.v. q 6–8 h
Ceftriaxone	1 g i.v. q 24 h
Ceftriaxone	1 g i.v. q 24 h
+ metronidazole	+500 mg i.v. q 8 h
Ciprofloxacin	400 mg i.v. q 12 h
Piperacillin/tazobactam	3.375 g i.v. q 6 h
Ampicillin	1 g i.v. q 4–6 h
Ampicillin	1 g i.v. q 4–6 h
+ metronidazole	+500 mg i.v. q 8 h
+ gentamicin	+1 mg kg i.v. q 8 h
Treatment of the underlying conditions will be done.	
Subsequently: semi-urgent endoscopic sphincterotomy with duct stone(s) extraction or stent drainage (before ulterior definitive management of the obstructing lesion)	
Elective cholecystectomy is suggested in most cases of biliary disease	
2. If antibiotics fail (<10% of cases): urgent drainage of the bile duct:	
Endoscopic (ERCP) sphincterotomy + removal of duct stones or stent insertion	
Transcutaneous biliary drainage (stent radiological route)	

6.6.3 Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, progressive disease of unknown origin, characterized by inflammation leading to stenoses of intra- and extrahepatic bile ducts. The vast majority (80%) of patients with sclerosing cholangitis suffer from an inflammatory colitis (ulcerative colitis or Crohn's disease). PSC will be discussed in ▶ Chap. 8.

Diagnosis The diagnosis is usually suspected on a blood test revealing cholestasis (elevated alkaline phosphatase). Magnetic resonance imaging of bile ducts (or more rarely ERCP) shows multiple stenoses of extra- and intrahepatic bile ducts.

Evolution The main complication is the development of biliary cirrhosis secondary to the biliary obstruction. Liver transplantation is required in a large number of patients to mitigate the liver failure. Cholesterol or bilirubin stones may form proximally to the biliary strictures (their growth is probably promoted by stasis due to obstruction). Cholangitis may develop; the risk of cholangitis is significantly increased after iatrogenic manipulation of the bile ducts (because of this complication, diagnostic ERCP has now been replaced by magnetic resonance cholangiography).

Cholangiocarcinoma develops in 10–15% of patients. Differentiating a malignant from a benign stenosis can be very difficult.

PSC is a very important risk factor in the development of colon cancer in patients with associated inflammatory colitis. A surveillance program for colon cancer is desirable for these patients.

Treatment There is no known treatment to influence or improve the evolution of PSC. Medical or surgical control of the associated inflammatory bowel disease does not appear to alter the course of the biliary disease. Liver transplantation is the ultimate solution for patients who develop cirrhosis or, in some cases, cholangiocarcinoma.

6.6.4 Autoimmune Cholangitis

Stenosing damage to the bile ducts is common in IgG 4 disease whether or not accompanied by pancreatitis (see autoimmune pancreatitis in ▶ Chap. 5). Inflammatory stenoses may respond to corticosteroid therapy.

6.6.5 "Atypical" Infectious Cholangitis

In an immunosuppressed patient, most often due to HIV virus (or in children with primary immune deficiency), infectious cholangitis due to CMV, *Cryptosporidium*, etc. may occur. In countries where parasitic infections are endemic, infection of the bile ducts by *Ascaris* or *Clonorchis* (Chinese fluke) is common.

6.7 Tumor Disorders

6.7.1 Cholangiocarcinoma

An adenocarcinoma can develop at various levels of the bile ducts:

- In the intrahepatic bile ducts (intrahepatic cholangiocarcinoma). See ▶ Chap. 8.
- In the right or left hepatic ducts (extrahepatic or proximal cholangiocarcinoma) or at the confluence of both ducts (perihilar cholangiocarcinoma or Klatskin's tumor).
- Along the common bile duct (cholangiocarcinoma or adenocarcinoma of the bile duct). If distal, this tumor presents like an adenocarcinoma of the head of the pancreas and is treated in essentially the same way (although the adjuvant chemotherapy is different).
- At the ampulla of Vater (ampullary carcinoma). This tumor normally presents as jaundice or anemia through blood loss from its ulcerated surface. It can

be localized on the intracanalar side of the ampulla or on its intestinal luminal side (it can then be easily visualized at duodenoscopy). An ampullary carcinoma may be associated with duodenal polyps found in patients with familial polyposis of the colon. This tumor is managed like an adenocarcinoma of the head of the pancreas, with similar adjuvant chemotherapy.

Clinical presentation The cholangiocarcinoma obstructs the bile duct and impedes passage of bile into the duodenum; jaundice is the most frequent clinical manifestation, regardless of the level of obstruction (hilum, bile duct or ampulla).

Diagnosis Blood tests reveal elevated conjugated bilirubin and alkaline phosphatase. Imaging techniques demonstrate dilatation of the bile duct in relation to the site of tumor obstruction along the bile duct pathway. Ultrasonography is a simple procedure, but it must most often be complemented by CT scan or MRI cholangiography in order to evaluate precisely the tumor and especially its extension allowing or not its surgical resection.

Endoscopic ultrasound (EUS) allows precise visualization of the tumor and a tissue diagnosis by needle biopsy.

Retrograde cholangiography (ERCP) is no longer used exclusively for diagnostic purposes (given the risk of infecting the bile ducts and inducing cholangitis) but is reserved for cases requiring therapeutic intervention (stent drainage, etc.).

Treatment Extensive surgical resections such as Whipple's duodeno-pancreatectomy are usually necessary and require the expertise of a team well-versed in this type of surgery. Extension of the tumor to local lymph nodes and/or vascular structures (or other surrounding structures) often precludes surgery and dictates a palliative therapeutic strategy.

Palliative treatment aims to remove the biliary obstruction and relieve the jaundice (often a source of intense pruritus). Drainage of the obstructed bile duct is most often achieved using prostheses (also called stents) installed at ERCP (plastic stents are less expensive than expandable metal stents but are susceptible to earlier clogging by bile plugs due to their smaller diameter) (see Fig. 6.11). Biliary drainage by percutaneous transhepatic route (radiological approach) is possible and allows placement of an internal stent, an external biliary drain, or an internal/external drain. Surgical drainage (biliary bypass through a "Roux-en-Y" bowel loop) is now rarely performed.

Palliative chemotherapy (cisplatin and gemcitabine) may somewhat improve the median survival of patients (11.7 versus 8.1 months) in whom curative treatment is not possible.

The prognosis of cholangiocarcinoma is poor with a 5-year survival of 5% in inoperable patients and 30–40% in curatively operated patients. However, the majority of patients (70%) are incurable at the time of diagnosis.

In children, rhabdomyosarcoma (botryoid sarcoma) is the most common tumor of the biliary tract. A survival rate of more than 75% is achieved after treatment with chemotherapy and surgery.

6.7.2 Gallbladder Cancer

Cancer of the gallbladder is associated with gallbladder stones. However, the long-term risk of developing cancer in the presence of gallstones is lower than the risk of elective cholecystectomy (and is therefore not an argument for supporting prophylactic cholecystectomy in silent gallstones bearers).

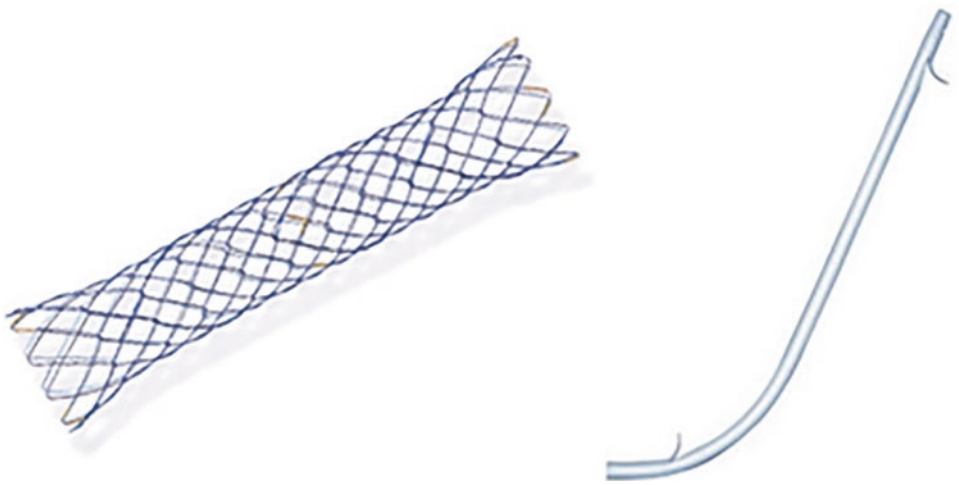


Fig. 6.11 Prostheses or stents to be introduced endoscopically into the bile ducts to palliate luminal obstruction. Expandable metal stent on the left figure; rigid plastic stent on the right figure

The tumor most often develops insidiously and is usually not operable by the time symptoms of abdominal pain in the right hypochondrium, weight loss, or jaundice appear. A palpable mass in the right hypochondrium may be detected on physical examination. Sometimes gallbladder cancer is discovered incidentally during a cholecystectomy or postoperatively when the pathologist examines the surgical specimen.

Imaging (ultrasound, CT scan, etc.) may show the tumor.

The treatment is surgical in the absence of vascular invasion or metastases; it includes extensive gallbladder excision with partial liver resection and lymph node dissection.

The prognosis is poor (5-year survival of 5%) in inoperable patients.

6.7.3 Benign Tumors/Polyps

Gallbladder polyps are asymptomatic.

They may be inflammatory (in chronic cholecystitis) or adenomatous.

A polyp larger than 1 cm justifies a cholecystectomy due to the risk of a malignant transformation of adenomas.

6.8 Function Disorders

The Rome IV classification of functional GI disorders (see ► Chap. 4) recognizes functional gallbladder as well as functional sphincter disorders. In both cases, the clinical presentation is that of biliary type pain, i.e., localized to the right upper or epigastric area, episodic, and unexplained by usual examinations including abdominal ultrasound in search of lithiasis or biliary sludge. Both topics however are highly controversial.

6.8.1 Functional Gallbladder Disorders

Delayed gallbladder emptying (perhaps due to chronic cholecystitis), when measured by HIDA-Tc 99 cholescintigraphy, is found in some of these patients and has been interpreted as the cause of their symptoms by some medical authorities who promoted cholecystectomy for treatment of the disease. However, this concept and plan of investigation/treatment are highly debated and contested by several gastroenterologists and surgeons who question the diagnostic value of isotopic cholecystography and the therapeutic benefits achieved with cholecystectomy in these patients.

6.8.2 Functional Oddi Disorders

Sphincter of Oddi (SO) dysfunction refers to a defect in the relaxation of the sphincter which therefore leads to an alteration in the emptying of gallbladder and/or bile duct with biliary type pain. Classically three types of Oddi dysfunction have been recognized:

- Type 1: Biliary pain with biochemical abnormalities (elevation of ALT, AST, alkaline phosphatase) *and* bile duct dilatation (on ultrasound or other imaging)
- Type 2: Biliary pain with biochemical abnormalities *or* bile duct dilatation
- Type 3: Biliary pain *without* biochemical abnormalities *or* bile duct dilatation

Manometry of the SO may reveal inadequate sphincter relaxation («Oddi's achalasia») in response to CCK administration with normal or increased basal sphincter pressure. Manometry, performed by sphincter cannulation using ERCP technique, is however a delicate procedure with a high risk of complications (pancreatitis, etc.) and is only available in a few ultra-specialized units in the world.

Treatment of the disease with pharmacological relaxants (nitroglycerin, calcium blockers, botulinum toxin) has been poorly studied. Sphincterotomy (per ERCP) gives good results in patients with type 1 dysfunction. However, this disease is rare (5–7% of SO dysfunctions), and it is likely that the pathology involves sphincter fibrosis possibly related to the previous passage of bile duct stones. In the case of type 2 dysfunction, sphincterotomy has provided encouraging results (60–90% success rate) in some patients with well documented high basal sphincter pressure. Type 3 dysfunction is by far the most common (80%); sphincterotomy has failed to relieve symptoms better than a sham procedure in this population, and rectal hypersensitivity (suggestive of IBS) has been identified in a large number of these patients. Sphincterotomy (and its complications) should be thus avoided in subjects with type 3 sphincter dysfunction, and the presence of other functional symptoms (such as IBS) should be sought.

SO dysfunction, apart from the rare type 1 form, is a concept that is now questioned by several investigators.

6.9 Miscellaneous

6.9.1 Chronic Cholecystitis

This histopathological term describes chronic morphological changes of the gallbladder most often related to lithiasis. There exists no clear clinical correlate for this histological finding.

6.9.2 Porcelain Gallbladder

Porcelain gallbladder is identified on simple X-ray or CT scan by calcification of the gallbladder walls. The increased risk of neoplastic transformation justifies cholecystectomy in this condition.

6.9.3 Acute Acalculous Cholecystitis

Occasionally (less than 10% of cases), acute cholecystitis occurs in the absence of lithiasis. This condition is most often seen in debilitated patients, often hospitalized, and therefore carries a high morbidity/mortality rate.

6.9.4 Emphysematous Cholecystitis

Emphysematous cholecystitis is due to cholecystitis involving gas-producing bacteria, most often anaerobic bacteria. Gangrene and perforation are frequent, and emergency cholecystectomy is required.

6.9.5 Mirizzi's Syndrome

Mirizzi's syndrome refers to the obstruction of the common hepatic duct by a gallstone lodged in the cystic duct or in the Hartmann's pouch. It is often mistaken for a malignant obstruction.

6.9.6 Isolated Bile Duct Dilatation

The common bile duct (CBD) normally measures less than 7 mm. Dilatation without symptoms (pain, jaundice, etc.) and without biochemical abnormalities (elevated alkaline phosphatase) is common in cholecystectomized patients (up to 1.2–1.4 cm).

Dilatation may also be noted in subjects with cystic dilatation of the bile ducts, which may take several forms as described and classified by Todani: the most common variety (80–90%; Todani type 1) involves saccular or fusiform (choledococele) dilatation of a portion or entire CBD; cysts may also present as an isolated diverticulum protruding from the CBD (type 2), arise from a dilatation of the duodenal portion of the CBD (type 3 or choledochocoele), and involve multiple dilatations of the intrahepatic and extrahepatic biliary tree (type 4a), multiple dilatations involving only the extrahepatic bile ducts (type 4b), or multiple saccular or cystic dilations of the intrahepatic ducts (type 5 or Caroli disease). Bile duct cysts are usually asymptomatic. With the exception of the choledocele and Caroli disease, surgical resection should be considered because of the long-term risk of malignant transformation.

6.9.7 Adenomyomatosis-Cholesterolosis

These focal thickenings of the gallbladder wall are most often found in patients operated for cholelithiasis.

Adenomyomatosis refers to a benign proliferation (without adenomatous changes, despite its name) of the gallbladder epithelium with possible formation of tissular nodules and protrusions (Rokitansky-Aschoff sinuses).

Cholesterolosis corresponds to a deposit of cholesterol in the gallbladder wall and results in a whitish staining (strawberry gallbladder).

Both conditions, although benign, can lead to polypoid formation. In the case of polyps larger than 1 cm and whose malignant nature cannot be excluded, a cholecystectomy will be justified.

PS: for complementary lectures on the biliary tree, see ► Chaps. 16 and 26.

The Anorectum

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Contents

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7.1 Macroscopic Anatomy

7.1.1 Rectum and Anus

The *rectum* is the most distal segment of the large intestine, extending from the sigmoid colon. The junction between the two is marked by the rectosigmoid angle located at the level of the S3 vertebra. It is approximately 15-cm-long in adults, ending distally in the anal canal. The rectum and the sigmoid form, at rest, a right angle (open at the back and whose angulation depends on the contraction of the puborectalis muscle) that will open (straighten) during defecation. The rectum is extraperitoneal in its lower two-thirds and follows the concave curve of the sacrum. In men it is located behind the bladder and the prostate, and in women it is behind the uterus and the vagina (◘ Fig. 7.1).

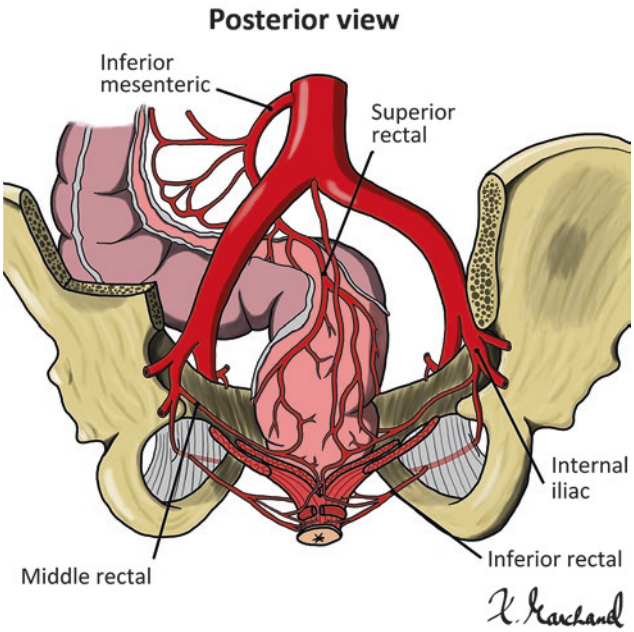
Inside the rectum, three semicircular valves (valves of Houston) are formed by folds of the rectum wall.

The *anal canal* is the terminal portion of the intestinal tract that extends from the lower end of the rectum to the anal orifice at the skin. It is a muscular cylinder about 2- to 4-cm-long that is angled down and toward the back. It is an area of high pressure with a key role in maintaining fecal continence. This high-pressure area is directly related to the presence of two sphincters: the internal anal sphincter and the external anal sphincter.

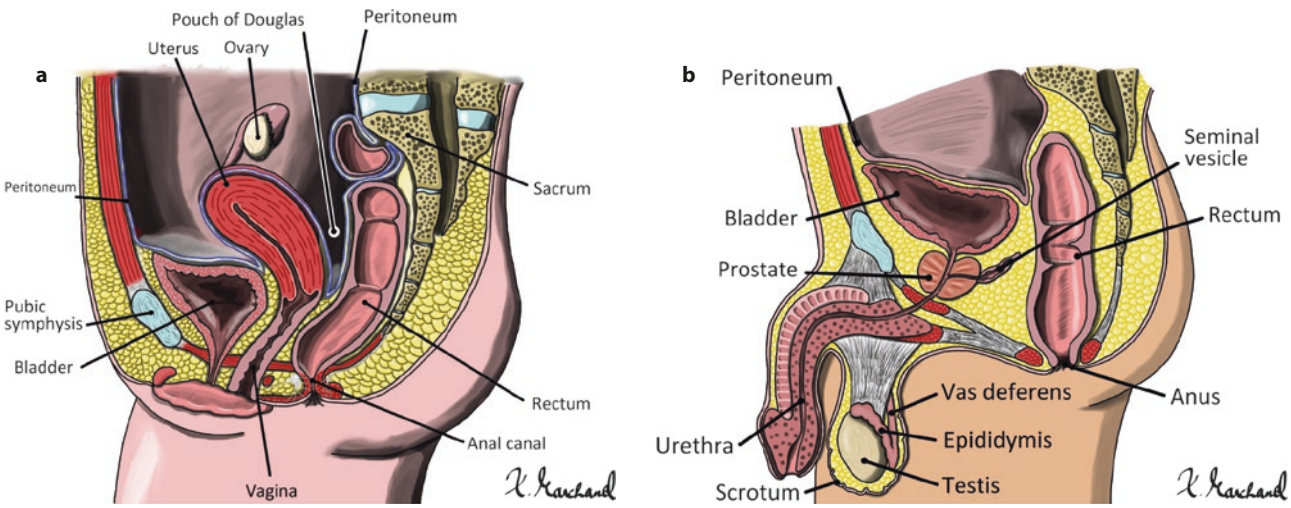
7.1.2 Vascular Supply

Arteries The rectum receives arterial supply from five arteries: the superior, middle (right and left), and inferior (right and left) rectal arteries (also called hemorrhoidal arteries). The superior rectal artery is the main one; arising from the inferior mesenteric artery, it is divided into two branches feeding the posterior and anterior sides of the rectum. The collateral branches penetrate the rectal muscular wall and descend to the anal canal. The rectosigmoid angle, the rectum, and the mucosa of the anal canal are fed by the superior rectal artery (◘ Fig. 7.2). The middle rectal artery originates from the internal iliac artery. It supplies blood to the rectum and the genital area, but it only exists in about one in two cases.

The inferior rectal artery, a branch of the internal pudendal artery (which arises from the internal iliac



◘ **Fig. 7.2** The arteries supplying blood to the rectum and anus (called rectal or hemorrhoidal arteries) originate from a branch of the inferior mesenteric artery for the upper rectum and from branches of iliac arteries for the more distal areas



◘ **Fig. 7.1** Anatomy of the pelvis (lateral view) in woman (**a** on left) and in man (**b** on right)

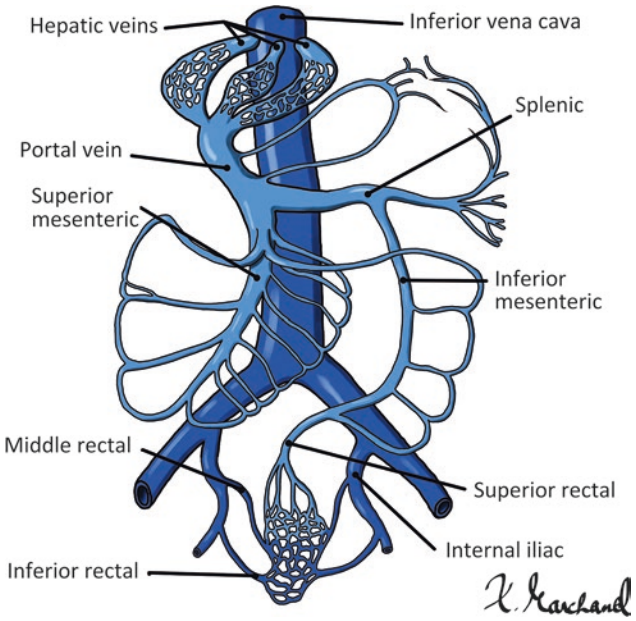


Fig. 7.3 Veins from the lower rectum and anus drain blood into iliac veins to the systemic circulation via the iliac veins. The upper rectum drains into portal system via the lower mesenteric vein to the splenic vein (which joins the upper mesenteric vein to form the portal vein going to the liver)

artery) vascularizes the external and internal sphincters as well as the levator muscle of the anus.

Veins Venous vascularization follows the arterial system (Fig. 7.3). Thus, the superior rectal vein forms, with sigmoid veins, the inferior mesenteric vein which then joins the splenic vein and the portal venous system.

The middle and inferior rectal veins are not always present. They drain the lower part of the rectum and the anal canal to the internal iliac veins connecting to the inferior vena cava.

The rectum drains to the portal as well as to the systemic venous system. Since the five rectal veins connect (anastomose) with each other in the submucosa of the lower rectum (forming the hemorrhoidal plexus), anastomoses between portal and vena cava systems result. These anastomoses explain the presence of rectal varicose veins in portal hypertension due to liver cirrhosis.

Lymphatics Lymphatic plexuses of the rectal and anal walls are the starting point of lymphatic vessels that join lymph nodes in the perirectal adipose tissue. Lymphatic drainage follows the arteries in the mesorectum for most of the rectum and ascends to the inferior mesenteric artery. The lower part of the rectum and the ano-perineal region are drained to the inguinal region. Cancer of the rectum has a high risk of lymph node metastasis as soon as the cancer spreads beyond the muscularis mucosae. This characteristic of rectal cancer associated with its double lymphatic drainage (i.e., "portal" and systemic) helps to understand the high risk of locoregional recurrence of rectal cancers after surgery, as well as the increased prevalence of metastatic spread in systemic territories (independent from the portal system) such as the lungs.

7.1.3 Innervation

As in the entire digestive tract, rectal innervation has both intrinsic and extrinsic architecture (Fig. 7.4).

(a) Intrinsic innervation is provided by the enteric nervous system (ENS), which is present all along the intestinal wall (as already described in previous chapters of this book). Sphincter relaxation is mainly ensured by VIP and ATP neurotransmitters.
(b) Extrinsic somatic innervation reaches the striated muscles of the pelvis and consists of the motor bundles (S2, S3, S4) of the pudendal nerve. The pudendal nerve transmits motor function for the external sphincter of the anus and sensation for the perineum.
(c) Extrinsic autonomous innervation depends on parasympathetic and sympathetic fibers, both efferent and afferent, connected to the central nervous system, including the hypothalamus.

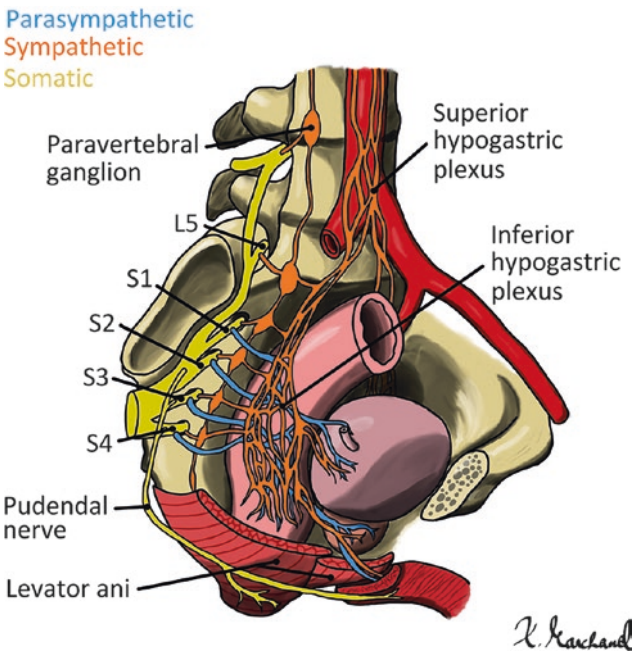


Fig. 7.4 Innervation of the anorectal region: sympathetic fibers from paravertebral ganglia synapse in hypogastric ganglions (superior and inferior) before reaching their target organs. The parasympathetic fibers come from sacral roots S1 to S4. Somatic innervation is provided by the pudendal nerve (a branch of the nerve roots forming, among others, the sciatic nerve)

Parasympathetic fibers Central parasympathetic fibers synapse with cells from the vagal dorsal nucleus on the floor of the fourth ventricle to give rise to the 10th cranial nerve, the pneumogastric or vagus nerve, which travels down along the esophagus until the proximal colon. Parasympathetic fibers also descend into the spinal cord to synapse with sacral roots from S2 to S4 and innervate the distal colon, i.e., the sigmoid and rectum. Sacral parasympathetic fibers, both motor and sensory, play an important role in the defecation (cholinergic parasympathetic stimulation relaxes the internal anal sphincter).

Sympathetic fibers Sympathetic fibers all go down from the brain to the abdomen through the spinal cord and intervertebral nerve roots. Fibers issued from the spinal cord are called "preganglionic" fibers since they all go to nerve ganglia from where the so-called postganglionic fibers emerge to reach the various digestive organs. There are five important neurological ganglia (or plexuses) in the abdomen:

- The celiac ganglion, located close to the aorta at the origin of the celiac trunk artery, receives thoracic splanchnic nerves synapsing to generate postganglionic fibers that innervate the foregut organs (stomach, duodenum, pancreas, etc.). Celiac ganglion block can be done to alleviate pain from pancreatic cancer. Interruption of sympathetic activity can cause diarrhea.
- The superior mesenteric ganglion located at the junction between the aorta and the superior mesenteric artery receives lower thoracic splanchnic nerves (from T6 to T12) to give rise to postganglionic fibers innervating the midgut, i.e., the small bowel and the proximal colon.
- The inferior mesenteric ganglion, at the aortic root of the artery, receives lumbar fibers from L1 to L3 to innervate the left colon.
- The superior hypogastric ganglion, located in front of the aortic bifurcation, receives preganglionic fibers from L4 to L5 and gives postganglionic axons innervating the sigmoid and the rectum.
- The inferior hypogastric (or pelvic) plexus receives sacral fibers from S1 to S3 destined mainly to the anorectal region and pelvic organs such as the prostate, bladder, seminal vesicles, etc. Damage to these pelvic nerves during surgery with rectal dissection can lead to erectile or bladder dysfunction. Alpha-adrenergic sympathetic stimulation contracts the internal anal sphincter, while beta-adrenergic stimulation relaxes it.

7.2 Microscopic Anatomy

7.2.1 Mucosa

Rectal mucosa The mucosa of the rectum is similar to the rest of the colon. The epithelium is columnar and lies on a basal membrane. In the upper part of the crypts, so-called enterocytic absorptive cells and mucus cells (or goblet cells) are predominant, while at the bottom of the crypts, more undifferentiated cells and some endocrine cells are present. Muscularis mucosae separate the mucosa from the submucosa as in the rest of the colon.

Anal mucosa The anus is covered by a squamous epithelium which meets the columnar colonic epithelium (anorectal line or squamocolumnar junction) just above the columns of Morgagni and extends down 4–5 cm to the anal margin (ano-dermal line) where the skin (rich in hair follicles, sweat glands, etc.) begins.

About halfway up the anal canal (2–3 cm from the anal margin), the pectinate or dentate line, is clearly visible. It is made of 10–12 half-moon-shaped valves called Morgagni's columns that cover crypts where channels emerge from glands located in the rectal wall (called Hermann and Desfosses' glands). These glands reside in the inter-sphincter space and are the starting point for abscesses and anal fistulas.

Above the pectinate line, the mucosa takes on a reddish-purple appearance due to the internal hemorrhoidal plexuses located in the submucosa.

Below the pectinate line, a non-keratinized squamous cell type epithelium is present. This 1 cm transitional zone (also called anal pecten) is richly innervated and continues downward to blend with the keratinized skin, gradually changing from being initially smooth to become more pigmented and rich in hairs and sebaceous and sweat glands.

The pectinate line corresponds to the junction of the endoderm and the ectoderm structures during the development of the embryo.

7.2.2 Muscularis

(a) Muscles of the rectum The rectal muscularis is made up of a circular inner layer and a longitudinal outer layer different from those of the colon. In the colon, the longitudinal layer does not cover the whole circumference of the colon and is reduced to three strips called taenia coli; in the rectum, the outer layer is continuous as elsewhere in

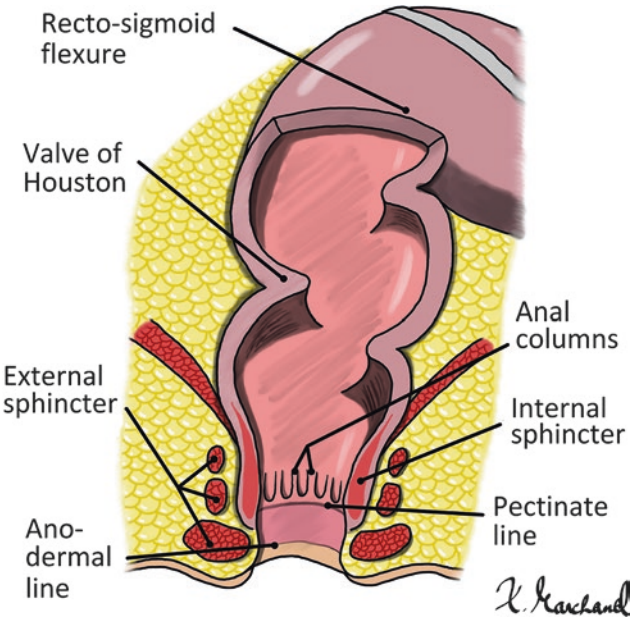


Fig. 7.5 Anus, pectinate line, sphincters, Houston's valves

the digestive tract. The circular and longitudinal muscle layers will, in the part distal to the rectum, merge to form the internal sphincter. The Auerbach's myenteric plexus is located on the outer surface of the circular muscle.

In the rectum, three transverse folds of the mucosa and circular muscles form semilunar valves (valves of Houston) that take up about 1/3 of the lumen. The upper and lower valves are located on the left side wall; the middle valve is on the right. The three valves are located 2–3 cm, 6–7 cm, and 10–11 cm, respectively, above the pectinate line (Fig. 7.5). The function of these valves is uncertain.

(b) External anal sphincter The external anal sphincter is a muscle structure, made of three concentric layers (deep, intermediate, and subcutaneous) of striated muscles which surround the virtual space of the anal canal, forming a ring about 1-cm-thick along the entire length of the canal and specifically at its lower third. The external sphincter is a striated muscle and is under conscious control (e.g., relaxation during defecation and contraction during retention efforts) by the somatic nervous system via the pudendal nerve.

(c) Internal anal sphincter The internal anal sphincter is made of smooth muscle about 4-mm-thick that surround the upper two-thirds of the anal canal. It is an inseparable extension of the internal circular muscles of the rectal wall. It is responsible for the resting tone of the anal canal. It is almost always contracted, relaxing only for brief moments in response to certain stimuli. Sphincter tone is regulated by the autonomic nervous system: lowered by the cholinergic parasympathetic nerves (from S2 to S4) and raised by the alpha-adrenergic sympathetic fibers (from L5).

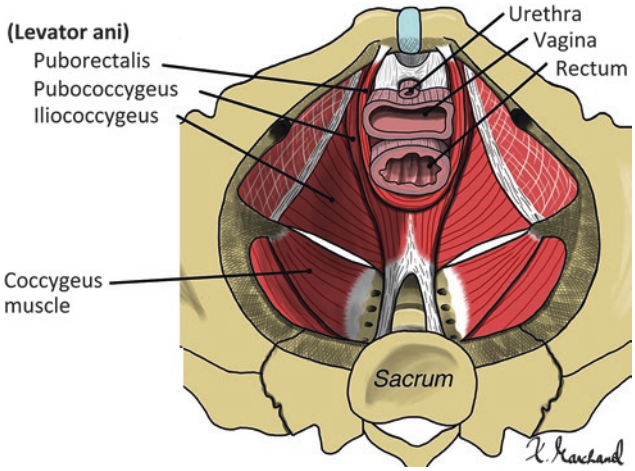


Fig. 7.6 The levator ani is a muscle structure made of three muscles (pubococcygeus, iliococcygeus, and puborectalis) attached in the front at the pubis, to the sacrum at the back, and to the sides of the pelvis to constitute the pelvic floor, which supports the pelvic viscera like a hammock

(d) Levator ani The levator ani is a muscle structure involved in the formation of the pelvic diaphragm, which separates the pelvis into an upper and a lower (perineal) compartment and which forms a thin hammock supporting the pelvic organs (Fig. 7.6). It originates in the front at the pubis and has three muscle components: the pubococcygeus and the iliococcygeus which attach to the sacrum at the back and to the inner surface of the pelvis to support the pelvic viscera (pelvic floor). The puborectalis is the third component muscle which, from the pubis, passes behind the top of the anal canal, in the form of a U-shaped loop that pulls the rectum forward and closes the anorectal angle, thus obstructing the passage of stools and promoting continence. During defecation, the muscle is relaxed to open the anorectal angle, allowing the rectum to be aligned with the axis of the anus and facilitating the expulsion of the rectal contents. The important contribution of the puborectalis muscle to continence is illustrated in Fig. 7.7.

7.2.3 Serosa

The rectum has no serosa in its extraperitoneal segment (the lower two-thirds).

7.3 Embryology

7.3.1 Normal Development

From the primitive digestive tract (derived from the endoderm), three regions (foregut, midgut, hindgut) are formed according to the territories irrigated by the main three arteries of the digestive tract (celiac trunk, superior

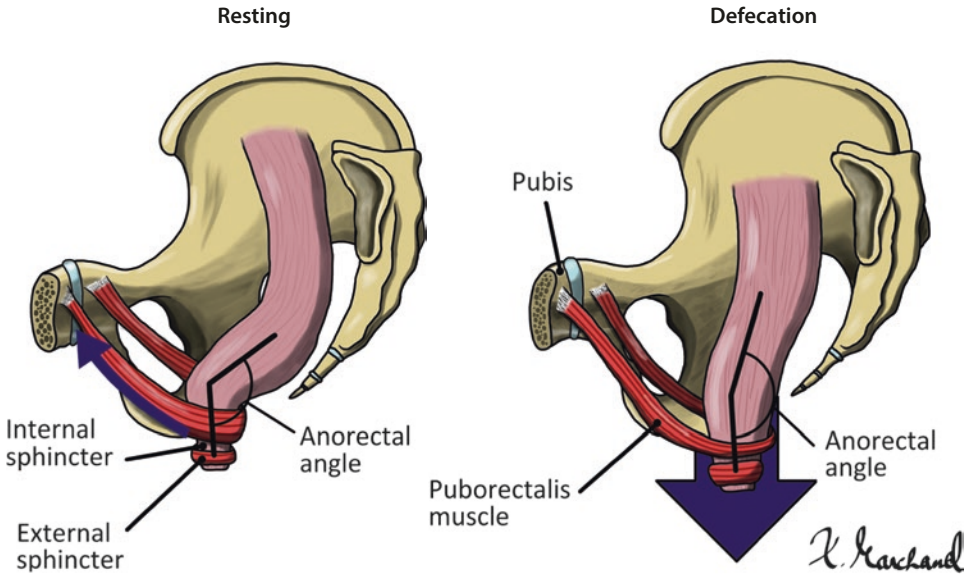


Fig. 7.7 Anus muscles for fecal continence: **a** the internal sphincter provides basal tone for the anal canal (and relaxes during defecation); **b** the external sphincter is made of striated muscles subject to voluntary control (relaxation during defecation or contraction during retention efforts); **c** the puborectalis muscle pulls the anal canal forward and tightens the anorectal angle to help maintain continence (relaxes to open the anorectal angle and facilitate passage of stools during defecation)

mesenteric artery, inferior mesenteric artery). The descending colon and the rectum arise from the hindgut. Between weeks 4 and 6 of embryonic development, from the distal part of the hindgut, the cloaca will divide into an anterior urogenital sinus and the posterior rectum.

The upper two-thirds of the anal canal also originates from the most distal part of the endodermal hindgut. Its lower third derives from the ectoderm where, facing the endodermal anal canal, an "anal depression" will appear. Endodermal and ectodermal portions of the anal canal are separated by an anal membrane until week 8. In adulthood, the area where this membrane was located can be identified as the pectinate line. The double origin of the anorectum has consequences in its vascularization since the upper part of the rectum is irrigated by abdominal vessels (blood coming from the inferior mesenteric artery and drained to the portal vein), whereas its lower part depends on peripheral internal iliac arteries and veins.

7.3.2 Atresias

Atresias of the anorectal region are present in 1/5000 births. The most frequent abnormalities are the following:

- Failure to separate the distal hindgut (which normally gives the urogenital system in front and the rectum behind). The abnormality observed is then a cloaca (i.e., as in birds where the urinary and fecal waste ends up in a common reservoir).
- Defect of fusion between the ectodermal anus and the endodermal anorectal apparatus. This is called imperforate anus and may present with or without a gap between the anus and the rectum.

The diagnosis of atresia is usually made at birth, when an inspection of the perineum reveals anal imperforation. Other associated malformations must be looked for, such as those affecting the pelvis, vertebrae, as well as urinary, genital, digestive, bone, or muscle systems. The surgical treatment for reconstruction will depend on the anatomical assessment.

7.3.3 Hirschsprung's Disease

Hirschsprung's disease is due to an absence of enteric nervous system plexus ganglions in the distal intestine. The affected length of intestine varies. Its prevalence is 1/5000 births. It is more common in boys. There may be a genetic component and it is also more frequent in trisomy 21.

Pathophysiology is caused by a halt, during the first 12 weeks of the embryonic gut development, in the migration of neuroblasts from the neural crest to the digestive tract. This migration of the precursor cells of the intestinal neurons takes place in the cranio-caudal direction, and the aganglionic zone will thus start at the bottom from the internal anal sphincter and extend proximally over a more or less long segment of the gut. It most often affects the rectum and the distal sigmoid,

but sometimes it can involve the entire colon (or even the small intestine).

Many genetic mutations are associated with Hirschsprung's disease, including those affecting RET gene coding for proteins assisting movements of neural crest cells.

From a functional or clinical point of view, the aganglionic zone is in permanent contraction creating a narrow and rigid intestinal segment acting as an obstacle to the progression of the endoluminal content. The result is an upstream gut distension, hence the name of congenital megacolon which was given to Hirschsprung's disease. Diagnosis is obtained with anorectal manometry testing, since relaxation of the internal anal sphincter upon defecation is always impaired in all patients. The so-called recto-anal inhibitory reflex (relaxation of the internal anal sphincter in response to rectal distension) can easily be observed during anorectal manometry, an examination which can be carried out in newborns. This reflex is innate and can be detected in a newborn baby even under sedation by distending the rectum with a small balloon. In Hirschsprung's patients the inhibitory recto-anal reflex is absent. Rectal biopsy may also be easily performed trans-anally to demonstrate the absence of nerve cells (Meissner's plexus) in the submucosa.

Hirschsprung's disease is often revealed by delayed evacuation of meconium, as the vast majority of newborns evacuate their first meconium within the first 24 h of life. This will be followed by signs of digestive obstruction (vomiting, abdominal distension, etc.). The disease can also cause constipation in children.

7.4 Secretion/Absorption

Secretion and absorption functions of the rectum are identical to those of the colon. In practice, however, stools are already formed by the time they arrive in this short segment of the digestive tract, and the rectum serves primarily as a reservoir (before scheduled and controlled emptying) rather than as an absorbing or secreting organ.

The absorptive function of the rectum can be used when administering medications rectally (suppositories or enemas). Fecal impaction (hardened stool in the rectum) may result from increased fluid absorption during prolonged stool retention in the rectum.

Rectal secretion may be increased during pathological processes such as inflammatory proctitis. Exaggerated rectal secretions result in defecations that are often frequent, but of small volume, that may contain only mucus (and blood) and where stools may be surprisingly soft (not frankly diarrheic or liquid) or even of normal consistency.

7.5 Motility/Sensitivity

The main function of the anorectum is to control the evacuation of fecal material. This motor action is inseparable from anorectal sensitivity, which has the unique feature of being a conscious sensation unlike the rest of the digestive tract. This awareness of the physiology of the anorectal sphere is essential to maintain continence and to allow defecation at appropriate times and places. Any disruption in this control could have consequences on the individual's social life.

7.5.1 Anorectal Physiology

The rectum is physiologically empty. One to three times a day, contractions of the sigmoid push the intestinal content of the colon into the rectum, which triggers the following sequence of events:

(a) *Sensation and need for defecation:* The arrival of stools in the rectal ampulla distends the rectum. Tension receptors in the rectal wall are then stimulated and send information, via the spinal cord, to the cerebral cortex informing the individual about the presence of materials in the rectum and a need for a bowel movement. Rectal hyposensitivity may be a cause of constipation in some patients who do not feel the presence of stools in the rectum and therefore "forget" to defecate.

(b) *Accommodation:* The pressure rise on the rectal wall by stools reaching the rectum is temporary. After few seconds, a phenomenon of accommodation appears, characterized by a relaxation of the parietal tension and therefore a decrease in the intraluminal pressure (at constant volume). This accommodation capacity is very important since it allows defecation to be put off temporarily. Accommodation capacity can be reduced in conditions such as inflammatory or radiation proctitis (causing frequent defecations of small stools), as well as, probably, in IBS (provoking a sensation of incomplete rectal evacuation).

(c) *Recto-anal inhibitory reflex*: In reaction to the pressure rise in the rectum, the internal sphincter will relax, opening the upper part of the anal canal (this sphincter will then regain its baseline tone in 30–60 s). During relaxation of the internal sphincter, some rectal contents may descend into the upper part of the anal canal, allowing the sensory squamous epithelium to perceive the nature of the contents (liquid, gas, or solid). This information travels up through the neurological pathways of the spinal cord to the cerebral cortex and informs the individual on the nature of the contents, which will enable him/her to eventually adapt his/her behavior (e.g.,

evacuation of gas vs. retention of a solid or liquid stool). The recto-anal inhibitory reflex is innate and depends only on the intrinsic nervous system (hence its absence in Hirschsprung's disease).

(d) *Recto-anal excitatory reflex*: Simultaneously with the recto-anal inhibitory reflex relaxing the internal anal sphincter, the excitatory reflex (also induced by rectal distension) contracts the external anal sphincter to close the lower part of the anal canal and prevent leakage of rectal content out of the body. This reflex passes through the spinal cord and is essential for immediate continence; it is not innate and is acquired during childhood (hence the normal physiological incontinence of the child before reaching a certain degree of development).

7.5.2 Defecation

When rectal pressure increases, the individual feels the need to evacuate and, at the same time, is informed about the nature of the rectal contents to be evacuated. If the individual accepts this evacuation, there is then a voluntarily sequence of actions: (1) relaxation of the puborectalis muscle opening the recto-anal angle to align the axis of the rectum in the axis of the anal canal and thus facilitate passage of the luminal content, (2) relaxation of the internal and external sphincters, (3) contractions of the rectal wall promoting rectal emptying, and finally (4) voluntary contractions of the abdominal wall against the diaphragm to increase intra-abdominal pressure to help push the stool outward through the anal orifice.

When defecation is not allowed, reverse phenomena occur and the individual has the ability to close the external sphincter, contract the puborectal muscle, etc. If the rectal contents are not expelled, the phenomenon of rectal accommodation is such that the sensation of needing to defecate regress (until next time the rectal volume increases). Refraining from defecation also induces reduction of proximal colonic motility and backflow of distal content.

Knowing this physiology, we understand the importance of the integrity of the muscular system and of the sensory and motor nervous systems in order to secure fecal continence.

7.6 Inflammation Disorders

7.6.1 Rectal Inflammation (Proctitis, Rectal Ulcers)

(a) Proctitis Inflammation of the rectum is called proctitis (less commonly rectitis). In clinical practice, it defines an inflammation limited to the rectum.

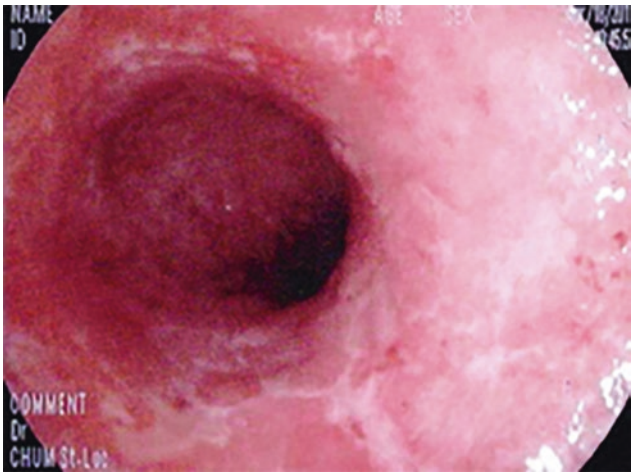


Fig. 7.8 Ulcerative proctitis in endoscopy: the rectal mucosa is erythematous, friable, erosive, covered with mucus or pus. (Photo by P. Poitras)

Symptoms of proctitis include:

- Presence of blood in the stools
- Discharge of mucus or pus, feeling of rectal fullness
- Tenesmus (sensation of frequent urges to have a bowel movement)
- Frequent defecation with false urges, i.e., numerous defecations, often of mucosanguineous secretions with stools in small quantity, which may be either of soft or normal consistency, or even dry and hard as in constipation. In proctitis, there is no classic diarrhea with large amount of liquid stools that could lead to dehydration but rather frequent defecations (q 1 h day or night!) that compromises quality of life. Loss of compliance of the rectal reservoir (caused by inflammation of rectal walls), associated with very distal secretions without any capacity for reabsorption, explains the clinical symptomatology.

The diagnosis of proctitis is obtained by endoscopy (Fig. 7.8) which shows inflammation of the rectum (over a maximum distance of about 15 cm). Depending on the type and severity of the disease, mucosal breaks (erosions, ulcerations, ulcers) can be present.

Types of Proctitis

- *Inflammatory proctitis* may be caused by inflammatory bowel disease (IBD) such as ulcerative colitis (ulcerative proctitis) or Crohn's disease.

When an individual presents with ulcerative proctitis, it is estimated that the disease will remain limited to the rectum in 50–70% of cases; in others, over the following years, it may spread to more proximal areas of the colon and digestive tract.

Ulcerative proctitis is usually treated with local 5ASA or steroid therapies in the form of a suppository (Salofalk® or Pentasa®), foam (Mezera®, Cor-

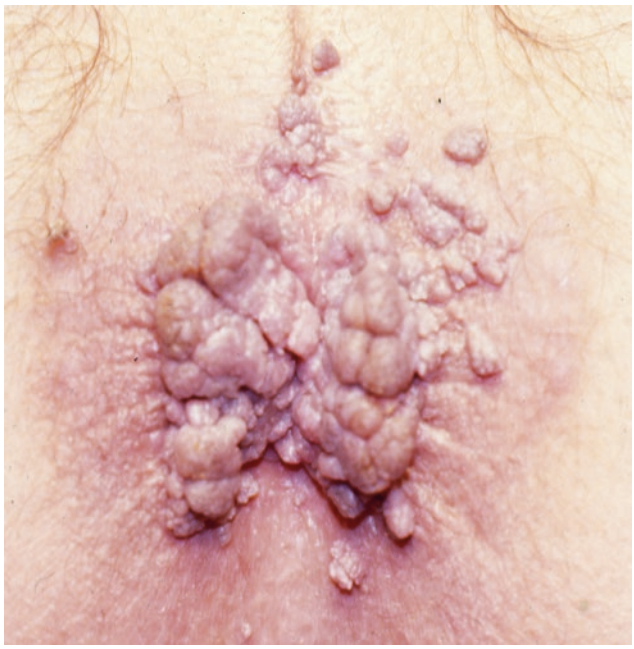


Fig. 7.9 Condyloma (genital warts due to human papilloma virus) of the anus and perianal region. Condyloma within the rectum should be looked for during endoscopic examination. (Photo from D. Bernard)

tifoam®), or enema (Salofalk®, Pentasa®, Cortenema®, Entocort®).

- *Infectious proctitis.* The rectum, during anal intercourse, can be infected by sexually transmitted diseases such as syphilis, gonorrhea, chlamydia (with or without lymphogranuloma venereum), herpes, and papilloma virus (Fig. 7.9).

  Various lesions (diffuse or circumscribed inflammation or ulceration, etc.) can be seen at rectoscopy. Viruses or bacteria can be identified by histological or bacteriological analysis of rectal biopsies. Treatment will depend on the causal organism.
- *Radiation proctitis* is seen mainly after irradiation for prostate cancer. Small caliber vascular damage is seen, rather than inflammatory changes. Rectal bleeding is the most common sign (in some cases, it can be severe enough to justify blood transfusions). Endoscopic treatment (electrocoagulation, etc.) may be required.
- *Chemical proctitis.* Damage to the rectal (and colonic) mucosa can be caused by instillation of enemas containing "irritating" substances such as soap, hydrogen peroxide, ginger, etc. The use of such agents should be discontinued.

(b) Solitary ulcer of the rectum A solitary ulcer of the rectum describes, as its name suggests, an isolated ulcer in an otherwise normal-looking rectum and corresponds to an "ischemic," chronic ulcer associated with a rectal prolapse (to be identified by clinical examination and/or radiological defecography). Histological analysis often reveals proliferation of fibroblasts and smooth muscle fibers in the chorion of the mucosa. Treatment involves correction of the causal prolapse.

The solitary ulcer of the rectum must be differentiated from other unique lesions of the rectum including:

- Cancer of the rectum (to be confirmed by biopsy)
- Crohn's disease (to be confirmed by biopsy and investigation of the digestive tract
- Infectious ulcer such as syphilis, etc. (to be confirmed by histological or microbiological analysis)
- Traumatic ulcer, following the misuse of enema cannulas or other foreign bodies

7.6.2 Anal and Perineal Inflammation (Abscess, Fistulas, Anal Pruritus)

(a) Abscess Anal abscesses are caused by an infection of a gland (Hermann and Desfosses glands) of the anal canal. These glands located in the anorectal wall opening the intestinal lumen at the level of the Morgagni crypts through a main glandular canal. The infection starts in glandular ducts and then proceeds to the inter-sphincteric space. The germ is most often of intestinal origin. In all cases, a primary or internal orifice (which sometimes may be difficult to find) is always present at the level of the pectinate line.

Clinical presentation The clinical picture is dominated by anal or perianal pain. The pain is initially moderate, then increases, and can become severe, insomniant. It is not associated with defecation (as is anal fissure). The pain can radiate to the perineum or the genitals and be associated with painful tenesmus (painful desires to evacuate stools) or dysuria. An infectious syndrome (with fever, etc.) may be present. On perineal examination (Fig. 7.10), the abscess may be visible, consisting of an indurated, inflammatory mass, more or less important, which can erase the plicated folds of the anus; localization is more difficult when the abscess is deeply located, but palpation of the surrounding tissues may reveal abnormal firmness and localized pain. Pus discharge from the primary endoluminal opening may sometimes be noted when examining the anal margin. Digital exam may reveal the same on palpation but, as with endoscopy in this situation, may be difficult because of pain.

Treatment of abscess The ideal treatment is to drain the abscess and treat the associated fistula (see below). Simple drainage of the abscess without addressing the fistula leads to recurrence in 14–40% of cases in randomized

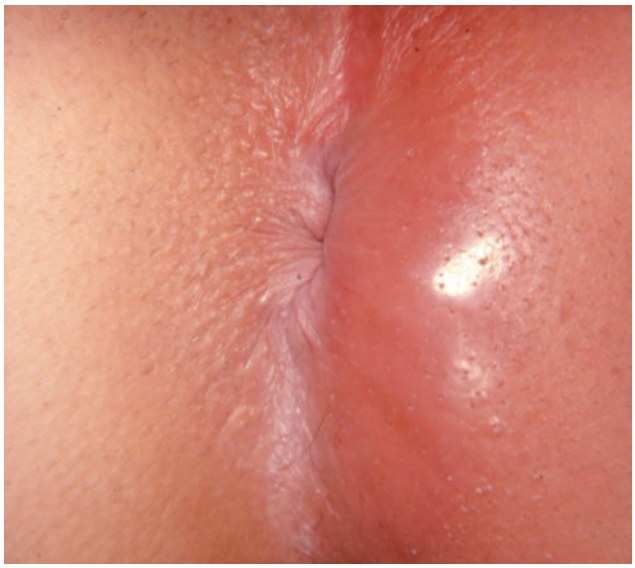


Fig. 7.10 The anal abscess presents as an inflammatory swelling (red, hot, painful, etc.) of the immediate perianal area (here on the right side of the anus). (Photo from D. Bernard)

trials. Treatment should be surgical as often as possible, as antibiotic therapy alone is rarely curative.

Antibiotic treatment of perineal abscess has, curiously enough, rarely been studied in the scientific literature. It is often used (beta-lactams and metronidazole are the most common agents) in presence of systemic infection, significant cellulitis, or in patients with risks of infection extension such as immunocompromised or diabetic patients. Antibiotic treatment (most often ciprofloxacin + metronidazole) also appears to be effective in reducing infection in complicated abscesses of Crohn's disease.

(b) Fistulas A fistula is defined as an abnormal communication between two epitheliums. Most anal fistulas are a complication of an anal abscess which has drained (either spontaneously or through a therapeutic gesture) to the perianal region, spreading along a sinuous path in or through the sphincter apparatus or to the skin (Figs. 7.11, 7.12, and 7.13).

Clinical presentation The fistula may follow the acute phase of an abscess, or it may set in immediately. It is responsible for a flow of serosanguineous or fecal matter to the skin. On clinical examination (Fig. 7.13), there is an external orifice (known as the secondary orifice) located on the skin and allowing secretions to flow out. Palpation of surrounding soft tissues may reveal induration that corresponds to the path of the fistula. There may be several secondary openings, or double fistulas; openings located on both sides of the midline suggest a horseshoe shaped fistula encircling the anus.

Treatment of fistula In all cases, treatment of an anal fistula has two goals: to heal the fistula and to preserve continence. The primary orifice is typically the source of recurrence if the abscess is treated without treating the fistula.

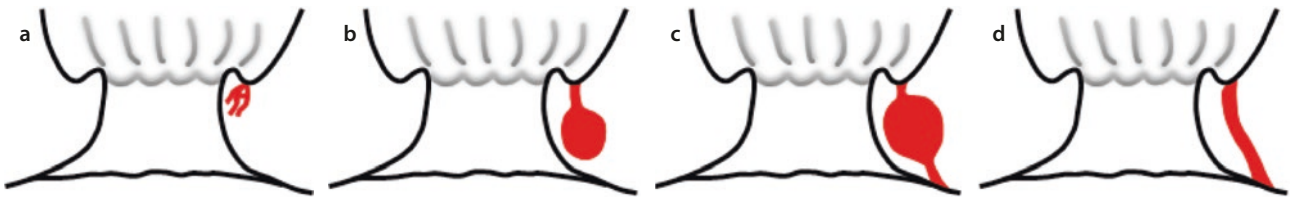


Fig. 7.11 From an internal (primary) opening **a**, an anal gland becomes infected and forms an abscess **b**; the abscess drains by (secondary) opening to the skin **c**, leaving a fistulous path between the internal and external openings **d**

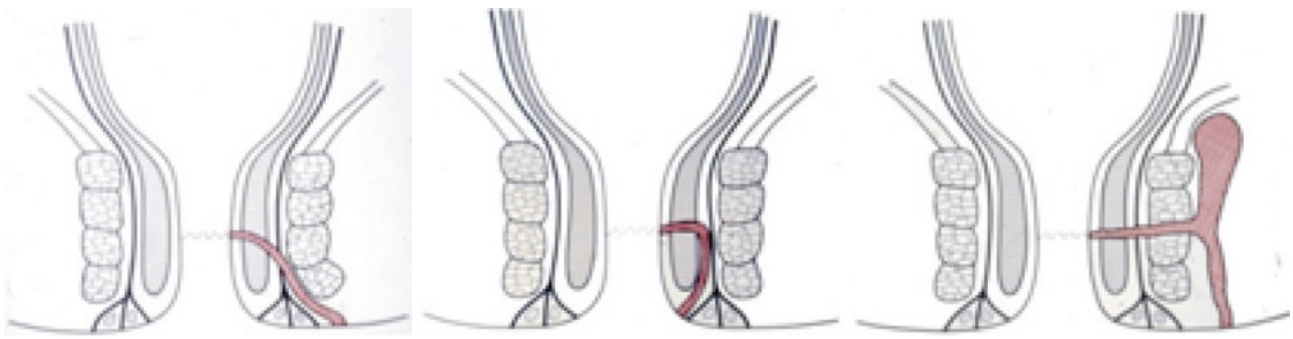


Fig. 7.12 Different fistula paths are possible: sparing the sphincters (two illustrations on the left) or trans-sphincteric (illustration on the right)

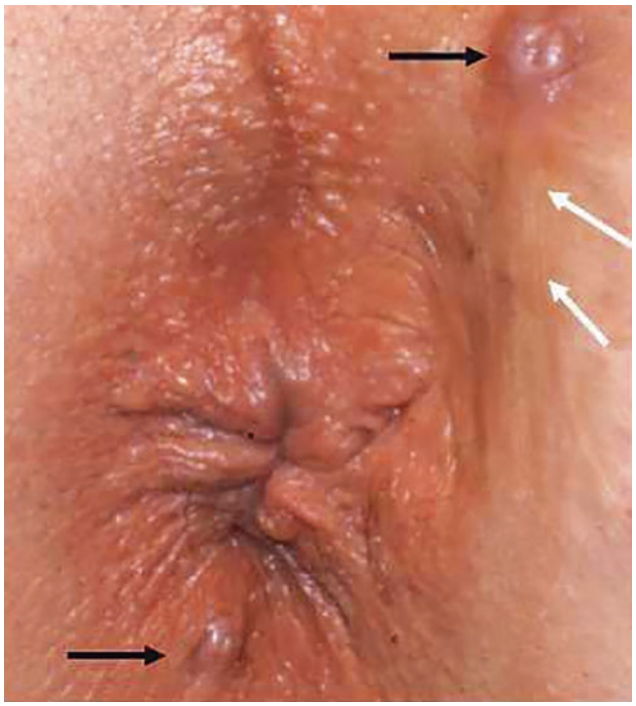


Fig. 7.13 Fistulous openings (black arrows) around the anus; a fistulous path (white arrows) is visible from the anus to the opening. (Photo from D. Bernard)

Conventional treatment is fistulotomy, the techniques of which vary according to the height of the fistula and its path, since treatment must be performed with minimal sphincter trauma. There are also some surgical alternatives whose main goal is to avoid extensive sectioning of the sphincter muscle. In some complex cases, sphincter reconstructions may be required.

(c) Perineal necrotizing fasciitis (or Fournier's gangrene) is an acute bacterial infection with extensive necrotic infection of perineal soft tissues. It is an emergency, both medical and surgical. It most often arises as a complication of an operation in the area (anal surgery, etc.) or a soft tissue trauma in patients with diabetes, alcoholism, immunosuppression, etc.

Germs involved are usually bacteria from the normal anorectal flora (aerobic or anaerobic, including *Escherichia coli*, *Streptococcus*, *Staphylococcus*, *Proteus*, *Bacteroides fragilis*, or clostridiums). The first clinical signs are a localized, constant, and intense perineal pain associated with a septic syndrome that quickly becomes severe. Clinical examination reveals necrotic skin damage. On palpation, a crepitation can be felt, indicating subcutaneous emphysema by air-producing bacteria. The infection may spread rapidly throughout the perineum and upward to the abdomen or lumbar regions or downward to the thighs.

Medical treatment of necrotizing fasciitis combines broad-spectrum antibiotic therapy (a third-generation cephalosporin combined with an aminoside and metronidazole) and surgical treatment with extensive (often mutilating) debridement, instituted rapidly and which may need to be repeated to remove all necrotic tissues. Colostomy is often necessary, and some people use hyperbaric oxygen therapy to treat this gangrene whose mortality, despite treatment, has been estimated at 16%.

(d) Pilonidal disease The pilonidal sinus is a pseudocystic cavity of the subcutaneous tissue that communicates with the skin through a duct that opens into small orifices on the midline of the gluteal cleft (butt crack). This cavity does not have hair follicles but contains hairs; it can become infected and produce an abscess that will fistulize to the skin. It is not strictly speaking a digestive nor an anorectal pathology.

Pathogenesis The congenital theory has long been predominant and considered these cavities as embryological scars. However, the acquired theory is now generally accepted, especially since the description of Jeep Disease during the Second World War, when nearly 79,000 Jeep drivers of the US Army were hospitalized for pilonidal disease, which is therefore considered an inflammatory reaction secondary to the penetration of a hair in the gluteal furrow with secondary suppuration promoted by various phenomena such as friction (prolonged sitting, etc.).

Clinical An inflammatory and painful swelling is present in the gluteal fold. The swelling may resolve spontaneously or may progress to release pus and pilar content (corresponding to the fistulization of the abscess). The drainage may flow through one of the median orifices, or sometimes through lateral fistulization orifices, and may occur chronically or repeatedly.

Treatment Treatment of a pilonidal sinus is surgical to prevent recurrence.

(e) Hidradenitis suppurativa (HS, Verneuil's disease, acne inversa) is a skin disease that can be fistulizing and may be mistaken for perineal Crohn's disease. In fact, it is a hyperkeratinization of hair follicles with a secondary infectious process (by bacterial colonization).

HS is a rare infection (prevalence of 0.3%) and more frequent in women than in men (4/1), as well as in Crohn's disease.

Clinical presentation HS lesions are located mainly in underarms, under the breasts and groin areas.

The elementary lesion consists of a hypodermal nodule which is generally hard on palpation, well-limited, and mobile with deep planes. This nodule may be isolated or associated with several nodules forming growths and/or scars on the skin. Most often, one of these nodules will open to the skin with a seropurulent discharge.

The disease will evolve with subcutaneous extension and the appearance of new localizations forming new nodules with more and more suppurative orifices communicating with each other. These cutaneous suppurations and fistulas may be suggestive, when occurring in perianal area, of fistulizing Crohn's disease.

Treatment Antibiotics do not treat the disease but may be helpful to prevent progression of infection. The treatment is surgical and based on resection of the lesions with the widest and earliest possible excision. TNF inhibitors (e.g., adalimumab) have a positive effect on HS lesions and are a more and more popular treatment.

(f) Anal pruritus Itching sensation in the anal or perianal region that causes the patient to scratch (generally with traumatic erosions that promote licking of the skin, which itself is a source of pruritus) is a common reason for consultation. Its prevalence is poorly known, but it is thought to affect about 1–5% of the population, with a male prevalence of 4 to 1.

Causes for anal pruritus are numerous:

- Infectious: *Candida albicans* (favored by antibiotics, diabetes), bacteria (group A beta hemolytic *Streptococcus*, *Corynebacterium minutissimum*), virus (human papillomavirus, herpes), and parasites (pinworm) are causes of skin infection with anal itching.
- Inflammatory: Contact dermatitis or eczema most often related to toiletries (e.g., soap or other hygiene products) or to fecal contamination (sticky stools, lack of hygiene, etc.) is common. Psoriasis should be considered in presence of red, squamous lesions, often with lesions at distance in other locations. Shiny whitish papules in women may be due to lichen sclerosus present in the anal area but also in the vulva.
- Tumoral: Bowen's disease (squamous cell carcinoma of the epidermis) and Paget's disease (intraepithelial adenocarcinoma of the epidermis) are possible. Resistant to topical steroids, these lesions are usually infiltrative, keratotic, and inflammatory.
- Proctologic: Conditions with anorectal suppurations such as fistulas, abscesses, Verneuil's disease, pilonidal cyst, anal fissure, and rectal prolapse may promote pruritus. Hemorrhoidal prolapse or oozing can cause pruritus, as can skin tags due to difficulty in maintaining good hygiene. Hemorrhoids may be responsible for 20% of itching in adults.
- Idiopathic: a quarter of cases remain unexplained. A psychological origin (with neurodermatitis) is frequently suspected. Excessive or aggressive hygiene of the perianal area may also cause or maintain pruritus in some patients.

Management of pruritus Extensive investigations are rarely necessary at first consultation. A good clinical examination should be able to identify the main causes; a "Scotch tape" test for pinworms and/or swabs for bacteriological, mycological, or virological examinations can be considered.

Treatment of anal pruritus Hygiene rules are of primary importance and should insist on keeping the perianal area clean and dry. Cleanliness should be best achieved without soap or antiseptic products and only with water. Wiping should be done with a soft paper, ideally slightly moistened and without rubbing. Drying should be done with a towel without rubbing. Creams and intra-channel cleaning after defecation should be avoided. No diet regimen is known to be effective.

Medicated treatment depends on the cause. Antifungal ointments or creams (nystatin, miconazole, etc.) or antibiotics (metronidazole, bacitracin, etc.) can be applied locally in case of superinfection. Test treatment against pinworms can be undertaken (mebendazole 100 mg, two doses 14 days apart). Some authors have proposed type 1 antihistamines for predominantly nocturnal pruritus. When acute dermatitis is present, dermatologic advice may be required, and a small dose of a topical steroid (hydrocortisone 0.1%) may be used; it is, however, best to avoid the long-term use of these creams, which in the long run lead to skin atrophy and can make the condition even more difficult to treat. Recently, capsaicin ointment (topical analgesic) has been reported to be effective.

In children, perianal erythema is a frequent reason for consultation; it may involve specific pediatric conditions:

- Perianal *Streptococcus* A dermatitis is a lesion starting from the anus and extending into the perianal region for 2–3 cm. The erythema is bright red with clear borders, sometimes associated with edema or oozing. Local swabbing with a bacteriological culture swab confirms the diagnosis. The treatment consists of antibiotic therapy directed against *Streptococcus* A.
- Diaper psoriasis is characterized by an intense, varnished, sometimes dry and scaly erythema, which is very limited in infants with diapers. Superinfection or maceration often makes the diagnosis difficult. The existence of distant psoriasis lesions and of family history helps in the diagnosis. It is probably a reaction triggered by any other cause of diaper rash

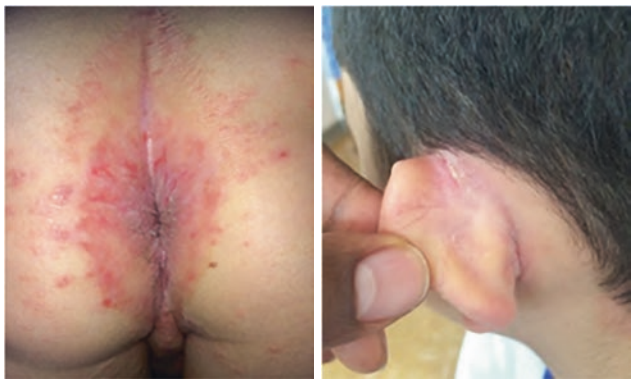


Fig. 7.14 Perianal and retroauricular psoriasis lesions. (Photos from P. Jantchou)

- in children with a psoriasis trait. The treatment is based on topical steroids and skin emollients.
- Anti-TNF induced psoriasis is a complication increasingly observed in children treated with these biologic drugs (infliximab, etc.). Perianal involvement is manifested by an intense, dry, scaly, pruritic erythema, sometimes associated with micro-ulcerations (scratching lesions). Extra-perineal lesions, particularly in retroauricular areas, may be present (Fig. 7.14).

7.7 Tumor Disorders

7.7.1 Rectum Cancer

- *Adenocarcinoma* of the rectum is a form of colorectal cancer (discussed in ▶ Chap. 4). Symptoms of rectal adenocarcinoma include rectal bleeding, stools of reduced diameter (pencil-shaped), dyschezia, or pelvic discomfort.

Any of these symptoms should prompt a digital rectal examination, since many rectal tumors are located distally enough to be felt on digital palpation. Endoscopy with biopsies will confirm the diagnosis (Fig. 7.15).

Progression of rectal adenocarcinoma may lead to metastasis through the lymphatic and venous drainage systems of the rectum, which can lead to locoregional spread to pelvic and inguinal lymph nodes, or more distantly to the liver but also to the lungs due to venous drainage bypassing the portal circulation.

Treatment of adenocarcinoma of the rectum is surgical and almost always combines preoperative (neoadjuvant) radiotherapy and chemotherapy. Surgical therapy is complex because of the desire to fully and uncompromisingly resect the tumor while preserving normal bowel function (i.e., keeping the anal sphincter intact and avoiding a permanent colostomy), as well as avoiding damage to other pelvic mechanisms (including erection, urinary function, etc.). Colorectal and even colo-anal anastomosis techniques, combined with radiotherapy, now make it possible, in a large number of cases, to avoid proctectomy with definitive colostomy that was previously performed in these cases.

- *Neuroendocrine tumors* (*NET*) can be found in the rectum. They are most often nonsecreting.

7.7.2 Anus Cancer

Squamous cell (epidermoid) carcinoma of the anus is very frequently associated with the human papillomavirus (HPV) responsible for condylomas (and cervical cancers in women) and is therefore more similar to genital neoplasia than to other digestive cancers. Among the more than 40 known types of HPV, types 16 and 18 are more frequently associated with neoplasm. Epider-

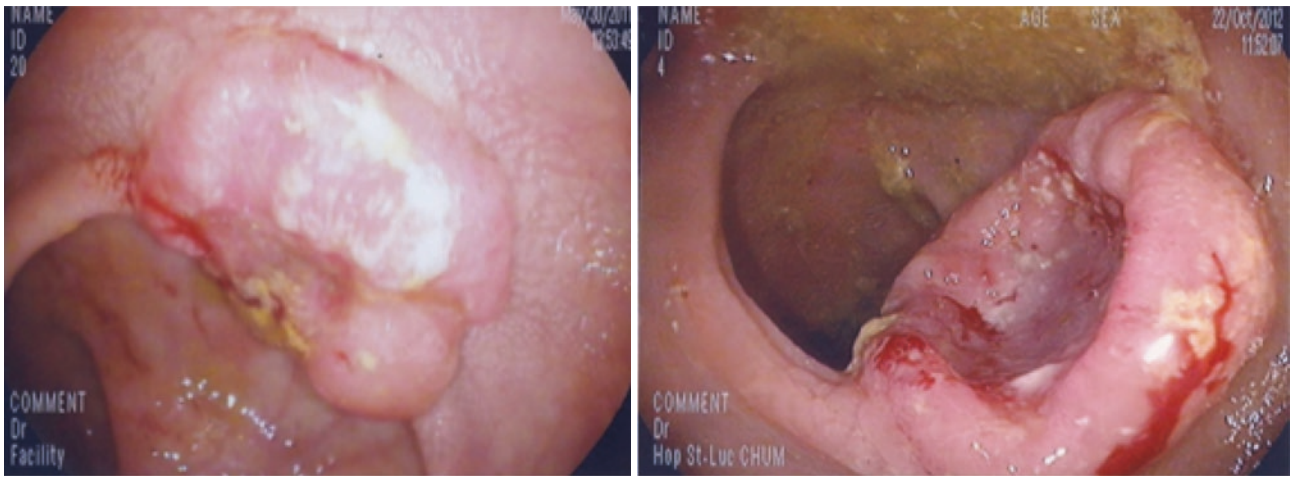


Fig. 7.15 Malignant polyps seen during rectal endoscopy. (Photos by P. Poitras)

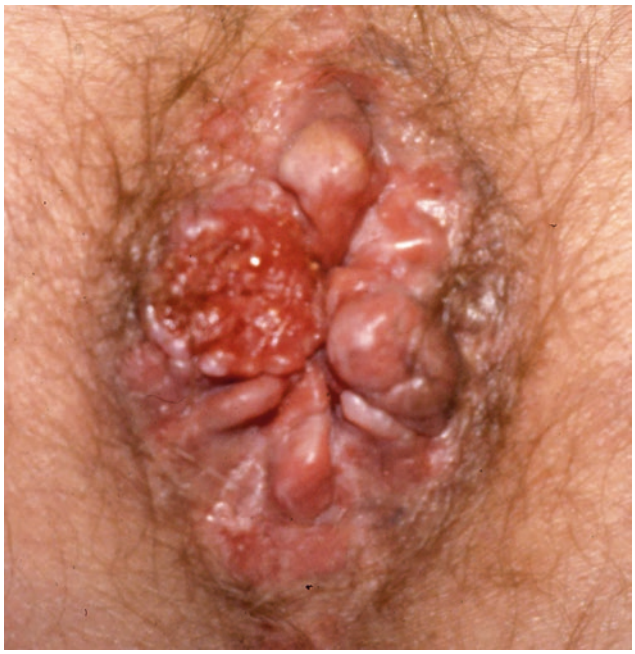


Fig. 7.16 Epidermoid neoplasia of the anus presented here as an ulcerated lesion. (Photo from D. Bernard)

moid cancer of the anus (Fig. 7.16) can reach the anal canal as well as the perianal skin region. It presents with rectal bleeding (40% of patients) and sensation of anal pain or mass (30%) and also may be found in asymptomatic subjects.

Tumors of the anal canal were previously treated by proctectomy and colostomy. Treatment with radiotherapy and chemotherapy is now preferred with a 5-year survival of 70–90%.

Perianal cancer, which is rarer, is most often presented with an itchy or eczematous lesion. Perianal tumors are considered and treated as skin lesions.

Bowen's disease is a dysplasia of the epidermis without infiltration of the dermis and corresponds to in situ squamous cell neoplasia related to HPV virus. It may present as an erythematous plaque suggestive of psoriasis and has a good prognosis.

Paget's disease (extramammary) is an intraepithelial adenocarcinoma that originates from an anal gland and most commonly presents as an eczematous plaque of the anal margin. Its prognosis is poor considering its invasive and/or metastatic potential.

Cloacogenic carcinoma is a rare (2% of epidermoid lesions) tumor originating from a persistent remnant of the embryological cloacal membrane located in the transitional zone 1 cm above the dentate line.

Melanoma is rare (1% of anal tumors) but can occur.

7.8 Function Disorders

7.8.1 Proctalgia Fugax

Proctalgia fugax is a painful syndrome in the anus or lower rectum. It is a cramp-like pain that appears suddenly, at first of maximum intensity, and lasts for few seconds or minutes (less than 5 min in 90% of people), and then disappears quickly without leaving any residual discomfort between attacks. These paroxysmal pains are recurrent (more than five attacks/year in 50% of patients). They often occur during the night and can of course wake the patient up; they can also appear after certain situations such as defecation or sexual intercourse or spontaneously. Proctalgia fugax is common (10–20% of people are said to suffer from it) but may be underreported by patients who feel ashamed to talk about it.

Pain may be associated with classic neurovegetative manifestations of pain such as pallor, sweating, nausea, and faintness. Often attributed to spasms of the anal muscles, the physiopathology of this pain is not known. Its acute and brief cramp-like nature is reminiscent of calf muscle cramps.

Other causes of ano-rectal pain (e.g., hemorrhoids, fissure, abscess, etc.) must be excluded, but in most cases, with typical episodic pain, investigation other than digital rectal examination is rarely necessary.

The treatment is not well codified. Postural techniques have been identified spontaneously by patients, such as sitting with flexion of the lower limbs but sometimes also gas or stool emission or digital rectal introduction. Medications (aiming to relax the anal sphincter) are rarely effective for this brief pain (because of their delayed onset of action); topical or sublingual nitroglycerin or inhaled salbutamol may possibly help. Baths in warm water have been suggested, as well as relaxation techniques (self-hypnosis, autogenic training, etc.). Patients are often worried about this sharp pain and may be ashamed to talk about it; reassurance is crucial for this frequent and typically benign condition.

7.8.2 Levator Ani Syndrome

Levator ani syndrome is a painful syndrome in the upper part of the anal canal, with a sensation of heaviness or sometimes of an intrarectal foreign body. The pain may extend to the genital or urinary sphere, being sometimes accompanied by dysuria; it may also radiate posteriorly in the gluteal fold. The pain is moderate, prolonged

(more than 20 min; in contrast with the brief pain of proctalgia fugax), with a tendency to worsen over the course of the day. Like proctalgia fugax, the pain may be promoted by certain events such as sexual intercourse or after defecation.

This pain is attributed to chronic or prolonged tension or spasm of the levator ani muscle, particularly of the pubococcygeus bundle. On examination, digital palpation and posterior traction of the levator ani muscle are often painful. Manometry, which is not essential, may reveal hypertonia of the anal canal. Pelvic examinations (CT scan, MRI, sigmoidoscopy, etc.) may be required to eliminate visceral or other lesions.

Treatment remains empirical for this rare condition. Digital massages of the levator ani muscles have been reported to be effective, as well as medical treatments with muscle relaxants (cyclobenzaprine, diazepam) or relaxation techniques (hot baths, etc.).

7.8.3 Anorectal Dyssynergia/Anismus

Anorectal dyssynergia is a paradoxical contraction (or lack of relaxation) of the external anal sphincter during defecation. Fecal evacuation must therefore take place through expulsion thrusts fighting against an obstacle made by an abnormally high sphincter resistance. This asynchrony in the defecation maneuver can lead to dyschezia (difficulty in evacuating stool, with exaggerated defecation efforts, use of digital facilitation, etc.), sensation of incomplete rectal emptying after defecation, or constipation.

There are two main causes of anorectal dyssynergia: neurological causes are rare but can involve spinal or root damages (cauda equina syndrome, multiple sclerosis, pudendal nerve trauma, etc.). In the vast majority of cases, a behavioral cause is identified. A high frequency of sexual abuse is found in anismus (which is a sensitive but nonspecific marker of sexual abuse). The term anismus should be reserved for behavioral causes of anorectal dyssynergia.

Clinically, anorectal dyssynergia is suspected constipation, especially if accompanied by difficulties in stool evacuation. During physical examination, at the time of the digital rectal examination, the examiner may ask the patient to push in order to simulate defecation; if during this test there is no paradoxical contraction perceived with the finger, this eliminates, with good sensitivity, the possibility of having anismus. Anorectal manometry is the ultimate test to reveal paradoxical contraction of the external sphincter during defecation; inability to expel a water-filled balloon is usually present as well.

First-line treatment is typically that for constipation. If unsuccessful, reeducating the defecation maneuver with the help of physiotherapy or biofeedback may be used.

7.8.4 Hirschsprung's Disease

Hirschsprung's disease is due to a defect in the migration of neural crest cells (precursors of intestinal ganglion cells) during embryonic gut development as discussed in ▶ Sect. 7.3.3. The absence of ganglionic myenteric plexus most often affects the rectosigmoid region (80% cases) but can extend to the entire colon and sometimes even to the small intestine (5% cases). Aganglionosis causes permanent contracture without relaxation of the affected areas and results in distension of the normal intestine upstream of this functional obstacle (hence the name congenital megacolon).

The condition is usually suspected in a newborn with intestinal occlusion and without passage of meconium and/or stool. The diagnosis can sometimes be suspected later in a constipated child or even (rarely) in adulthood.

The diagnosis is suspected by a barium enema X-ray that shows colonic occlusion on a contracted distal (usually rectal and lower sigmoid) segment. Anorectal manometry demonstrates the absence of the recto-anal inhibitory reflex (reflex relaxation of the internal anal sphincter during rectal distension by a balloon). Rectal biopsy confirms the absence of neurological ganglionic cells.

Surgical treatment is required, in early life, to resect the aganglionic intestinal segment and bring the normal intestine to the anal sphincter, to allow a future life without colostomy and as normal as possible.

7.8.5 Fecal Incontinence

Anal continence requires four conditions: (1) solid stool consistency (liquids stools are more difficult to contain), (2) good rectal compliance (to act as a reservoir for temporary holding of waste material present in the rectum), (3) strong sphincter muscles (to effectively close the exit aperture), and (4) effective regulatory nerves (to control muscle activity).

Fecal incontinence is discussed extensively in ▶ Chap. 18.

7.9 Miscellaneous

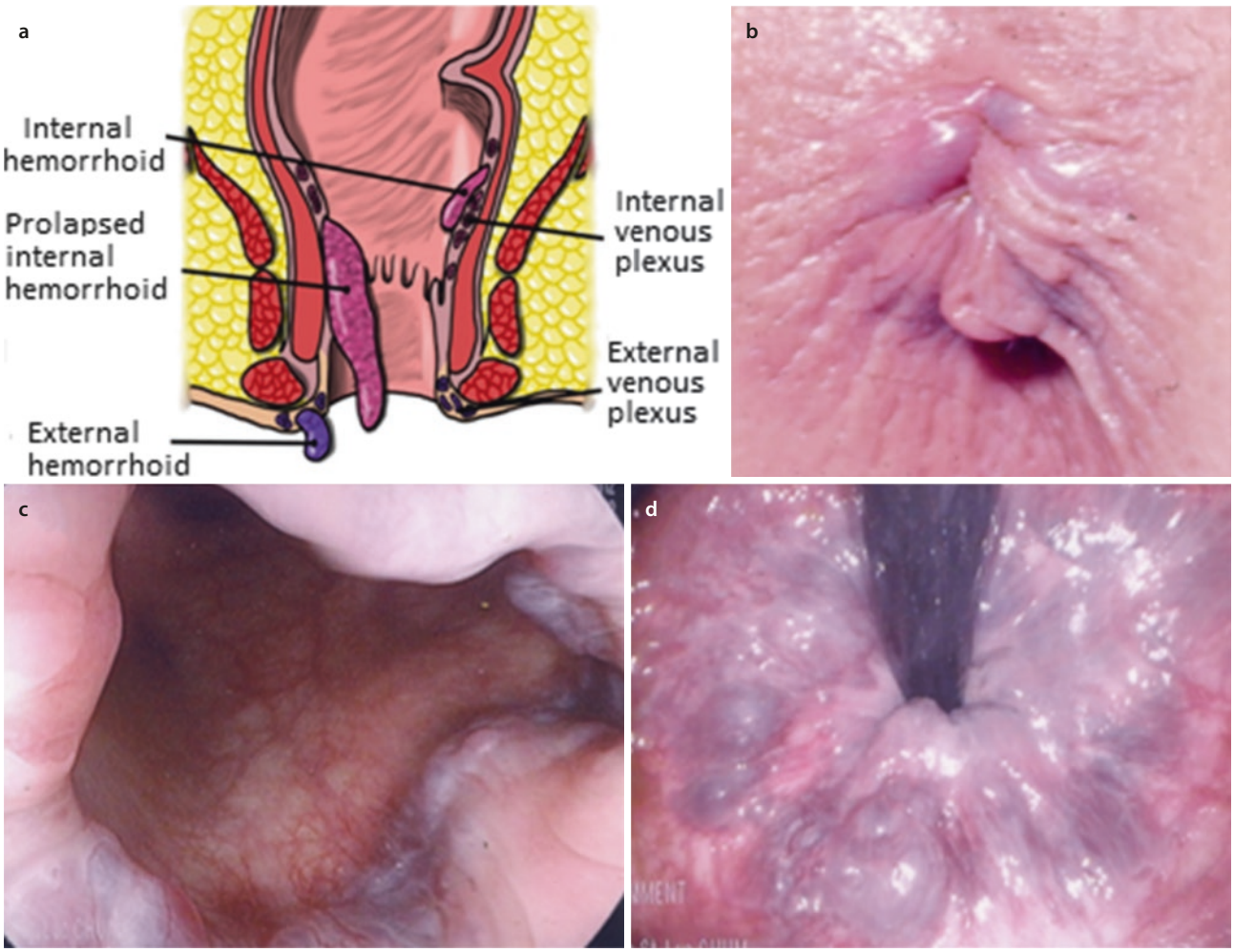
7.9.1 Vascular Diseases: Hemorrhoids/Varices

(a) Hemorrhoids The prevalence of hemorrhoids is not well-known and varies from 4.4% to 86%, depending on the studied population. Hemorrhoidal pathology (i.e., hemorrhoids with symptoms) typically appears in the third decade and increases with age, peaking between the

ages of 45 and 65. No ethnic or gender differences are seen. Factors contributing to hemorrhoidal disease include family history, constipation, and, in women, pregnancy and delivery; hormonal factors may be involved (especially since estrogen receptors are present in hemorrhoidal tissues), but mechanical factors are obvious (e.g., pressure of the fetus on pelvic veins limiting venous drainage of hemorrhoids during pregnancy, or baby delivery which is accompanied, one out of three times, by hemorrhoidal thrombosis).

Hemorrhoids are normal vascular plexuses located in the anus and present from birth (although poorly developed before the age of 10). Internal and external hemorrhoids are identified (see ◘ Fig. 7.17). External hemorrhoids are located below the pectinate line, at the epidermal anal margin, and their vascularity depends on the internal pudendal artery (a branch from the internal iliac artery). Internal hemorrhoids are located in the submucosal space of the anal canal above the pectinate line. They are classically arranged in three bundles emerged from branches of the superior rectal artery. The venous blood return from hemorrhoids is provided by the upper, middle, and lower rectal veins to abdominal portal circulation and to systemic inferior vena cava circulation. Hemorrhoidal plexuses are histologically made up of collagens, sinusoid vessels, and arteriovenous shunts sometimes including a corpus cavernosum structure. Internal hemorrhoids are normally fixed inside the anal canal against the internal sphincter. Sensitive receptors are present on hemorrhoids, including mechanoreceptors and thermoreceptors, which are essential for discrimination of rectal contents (gas, liquid, solid).

Physiopathology The physiopathology of hemorrhoidal disease is explained by two theories, one vascular and one mechanical. The vascular theory is based on the existing arteriovenous capillary-type shunts that could undergo



◘ **Fig. 7.17** Hemorrhoids: **a** schematic illustration; **b** external hemorrhoids on visual examination of the anus; **c** internal hemorrhoids on endoscopic examination (direct vision), **d** seen under retroflexion (black endoscope in the anus and retroflexed in the rectum). (Photos by P. Poitras)

significant variations in arterial flow under the influence of variable factors such as pregnancy or childbirth. The mechanical theory considers a degradation (with age) of supporting connective tissues as the essential cause for the appearance of rectal bleeding and prolapse of the hemorrhoidal tissue over time.

Clinical The limit between physiological hemorrhoids and hemorrhoidal disease is often thin. Hemorrhoidal disease is characterized by symptoms related to hemorrhoids.

- Hemorrhoidal thrombosis (Fig. 7.18) is the most important manifestation of *external hemorrhoids* with sudden onset of anal pain associated with swelling and a blood clot visible under the skin. The pain is continuous, non-pulsating and not related to defecation (in opposition to anal fissure pain). Without treatment, the pain will typically progress, in 1–5 days, toward the disappearance of the pain and of hemorrhoid swelling. During spontaneous healing, external hemorrhoid thrombosis can leave a fold of skin called skin tag which, most often, is not a medical problem but may be responsible for aesthetic discomfort or pruritus due to difficulty in cleaning. If treated early, external hemorrhoidal thrombosis can benefit from excision of the skin to remove the clot, resulting in immediate relief.
- Rectal bleeding is the most common manifestation of *internal hemorrhoids*, made of bright red blood occurring with defecation. Blood may be on the stool, on paper when wiping, or sometimes dripping after defecation. The rectal bleeding is painless and stops spontaneously, although, in rare cases, chronic bleeding may be responsible for anemia.
- Hemorrhoidal prolapse is a situation where externalization of internal hemorrhoids outside the anal canal occurs. It can happen with a single hemorrhoid or with several hemorrhoids. Prolapse most often occurs during defecation and is more common in chronic constipation with straining efforts. The prolapse may be spontaneously retractable, require manual reinsertion after a bowel movement, or be permanent. It may be associated with other symptoms such as oozing, bleeding, discomfort, and pruritus. It can sometimes resemble a rectal prolapse (having a circular groove, while the hemorrhoidal prolapse has radiating grooves).

  Hemorrhoids are classified into four stages: stage I, simple hemorrhoids with rectal bleeding and without prolapse; stage II, hemorrhoids prolapsing at defecation with spontaneous reintegration; stage III, hemorrhoids prolapsing during bowel movements and requiring manual reintroduction; and stage IV, hemorrhoids with permanent prolapse.
- Pain other than thrombosis: Hemorrhoids are rarely painful but may cause discomfort, sensation of anal heaviness, which is particularly exacerbated during the premenstrual period in women. There is no particular treatment for this symptom.
- Skin tags (Fig. 7.19) are sequelae of hemorrhoidal thrombosis, as are hypertrophic papillae that may be associated with it and may persist after hemorrhoidal

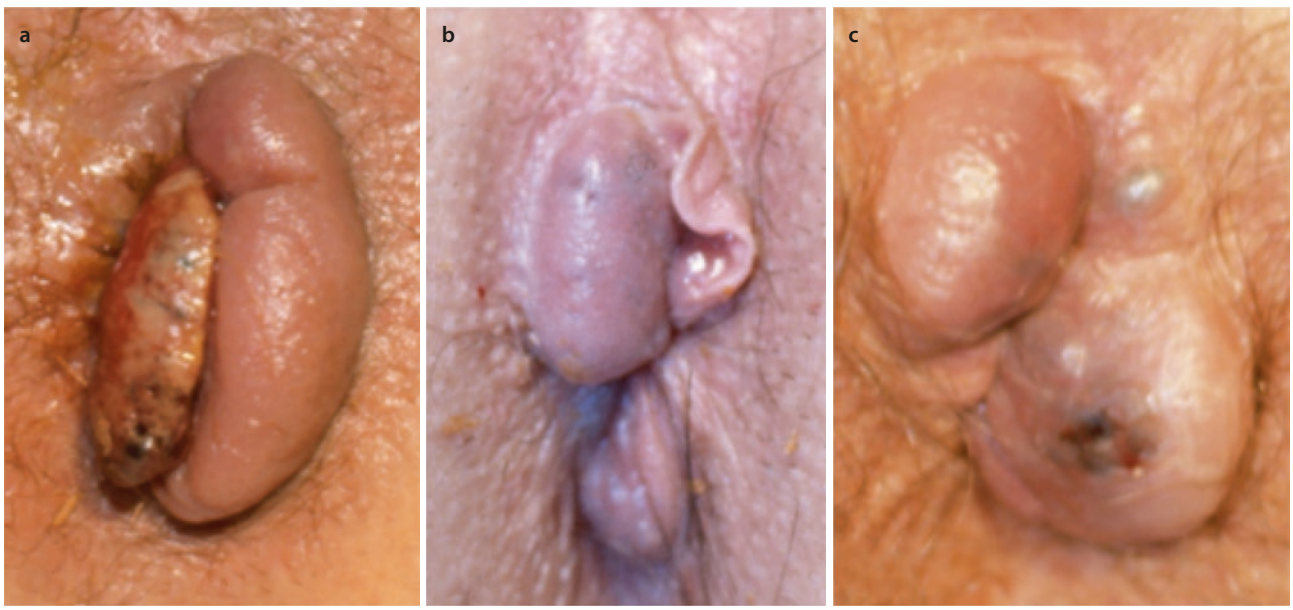


Fig. 7.18 Thrombosed hemorrhoids: **a** necrotic internal hemorrhoid (ischemic yellowish coloration; left side of anus) and edematous external hemorrhoid (right side of anus). **b** Thrombosed external hemorrhoid **c**, thrombosed hemorrhoid with spontaneous rupture that has caused partial evacuation of the clot. (Photos from D. Bernard)

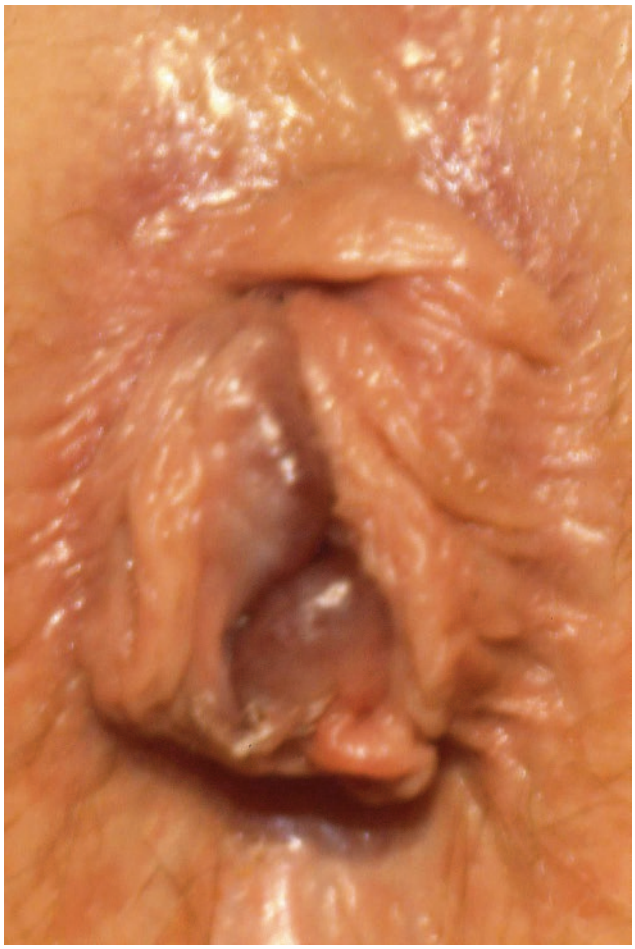


Fig. 7.19 Skin tag: a skin flap at the outer part of the anus (sequelae of an old hemorrhoidal thrombosis) surrounding hemorrhoids. (Photo from D. Bernard)

thrombosis. These may cause local discomfort, either aesthetic or due to difficulty in maintaining proper hygiene. They can be surgically resected, but any surgery in this area should be considered with caution since it can be very uncomfortable and can be complicated by infection, sometimes very serious.

- Anal fissure is not uncommon with hemorrhoids. The fissure syndrome is often clinically predominant and is not a complication of hemorrhoids.

Treatment Hemorrhoid treatment is only indicated if the hemorrhoids are symptomatic:

- Topical ointments or creams, although very popular, have not proven to be effective in the treatment of hemorrhoidal disease. Oral diosmin (from *Citrus sinensis* fruit; with antiinflammatory and venotonic properties), popular in Europe, is now available in Canada.

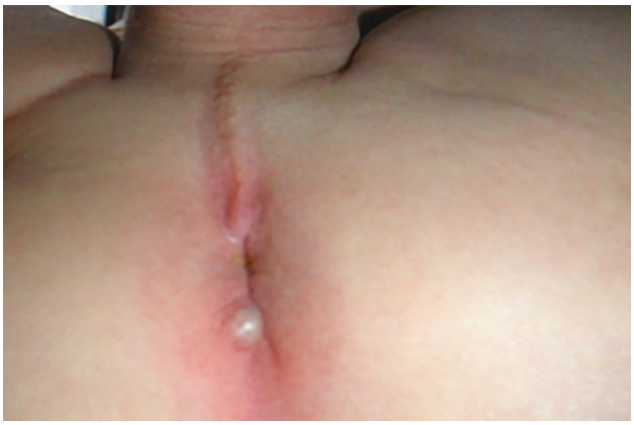


Fig. 7.20 5-year-old boy with an anal venous dilatation due to constipation. (Photos from P. Jantchou)

- Hemorrhoidal thrombosis is treated with analgesics and anti-inflammatory drugs during the painful period. During the first 48 h, incising the hemorrhoid to release the clot is a simple procedure, performed under local anesthesia, which provides immediate pain relief.
- Hemorrhagic hemorrhoids can be treated with a variety of instruments. The most commonly used and effective is the rubber-band ligation; this is a simple procedure performed on an outpatient basis and does not require sedation or preparation. Infrared photocoagulation or sclerosing injections are less popular.
- Surgical treatment by hemorrhoidectomy or hemorrhoidopexy (10% of symptomatic hemorrhoids) is used when other therapeutic treatments have failed, or with stage IV or III hemorrhoids.

In pediatrics, hemorrhoidal pathology is almost nonexistent in children under 10 years of age due to the poor development of the hemorrhoidal plexus before this age. It occurs only in situations of portal hypertension, a context in which rectal varicose veins can be observed (see below). Venous dilatations related to excessive abdominal straining in chronic constipation can sometimes be mistaken for hemorrhoid (Fig. 7.20).

(b) Rectal varices Rectal varicose veins are dilatations of the rectal veins. Diagnosis is made by rectal endoscopy, which easily sees non-pulsatile venous cords (Fig. 7.21). They are usually diagnosed in cirrhotic patients with portal hypertension. Complications, although rare, are dominated by hemorrhage, the treatment of which is not clearly codified but may include treatment of portal hypertension by TIPS or other means (see ▶ Chap. 8).

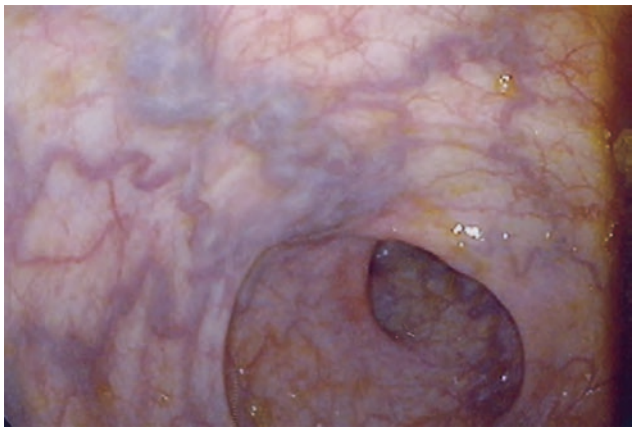


Fig. 7.21 Rectal varices (dilated varicose veins) seen during endoscopy. (Photo by P. Poitras)

7.9.2 Anal fissure

The anal fissure is a longitudinal tear in the mucosa of the anal canal, most often on its posterior side (Fig. 7.22).

Pathophysiology The pathophysiology of anal fissure is not fully elucidated, but it is probably multifactorial.

A "mechanical" factor is usually the initial triggering factor. It is often a trauma related to a hard or bulky stool, which results in tearing the anoderm, often at the posterior commissure of the anus, an area of weak anatomical resistance and relatively poor vascularization.

The "sphincter" factor is related to high-pressure contraction of the internal sphincter, which could be a primary factor in fissure creation, or could be secondary to the pain induced by the fissure, as well as to the stress or anxiety of new stools generating this pain.

The "vascular" factor is related to the fact that the posterior commissure of the anus is an area with limited blood supply and that hypertonia of the internal sphincter can limit blood flow further, all of which lead to delayed or incomplete healing of the fissure. One treatment option, lowering sphincter pressure by surgical sphincterotomy, results in an improvement in sphincter blood flow, thus promoting healing of the fissure.

Clinical Three elements of the diagnosis are linked in a variable manner:

- The fissure is an epithelial ulceration that sits in the anus, usually in the shape of a paper cut or of a tennis racket (with the widest part at the exterior margin and the handle tapering upward in the anal canal). It is located posteriorly in the majority of cases.
- Sphincter contracture results in a hypertonic anal canal and makes digital rectal examination difficult.

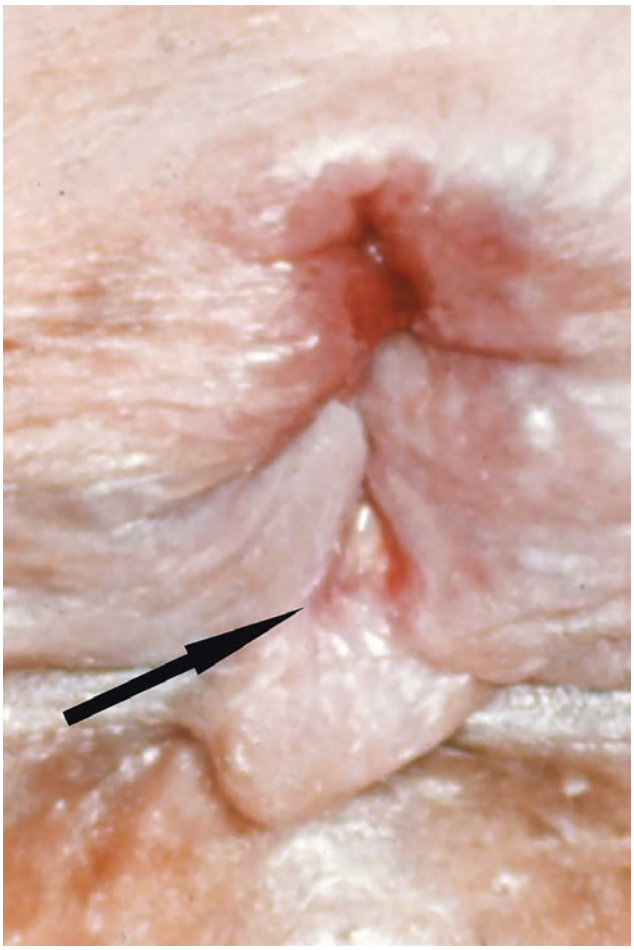


Fig. 7.22 Anal fissure (indicated by the arrow) is a longitudinal, most often posterior, tear in the anal mucosa. (Photo from D. Bernard)

- The pain syndrome typically evolves in three stages: (1) pain is triggered at the time of defecation by the passage of stools, (2) and then there is a decrease or even disappearance of this pain for a few minutes, and (3) finally, there is a secondary reappearance of the pain, often prolonged.

With the passage of the stools, bright red rectal bleeding (in the toilet or on toilet paper) is frequent.

Diagnosis of anal fissure It is most often detected by visual examination of the anus (by spreading the buttocks apart and asking the patient an abdominal thrust to push the anal sphincter out).

Anal fissure must be differentiated from tumor lesions (epidermoid or adenocarcinoma), inflammation (Crohn's, etc.), infection (syphilis, herpes, chlamydia, etc.), or skin lesions (eczema, etc.).

The fissure can be *acute*. The ulceration is superficial, the crater floor is pinkish, and the edges are thin and barely raised; on examination circular fibers of the inter-

nal sphincter may be seen. The pain is usually intense, with its characteristic three-step pattern. The contracture of the internal sphincter is palpable, and rectal examination is almost impossible. This type of fissure can heal spontaneously. The risk of recurrence is significant, and it can also evolve into a chronic (nonhealing) anal fissure.

In the case of *chronic* fissure, the ulceration is deep, with elements of fibrosis around the fissure (raised and sclerotic edges, hypertrophic papilla close to the pectinate line, skin tag on the cutaneous side). Spontaneous healing rate occurs in only 30% of cases.

Treatment of anal fissure Medical treatment is the first-line treatment since it is safe and effective in up to 85% of cases. However, recurrences are frequent (around 50%). Medical treatment consists of:

(a) Regularize stool transit and avoid constipation or large, hard stools that cause anal trauma with tearing. "Soft" (non-stimulant) laxatives are often helpful (fibers (psyllium), emollients (mineral oil), osmotic agents (PEG)) to generate stools of soft consistency.
(b) Decrease pain with oral pain relievers (acetaminophen or NSAIDs, but avoid narcotics that will aggravate constipation). Suppositories or ointments for analgesic purposes, particularly those with a xylocaine base, can be used for a short period of time.
(c) Relax the anal sphincter (to promote tissue oxygenation and healing) through:
   - Sitz baths with lukewarm water (three to four times/day).
   - Nitro derivatives (nitroglycerin 0.2–0.4% in ointment qid) induce the release of nitric oxide (NO), a neuro-mediator relaxing the internal anal sphincter. Side effects of nitrate derivatives, including headache, lead to discontinuation of treatment in more than 30% of cases.
   - Calcium channels blockers (in ointment or gel, such as nifedipine 0.2% bid or diltiazem 2% bid) for 8 weeks are better tolerated than nitrates and give good results in 75–90% of cases.
   - Botulinum toxin (Botox) is a neurotoxin that induces muscle relaxation (presynaptic blocking of acetylcholine at the neuromuscular junction) and can be injected into the anal sphincter. Its long-term efficacy is controversial.

Surgical treatment is indicated in cases of fissures that are resistant to medical treatment or are recurrent after medical treatment. Lateral leiomyotomy (or sphincterotomy) is still the reference technique. It consists in a partial section of the internal sphincter to reduce sphincter tension and thus promote vascularization and oxygenation of anal tissues to heal the fissure. Results are 90% successful. However, its inconvenience is the potential appearance of incontinence, particularly gas incontinence (up to 15–40% of cases).

7.9.3 Neurological Diseases with Anorectal Impact

Neurological diseases can have repercussions on anorectal function.

After a *stroke*, fecal incontinence symptoms are present in 20% of patients after 6 months. Many cofactors can contribute to fecal incontinence, such as age, diabetes, pre-stroke neurological status, injured brain territory, etc.

In *multiple sclerosis*, fecal continence, intestinal transit disorders, and bladder and bowel dysfunction are present in almost half of cases, and these disorders may be presenting symptoms of the disease in 1/3 of cases.

In *Parkinson's disease*, constipation is frequent. Continence disorders are more rare.

In *spinal cord injury*, the neurological alteration can be complex since the lesion may be complete or incomplete, affecting sensory or motor pathways, autonomic or somatic innervation. In complete spinal cord lesions, where supraspinal control of the sensory-motor functions is absent, sphincter dyskinesia affecting both urinary and anal organs may impair evacuation function. In high spinal cord lesions, constipation, due to reduced colonic motor activity, is often the main symptom. Lower spinal cord injuries, as in cauda equina syndrome, may reduce rectal perception of need to defecate and result in constipation and/or encopresis.

7.9.4 Pelvic Floor Disorders

The pelvic organs lie on a muscular floor or diaphragm made of four main muscles: the pubococcygeus, the iliococcygeus, the puborectalis (all three forming the levator ani muscle), and the coccygeus which attach to the pubis in the front, the sacrum at the back, and the inner surface of the pelvic skeleton forming a thin hammock to support them. The pelvic floor may be altered by childbirth, defecation, age, menopause, or certain surgical procedures. Pelvic floor disorders are clinically characterized either by problems with rectal evacuation (constipation), fecal incontinence, or pain or abnormal sensations in the lesser pelvis.

(a) Rectocele A rectocele is a herniation of the front wall of the rectum into the back wall of the vagina (see

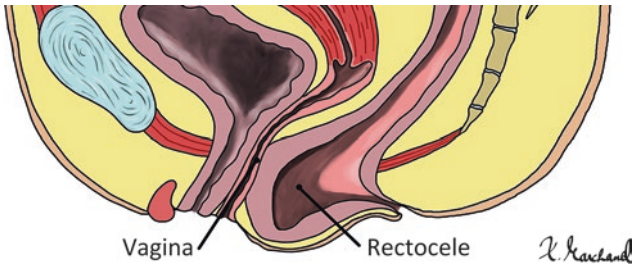


Fig. 7.23 Rectocele is a saccular deformation and bulging of the rectum toward the vaginal cavity and where stools can be trapped and difficult to evacuate

Fig. 7.23). It can be promoted by various factors including age, pregnancy, hysterectomy, or chronic constipation. The rectocele is manifested by dyschesia (difficulty in passing stools); perception of need to defecate is not affected, and the frequency of bowel movements remains normal. Signs associated with dyschezia are as follows:

- Excessive straining to evacuate stools
- Need to use digital pressure in the vagina or to apply pressure on the pubic (or perineal) area to facilitate emptying of the rectocele and stool evacuation from the rectum
- Incomplete stool evacuation after defecation, forcing the patient to return several times to the bathroom to finish emptying, or with staining of undergarments after defecation due to persistent stools in the rectocele

Diagnosis of rectocele It is based on the symptomatology and perineal examination (in supine or gynecological position, during a rectal examination with the finger forward, when the patient is asked to push, the finger gets into the rectocele and may protrude into the vagina).

Investigation by defecography is useful when surgical treatment is considered. This X-ray examination films the defecation of a barium paste introduced into the rectum. A rectocele will be considered significant when its depth during straining exceeds 3 cm, and if, after defecation, there is still contrast material left in the rectocele.

Treatment of rectocele It should be done in a stepwise fashion and according to symptoms. Medical treatment begins with a precise explanation of the anatomical abnormalities to the patient. Manual maneuvers, if they are not disturbing, can be continued by the patient and the best anatomical knowledge will allow them to be maximized. Rectal emptying of hard stools maybe difficult and osmotic laxatives in combination with fiber are often helpful; rectal suppositories, e.g., glycerin-based suppositories, can be used to promote complete evacuation.

Most rectocele surgeries are performed by gynecologic surgeons and aim to strengthen the posterior vaginal wall.

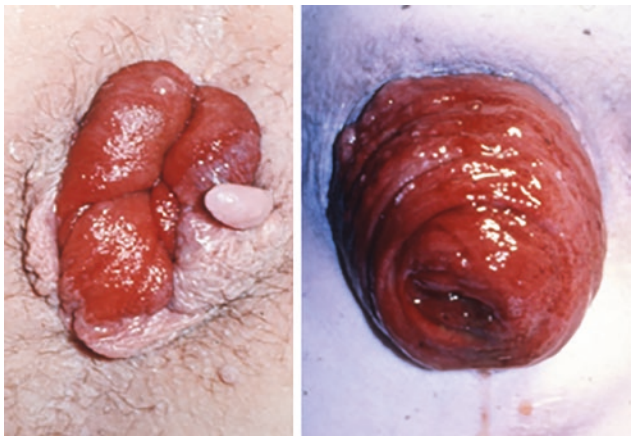


Fig. 7.24 Rectal prolapse can be partial, i.e., made of mucosal and submucosal layers only, giving rise to radiating folds (left image); it can also be complete, i.e., include all rectal wall layers, including the muscularis, and be recognizable by its circular folds (right image). (Photos from D. Bernard)

(b) Rectal prolapse Rectal prolapse is the exteriorization of the rectum through the anal opening.

Rectal prolapse is ten times more frequent in women than in men, with a peak prevalence between the ages of 60 and 70 years; it seems to be associated with chronic constipation with straining during defecation, previous obstetric damage (which may have occurred decades prior), previous perineal surgery, weakness of pelvic floor muscles, etc.

In children, a recurrent prolapse should be investigated for three conditions: chronic constipation, celiac disease, and cystic fibrosis.

Clinical diagnosis of rectal prolapse The patient usually consults for a lump or swelling in the anus (Fig. 7.24). This swelling is initially often intermittent, occurring at the time of defecation. Initially, it spontaneously reduces at the end of defecation but may over time need to be reduced manually by the patient. Prolapse can also become permanent or occur under various circumstances such as stress or walking.

The patient may also consult for complications related to this prolapse such as oozing, discharge, incontinence, obstructive constipation, or "false" diarrhea. Rectal prolapse is not accompanied by pain except in the case of strangulation with an irreducible prolapse, a complication leading to prolapse ischemia and requiring urgent surgical treatment.

The diagnosis of a prolapse is obvious when it is visible. It is sometimes difficult for the physician to identify it when it is intermittent, but it may be revealed during a defecation thrust from the patient.

Treatment of rectal prolapse Conservative medical treatment can be used if the prolapse is not very disabling,

easily reducible, and without significant medical or quality of life consequences. In the case of external prolapse with strangulation, manual reduction should be attempted as soon as possible. The best technique is to apply powdered sugar on the prolapse in order to reduce the edema by an osmotic effect; then, a manual reduction with gradual gentle pressure to retract the prolapse usually avoids emergency surgery.

Surgical treatment is the only curative treatment for an externalized or disabling rectal prolapse.

(c) Enterocele The enterocele is a hernia of the small bowel in the pouch of Douglas. It is characterized by a sensation of pelvic heaviness, pain in sitting position, urinary symptoms, or constipation. The main risk factor is hysterectomy.

The diagnosis can sometimes be made clinically by a bi-digital examination with a rectal and vaginal examination; during bearing down, an intestinal loop can be felt between the two fingers. Defecography most often confirms the diagnosis by showing small intestinal loops descending into the lesser pelvis.

(d) Excessive perineal descent (or descending perineum syndrome) will present clinically either by constipation or by incontinence. Its diagnosis is difficult on clinical examination and is essentially made by defecography (on lateral views) showing the anorectal angle in an abnormally low position. Excessive perineal descent is rarely isolated and is most often accompanied by other disorders of the pelvic floor, including pudendal neuropathy due to repeated tension on the nerve as the perineum stretches downward.

7.9.5 Fecaloma

A fecaloma is a hardened bulk of feces accumulated in the rectum (sometimes higher up in the sigmoid). It is due to excessive stagnation of stools in the rectal ampulla and is therefore usually related to prolonged constipation and to defecation needs not felt or relieved by the patient. Adult fecal impaction is most often found in an individual with a central or peripheral neurological condition that alters rectal perception and defecation. In children, it can be found in functional constipation with or without encopresis (incontinence or fecal leakage in underwear).

Fecal impaction can induce:

- Constipation.
- Intestinal obstruction (bloating, vomiting, cramps, etc.).
- Incontinence or paradoxical overflow diarrhea (fecaloma is always to be considered in a diarrheic old man or in an encopresis child).
- Pelvic or perineal pain in the form of pressure, heaviness.

Digital rectal examination reveals a rectal ampulla full of hardened stools.

Treatment of fecaloma consists of emptying the rectum, preferably with laxatives administered rectally (enema, etc.) or combined with oral laxatives (if no obstruction). Digital disimpaction is certainly effective but often painful for the patient (and "uncomfortable" for the doctor).

PS: for complementary readings on the anorectum, see ► Chaps. 18, 19, and 20.

The Liver

M. Bilodeau, J. Bissonnette, H. Castel, D. Corsilli, D. Fenyves, C. Fournier, J. M. Giard, G. Huard, P. M. Huet, D. Marleau, G. Pomier-Layrargues, J. P. Villeneuve, C. Vincent, B. Willems, F. Alvarez, and Mark G. Swain

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8.1 Macroscopic Anatomy

8.1.1 Shape and Structure

(a) Liver The liver is situated behind the lower right rib cage, under the diaphragm. Therefore, it is typically only palpable during inhalation. Its border feels sharp but flexible in the normal state. It has the shape of an elongated triangle across, from the right hypochondrium to the epigastric hollow. The liver is the largest organ of the human body, weighing between 1 and 2 kg, depending on body weight. The liver is reddish-brown in color due to its high concentration in ferric pigments. Its smooth surface consists of a very fine capsule (<1 mm on histological sections), called Glisson's capsule.

In humans, the liver has two main lobes. Traditionally, the liver was divided into left and right liver lobes separated by the falciform ligament (◘ Fig. 8.3). However, Couinaud's anatomical work and the development of liver surgery required a nomenclature based on liver vascularization. The right lobe is vascularized by the right branch of the portal vein and the left lobe by the left branch of the portal vein. The right lobe is larger than the left lobe (65% vs. 35%), and the delineation between these two lobes is well known to surgeons (particularly in liver transplantation surgery using "living donors" where one lobe, usually the right lobe, is removed for grafting in the recipient).

The hepatic lobes are subdivided into segments that represent true anatomical units which are readily identified and independent of each other. This division is complex and essential for surgeons to know. The liver is composed of eight segments identified as a clockwise spiral, from segment I, central and located behind the liver, to segment VIII, located in front of the hepatic dome, as shown in ◘ Fig. 8.1.

Segment I (caudate or Spiegel's lobe) is located in the center of the organ, behind the bifurcation of the right and left branches of the portal vein, just in front of the inferior vena cava.

In contrast to other liver lobes, the caudate lobe drains directly into the inferior vena cava rather than into the hepatic veins. This anatomical feature explains why, in some cases of thrombosis of the main hepatic veins (Budd-Chiari syndrome), this segment is preserved and becomes hypertrophic to maintain normal compensatory hepatic function.

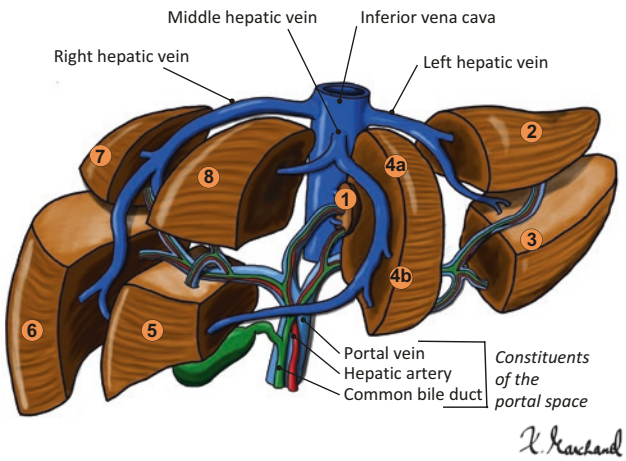
Segments II and III form the anatomical left lobe. Their afferent vascular supply comes from two branches of the left portal vein and branches of the left hepatic artery. These two segments are difficult to distinguish, and, during tumor surgery of the left hepatic lobe, they are resected together (left lobectomy). The venous drainage for these segments is through the left hepatic vein.

Segments II and III are separated from segment IV by a ligament called the falciform ligament, clearly recognizable on the surface of the liver, following the suspensory ligament of the liver.

Segment IV (IVa and IVb or square lobe), located to the right of the falciform ligament, is part of the left liver lobe and receives its blood supply from the left branches of the portal vein and hepatic artery. Its venous drainage occurs via the median hepatic vein, which also frequently drains segments V and VIII of the right lobe.

Segments V, VI, VII, and VIII form the anatomical right lobe and are subdivided into an anterior right sector (V and VIII) and a posterior right sector (VI and VII). These latter segments (Riedel's lobe) can sometimes be palpated in the right iliac fossa. The venous and arterial vascularization of these segments occurs through the right branches of the portal vein and hepatic artery. Venous drainage of segments VI and VII occurs through the right hepatic vein; for segments V and VIII, this occurs mainly through the middle hepatic vein.

This anatomical description is of particular importance during segmental or lobar hepatic resections, which most often occurs in the context of surgery for primary or secondary liver tumors.



◘ **Fig. 8.1** Macroscopic anatomy of the liver with its eight segments

(b) Gallbladder The gallbladder is oblong in shape and is located below the liver, in the cystic fossa between segments IV and V. The gallbladder fundus can be seen at the front of the liver, and its body extends backward and to the left toward the hepatic hilum. Gallbladder cancers therefore typically locally invade segments IV and V due to proximity.

8.1.2 Vascular Supply

(a) Afferent vascularization The liver is in a unique situation, benefiting from a double blood supply, arterial and venous, which provides it with approximately 1.0–1.5 liters of blood per minute (35% of the cardiac output).

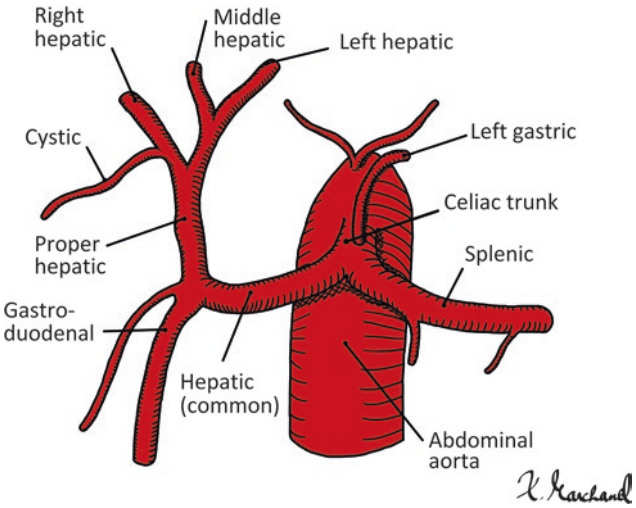


Fig. 8.2 Arterial vessels connecting the liver come from the common hepatic artery, one of the three main branches of the celiac trunk along with the splenic artery and the left gastric artery

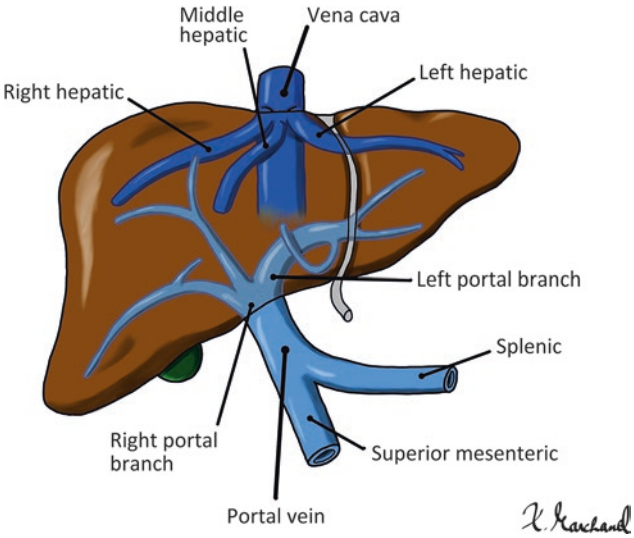


Fig. 8.3 Veins entering the liver (portal vein draining the intestine and formed by the splenic and mesenteric veins) and veins exiting the liver (hepatic veins leading to the inferior vena cava)

- ***Arteries:*** like all other organs, the liver is supplied by an artery, the hepatic artery, which normally originates from the celiac trunk, after division into the splenic artery and the gastroduodenal artery (Fig. 8.2). The hepatic artery supplies the liver with oxygenated blood and follows the portal vein on its extra- and intrahepatic route, all the way to its terminal branches.
- ***Veins:*** the main blood supply of the liver comes from the portal vein, formed by the union of the splenic and mesenteric veins (inferior and superior). The portal vein enters the liver inferiorly, in association with the hepatic artery, via the hepatic hilum, after which the two vessels divide to enter the two hepatic lobes and then branch to enter the different hepatic segments (Fig. 8.3). The portal vein blood flow is important, corresponding to 70–75% of the total hepatic blood flow, the remainder being provided by the hepatic artery. Blood within the portal vein has a low oxygen tension ($pO_2 \pm 60\%$) but is well saturated in oxygen (90%). The portal vein drains all the blood from the intra-abdominal organs (lower esophagus, stomach, pancreas, spleen, duodenum, small intestine, colon, and rectum to the junction with the anus). It brings to the liver all substances and nutrients absorbed by the intestine (except lipids which are absorbed in the form of chylomicrons and pass into the lymph).

In the liver segments, branches of the portal vein and the hepatic artery divide into first-, second-, and third-order branches ending in the hepatic lobules which are the true functional units of the liver, as outlined later.

(b) Efferent vascularization The venous drainage of the liver occurs via the hepatic veins (formerly called sus-hepatic veins). They originate at the exit point from the hepatic lobules (centrilobular vein) forming the left (draining segments II and III), middle (or median, draining segments IV, V, and VIII), and right (draining segments VI and VII) hepatic veins, which are all tributaries of the inferior vena cava.

(c) Lymphatics The hepatic lymphatic channels originate in the portal space within the liver and follow the extracellular hepatic space between the liver cells (hepatocytes) and the cells of the vascular wall (endothelial cells), whose architecture is very particular to the liver and will be described later. These channels, poorly identified by light microscopy, run along the terminal branches of the portal veins, ultimately arriving at the hepatic hilum. Lymph flow in the liver is in the opposite direction to blood flow, moving toward the first set of lymph nodes that are located near the bifurcation of the portal vein. Due to their anatomical location, these lymph nodes are the first metastatic sites in the case of malignant liver tumors. These hepatic lymph nodes then join the large cistern and subsequently empty into the thoracic duct with lymph flowing toward the left subclavian vein.

8.1.3 Innervation

The liver is innervated by splanchnic (sympathetic) and vagal (parasympathetic) nerves. The splanchnic nerves originate between the sixth and ninth dorsal vertebrae

and the parasympathetic vagal nerves in the medulla oblongata. Both types of nerve fibers are present in the connective tissue of the portal spaces, in close relationship to hepatic vessels and bile ducts; some nerve fibers extend from the portal space into the hepatic lobule where their nerve endings form close relationships with the cells within the hepatic lobule. Both systems have afferent and efferent fibers. The efferent nerve fibers are believed to be involved in the regulation of the hepatic microcirculation as well as in hepatic metabolism and biliary secretion. Afferent nerve fibers are involved in sensory and osmotic regulatory functions as well as in carbohydrate homeostasis. However, the importance and the role of hepatic innervation are poorly understood: the fact that, after liver transplantation (and thus sectioning of all hepatic extrinsic innervation), all normal liver functions are maintained suggests a relatively minor role of this innervation in liver function.

The liver has no sensory fibers. Glisson's capsule is the only hepatic structure containing some neural sensory afferents (that arise via the phrenic nerve which also innervates the diaphragm). This neural innervation of the liver capsule can give rise to intense pain when it is distended (as in acute inflammatory processes of the liver). The liver parenchyma itself does not contain sensory nerves and, therefore, does not contribute to the generation of hepatic pain sensations, even during major insults (such as in primary or secondary cancers).

8.2 Microscopic Anatomy

The liver is mainly composed of hepatocytes (65% of total cell number); sinusoidal endothelial cells (25%); Kupffer cells (5–7%); stellate cells (2–4%), formerly called Ito cells or fat-storing cells; and liver-associated lymphocytes (less than 1%).

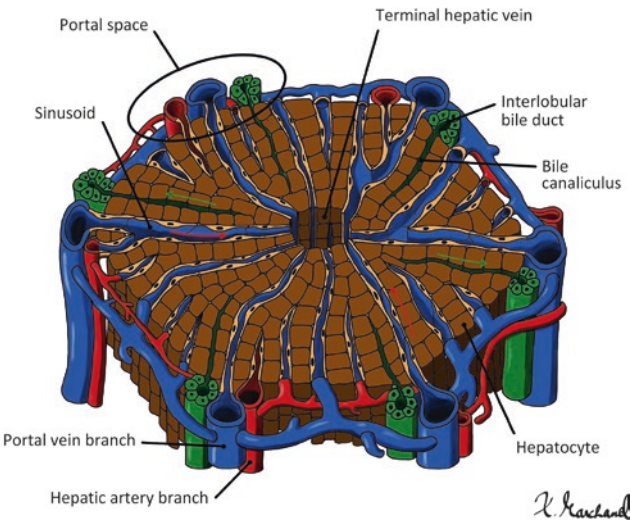
The liver can be seen as a processing factory, located between the intestine and the systemic bloodstream, that modifies the blood coming from the intestine before it enters the general circulation and integrates the whole body. The blood entering the liver via the portal vein needs to be in close contact with the factory cells, the hepatocytes, for its transformation. When it passes through the hepatic veins and into the systemic circulation, the (intestinal) blood has been modified so that toxic components are removed by hepatocytes (e.g., gut-derived bacterial products), and hepatocyte-synthesized products have been added (e.g., albumin). The hepatocytes are therefore anatomically located according to a precise anatomical plan (the hepatic lobule) that allows the liver (and especially the hepatocytes) to fulfill its complex and essential physiological role.

8.2.1 Organization of Hepatocytes: Lobules and Acini

(a) Hepatic lobule The hepatic lobule is the functional anatomical unit of the liver. Hepatocytes are arranged in rows between the afferent and efferent blood vessels of the liver. The afferent vessels, arising from the portal vein and hepatic artery, are located at the periphery of the lobule, in the portal space (this area also contains the interlobular bile duct). The efferent blood vessels originate in the center of the liver lobule, in the terminal hepatic veins, and drain blood into the hepatic veins. A liver lobule therefore consists of a terminal hepatic vein at the center of hepatocyte trabeculae bordered at the periphery by four to six portal spaces (◘ Figs. 8.4 and 8.5).

Blood arrives in the liver at the periphery of the lobule, in the portal space, and travels to the terminal hepatic vein in the center of the lobule through vessels, called sinusoids, which are bordered by rows of hepatocytes (◘ Figs. 8.4 and 8.5). The transit of substances present in the blood compartment to the hepatocyte must go through (1) the wall of the sinusoids composed of sinusoidal endothelial cells and (2) the Disse space, a virtual space between endothelial cells and hepatocytes, containing loose collagen fibers.

The hepatic lobule, despite its functional inaccuracy (see the acinus described below), remains the classic anatomical marker used clinically.



◘ **Fig. 8.4** The hepatic lobule is a three-dimensional structure with the terminal hepatic vein in the center of rows of hepatocytes bordered by four to six portal spaces. The blood travels through the liver from the periphery of the lobule, in the portal space, and is directed toward the terminal vein in the center of the lobule through sinusoids bordered by hepatocytes. The bile secreted by hepatocytes in the bile duct flows in the opposite direction, from the center of the lobule to the interlobular bile duct located at the periphery, in the portal space

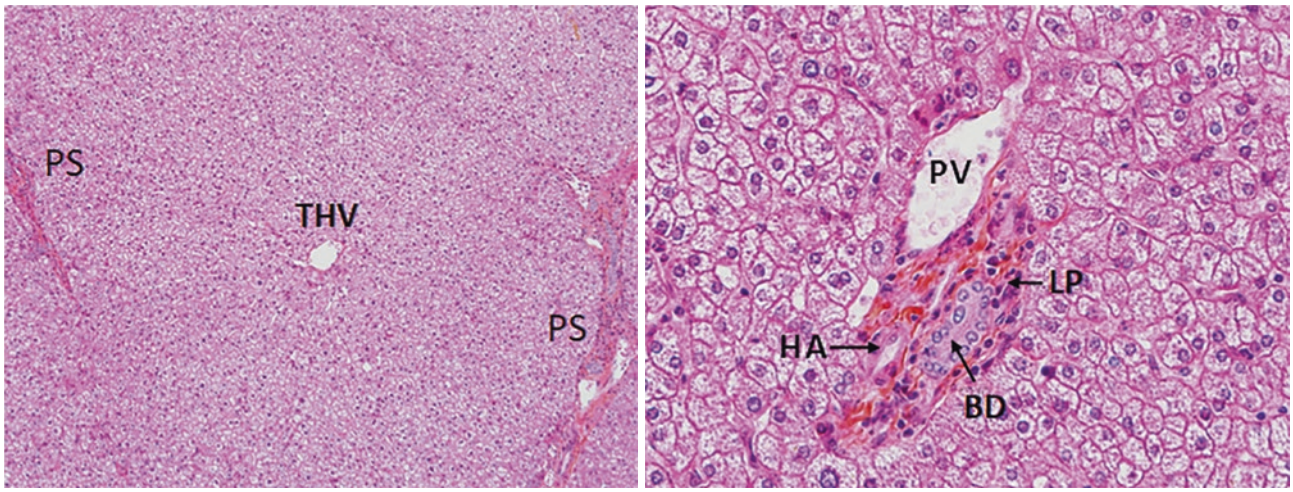


Fig. 8.5 Hepatic histology. Left: hepatic lobule with terminal hepatic vein (THV) and hepatocytes bordered by portal spaces (PS). Right: portal space seen at higher magnification with portal venule (PV), hepatic arteriole (HA), and interlobular bile duct (BD), all bordered by the limiting plate (LP, interface between portal space and hepatocytes)

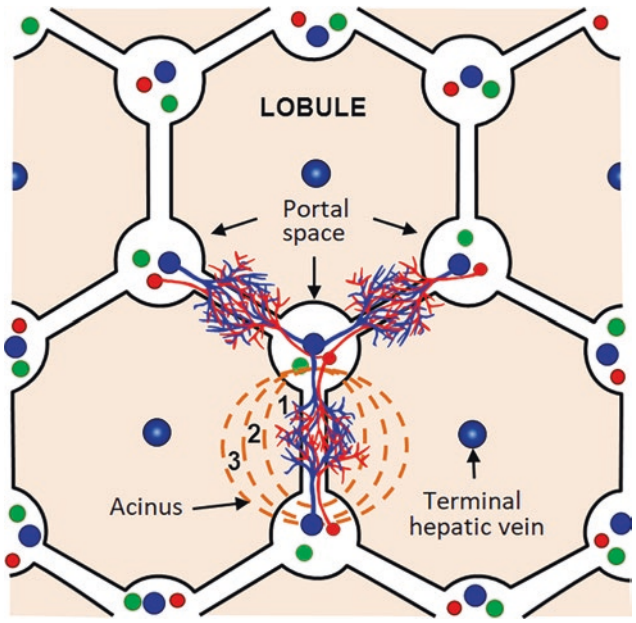


Fig. 8.6 In hepatic acinus, according to the Rappaport model, blood entering the liver circulates primarily between two portal spaces and travels to at least two terminal hepatic venules, passing through various zones (1, 2, 3) where hepatocytes have different metabolic activities

(b) Hepatic acinus The pattern of blood circulation in the normal liver was defined through the work of Toronto researcher Aron Rappaport around 1955 (Fig. 8.6). He demonstrated that liver blood flow does not follow the classical anatomical model of the lobule. Actually, blood circulates from the portal spaces to the terminal hepatic veins, but this flow is not straightforward: blood flows from a terminal branch of the portal vein (third order) to at least two terminal hepatic venules through a functional microcirculatory unit of the liver, the hepatic acinus, which comprises several layers of hepatocytes divided into zones 1 (periportal), 2, and 3 (pericentrolobular), each with different metabolic activities (e.g., gluconeogenesis in zone 1 and glycolysis in zone 3). Zone 1 is closer to afferent oxygen-carrying blood vessels and therefore is well oxygenated. The level of oxygen and nutrients contained within the blood is thought to determine the type of metabolic activity taking place in each zone. The blood circulates in the acinus through capillary vessels called sinusoids, which, because of their particular structure, ensures maximum contact between hepatocytes and the sinusoidal blood.

8.2.2 Sinusoids

Sinusoids (Fig. 8.7) begin at the third-order portal venules and have an average diameter of 4–6 mm. These blood vessels are formed of sinusoidal endothelial cells (SECs) which have two atypical characteristics: (1) they are perforated with a multitude of fenestrae 50–150 nm in diameter and (2) they do not rest on a basement membrane (unlike endothelial cells of capillaries of other organs such as the brain, lung, and heart). These SECs express a large number of receptors and molecules that are involved in the adhesion of various substances and leukocytes to the endothelium.

Between SECs and hepatocytes lies a virtual territory, the space of Disse, representing about 10–15% of the volume of the liver lobule. This space is the site of formation of hepatic lymph, which circulates in the opposite direction from the sinusoidal blood flow, moving toward the portal spaces and hepatic hilum. In the normal liver, only a few rare collagen fibers are visible

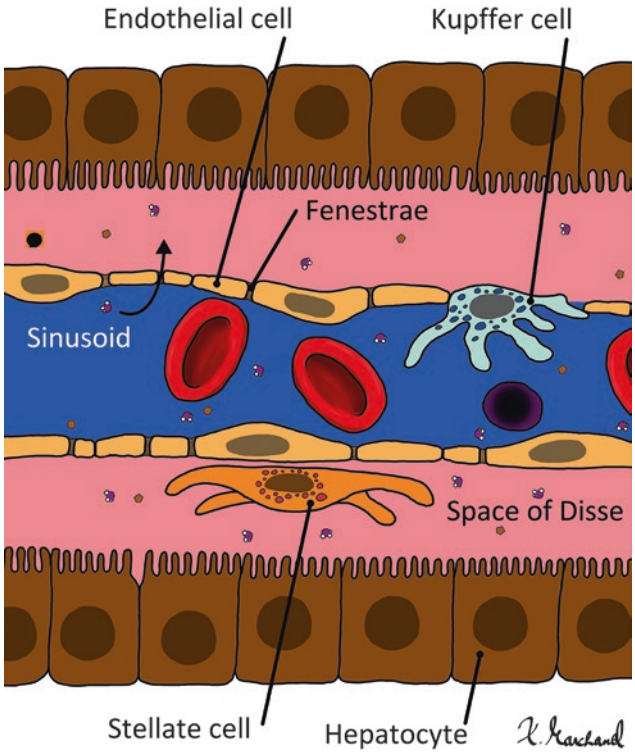


Fig. 8.7 The sinusoids are blood vessels bordered by sinusoidal endothelial cells (SECs) perforated with a multitude of fenestrae through which small substances (less than 100 nm) can reach hepatocytes, after having crossed the space of Disse. When cirrhosis develops, collagen accumulates in the space of Disse (produced by stellate cells) which transforms the sinusoidal wall into a tight capillary, disturbing the movement of substances to and from hepatocytes

under electron microscopy in the space of Disse, which also contains other components of the extracellular matrix (such as laminin, fibronectin, collagens, hyaluronan, and perlecan which are well identified in immunohistochemistry). This matrix acts as a semipermeable gel through which substances dissolved in plasma diffuse, according to their molecular weight, coming into contact with hepatocytes (where the uptake processes can then take place).

Red and white blood cells as well as large lipoproteins (chylomicrons, which have a diameter of 100–1000 nm) are bigger than the fenestrae in the SECs (50–150 nm) and therefore do not normally have access to the space of Disse. Interestingly, SEC fenestrations can expand and contract due to the presence of actin and myosin filaments, especially as a result of effects of alcohol and nitric oxide (NO).

Changes in the sinusoids occur in the context of chronic liver damage (cirrhosis). "Capillarization" (loss of fenestrations and the formation of a basement membrane) and "collagenization" (formation of dense collagen tissue in the space of Disse) of the sinusoids increase resistance to blood flow in the sinusoids, thereby leading to increased pressure within the portal vein (portal hypertension). Furthermore, the "capillarization" and "collagenization" of sinusoids will compromise the diffusion of substances present in the sinusoidal blood to hepatocytes, thereby limiting hepatocyte uptake processes.

8.2.3 Bile Ducts

Hepatocytes are polarized cells that are oriented toward sinusoids on one side and bile canaliculi on the other. Bile canaliculi are actually a virtual space devoid of a cell lining and delimited by invagination of hepatocyte membranes (Fig. 8.8). Substances secreted by hepatocytes into the bile canaliculus will flow in the direction opposite to blood flow, moving from the center of the lobule to the peripheral portal space where the interlobular bile duct is located, being formed by a lining of bile duct cells.

8.2.4 Hepatocytes

Hepatocytes are polyhedral cells, measuring approximately 20 by 30 mm, arranged in single-cell plates. They can regenerate and multiply either spontaneously, after a half-life of about 150 days, or when stimulated after

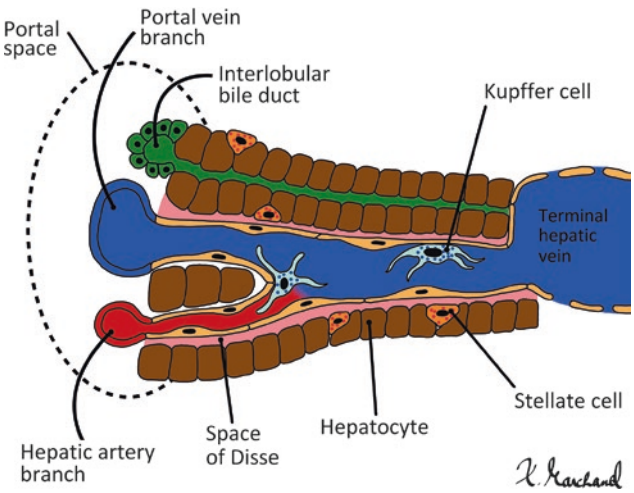


Fig. 8.8 The hepatocyte trabeculae are bordered on one side by a sinusoid and on the other by a bile duct. Blood enters the liver via the portal space vessels at the periphery of the hepatic lobule and travels to the terminal vein at the center of the lobule to reach the hepatic veins and the inferior vena cava. Along the way, unconjugated bilirubin, contained in blood, passes through the fenestrae of the sinusoidal endothelium to be captured by the apical membrane of the hepatocytes where it is enzymatically transformed and conjugated. Conjugated bilirubin is then transported through the basement membrane of the hepatocytes into the bile canaliculus and ascends, through the interlobular bile duct and subsequently via the bile ducts, to the duodenum

Table 8.1 Main hepatic organelles and their functions

Mitochondria	Oxidative phosphorylation and oxidation of fatty acids
Rough endoplasmic reticulum	Synthesis of albumin, fibrinogen, inflammation, and clotting proteins
Smooth endoplasmic reticulum	Conjugation of bilirubin, esterification of fatty acids, glycolysis, synthesis of cholesterol and bile acids
	Main site for the oxidative microsomal system (P450) involved in the metabolism of lipids, drugs, and steroids
Golgi apparatus	Lipid transport to plasma; catabolic role?
Lysosomes	Acid phosphatase activity, hydrolysis of foreign bodies, iron storage
Peroxisomes	Metabolism of hydrogen, purines, lipids, alcohols; gluconeogenesis

loss of cell mass (either because of cell injury or of surgical partial hepatic resection). The liver can regenerate 70–80% of its original mass within a week.

Hepatocytes are in contact with the space of Disse and the sinusoids, on at least two of their sides, and their sinusoidal wall is made up of microvilli. At their apical portion, they form, with each adjacent hepatocyte, a bile canaliculus, a structure that has no wall of its own and is separated from the hepatocyte intercellular space by tight junctions. The canalicular side of the hepatocyte is also covered with microvilli. These microvilli increase the surface of exchange between the inside and outside of the hepatocytes.

There are approximately 1×10^8 hepatocytes per gram of human liver. Hepatocytes possess all the organs and enzymatic material necessary for the synthesis and biotransformation of a large number of substances, both endogenous and exogenous, and also facilitate their elimination through bile or blood (Table 8.1).

8.2.5 Kupffer Cells

Kupffer cells are resident hepatic macrophages, which originate in the bone marrow and migrate and settle in the liver. They make up ~80% of the macrophage population in the body. Kupffer cells are located in the space of Disse but can be attached to the sinusoidal wall in order to better facilitate their functional role as of phagocytes (viruses, bacteria, etc.). They have a longer half-life than hepatocytes and are also capable of regeneration or multiplication during liver injury. In addition to phagocytosis, these cells have important metabolic activities and are involved in immune and inflammatory responses through the secretion of cytokines (TNF-a, interleukins, interferons), eicosanoids (prostaglandins and thromboxane), and reactive oxygen derivatives. They also have a tumoricidal action against cancer cells. After hepatic transplantation, the donor's Kupffer cells are gradually replaced by those of the recipient, while hepatocytes remain of donor origin.

8.2.6 Hepatic Stellate Cells

Hepatic stellate cells (also called Ito cells) are difficult to see with light microscopy, except when they are loaded with fat (storage of vitamin A, a lipid compound, is the primary function of these cells at rest). As their name indicates, stellate cells have very fine cytoplasmic projections, extending by filaments into the space of Disse where they are located, connecting with hepatocytes, SECs, and Kupffer cells. Stellate cells play an important role in the regulation of the hepatic microcirculation due to their expression of numerous vasomotor receptors, for both vasodilators and vasoconstrictors (thromboxane, prostaglandins, endothelin, NO, etc.). Moreover, they are endowed with contractile capacities.

During repeated liver injury, these cells transform, losing their capacity to store vitamin A. They start producing extracellular matrix components, thus modifying the sinusoidal architecture through the deposition and accumulation of collagen in the space of Disse (leading to the processes of collagenization and capillarization) and eventually giving rise to cirrhosis (which we will see later in this chapter).

8.2.7 Liver-Associated Lymphocytes (LAL)

These cells (also called pit cells) are derived from circulating lymphocytes and are immobilized in the space of Disse where they have intimate contact with other liver cells. Their composition differs from that of circulating lymphoid cells (increased population of T lymphocytes, "natural killers"), and they appear to have significant cytotoxic activity and a major role in antiviral and antitumor defense.

8.3 Embryology/Development

The liver and bile ducts develop from a bud, which appears around the 18th day of embryonic life on the ventral face of the duodenum. This bud consists of an upward ventral part (pars hepatica) and a downward dorsal part (pars cystica). The pars hepatica represents

the origin of the hepatic parenchyma, the intrahepatic bile ducts, and the right and left hepatic ducts.

From the end of the first month, the embryonic cells of the pars hepatica form trabeculae and hepatoblast corpuscles that penetrate a capillary vascular bed, thus forming the sinusoid outline. Parallel to this, the pars cystica also penetrates the septum transversum and gives rise to the gallbladder, the cystic duct, and the common hepatic duct. Abnormalities in the development of the bile ducts have been described in ▶ Chap. 6.

The final organization of the hepatic circulation is complex and results from the abrupt transition occurring at birth from a system where venous blood is brought to the liver mainly through the umbilical vein (mother's blood) to a system where venous blood is brought to the liver mainly through the portal vein (child's blood). In utero, a vessel (the ductus venosus) derived from the umbilical vein connects the left branch of the portal vein with the vena cava. The liver is thus vascularized by the portal vein, but the umbilical vein is the main venous blood source until the end of the pregnancy. At birth, the ductus venosus and the left umbilical vein close. In cases of portal hypertension, this left umbilical vein can recanalize (in fact, new veins surrounding the obliterated umbilical vein open up, leading to the Cruveilhier-Baumgarten syndrome (caput medusae) bringing blood from the left branch of the portal vein to the periumbilical venous system).

During fetal life, the liver functions mainly as a hematopoietic function, beginning around the second month and reaching a maximum around the seventh month. At birth, the main metabolic functions of the liver are present but are still immature. Hence, bilirubin conjugation, which occurs via the enzyme glucuronyltransferase, is not yet fully functional; in this case, unconjugated bilirubin will accumulate in the plasma and be responsible for jaundice in the newborn.

8.4 Hepatic Catabolism

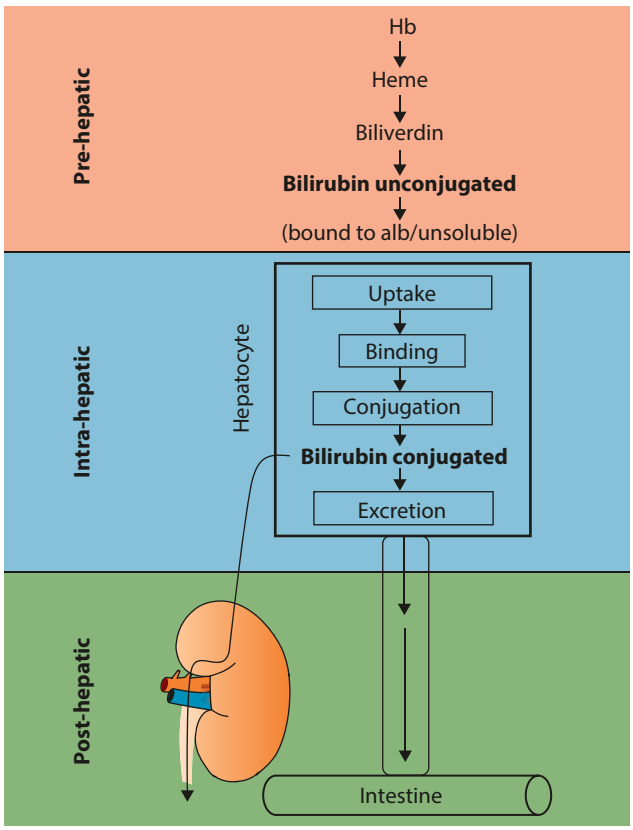
The liver plays a vital role in bodily homeostasis. The liver can be viewed simplistically as a factory that metabolizes many substances transported via the portal vein (70–75% of the hepatic output) from the intestine (e.g., absorbed nutrients or drugs) or via the hepatic artery from extra-digestive tissues (e.g., toxic waste such as bilirubin, urea, or injected drugs) and that produces new compounds useful to the body (e.g., albumin, clotting factors, etc.). The catabolic and synthetic functions of the liver can affect not only the digestive system but all organs.

8.4.1 Heme-Bilirubin

The metabolism of bilirubin is the most obvious and best-known example of the process of catabolism and synthesis exerted by the liver. This is the most complex biological process, and an appreciation of how this process occurs is of prime importance for understanding and managing icterus (jaundice).

Bilirubin is a yellow pigment that is a waste product from the metabolism of heme. It has, in humans, a remarkable path, starting in senescent red blood cells and ending in the stool. During this journey, the original pigment, heme, is progressively transformed into fat-soluble bilirubin, which is made water-soluble through conjugation in the hepatocyte, and is then excreted in bile into the intestine. The initial red pigment, heme, changes color several times, from green (biliverdin), to yellow (bilirubin), to "white" (colorless urobilinogen), to orange (urobilin that colors urine), and finally to brown (stercobilin that colors stool).

The metabolism of bilirubin takes place in several stages (◘ Fig. 8.9), each of which can be altered, leading to an increase in blood bilirubin levels and hence



◘ **Fig. 8.9** Bilirubin metabolism: prehepatic, hepatic, and posthepatic stages

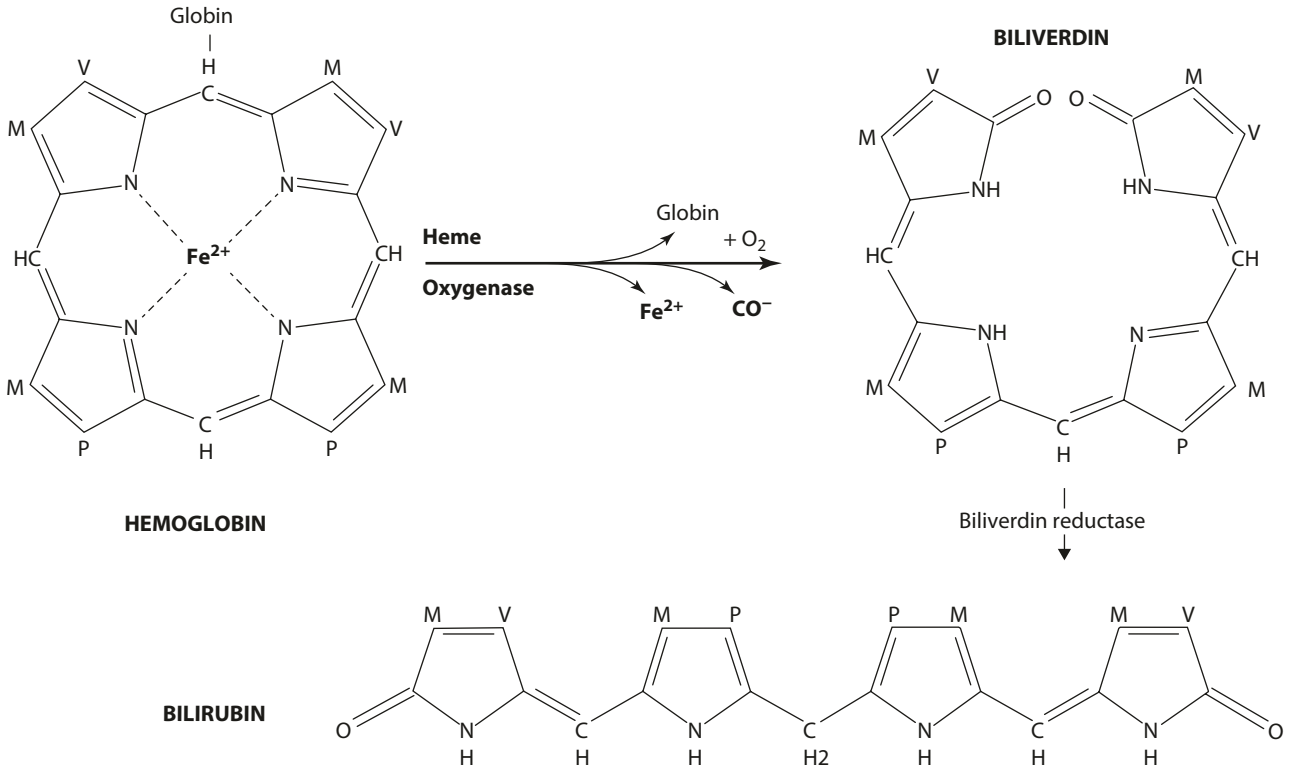


Fig. 8.10 Hemoglobin is destroyed within the reticuloendothelial system and transformed into bilirubin (unconjugated), which circulates in blood bound to albumin

jaundice. The clinical approach to jaundice is discussed in ▶ Chap. 27. Here we will review the physiology and pathophysiology of bilirubin metabolism.

(a) Formation of bilirubin (prehepatic process) Heme comes from the breakdown of hemoglobin in senescent red blood cells destroyed within the reticuloendothelial system (80%) and from myoglobin, cytochromes, and catalases (20%). Heme, with its iron molecule, is a red pigment. In the reticuloendothelial system of the spleen and hepatic Kupffer cells, the enzyme heme oxygenase catalyzes the opening of the heme nucleus, releasing iron and producing biliverdin (a green pigment). Biliverdin reductase then converts biliverdin into bilirubin (yellow pigment) (Fig. 8.10).

This form of bilirubin, called nonconjugated or indirect bilirubin, is a nonpolar compound and therefore is not soluble in water. Unconjugated bilirubin is potentially toxic (especially to the brain) at high concentrations and is transported in plasma bound to albumin, preventing it from entering other tissues such as the brain and kidney.

An increase in unconjugated bilirubin production (which can lead to mild to moderate jaundice) occurs with any increase in red blood cell destruction, particularly during hemolysis (hemolytic anemia) or during resorption of large hematomas. Unconjugated hyperbilirubinemia can also occur when certain albumin ligands compete for the same transport site used to bind unconjugated bilirubin. These compounds (in particular, nonsteroidal anti-inflammatory drugs, sulfonamides, and some anticoagulants) can displace unconjugated bilirubin, thereby preventing it from reaching hepatocytes for further metabolism.

(b) Transformation of unconjugated bilirubin (hepatic process) Unconjugated bilirubin is transported in plasma bound to albumin (and therefore cannot be eliminated as such into urine). At the surface of the hepatocyte sinusoidal membrane, unconjugated bilirubin separates from albumin and enters the hepatocyte where it is converted to conjugated (or direct) bilirubin in several steps, each of which can lead to a disorder resulting in jaundice (Fig. 8.11):

1. *Bilirubin uptake* and entry into the hepatocyte are achieved by simple diffusion or by a facilitated transport mechanism involving the OATP-1 (organic anion transporting polypeptide) transporter.

   Some drugs such as rifampicin or flavaspidic acid (contained in medicinal plants) can interfere with the transporter and cause unconjugated hyperbilirubinemia. This mechanism has also been suggested as a partial explanation for Gilbert's syndrome (see below).

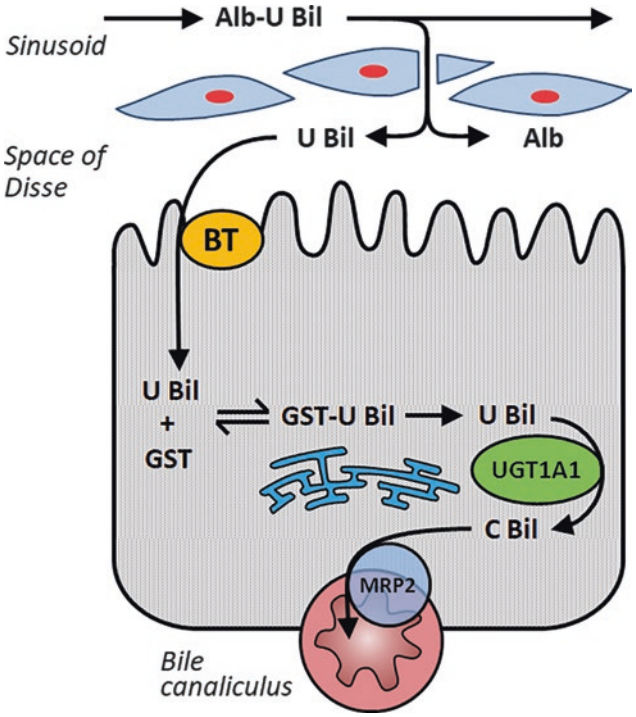


Fig. 8.11 Hepatocyte bilirubin pathway in four steps: **a** unconjugated bilirubin (UCbil) is taken up at the hepatocyte sinusoidal membrane and enters the hepatocyte via a transporter (BT) and **b** then binds to cytosolic proteins (glutathione S-transferase, GST), **c** to reach the endoplasmic reticulum where it is enzymatically conjugated (by glucuronyltransferase, GT) to glucuronic acid to become conjugated bilirubin (Cbil), **d** which is finally excreted by a transporter through the hepatocyte membrane into the bile duct

2. *Intracellular binding* of bilirubin to glutathione S-transferase allows unconjugated bilirubin to travel into the cytosol.

   Intracellular binding by glutathione S-transferase can be disrupted by certain drugs and cause unconjugated hyperbilirubinemia.
3. *The conjugation of bilirubin* to glucuronic acid is critical. It occurs in the endoplasmic reticulum by means of the enzyme BRB-UGT1A1 (bilirubin-uridine-diphospho-glucuronate-glucuronyltransferase A1), which conjugates several substrates, including drugs, to glucuronic acid. This process renders bilirubin more water-soluble.

   Disruption of glucurono-conjugation of bilirubin (leading to unconjugated hyperbilirubinemia and, potentially, jaundice) can occur in many situations:
   - Neonatal jaundice: Most newborns experience unconjugated hyperbilirubinemia due, among other things, to a quantitative insufficiency of glucuronyltransferase in the still immature liver, especially in premature infants. Jaundice in infants is usually mild and transient. In more severe cases, phototherapy is used. This treatment exploits the effect of blue light (460–490 nm) on unconjugated bilirubin. Several photochemical reactions generate stereoisomers of bilirubin (Fig. 8.12) and other derivatives which can then be excreted in the bile or urine without the need for conjugation by the liver.
   - Gilbert's syndrome refers to a benign unconjugated hyperbilirubinemia that affects 5–8% of the population. Familial transmission is autosomal recessive with variable expression. Glucuronyltransferase activity is decreased (30%), and there is also, in some individuals, a defect in the uptake of unconjugated bilirubin by hepatocytes. These individuals (6 males to 1 female) are normal and asymptomatic. There is no hemolysis (normal blood count); liver tests are normal (AST, ALT, alkaline phosphatase). There is no liver injury, and the liver biopsy (which is never done) is normal. Total bilirubin is slightly elevated, usually in the range of 17–85 µmol/L (normal <17 µmol/L), with an increase in unconjugated bilirubin alone. Fasting can increase bilirubin levels; glucuronyltransferase-inducing drugs, such as phenobarbital, can decrease it. Genetically, a dinucleotide thymine and adenine are inserted into the TATA box of the UGT1A1 gene.
   - The Crigler-Najjar syndrome is fortunately extremely rare. It is a very severe unconjugated hyperbilirubinemia, incompatible with prolonged survival without liver transplantation. Glucuronyltransferase activity is either absent (in type 1) or greatly diminished (in type 2). The infant presents with deep jaundice and very high levels of unconjugated bilirubin. Kernicterus is a neurological complication of severe unconjugated bilirubin (>350 µmol/L) and is typically seen in type 1 Crigler-Najjar. It is characterized by deafness, oculomotor paralysis, ataxia, choreoathetosis, mental retardation, convulsions, spasticity, and death and results from the neurotoxicity of unconjugated hyperbilirubin. Treatment involves phototherapy while awaiting liver transplantation.
   - Some drugs interfere with UGT1A1 [in particular atazanavir and indinavir (used for the treatment of HIV) and gemfibrozil (a hypocholesterolemic)] and are responsible for jaundice with unconjugated hyperbilirubinemia.

   The majority of the cytosolic conjugated bilirubin is normally directed to the canalicular pole of the hepatocyte as presented in the section below. However, some conjugated bilirubin can be secreted into the blood at the sinusoidal pole, before being reabsorbed by the OATP-1 transporter. This can result from a deficiency in a

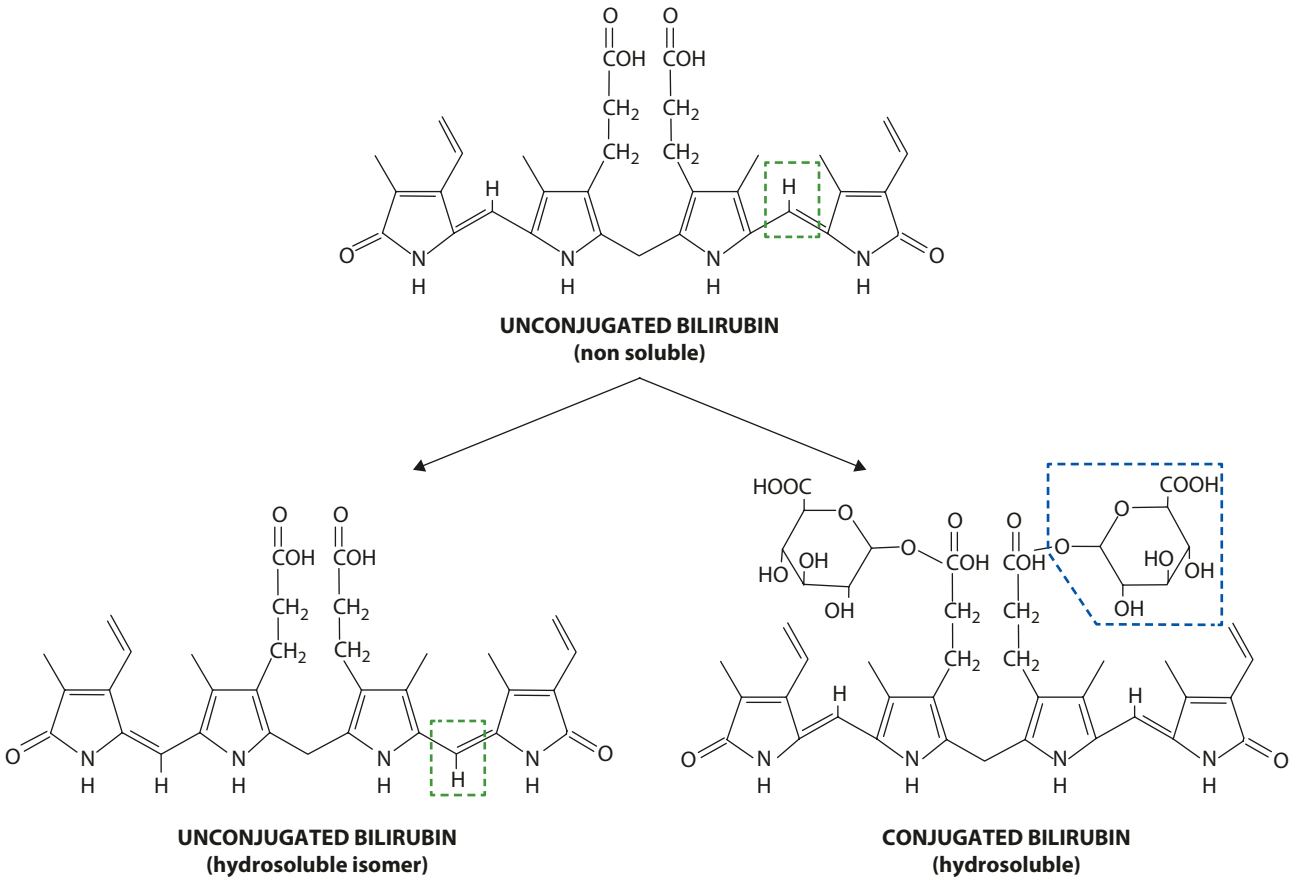


Fig. 8.12 Unconjugated bilirubin is non-soluble; therefore, it is not excretable in water, and its accumulation is toxic. Unconjugated bilirubin is made soluble by conjugation with glucuronic acid (conjugated bilirubin) or modified into a water-soluble isomer by blue-light phototherapy

protein responsible for the hepatocellular storage of conjugated bilirubin that, then, leaks into plasma. Such defects appear to explain the rare familial Rotor syndrome, characterized by a moderate and benign accumulation of conjugated and unconjugated bilirubin.

4. *Transport and excretion of conjugated bilirubin* occur at the hepatocyte canalicular membrane due to an ATP-dependent mechanism involving the canalicular transporter cMOAT/MRP2/ABCC2 (multispecific organic anion transporter, also called multidrug resistance protein 2, or ATP-binding cassette C2).

Disturbances in the transport and excretion of conjugated bilirubin into the bile canaliculus are frequent and can lead to hyperbilirubinemia:

- This is the main mechanism of jaundice in viral hepatitis, alcoholic hepatitis, some drug-induced causes of hepatitis, or cirrhosis.
- Dubin-Johnson syndrome is a rare, benign familial conjugated form of hyperbilirubinemia of autosomal recessive transmission. The defect is located in the expression of the canalicular bilirubin transporter CMOAT/MRP2/ABCC2. Blood conjugated bilirubin levels are usually between 35 and 85 µmol/L but can reach 400 µmol/L with impressive jaundice in a completely asymptomatic individual. Urine is dark, colored by conjugated bilirubin. Liver tests are normal. The liver often has a black pigmentation due to the accumulation of a pigment derived from adrenaline metabolism.

(c) Bilirubin in bile and intestine (posthepatic process) Conjugated bilirubin is found in the bile canaliculus and then in the biliary tree on its way to the intestine. Being water-soluble, conjugated bilirubin cannot be absorbed by the lipid membranes of the small intestine. Certain bacterial enzymes, such as b-glucuronidases, reduce bilirubin to urobilinogen (20%) and stercobilinogen (80%) which are colorless. Part of the urobilinogen is absorbed by the intestine and, after transformation into urobilin, is found in the urine, giving it an amber coloration. Stercobilinogen undergoes reoxidation to stercobilin, which is responsible for the brown color of the stool.

Any mechanical obstructions in the bile ducts, intra- or extrahepatic, will lead to conjugated (often mixed)

hyperbilirubinemia. In cases of complete biliary obstruction, the stools are no longer colored (mastic-colored acholic stools). The main causes of obstructive jaundice are gallstones, cancer of the bile ducts or pancreas, and surgical trauma to the bile ducts. Sclerosing cholangitis, whether or not associated with inflammatory bowel disease, should also be considered. In obstructive jaundice, serum alkaline phosphatase is typically increased, and transaminases are low. Abdominal ultrasound usually shows dilated bile ducts. Additional imaging techniques such as magnetic resonance cholangiography, endoscopic retrograde cholangiography (ERCP), transhepatic cholangiography, or endoscopic ultrasound (EUS) can help localize the level of obstruction. The treatment is the removal of the blockage of bile flow, whenever possible.

The clinical, diagnostic, and therapeutic approach to hyperbilirubinemia is discussed in the ▶ Chap. 26 in the second part of the book.

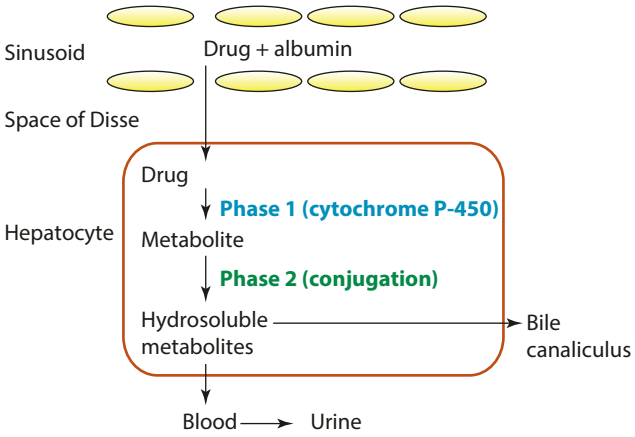
8.4.2 Urea-NH_4^+

Nitrogen is a constituent of all amino acids. When these are broken down, the nitrogen atom cannot be reused and must therefore be eliminated from the body. The liver is the main site of amino acid degradation. These are first transaminated to form glutamate which is then deaminated by releasing an ammonium ion (NH_4^+). The ammonium ion (or ammonia, NH_3, in its unionized form) is toxic to the brain and causes encephalopathy if it accumulates in excessive amounts. Ammonia is therefore rapidly converted, via the urea cycle, into urea (NH_2-CO-NH_2) which is then eliminated in the urine. The urea cycle (or Krebs/Henseleit cycle) depends on four enzymes: enzyme deficiencies have been described for each of these enzymes, which lead to states of congenital hyperammonemia (see ▶ Sect. 8.9 Function Disorders).

Hyperammonemia is most often found as a complication of cirrhosis with portal hypertension. In this situation, hyperammonemia is due to a decrease in the capacity of the liver to eliminate ammonia. The decrease in muscle mass commonly observed in cirrhotic patients also leads to a decreased capacity to detoxify ammonia in the periphery.

8.4.3 Drugs

The liver plays a central role in the elimination of fat-soluble compounds. Liposolubility allows drugs to be absorbed by passive diffusion through the cell membrane of the digestive epithelium. Once absorbed, the drugs need to be biotransformed by the liver into water-soluble metabolites that can then be eliminated in the urine or bile (◘ Fig. 8.13).



◘ **Fig. 8.13** Liver metabolism of drugs

There are two types of drug biotransformation reactions. In phase 1 reactions, drugs are oxidized (by cytochrome P450) into products that are usually inactive or less active than the parent substance (but some may be activated, e.g., clopidogrel). Phase 2 reactions consist of conjugation of the drug or metabolite with glucuronic acid, glutathione, or sulfate groups. Most often, drugs are biotransformed by phase 1 and then phase 2 reactions, but some drugs are eliminated directly by phase 2 reactions only (e.g., benzodiazepines such as oxazepam or lorazepam).

In some cases, hepatic biotransformation will not be used for the inactivation of a pharmacotherapeutic molecule, but rather for its transformation into an active metabolite. This is the case, for example, with clopidogrel, a prodrug that can only express its antiplatelet function after biotransformation into an active metabolite by CYP2C19. The liver also transforms prednisone into its active form prednisolone, codeine into morphine, or azathioprine into 6-mercaptopurine.

Cytochrome P450s (CYPs) are hemoproteins located in the endoplasmic reticulum of the liver. They use oxygen to generate oxidation or hydroxylation reactions. CYPs are a superfamily of enzymes. In humans, about 20 families of CYPs have been identified, but the specific families 1, 2, and 3 are responsible for drug metabolism (CYP1, CYP2, and CYP3). Within each family, subfamilies are identified by a capital letter (i.e., 3A, 2C, 1A) and individual members of a subfamily by a number (i.e., CYP2C9, CYP3A5). CYP3A4 and CYP3A5 are responsible for the metabolism of approximately 50% of drugs currently used in clinical practice.

Each CYP can metabolize multiple drugs, which can lead to competition for the metabolism of co-administered drugs. For example, cimetidine and omeprazole, which

are metabolized by CYP2C19 (which also metabolizes warfarin), may therefore slow the catabolism of the anticoagulant and increase INR values.

Several CYPs are influenced by genetic polymorphisms. For example, approximately 5% of Caucasians and 20% of Asians have decreased CYP2C19 activity (i.e., slow metabolizers), which may lead to increased omeprazole efficacy.

Some drugs may specifically increase the concentration and activity of a CYP (inducers), while others may inhibit their activity. For example, phenytoin induces CYP3A4, while ketoconazole inhibits it. These phenomena are responsible for drug interactions that are often difficult to manage.

In vivo, some drugs are extensively and rapidly metabolized by the liver (high hepatic extraction), while others are less so (low hepatic extraction). When a drug with high hepatic extraction (e.g., propranolol) is administered orally, a significant fraction of the dose will be eliminated by the liver before reaching the systemic circulation. This is called the "first-pass effect." For drugs with low hepatic extraction (e.g., metronidazole), the plasma concentrations of the drug will be similar after oral or intravenous administration (i.e., no first-pass effect). Obviously, drugs that are poorly metabolized by the liver will have their pharmacological profile less influenced in cases of liver disease (cirrhosis, etc.).

8.4.4 Hormones

Many hormones are metabolized by the liver. Serotonin, a hormone secreted by enterochromaffin cells of the intestine, is metabolized in the liver to 5-hydroxyindoleacetic acid (5HIAA), which can be measured in the urine of people with carcinoid tumors. The metabolism of serotonin during its passage through the liver is thought to explain the rarity of the carcinoid syndrome (diarrhea, flushing, etc.) in patients with a carcinoid tumor limited to the intestine and not metastatic to the liver. Many hormones produced in the digestive tract, such as gastrin secreted from the stomach, also undergo hepatic catabolism.

However, the disruption of hepatic metabolism is not the exclusive cause of hormonal alterations in cirrhotic subjects. The decrease in testosterone levels is explained by a decrease in testicular production, while the rise in estrogen is explained by an increase in peripheral production.

8.4.5 Lactic Acid

The liver has the ability to regenerate lactate produced by the incomplete metabolism of glucose in muscles: this is called the Cori cycle. Lactate is then converted back into glucose, which can be used by the liver or exported to other organs. It is estimated that the liver removes 50–70% of the lactic acid produced daily. Lactic acidosis is frequently observed in cirrhotic patients in hypovolemic or septic shock. Lactic acidosis can also occur independently of the hemodynamic status in acute severe liver failure, in which the presence of lactic acidosis is a negative prognosticator.

8.5 Hepatic Synthesis

The liver functions not only in a catabolic role but also includes the synthesis activity (anabolism) of several substances.

8.5.1 Proteins

Albumin is the most abundant protein in plasma. It is synthesized exclusively by hepatocytes in adults. The main functions of albumin are to act as an osmotic agent and to bind (and therefore transport) various endogenous substances (bilirubin, fatty acids, T4, ions, etc.) and drugs. When bound to albumin, these compounds are biologically inactive.

Alpha-fetoprotein is the protein analogue of albumin during the fetal period. It is found in the blood of pregnant women (in which case it is of fetal origin), in certain embryonic tumors (teratomas, choriocarcinomas, testicular tumors), and in malignant liver tumors (hepatocarcinoma, hepatoblastoma) and when the liver is the site of intense regenerative activity (e.g., in the case of viral hepatitis).

Haptoglobin binds to the free hemoglobin produced by hemolysis. The haptoglobin/hemoglobin complex is then degraded by cells of the reticuloendothelial system. Low haptoglobin levels are a sign of increased hemolysis. However, decreased hepatic synthesis of haptoglobin is frequently observed in individuals with liver disease, resulting in lower haptoglobin levels in the absence of hemolysis.

Transthyretin is also produced by the liver. This protein is used to transport thyroxine and retinol. Blood levels of this protein are often used to assess a patient's nutritional status. However, it should be noted that levels of this protein are affected by liver disease, regardless of the nutritional status of the patient.

Ferritin is the main protein that stores iron, which mainly takes place in the liver. Ferritin is synthesized by hepatocytes. Increased ferritin levels are frequently observed in the context of liver disease, particularly in states of overload (hemochromatosis), chronic inflammation and in the presence of liver cell injury (in which case, ferritin is released from hepatocytes).

Coagulation proteins are all synthetized within the liver, except for von Willebrand factor and factor VIIIc.

This synthesis takes place in the hepatocytes. Importantly, not only procoagulant factors are synthesized by the liver but also the anticoagulant factors such as antithrombin III, protein C, protein S, etc.

Half-life of clotting factors varies from one to another and can sometimes be very short. The INR, commonly used as an indicator of coagulation factors' activity, is prolonged early in the setting of liver failure. However, the INR is a poor indicator of the actual overall coagulation status of patient with liver failure since it does not take into account the deficit in liver production of anticoagulant factors mentioned above.

Coagulation factors II, VII, IX, and X are considered to be vitamin K-dependent because vitamin K is required as a cofactor for the enzymatic activity of the carboxylase important for the activity of these factors. Vitamin K is a lipid-soluble vitamin whose absorption requires the presence of a sufficient amount of bile in the digestive tract. In the presence of cholestasis and associated impaired bile flow, less vitamin K is absorbed, which decreases the activity of the vitamin K-dependent coagulation factors II, VII, IX, and X and lengthens INR. Parenteral administration of vitamin K is often used to differentiate between INR prolongation caused by cholestasis and that caused by liver failure (in which vitamin K administration does not correct INR).

Fibrinogen is also manufactured by the liver. It is the essential substrate of the protein portion of a blood clot. Fibrinogen is converted into fibrin monomers by thrombin; factor XIII then polymerizes fibrin. Fibrinogen levels only become low in patients with end-stage liver failure.

Inflammation proteins also originate in the liver. The liver responds to the presence of inflammation (even when located outside the liver) by secreting a variety of proteins known to be markers of inflammation [such as tumor necrosis factor alpha (TNF-a), C-reactive protein, and heat shock proteins (HSP) produced by liver macrophages]. When the liver begins to secrete these proteins, it goes to a state that makes it less able to perform its usual functions (e.g., albumin synthesis is reduced).

8.5.2 Hormones and Pro-hormones

Several hormones or pro-hormones are synthesized by the liver. Among the most important are IGF-1, angiotensinogen, hepcidin, and thrombopoietin.

IGF-1, formerly known as somatomedin, is synthesized by the liver in response to stimulation by growth hormone (synthesized in the pituitary). IGF-1 levels are decreased in patients with cirrhosis.

Angiotensinogen is the precursor of angiotensin II, a hormone that is very important in the regulation of vascular tone. Angiotensinogen levels are not altered significantly by cirrhosis, but the renin-angiotensin system is overactivated as a component of vascular dysfunction commonly occurring in cirrhotic patients.

Hepcidin is a central hormone in the regulation of iron metabolism. It is synthesized in response to iron overload (iron is mainly stored in the liver) and during systemic inflammation. This leads to a decrease in intestinal iron absorption.

8.5.3 Bile Salts

Bile salts (see ▶ Chap. 6) only constitute a small proportion of the bile (1% of hepatic bile and 6% of bile concentrated in the gallbladder). They are made from cholesterol through hydroxylation via cholesterol-7-hydroxylase, the key enzyme in the synthesis of bile salts. Once conjugated with amino acids (either glycine or taurine), they become bile acids. Conjugation improves the solubility of these compounds, allowing them to form micelles (essential for lipid absorption) in the duodenum.

Bile salts produced by the liver are called "primary" bile salts: cholic and chenodeoxycholic acids which represent 80% of the total bile acid pool. Released in the intestine, bile acids can be transformed by bacterial dehydroxylation to become secondary bile acids: the most important are deoxycholic acid and lithocholic acid, which can be reabsorbed at the terminal ileum as part of the enterohepatic circulation of bile acids. Once reabsorbed, these secondary bile acids can undergo further transformation into tertiary bile acids, the most well-known of which is ursodeoxycholic acid (used as a drug to dissolve gallstones or to treat chronic cholestasis, such as in primary biliary cholangitis, because of its increased water solubility and reduced hepatotoxicity).

8.5.4 Cholesterol

Cholesterol is an essential component of cell membranes and bile salt synthesis. Blood levels of cholesterol, which are important in determining the risk of atherosclerosis, are determined by the dietary intake (20%), by intestinal reabsorption (20%), and, mainly, by de novo synthesis, the majority of which occurs in the liver (with a lesser proportion in the kidneys and other tissues). Cholesterol formation in the liver is dependent on compounds derived from the Krebs cycle (acetyl-CoA and acetoacetyl-CoA) and an enzyme, HMG-CoA reductase, which is expressed in hepatocytes and produces

mevalonic acid that provides the carbon atoms rings that make up cholesterol. There are several drugs that inhibit this enzyme activity and reduce serum cholesterol levels (statin drugs).

8.5.5 Glucose, Lipids, and Amino Acids

The liver is a key organ in energy metabolism. Located at the crossroads of the digestive system and systemic circulation, it receives compounds (nutrients, drugs, etc.) newly absorbed by the intestine and hormones secreted by the digestive glands into the portal blood. Hepatocytes are equipped with enzymatic systems for the conversion of amino acids and lipids into glucose (gluconeogenesis) and also for the conversion of sugars into lipids (lipogenesis) for possible export and storage in adipose tissue (◘ Fig. 8.14).

(a) Carbohydrates Carbohydrates are absorbed by the intestine in the form of monosaccharides (glucose, fructose, or galactose). Fructose and galactose are mainly metabolized in the liver, converting them into glucose or metabolizing them through glycolysis. Deficiency in the main enzyme of galactose metabolism (mainly expressed in the liver) causes congenital galactosemia, a cause of hereditary cirrhosis.

Glucose can be metabolized by almost all tissues and is the sole source of energy for erythrocytes and the brain in a normal state. Absorbed by the intestine, glucose transits through the portal vein. When the portal vein glucose concentration rises above 10–15 mM, the affinity of glucose for the GLUT2 transporter increases enormously and promotes the entry of glucose into hepatocytes. In total, 35–50% of dietary glucose is metabolized by the liver. The remaining dietary glucose is either used as an energy source (e.g., by the brain) or to replenish tissue glycogen stores (e.g., in the muscle).

Glucose absorbed by hepatocytes can:

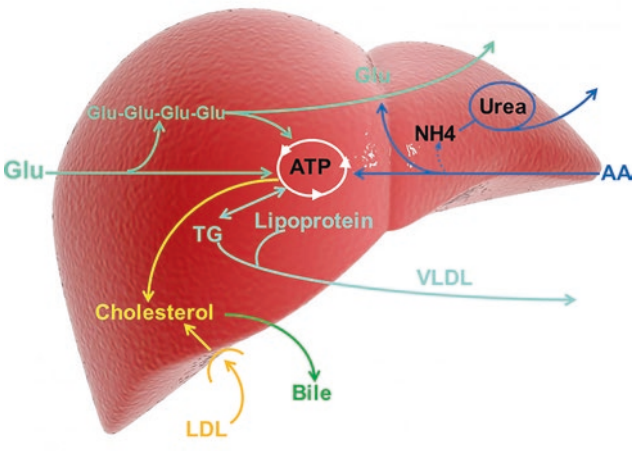
- Be transformed (glycogenosis) and stored as glycogen (chain of glucose molecules linked together by 1–4 bonds and with side chain branches through 1–6 bonds)
- Be used for glycolysis (transformation via the Embden-Meyerhof pathway of glucose into pyruvic acid which will be integrated into the Krebs cycle for the production of ATP which is essential for cellular energy)
- When excess, lead to the formation of fatty acids (section below on lipids)

In fasting states (i.e., during sleep or between meals), the liver becomes a very important source of glucose for peripheral tissues. This is achieved through the release of glycogen from liver stores (75%) and gluconeogenesis (i.e., the ability of the liver to form glucose from lactate, amino acids, or glycerol derived from fatty acids). It is estimated that the liver alone constitutes more than 25% of the body's glucose reserves. In severe acute liver failure, hypoglycemia may occur due to the loss of hepatocyte glycogen stores and hepatic gluconeogenic capacity.

(b) Lipids Lipids can be found in hepatocytes either because they are newly formed from other energy sources, such as glucose or alcohol, or because they are absorbed by the liver as chylomicron residues.

"Endogenous" fatty acids are mainly synthetized by the liver from carbohydrates (called de novo synthesis), taking place in the hepatocyte cytosol in a state of abundant acetyl-CoA (produced during excess glucose). Acetyl-CoA is first metabolized to malonyl-CoA which, following a series of reactions including elongations via the FAS enzyme (fatty acid synthase), leads to the synthesis of palmitate (16-carbon fatty acid). Once synthesized, three fatty acids bind to a glycerol molecule to form triglyceride. Normally, the liver exports triglycerides to the periphery using very-low-density lipoproteins (VLDL) formed within the endoplasmic reticulum of the hepatocytes through the addition of triglycerides, proteins (apolipoproteins B100, C1, and E), and cholesterol to the molecule. The accumulation of triglycerides within the hepatocytes can lead to steatosis.

Dietary fatty acids are not metabolized by the liver. They are transformed in enterocytes into triglycerides and packaged in chylomicrons so that they pass into the lymph (in addition to triglycerides, which make up 90% of their mass, chylomicrons contain apolipoproteins A,



◘ **Fig. 8.14** Liver metabolism of carbohydrates, amino acids, and lipids

B, C, and E, cholesterol, and phospholipids). Triglycerides within the chylomicrons in peripheral blood are released by the action of lipoprotein lipase found on the surface of vascular epithelia, particularly in skeletal striated muscles and cardiac muscle (due to their high energy requirements) and in adipose tissue (so that they can be stored). Fat lipoprotein lipase is used to hydrolyze triglycerides in fatty tissue when these energy stores need to be used. Fatty acids released from the fat tissue bind to albumin and are transported to other tissues. The action of lipase releases a glycerol molecule that can be used by the liver for glycolysis, gluconeogenesis, or the formation of new triglyceride molecules.

(c) Amino acids Amino acids are deaminated in the liver by producing $NH4^+$ which is then used in the urea cycle.

Liver functions of metabolism and catabolism are summarized in ◘ Table 8.2.

8.6 Inflammation Disorders

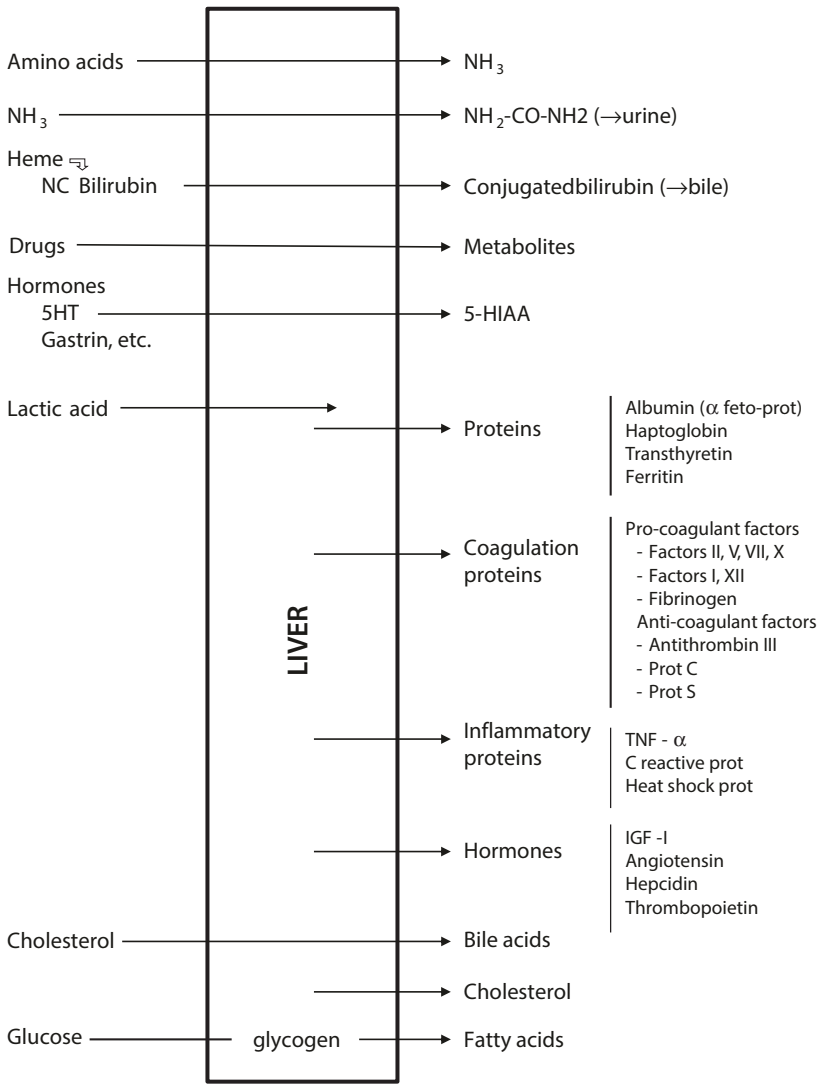
This section on inflammation disorders will contain three parts: (1) acute hepatitis, (2) chronic hepatitis, and (3) cirrhosis, an end-stage complication of inflammation damage to the liver.

8.6.1 Acute Hepatitis

Acute hepatitis is an acute inflammation of the liver, taking place mostly in a patient with no history of liver disease, which heals without leaving any identifiable sequelae.

Acute hepatitis is an inflammatory disorder of the liver, taking place mostly in a patient with no history of liver disease, jaundice being the main mode of presentation. It can heal without leaving any identifiable sequelae,

◘ **Table 8.2** Hepatic metabolism and catabolism



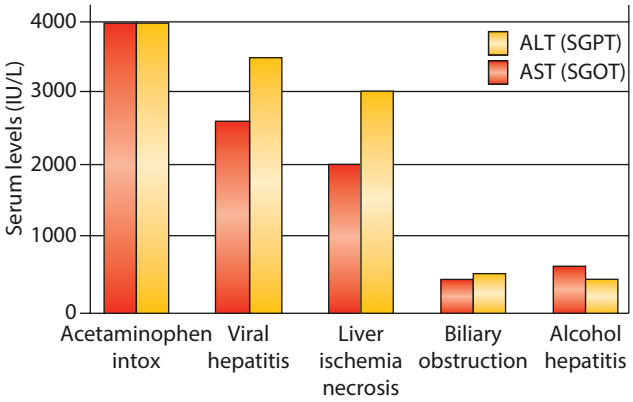


Fig. 8.15 Severity of cytolysis in various clinical situations

progress rapidly to liver failure, or lead to the development of chronic liver disease.

Pathology The predominant site of inflammation can vary within the hepatic acinus:

- When inflammation is found in the liver lobule, it creates hepatocyte damage which leads to cell lysis: this increases ALT and AST into circulation due to the breakdown of the membrane integrity of hepatocytes. This occurs in the majority of cases of acute hepatitis. The severity of cytolysis may help identify the etiology of the disorder (Fig. 8.15), but is not related to the risk of liver failure.
- When the predominant inflammation is found around the bile ducts, this results in a disruption of bile flow and cholestasis characterized by elevation of serum alkaline phosphatase levels, an enzyme found on the canalicular pole of hepatocytes and in bile ducts. This is known as cholestatic hepatitis. Examples are infectious mononucleosis hepatitis, certain forms of acute hepatitis A, alcoholic hepatitis, and certain drug-induced hepatitis.

As the legend of Prometheus taught us, the liver is an organ that can regenerate when cell loss is acute. Normally, hepatocytes are kept in the G0 phase of the cell cycle and rarely divide. In case of hepatectomy or liver cell damage, signal proteins will stimulate quiescent hepatocytes to enter the cell cycle. The stimulation of the replication will last as long as the liver has not reached its original cell mass. In acute self-limiting hepatitis, the liver recovers completely.

Clinical presentation of acute hepatitis The clinical presentation of acute hepatitis is highly variable and does not point toward a specific etiology. Hepatitis can be asymptomatic and, then, can only be identified through abnormal liver tests. When hepatitis is symptomatic, it can be icteric (with cutaneous and scleral jaundice, dark urine, and pale stools in case of a cholestatic component) or non-icteric. The clinical syndrome can also include fatigue, anorexia, malaise, pain/discomfort in the right hypochondrium, and, in the case of viral hepatitis, a flu-like syndrome (fever, myalgia, arthralgia, and sometimes diarrhea).

Depending on the severity and duration of hepatic injury, acute hepatitis can be complicated by (1) impairment of bilirubin excretion (mixed conjugated and unconjugated hyperbilirubinemia); (2) impairment of the synthetic functions of the liver, particularly clotting factors (decrease in factors II, V, VII, IX, and X and increased INR) and albumin; and (3) a decrease in the capacity to detoxify ammonia leading to hepatic encephalopathy clinically manifested by asterixis and impaired consciousness.

Fulminant hepatitis is defined as acute hepatitis of such severity that it leads to the development of liver failure and hepatic encephalopathy and impairment of the synthetic functions of the liver (e.g., coagulation) in the absence of underlying chronic liver disease. Hyperacute, acute, and subacute fulminant hepatitis can be distinguished according to the time between the onset of jaundice and the onset of encephalopathy. When hepatic encephalopathy occurs within 4 weeks of the onset of jaundice, it is called acute fulminant hepatitis. Acute fulminant hepatitis was once associated with a mortality risk of almost 80% without liver transplantation. With current advanced patient management, survival is now 60% of patients (even without liver transplantation in half of the cases). Patients with hyperacute hepatic failure (development of encephalopathy within 7 days of the onset of jaundice) have a higher risk of cerebral edema but a better chance of survival without liver transplantation. On the other hand, patients with subacute liver failure (development of encephalopathy within 4–12 weeks after the onset of jaundice) are more likely to present with ascites and portal hypertension and have a lower chance of survival without liver transplantation.

Etiology of acute hepatitis There are four main etiologies of acute hepatitis: (1) viral hepatitis, (2) toxic hepatitis, (3) autoimmune/metabolic hepatitis, and (4) vascular causes. However, in about 15% of cases, the cause remains unknown.

8.6.1.1 Viral Hepatitis (A, B, C, D, E, and Other Viruses)

Acute viral hepatitis can involve two categories of viruses:

- Viruses with *hepatic tropism*: hepatitis A, B ± D, C, and E
- *Systemic viral agents* that can cause liver damage as part of broader systemic disease, such as herpes

viruses [herpes simplex, varicella zoster, Epstein-Barr mononucleosis and cytomegalovirus (CMV), adenoviruses, parvovirus B19, enteroviruses, dengue virus]

(a) Acute hepatitis A Hepatitis A virus is an RNA virus and member of the *Picornaviridae* family of the genus *Hepatovirus*. Transmission is fecal-oral. Hepatitis A is mostly found in patients returning from travel to endemic areas but can be seen in limited epidemics in crowded conditions, in early childhood centers, in men who have sex with men, and in people who use drugs.

The incubation period is 2–6 weeks, and it is contagious until its peak in the 10 days preceding the onset of symptoms. Viral replication takes place in the liver, and the virus is excreted in bile before being passed in the stool. Clinical severity and the risk of developing an icteric form increase with age. Children are most often asymptomatic. Fulminant hepatitis is rare (<1/1000 cases). There is no transition to chronicity.

The *diagnosis* of hepatitis A is confirmed by a serum increase in IgM anti-HAV antibodies at the onset of the disease, followed by IgG anti-HAV antibodies (Fig. 8.16).

Supportive *treatment* is usually sufficient for managing patients with acute hepatitis A, which is usually self-limited and of moderate intensity. Progression to severe or fulminant hepatitis is very rare, observed more often in the elderly or those with significant underlying comorbidities.

Vaccination: Havrix®, Vaqta®, or Avaxim 160® vaccines specific to hepatitis A, or the Twinrix® vaccine effective against hepatitis A and B, are widely available and are very effective.

Relatives of patients suffering from acute hepatitis A should be vaccinated, ideally within the first 48 hours after contact, and receive a dose of specific anti-HAV immunoglobulins.

(b) Acute hepatitis B The hepatitis B virus is a DNA virus and member of the *Hepadnaviridae* family that can integrate into the host genome. It causes an acute, self-limiting infection in more than 98% of cases in adults (less than 1–2% transition to chronicity in immunocompetent adults). When acquired by vertical transmission at birth, the risk of chronicity is about 90%. In countries where universal vaccination against hepatitis B has been introduced, it has become a rare cause of acute hepatitis.

Transmission is (1) sexual, (2) through blood contamination (intravenous drug use, accidental injection, use of unsterilized medical equipment), (3) vertical (mother-to-child transmission), or (4) horizontal, person-to-person. The incubation period is approximately 4–20 weeks.

In acute hepatitis B, hepatocellular damage is caused by the host immune response. Hepatitis can be icteric or non-icteric. Inflammation and necrosis can be severe enough to lead to liver failure. In acute sympathetic hepatitis B, there is usually no transition to chronicity, and the liver recovers completely without treatment (see chronic hepatitis B below).

The *diagnosis* of acute hepatitis B is confirmed by blood tests revealing the presence of HBsAg and anti-HBc IgM antibodies (Fig. 8.17).

Supportive *treatment* is usually sufficient for this hepatitis, which is usually self-limited and of moderate intensity. When hepatitis is severe, which occurs in some

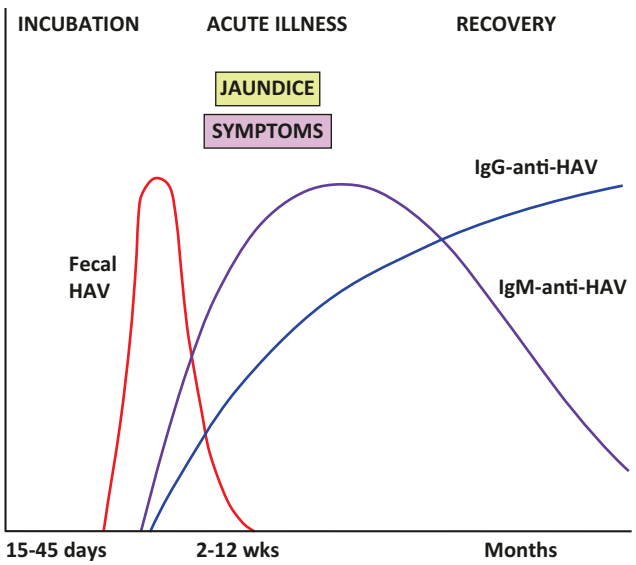


Fig. 8.16 Evolution of liver testing and serology in acute hepatitis A. (According to Robbins and Cotran. *Pathologic basis of disease*, 7th edition)

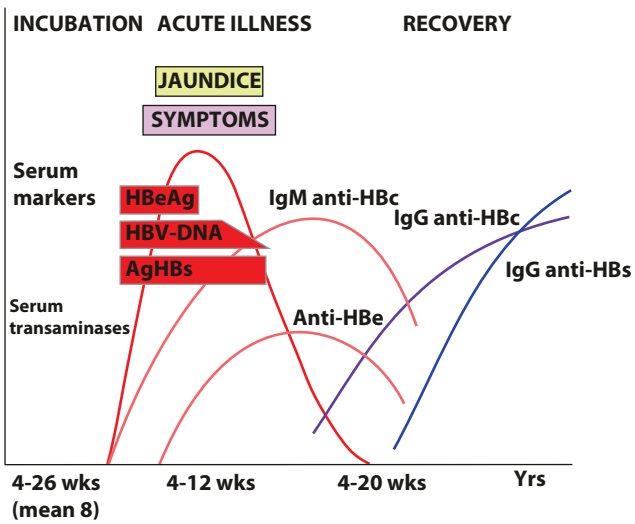


Fig. 8.17 Evolution of hepatic testing and serology in acute hepatitis B. (According to Robbins and Cotran. *Pathologic basis of disease*, 7th edition)

cases, antiviral treatment with entecavir or tenofovir is recommended.

Non-immune individuals who are in contact (unprotected sex, accidental needle stick, intravenous drug use) with a patient who is a carrier of acute or chronic hepatitis B need to be vaccinated with a hepatitis B-specific vaccine (Recombivax® or Engerix-B®) or a vaccine effective against hepatitis A and B (Twinrix®) and given hepatitis B hyperimmune immunoglobulins (HBIG) as soon as possible to prevent infection. HBIG is no longer recommended more than 14 days after exposure.

Vaccination against hepatitis A and B is recommended in any patient with chronic liver disease.

(c) Acute hepatitis D (hepatitis delta) The hepatitis D virus (HDV) is a 1700-nucleotide circular RNA virus, which is considered a satellite sub-virus (also called a viroid). It requires the hepatitis B replication apparatus. Furthermore, both HDV RNA and D antigen are coated with HBsAg. Acute hepatitis D occurs in co-infection with hepatitis B or in superinfection as it sometimes occurs in a chronic hepatitis B carrier. Co-infection is associated with an increased risk of fulminant hepatitis. In the case of co-infection, hepatitis delta resolves when hepatitis B is no longer active (HBaAg loss). Hepatitis delta cannot persist in the absence of chronic hepatitis B infection.

Diagnosis is made by detecting antibodies against the Delta virus (anti-HDV IgM type) and can be confirmed by the presence of HDV RNA.

(d) Acute hepatitis C Hepatitis C virus is an RNA virus of the *Hepaciviridae* family, discovered in 1989. The genome contains approximately 9600 nucleotides that code for a polyprotein of approximately 3000 amino acids composing structural (nucleocapsid, envelopes E1 and E2) and nonstructural proteins essential for replication, such as NS3-4A protease, NS5A protein, and NS5B polymerase (all three of these proteins are targets of antiviral agents). HCV is not directly cytopathic for hepatocytes; the disease is mediated by the host immune response. Viral replication takes place in the endoplasmic reticulum. The virus does not integrate into the host genome.

The incubation period is 2–16 weeks. Acute hepatitis C occurs primarily in the context of intravenous drug use or accidental needle stick injuries (65%). Sexual transmission is rare except in cases of co-infection with HIV. Drug snorting with shared straws is a recognized mode of infection. HCV infection is symptomatic in only 30% of cases and will progress to chronicity in about 70% of cases. Acute icteric presentation is associated with a better chance of spontaneous clearance.

Diagnosis is based on a positive HCV RNA assay, with or without anti-HCV antibodies (Fig. 8.18). RNA is detectable a few days after infection. Detection

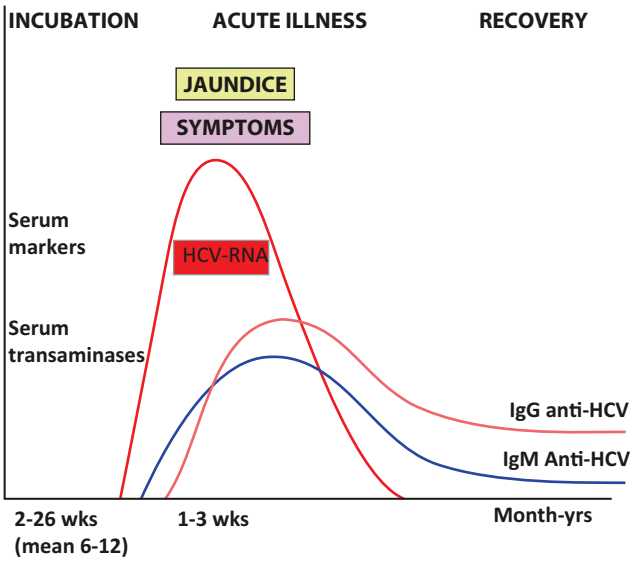


Fig. 8.18 Evolution of hepatic tests and serologies in acute hepatitis C. (According to Robbins and Cotran. *Pathologic basis of disease,* 7th edition)

of HCV RNA alone (without anti-HCV) indicates acute infection; the simultaneous presence of HCV RNA and anti-HCV indicates acute or chronic infection. In the presence of a highly suggestive clinical setting, despite negative tests, repeat testing for HCV RNA and anti-HCV must be performed.

Antiviral *treatment* with direct-acting antiviral drugs is recommended, as the time delay after onset of hepatitis is not clear. There is no vaccine against hepatitis C and no effective immunoglobulin in case of exposure. Universal precautions are recommended.

(e) Acute hepatitis E Hepatitis E is an RNA virus of the *Hepeviridae* family. Several genotypes have been identified. Infection is most commonly found in patients from countries at risk (North Africa, Southeast Asia, India, Mexico, the Middle East, and Pakistan). Europe and North America are considered low-endemicity areas. Contamination is fecal-oral, and outbreaks occur with the consumption of contaminated water. There is also an animal reservoir in pigs, wild boar, deer, swine, and perhaps other animal species.

The infection is usually self-limited, but, in pregnant women, a fulminant form occurs in 25% of cases. In 5% of cases, Guillain-Barré syndrome is associated with acute hepatitis E. There is no transition to chronicity except in immunocompromised (transplant, HIV) carriers of genotype 3.

Diagnosis is made by positive anti-HEV IgM antibodies and HEV RNA.

There is an effective recombinant hepatitis E vaccine developed in China (HEV 239 vaccine, Hecolin®), but it is not approved in Western countries.

(f) Acute hepatitis caused by systemic viral infection Several systemic viruses have the potential to induce liver damage in the context of viral illness, but hepatitis may be at the forefront. These agents include herpes viruses [herpes simplex, varicella zoster, Epstein-Barr infectious mononucleosis and cytomegalovirus (CMV), adenoviruses, parvovirus B19, and enteroviruses].

Acute herpes simplex hepatitis type 1 or 2 (and possibly HSV 6) in immunocompetent adults is rare but potentially fatal. Diagnosis is made by immunostaining of HSV or positive viral load on a liver biopsy. Typically, cytolysis is very important with ALT between 5000 and 10,000 IU/mL. Positive serum IgM antibodies to HSV are suggestive. Skin or mucosal vesicular lesions must be cultured, but are not always present. It is important to recognize this infection as it is treatable.

CMV hepatitis occurs mostly in immunosuppressed people but has been found in healthy subjects. Diagnosis is based on the presence of serum CMV viral load associated with IgM antibodies against CMV.

Epstein-Barr infectious mononucleosis is accompanied by hepatic cytolysis in 90% of cases and may be complicated by cholestatic jaundice in 5–7% of patients. Atypical lymphocytes, IgM-positive anti-VCA antibodies, and anti-EBNA are present.

There is no specific and recommended *treatment* for acute hepatitis caused by hepatotropic or systemic viruses except for very severe acute hepatitis B, hepatitis C, herpes simplex, and CMV hepatitis. Supportive treatment usually relieves symptoms and prevents complications. The disease is, in the vast majority of cases, self-limited. In rare cases of fulminant hepatitis, treatment may require a liver transplant.

8.6.1.2 Toxic Hepatitis (Drugs, Acetaminophen)

Toxic hepatitis can be caused by the intake of a toxic compound: medicinal drug (Table 8.3), natural product, recreational drug (cocaine, ecstasy, phencyclidine (PCP), anabolic steroids, ketamine, etc.), and mushrooms (from the Amanita family that can cause fulminant hepatitis and be fatal).

There are two types of hepatotoxicity:

- Predictable toxicity, either direct or most often induced by the formation of a toxic metabolite of the drug: this is dose-dependent and will occur in every subject taking a sufficient amount of the drug. The typical example is acetaminophen.
- Idiosyncratic reaction: this occurs only in certain exposed individuals. It is therefore unpredictable and dose-independent. This is the case with the majority of drug-induced hepatitis.

Table 8.3 Agents at risk of hepatotoxicity based on hepatic test disturbance

Hepatocellular (ALT ↑)	Mixed (Alk phos and ALT ↑)	Cholestatic (Alk phos and conj bilirubin ↑)
Acarbose	Amitriptyline	Amoxicillin-clavulanic acid
Acetaminophen	Azathioprine	Anabolic steroids
Allopurinol	Captopril	Chlorpromazine
Amiodarone	Carbamazepine	Clopidogrel
Anti-retrovirals	Clindamycin	Erythromycins
Baclofen	Cyproheptadine	Estrogens
Bupropion	Enalapril	Irbesartan
Fluoxetine	Flutamide	Ketamine
Herbs: kava, germander phenytoin	Nitrofurantoin	Mirtazapine
Isoniazid	Phenobarbital	Oral contraceptives
Ketoconazole	Phenytoin	Phenothiazine
Lisinopril	Sulfonamides	Terbinafine
Losartan	Trazodone	Tricyclics
Methotrexate	Trimethoprim-sulfamethoxazole	
NSAIDs	Verapamil	
Paroxetine		
Pyrazinamide		
Rifampin		
Risperidone		
Sertraline		
Tetracyclines		
Trazodone		
Trovafloxacin		
Valproic acid		

Hepatotoxicity can manifest itself with different clinical, biochemical, and histological patterns. The patient can have asymptomatic abnormal liver tests, clinical anicteric hepatitis (nausea, anorexia, right upper quadrant pain, impaired general condition, etc.), icteric hepatitis, or even fulminant hepatitis. Drug-induced hepatotoxicity is the primary cause in 25% of cases of fulminant hepatitis. When a cholestatic component is

observed, the patient may present with pruritus, pale stools, and dark urine and is more likely to be icteric. The picture may be accompanied by the classic signs of hypersensitivity: rash, fever, and hypereosinophilia.

The pattern of abnormal liver tests can be hepatocellular, cholestatic, or mixed (◘ Table 8.3).

Histological findings are diverse, but, typically, one observes an inflammatory infiltrate with eosinophilic predominance, with or without hepatocellular necrosis. Cholestasis, granulomas, steatohepatitis, phospholipidosis, vascular damage, etc. may also be found.

The majority of cases of toxic hepatitis are self-limited, but hepatocellular damage with jaundice is associated with higher mortality (about 10%). Cholestatic hepatitis is rarely fatal, but recovery is slower. Severe hepatitis (e.g., acetaminophen fulminant hepatitis) may require liver transplantation.

Hepatitis with acetaminophen Ingestion of acetaminophen is a frequent cause of hepatotoxicity. Two situations are encountered:

- Voluntary ingestion of a large quantity in a single dose, most often in a suicidal attempt.
- Therapeutic misadventure that occurs when a patient ingests slightly supra-therapeutic doses for a few days. This situation occurs more often in at-risk patients, particularly in chronic alcohol users.

The pathophysiology of acetaminophen hepatotoxicity is well understood. Acetaminophen is metabolized, via cytochrome P450 2E1, into N-acetyl-p-benzoquinone imine (NAPQI), which is highly hepatotoxic but inoffensive when conjugated with glutathione. However, glutathione has a conjugation capacity that is limited to approximately 4 grams of acetaminophen/day. When the conjugation capacity is exceeded, massive hepatocyte necrosis occurs. Toxicity begins to occur with a dose above 4 g. Toxicity is increased in the following situations:

- Induction of P450 during chronic alcohol intake, isoniazid intake, obesity, or diabetes.
- Depletion of glutathione during prolonged fasting.
- Delayed treatment with N-acetyl cysteine. A delay of more than 12 hours in the administration of N-acetyl cysteine is associated with an increased risk of hepatic failure.

Treatment of hepatitis with acetaminophen requires the administration of N-acetyl cysteine, which plays the same role as glutathione in binding the hepatotoxic metabolite. Its administration within 8 hours of acetaminophen ingestion prevents severe liver damage. This treatment should be instituted in every case where toxic acetaminophen intake is suspected and should not be delayed by waiting for the results of blood levels.

8.6.1.3 Autoimmune/Metabolic Hepatitis

(a) Autoimmune hepatitis Acute hepatitis, with or without liver failure, may be the mode of presentation of autoimmune hepatitis especially in young people. It can be spontaneous or triggered by drugs such as minocycline or statins.

Autoimmune hepatitis is primarily a chronic liver disease (see ▶ Sect. 8.6.2). Treatment consists of prednisone combined with azathioprine. Remission is the norm, but long-term treatment is required.

(b) Wilson's disease Wilson's disease is caused by a defect in the biliary excretion of copper and can manifest itself as acute hepatitis or even liver failure in patients under 50 years of age, as we will see in the ▶ Sect. 8.6.2.4 on chronic metabolic hepatitis.

8.6.1.4 Vascular Hepatitis

Acute hepatocellular injury can be the mode of presentation of Budd-Chiari syndrome or ischemic hepatitis. In both situations, there is no hepatitis as such, because there is no inflammatory infiltrate on liver biopsy.

(a) Budd-Chiari syndrome The Budd-Chiari syndrome is characterized by obstruction of hepatic vein outflow. The obstruction is secondary to thrombosis or fibrous thickening of the hepatic veins. The presentation may be acute, subacute, or chronic. In 90% of patients, a procoagulant underlying disorder will be identified. The main thrombotic disorders associated with Budd-Chiari are myelodysplastic syndromes, paroxysmal nocturnal hemoglobinuria, hereditary thrombophilia, antiphospholipid syndrome, and Behçet's disease. Budd-Chiari requires urgent medical attention.

Clinical presentation varies depending on the rapidity of occurrence of the obstructive phenomenon. In the case of an acute thrombosis of the hepatic veins, the patient presents with frank abdominal pain, ascites, and even fever. Very high levels of liver enzymes can then be observed (ALT, 1200–1500 IU/L), and liver failure can develop quickly. In case of chronic obstruction, progressive onset of ascites is the usual clinical finding.

Diagnosis is based on the absence of flow in hepatic veins on Doppler ultrasound or on the absence of opacification of the hepatic veins on contrast-enhanced abdominal CT scan (in the venous phase). The caudate lobe is hypertrophied in 25% of cases and ascites is present.

Treatment consists of urgent anticoagulation and management of the complications of portal hypertension. In presence of liver failure or nonresponse to

medical treatment, angioplasty of the hepatic veins, transjugular intrahepatic portosystemic shunt (TIPS), or a hepatic transplant may be performed.

(b) Ischemic hepatitis In cases of major hemodynamic instability, ischemic hepatitis or "shock liver" may occur. Liver injury is usually not in the foreground. Other signs of systemic hypoperfusion are usually observed such as systemic hypotension, acute renal failure, and acidosis. Typically, serum liver enzymes are very elevated (in the order of 3000–5000 IU/L) and rapidly decline. LDHs are also greatly increased. In severe cases, INR can increase and also rapidly decrease. Bilirubin and alkaline phosphatase rarely rise more than twice the normal values. The diagnosis is made in a patient with present or recent shock, usually of cardiogenic origin, in whom other causes of acute hepatitis have been ruled out. The picture is usually self-limiting once the hemodynamic instability has been corrected.

The diagnosis of acute hepatitis can require various biological tests, as shown in ◘ Table 8.4.

Table 8.4 Acute hepatitis: paraclinical evaluation

Baseline assessment (to be targeted according to the differential diagnosis formulated after clinical evaluation)
– Anti-HAV IgM
– HBsAg, anti-HBc IgM, anti-HBs
– Anti-HCV, HCV RNA
– CMV DNA, anti-CMV IgM
– Herpes simplex virus DNA
– Monotest
– Acetaminophen dosage
– Antinuclear antibodies, anti-smooth muscle, anti-liver-kidney-type (anti-LKM) microsomes
– Protein electrophoresis and IgG, IgA, and IgM assays
– Ceruloplasmin
– Abdominal ultrasound with hepatic Doppler or CT scan with contrast, if Budd-Chiari syndrome is suspected

8.6.2 Chronic Hepatitis

Chronic hepatitis is an inflammation of the liver which, by definition, lasts at least 6 months. The clinical picture is often vague and nonspecific, with symptoms of fatigue and/or right hypochondrium discomfort. Most patients are discovered through identification of abnormal, fluctuating transaminases. Inflammation and destruction of hepatocytes can lead to the development of fibrosis, which may progress to cirrhosis. The severity of liver damage will be established on a clinically and with non-invasive or invasive tests including biological parameters (bilirubin, albumin, INR, platelets), imaging (ultrasound, FibroScan® elastography, CT scan, MRI), and, possibly, histology. Liver biopsy remains necessary in some cases to make an etiological diagnosis or to establish the severity of the disease.

Several etiologies are possible, and diagnosis requires a number of tests.

8.6.2.1 Viral Hepatitis (B, D, C, E)

(A) Chronic Hepatitis B

Hepatitis B is a public health problem, since it affects more than 250 million people worldwide according to the WHO, which estimates that 350,000 new cases of hepatocellular carcinoma are attributable to it every year. It is estimated that there are 4 million chronic carriers of the hepatitis B virus (HBV) in Europe, 1.25 million in the United States, and 250,000–460,000 in Canada.

The prevalence of chronic HB antigen carriers is low (< to 0.5%) in developed countries, while it is higher in countries of the Mediterranean region (about 5%), Eastern Europe, Asia, and Africa (10–20%). The incidence and prevalence of the disease have significantly decreased thanks to the introduction of mass vaccination programs. It is the first effective vaccine to prevent hepatocellular carcinoma.

HBV is transmitted:

- By blood: intravenous or intranasal drug users, transfusion (hemophiliacs, hemodialysis patients, although transmission has become extremely rare thanks to screening tests), healthcare personnel with accidental blood exposure, and mass vaccinations.
- During sexual relations: since the virus is present in semen, the risk of transmission increases with the number of sexual partners.
- By vertical transmission, from mother to child.
- By contact with a chronic HBV carrier (close circle, in prisons, during fights). This mode of transmission prevails in Africa.

Clinical and biological expression of HBV infection depends on the age at which the patient contracted the disease. In Asian countries, where the prevalence of infection is high, the virus is acquired in the perinatal period. In this case, acute infection goes silent, and the progression to chronic disease occurs in more than 90% of cases, with a 40% risk of developing cirrhosis and hepatocarcinoma during a patient's lifetime. In Africa, transmission in early childhood is associated with a 15% risk of chronicity. In Western countries, the prevalence of the infection is low, and the virus is contracted mainly

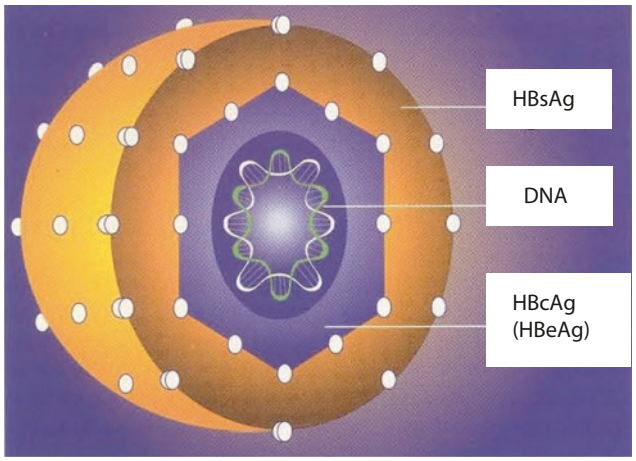


Fig. 8.19 Hepatitis B virus (HBV): The DNA and polymerase at the center of the virus are enveloped in a nucleocapsid containing various proteins, including HBcAg and HBeAg. The outer envelope of the virus contains, among other things, the surface antigen HBsAg

in adulthood. The risk of developing chronic disease is low, less than 2%.

The mode of acquisition remains unknown in one-third of cases.

(a) Virology The human hepatitis B virus (HBV) is a member of the *Hepadnaviridae* family, a DNA virus. It can persist for 7 days in the environment and is resistant to freezing.

HBV is a 42-micron-diameter particle (the Dane particle) at the center of which rests the viral genome made of circular, partially double-stranded DNA of about 3000 nucleotides (Fig. 8.19). The viral DNA is enveloped in a nucleocapsid (or core or HBcAg), which is itself surrounded by surface proteins (HBsAg).

Viral DNA contains the genetic information that enables the infected cell to produce the various proteins necessary for the synthesis of new viruses that can be detected in serum during viral replication:

- The core protein (HBcAg) is detectable in hepatocytes on liver biopsy, but is not exportable outside the cell and is therefore absent in the blood; only its antibody (anti-HBc) can be detected in the blood and indicates current or previous contact with the hepatitis B virus.
- The e antigen: HBeAg is a secreted protein that is translated from the C gene which is also the source of the core protein. It bears an additional portion (so-called pre-core protein) which is the N-terminal extension. Infected hepatocytes export the e antigen, which is measurable in circulation during viral replication (except in e antigen-negative active hepatitis B).
- HBsAg surface antigen: the virus is protected by an outer envelope composed of lipids and proteins, including the HBsAg surface antigen [originally called the "Australian antigen" when it was discovered in the serum of an Australian citizen in 1963 by B. Blumberg (Nobel Prize in Medicine in 1976)]. It allows the virus to bind to the hepatocyte membrane and enter the cell through the NTCP receptor. HBsAg, which is manufactured in excess by hepatocytes infected with the B virus, can circulate in the blood as an empty envelope, without the core proteins, polymerase, or viral DNA. Therefore, it cannot be used as a marker of active disease with viral replication (identified by an increase in viral DNA or the presence of HBeAg). Under electron microscopy, HBsAg polymers can form spheres or tubules.
- DNA polymerase is an enzyme that allows the virus to reproduce its DNA. It is not measured in clinical practice.
- Protein X is involved in replication and virus-induced oncogenesis. It is not measured in clinical practice.

The presence or absence of these proteins and their antibodies determines the phase of the disease. They are therefore important clinical biomarkers.

Viral cycle: virions circulating in the blood bind to hepatocyte membrane through its surface proteins; fusion of the two membranes allows the nucleocapsid to enter the hepatocyte through a receptor, NTCP (Na-taurocholate cotransporting polypeptide, which also acts as a bile salt transporter). The virus then moves toward the nucleus where it replicates through its own DNA polymerase. New viruses are thus manufactured and released into circulation before returning to the liver and infecting other hepatocytes. Viral DNA persists for many years in the nucleus of the infected hepatocyte; this is why viral reactivation and virological relapse can occur after cessation of antiviral therapy or following immunosuppressive treatment.

Pathophysiology: the hepatitis B virus is not cytopathic per se. Liver injury is due to the attack of infected hepatocytes by the host immune response. If the cellular immune response mediated by CD4 T lymphocytes is too weak, it fails to eliminate all infected cells. This result in persistence of viral replication and liver inflammation, leading to the development of chronic hepatitis and, possibly, with time, to the formation of cirrhosis and/or hepatocellular carcinoma.

Genotypes: the hepatitis B virus has nine viral genotypes, from A to I. These genotypes are linked to a distinct geographical distribution. The determination of these genotypes has only limited significance clinically (in contrast to hepatitis C genotypes, as discussed below).

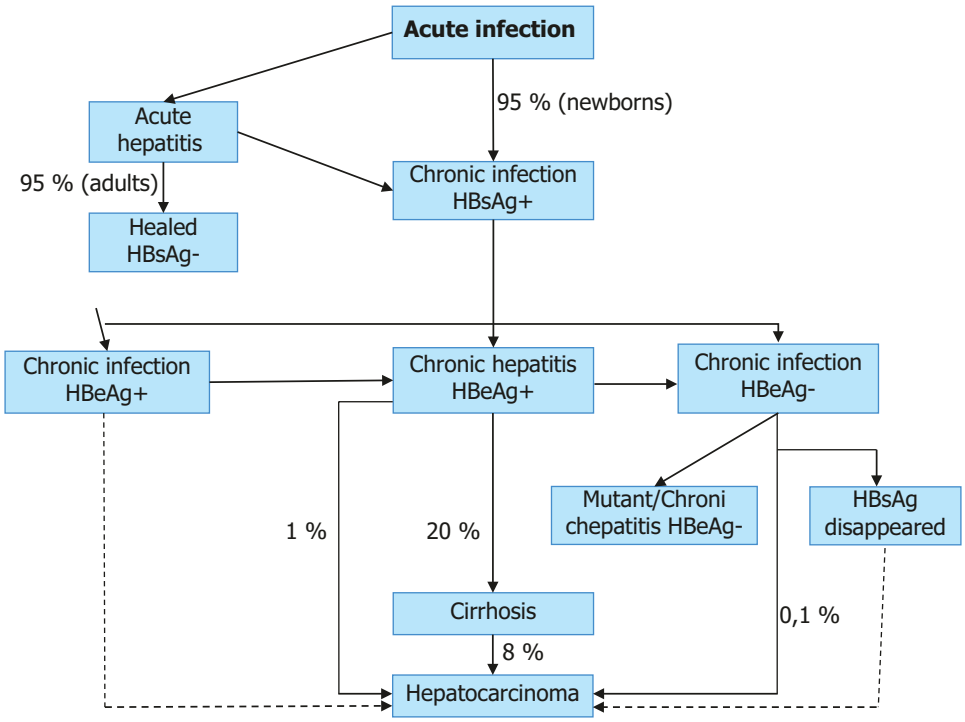


Fig. 8.20 Natural history of hepatitis B

(b) Natural history of B virus infection Chronic infection is defined by the persistence of the infection beyond 6 months after the initial acute phase. Different phases of the chronic infection have been described: they vary in duration and are not necessarily sequential (Fig. 8.20).

- *Phase 1 – Chronic HBeAg+ infection* (previously called the immune tolerance phase). This initial phase is common and prolonged (20–30 years) in Southeast Asian countries, where the virus is transmitted in the perinatal period. It is typically characterized by markers of intense viral replication (with a positive HBe antigen and extremely high serum viral DNA). However, due to the lack of immune response, there is no or minimal liver damage, and blood tests (AST and ALT) are normal. These patients are asymptomatic but, on the other hand, highly contagious. Screening of the entourage and vaccination of uninfected (HBsAg-, anti-HBc neg.) and non-immune (anti-HBs neg.) subjects are indicated.
- *Phase 2 – Chronic HBeAg+* hepatitis (formerly called the immunocompetent phase). This phase is characterized by the development of an immune response against the replicating virus, leading to liver inflammation and hepatocyte cell death. If the efficacy of the immune response is good, it can achieve partial or complete control of viral infection. In serum, markers of replication HBeAg and HBV DNA levels remain very high. Hepatocyte necrosis releases intracellular enzymes, and AST and ALT blood levels are elevated. Histology shows active hepatitis and a decrease in the number of cells expressing the virus. This phase can last a few weeks to several years. It is usually shorter if the infection is contracted during adult life. It is a phase of active hepatitis (or "wild-type" hepatitis), which can lead to a progressive and severe liver disease.

  HBeAg+ viral reactivation. Viral reactivation is defined as a reappearance of viral replication, with re-increased viral load, in a patient who has previously controlled viral replication. This situation (return to phase 2) is most often seen in immunosuppressed patients and is usually accompanied by an increase in transaminases. It is characterized by a seroreversion (reappearance of HBeAg in a patient who had previously seroconverted to develop anti-HBe antibodies) and may be associated with a severe hepatitic flare with the development of liver failure.
- *Phase 3 – Chronic HBeAg– infection* (previously called the inactive carriage phase). At the end of the immune clearance phase, which occurs either spontaneously or as a result of antiviral treatments, the immune system takes control of the viral infection. The low expression of viral antigens reduces the attack of infected liver cells by the immune response and leads to a new state of equilibrium. This phase is characterized by HBeAg/anti-HBe seroconversion, i.e., disappearance of the HBe antigen and appearance of anti-HBe antibodies. HBV DNA levels are

low (typically less than 10,000 UI/mL) or undetectable, and transaminases are normal. At this stage, the hepatitis is considered inactive; there is no evidence of liver inflammation on biopsy, and the risk of progression to cirrhosis is low.

In the course of this quiescent phase, various types of evolution can occur, and the patient can:

- Remain indefinitely in phase 3 of chronic HBeAg–/anti-HBe+ infection with the persistence of HBsAg+, normal transaminases, and very low or undetectable HBV DNA levels.
- Progress to phase 4 (HBeAg– chronic hepatitis B).
- Return to phase 2 (HBeAg viral reactivation with chronic HBeAg+ hepatitis).
- Move to phase 5 (resolved hepatitis B).

- *Phase 4 – HBeAg– chronic hepatitis B* (pre-core mutant hepatitis). This phase occurs late in the progression of chronic hepatitis B and usually takes place after the period of HBe/anti-HBe seroconversion. Reactivation of hepatitis occurs because of the selection and replication of a pre-existing mutant containing nucleotide substitutions in the pre-core region and/or promoter of the core region of the viral genome. These mutations allow the virus to replicate without expressing HBeAg and to escape the immune response. Over time, these mutants accumulate and become more numerous than the wild-type virus (which expresses HBeAg). Serologically, HBsAg is positive, anti-HBe antibodies are present (signaling a previous seroconversion against HBeAg), HBeAg is absent, HBV DNA levels are variable (10^4–10^7 UI/mL), and AST and ALT fluctuate. This phase reflects active hepatitis. These infections are usually discovered later and, therefore, are associated with a longer duration of the disease. The prevalence of cirrhosis on liver biopsy is higher than in other phases.
- *Phase 5 – Resolved hepatitis B*. This is characterized by the disappearance of HBsAg. Viral load becomes undetectable, and the patient's serology shows that HBsAg is negative and the appearance of anti-HBsAg antibodies (anti-HBs+). These antibodies may disappear over time; the only residual marker of a previous infection is then the presence of anti-HBc antibodies. Infection with hepatitis B is then considered resolved. The chances of spontaneous resolution of a chronic HBeAg– infection are estimated at 1–3% of cases per year (among patients with an undetectable viral load). However, cells with ccDNA integrated into their genome may persist indefinitely in the infected tissue. This can lead to viral reactivation in case of immunosuppression or to the development of hepatocarcinoma. In addition, liver fibrosis may be identified at this stage (sequelae of past infection).

(c) Complications of chronic hepatitis B

- *Cirrhosis:* 20% of chronic hepatitis B carriers will develop liver cirrhosis, which occurs approximately 20 years after the initial infection. Factors have been associated with a more rapid progression to cirrhosis in hepatitis B carriers:
  - Age: rare in children; progression to cirrhosis increases in teenagers and in adults.
  - Male sex.
  - High HBV DNA viral load.
  - Number of previous viral reactivations (risk increases with multiple reactivations).
  - Presence of infection with a pre-core mutant virus.
  - Immunosuppression.
  - Co-infection or superinfection with hepatitis C, hepatitis delta, or HIV.
  - Alcohol intake.
  - Presence of a metabolic syndrome.
- *Hepatocellular carcinoma:* Hepatitis B has been shown to be associated with the development of hepatocarcinoma. In most cases (80%), the cancer affects patients with advanced liver disease (cirrhosis). However, HBV is known to exert direct oncogenic effects, and the integration of the HBV genome into host cellular DNA explains the risk of developing cancer in the absence of cirrhosis. The incidence of hepatocarcinoma is estimated at 0.1% per year in inactive carriers, 1% in patients with chronic HBV without cirrhosis, and 1–8% in cirrhotic patients.
- *Extrahepatic manifestations:* Hepatitis B can develop extrahepatic complications. Among the most frequent are immune complex diseases: periarteritis nodosa (due to the presence of circulating immune complexes, i.e., HBV antigens bound to antibodies that are deposited in the wall of medium and small arteries), membranous glomerulonephritis, nephrotic syndrome, Guillain-Barré syndrome, myocarditis, and cryoglobulinemia. The treatment of these immune diseases relies primarily on antiviral drugs. Depending on the degree of inflammatory disease, the use of corticosteroids and/or plasmapheresis may be necessary.

(d) Diagnosisv of hepatitis B Serum HBs antigen and anti-HBs and anti-HBc antibodies are used to identify patients who are carriers, those who have been in contact with the virus, and those who have recovered from it (see Fig. 8.21).

- HBsAg+ is the diagnostic test for hepatitis B: it is the primary marker of HBV infection.

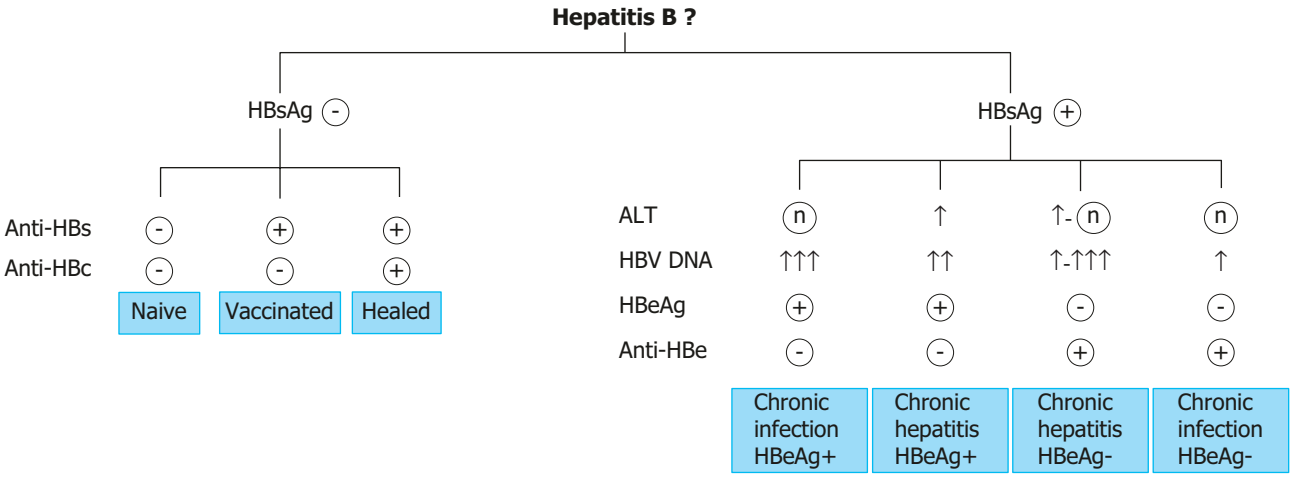


Fig. 8.21 Interpretation of serological tests for B virus

- Anti-HBs antibody (in the absence of HBsAg) confirms the resolution of hepatitis B or is a marker of the response to hepatitis B vaccine.
- The presence of anti-HBc antibodies indicates previous contact with the virus, whether the virus is still present or the infection has resolved.

It should be noted that vaccination induces anti-HBs antibodies but not anti-HBc antibodies, since there has been no exposure to the core proteins of the virus, but only to antigen proteins present in the vaccine.

Once the diagnosis of hepatitis B is made, it is important to determine the stage of the disease in order to determine the risk of progression to cirrhosis. The identification of progressive/aggressive disease mandates treatment. In the absence of signs of aggressivity, only regular monitoring can be applied.

To determine the stage of the hepatitis, one must look for signs of liver inflammation (increased AST and ALT) and active virus replication (quantitative HBV DNA by PCR in IU/mL, also referred to as viral load). If both conditions are present, identification of HBeAg and anti-HBe antibodies classifies the condition as HBeAg-positive or HBeAg-negative (pre-core mutant) chronic hepatitis. It should be noted that HBeAg-negative chronic hepatitis B (phase 4 of the disease) is characterized by fluctuating, sometimes transiently normal, AST/ALT levels and sometimes low or moderately high viral load: this profile is similar to that of the HBeAg-negative chronic infection phase. It is therefore necessary to look for variations in aminotransferases and HBe DNA by regular blood tests (every 3 months for 1 year).

In regions where access to viral load (HBV DNA) measurement is limited, a simplified score for the treatment of HBsAg+ subjects can be used (Table 8.5).

Table 8.5 Simplified score for the treatment of HBsAg+ subjects in regions where access to viral load (HBV DNA) measurement is limited (*J Hepatology* 2018)

ALT		HBeAg	
Value	**Score**	**Value**	**Score**
<20 IU/L	0	Negative	0
20–39	1	Positive	1
40–79	2		
>80	3		

A total score equal to or greater than 2 is an indication for treatment

(e) Treatment of chronic hepatitis B Only patients with active hepatitis benefit from treatment. Currently, it is recommended to treat patients in phase 2 and phase 4 (HBeAg+ or HBeAg– chronic hepatitis B).

How to treat? Two types of antivirals are approved in the treatment of chronic hepatitis B:

- Alpha-pegylated interferon: Used since the 1980s, its mode of action encompasses a direct antiviral effect, a stimulation of the T-cell immune response, an antiproliferative effect, and an antifibrotic effect. In patients in phase 2 (HBeAg+ chronic hepatitis B), it can induce HBeAg seroconversion (loss of HBeAg and appearance of anti-HBe antibodies) and clinical remission in approximately 25% of patients, but does not eradicate the virus: the patient moves from phase 2 to phase 3, and long-term clinical benefit has been well demonstrated. Interferon has two advantages: it does not generate treatment-resistant variants, and the treatment has a limited duration of 48 weeks. However, the treatment requires weekly subcutane-

ous injections and causes significant physical (flu-like symptoms, fatigue, headaches, skin rash), psychological (irritability, depression), and biochemical (anemia, neutropenia, thrombocytopenia, autoimmune disorders) side effects, which require careful selection of patients and strict monitoring.

- Nucleoside/nucleotide analogues (NAs): These agents are very well tolerated. They inhibit the activity of the HBV viral polymerase, thus blocking viral replication. The first-generation analogues (lamivudine, adefovir, emtricitabine) were associated with the progressive selection of treatment-resistant mutants. Currently, entecavir, tenofovir, and tenofovir alafenamide are used. The NAs suppress viral replication (undetectable viral load) in the vast majority of cases (75–93% of patients) and lead to HBe seroconversion in one-third of patients. The control of viral replication is accompanied by normalization of transaminases and stabilization or even regression of histological lesions and sometimes resolution of cirrhosis. Regular follow-up is recommended. Duration of treatment varies from case to case. Treatment can be discontinued if HBeAg seroconversion occurs, but regular follow-up is required thereafter to identify the possible development of HBeAg– hepatitis. In most cases, long-term treatment is necessary (several years or even life). Patients should therefore be informed not to stop follow-up.

(f) Hepatitis B prevention Vaccination is the best way to prevent this infection. The vaccine is very effective and safe. Vertical transmission from mother to child can be prevented to 95% with administration, within the first 12 hours of life, of one dose of vaccine against hepatitis B and hyperimmune gamma globulin against hepatitis B (for immediate prevention while waiting for development of vaccine-induced immunity). Pregnant women with viremia >200,000 IU/mL should also receive a non-teratogenic nucleotide analogue such as tenofovir from 24 weeks of pregnancy to decrease the viral load, the level of which correlates with the risk of vertical transmission.

Since the risk of chronic infection is highest when the infection is acquired in infancy or early childhood, it is recommended that vaccination be performed in every child as early as possible. A pentavalent vaccine (including HBsAg) can be used in infants at 2, 4, and 18 months of age.

In general, testing for response to the vaccine (HBsAg >10 IU/L) is not recommended. However, response should be tested in people who remain at risk of infection, such as children of HBsAg+ mothers, at-risk healthcare workers, sexual partners of infected patients, and hemodialysis patients. In these patients, the progressive decrease in anti-HBsAg titer below 10 IU/L requires a booster vaccination.

All patients with chronic hepatitis B infection should receive the hepatitis A vaccine unless they already have HAV antibodies (+). They should abstain from drinking alcohol.

Immunosuppression and chemotherapy: Corticosteroids and other immunosuppressive drugs should be used with great caution in HBsAg individuals since they can induce viral reactivation in a patient in phase 3 (chronic HBeAg– infection), which can lead to severe or even fulminant hepatitis. Any patient undergoing immunosuppressive treatment or cancer chemotherapy *must* be tested for HBsAg beforehand. If the test is positive, preventive antiviral therapy should be initiated. This is also true in HBsAg- but anti-HBc + (i.e., resolved hepatitis B) patients who will receive heavy chemotherapy with B-cell-depleting agents (e.g., rituximab) or anti-PD1 immunotherapy agents.

(B) Chronic Hepatitis D

The hepatitis D virus is a small circular RNA virus with 1700 nucleotides, considered a satellite or viroid subvirus. It requires the hepatitis B replication apparatus and the HBsAg which is known to coat RNA and D antigen.

Acquired by co-infection with the B virus or by superinfection in a patient already infected with HBV, the D virus is responsible for chronic hepatitis, most often severe, which progresses rapidly to cirrhosis and its complications (liver failure and hepatocellular carcinoma) in 80% of cases.

The diagnosis is made in an HBsAg+ patient by the presence of anti-Delta antibodies and D virus RNA.

Prolonged treatment with pegylated interferon can be attempted, albeit with limited success. New therapeutic options, such as surface antigen entry inhibitors, are expected to be available soon.

(C) Chronic Hepatitis C

(a) Epidemiology Widespread throughout the world, chronic hepatitis C is one of the main causes of chronic liver disease. The World Health Organization estimates that more than 170 million people are infected with the hepatitis C virus (HCV) worldwide and 400,000 deaths per year are attributable to it. Prevalence is highly variable across regions and even within a given population. The prevalence is around 0.4–3% in Western Europe, while it is up to 9% in Egypt. In North America, the infected population is estimated at four million individuals. In Canada, it is estimated between 178,000 and 315,000 individuals.

HCV transmission is almost exclusively caused by contact with contaminated blood. Prior to the 1990s, the main route of transmission of HCV was through blood transfusion (hemophiliacs, transplanted patients, hemodialysis units, etc.). Since the discovery of the virus and

availability of a widely accessible screening test (anti-HCV antibodies), there has been a drastic reduction in the number of patients infected by transfusions, the current risk being estimated at less than one per one million donations.

Current sources of contamination are mainly the use of contaminated recreational drug equipment (intravenous or intranasal) or, more rarely, tattoos, invasive procedures (e.g., dentistry), piercing, or acupuncture. In some developing countries, the use of non-sterile or recycled medical equipment remains a source of infection. Perinatal and heterosexual contamination is rare (2–5%). It is reported more frequently in men having sex with men, especially in HIV-infected patients. In 10–30% of cases, the origin of the infection remains unknown.

(b) Virology and pathophysiology The hepatitis C virus (HCV) is a single-stranded (positively oriented) RNA virus of the *Hepaciviridae* family that exclusively infects humans. HCV penetrates hepatocytes. Its replication takes place in the endoplasmic reticulum where the viral RNA incorporates directly into the ribosome, like a messenger RNA. The virus does not integrate into the host genome. It is not directly cytopathic for hepatocytes. The damage is mediated by the host immune response. The attack on hepatocytes by the immune system leads to their destruction and induces a necrotico-inflammatory reaction that stimulates the hepatic stellate cells to produce an extracellular matrix and fibrogenesis. Persistence of the virus is due to an inadequate immune response by CD4+ helpers and cytotoxic T lymphocytes.

There are currently 8 known genotypes (1–8) of HCV and more than 100 subtypes (identified by a lowercase letter: 1a, 1b, etc.). Genotype 1 is by far the most common (subtype 1a in America and 1b in Europe). Genotype 3 is prevalent among intravenous drug users. Genotype 4 is very common in Egypt and Central Africa, while genotypes 5 and 6 are found mainly in Africa and Southeast Asia, respectively. The various genotypes respond very well to the various "pan-genotypic" therapeutic regimens currently available.

(c) Natural history of hepatitis C Chronic HCV infection is defined by the persistence of viral replication beyond 6 months.

A minority of infected individuals recover from hepatitis; approximately 70% will remain chronic carriers.

Hepatitis C virus infection has a variable course. Among patients with chronic HCV infection, 15–20% have a mild disease, normal transaminases, and minimal histological lesions, do not develop fibrosis, and have a good prognosis; 60% will have abnormal liver transaminases and variable degree of chronic hepatitis on liver biopsy (mild to severe); and 20% will develop cirrhosis after 20 years. When cirrhotic, the risk of developing hepatocellular carcinoma is 1–4% per year.

(d) Symptoms and complications of hepatitis C Fatigue is the main symptom associated with hepatitis C; though it does affect the quality of life of patients, it does not correlate with the severity of liver damage.

- Extrahepatic manifestations can complicate the course of HCV infection. Among the most frequent are mixed cryoglobulinemia types 2 and 3 (present in one-third of patients with HCV, but rarely associated with symptomatic cryoglobulinemia vasculitis), membranoproliferative glomerulonephritis, arthralgia and myalgia, porphyria cutanea tarda, sicca syndrome, and non-Hodgkin's B-cell lymphomas. Autoantibodies (rheumatoid factor, antinuclear antibodies, anti-smooth muscle, anti-thyroglobulin, anti-cardiolipin) are frequently observed but do not translate into autoimmune disease. Hepatitis C should therefore be tested for and treated in patients presenting with these pathologies, since viral eradication is associated with a regression of these pathologies in the majority of cases.
- Cirrhosis is a well-known complication of HCV. Risk factors for progression to cirrhosis include male sex, advanced age at the time of infection, alcohol consumption, immunosuppression, co-infection with the hepatitis B virus or HIV, overweight, and non-alcoholic steatohepatitis (NASH). HCV-induced cirrhosis can progress to end-stage liver failure, which may require liver transplantation. Treatment with direct-acting antiviral drugs can prevent this fatal development when administered early enough. Treatment can also take place after transplant and is effective in preventing or treating severe recurrence of the infection.
- Hepatocellular carcinoma is more frequent in the presence of cirrhosis, with an incidence of 1–4% per year. Screening (abdominal ultrasound and measurement of serum alpha-fetoprotein every 6 months) is recommended in patients with advanced fibrosis or cirrhosis.

(e) Diagnosis of chronic hepatitis C Serological tests detect anti-HCV antibodies to various HCV epitopes, regardless of the genotype, and confirm previous exposure to HCV.

HCV RNA detection and quantification techniques (PCR) are currently available and are used to determine the active (RNA+) or resolved (RNA-) status of hepatitis. The simultaneous presence of anti-HCV antibodies and viral RNA is the signature of HCV infection.

Tests for the detection of virus C antigens are available in countries where molecular PCR tests are too expensive or inaccessible. They are not routinely available in Western countries.

HCV genotyping is done by sequencing specific regions of the viral genome.

Evaluation of liver fibrosis by liver biopsy has long been considered the gold standard in the evaluation of chronic hepatitis C. It has now been replaced by less invasive methods, such as liver elastography, which has become the test of choice for the investigation and follow-up of patients with chronic hepatitis C.

(f) Treatment of hepatitis C Major pharmacotherapeutic developments are currently revolutionizing the treatment of hepatitis C.

Molecules that block viral replication and assembly are available: they are powerful and effective against all genotypes. There are three classes of anti-HCV agents: (1) nucleotidic or non-nucleotidic inhibitors of polymerase (-buvir: sofosbuvir, dasabuvir), (2) inhibitors of the NS3-4A protease (-previr: glecaprevir, voxilaprevir), and (3) inhibitors of the NS5A protein, a component of the viral replicase (-asvir: pibrentasvir, velpatasvir). By using various combinations of these agents, rates of sustained virological response (i.e., cure of hepatitis C) are achieved in more than 95% of cases, with minimal side effects.

Until recently, treatment was only given to patients with evidence of progressive disease determined by the stage of fibrosis, due to side effects of older antiviral agents and cost. Nowadays, treatment with antiviral drugs is generally reimbursed in all cases, regardless of the stage of fibrosis. Once cured, hepatitis C does not recur, since the virus genome does not integrate into the host genome (unlike the B virus). However, the patient may re-infect as a result of risky behaviors.

There is currently no vaccine against hepatitis C, and immunoglobulins are ineffective in preventing transmission.

(D) Chronic Hepatitis E

Hepatitis E virus (HEV) genotype 3 is widespread in pigs raised in certain regions (including North America). HEV genotype 3 can cause acute hepatitis (mostly subclinical) or chronic hepatitis in immunocompromised (transplanted or treated for autoimmune or inflammatory diseases) individuals (children and adults). In these patients, evolution to cirrhosis and liver failure is not uncommon. The detection of viral RNA, signaling active viral replication, should lead to antiviral treatment.

8.6.2.2 Toxic Alcoholic Hepatitis

Liver damage secondary to excessive consumption of ethyl alcohol (ETOH) represents a continuum of lesions that can evolve over time, ranging from simple steatosis to alcoholic hepatitis and then cirrhosis.

The development of chronic liver damage secondary to alcohol consumption depends on several factors: the total amount of alcohol consumed, the duration of alcohol consumption, and sex (females are more at risk). There are, however, inter-individual genetic (e.g., cytochrome P2E1 polymorphism) or metabolic variations. Studies in the general population have shown that there is an increased risk of chronic liver disease beginning with a daily consumption of 40–80 g per day of pure alcohol for 10 years in men and 20–40 g per day for 10 years in women (Table 8.6).

Alcohol metabolism: the liver is the main organ of alcohol metabolism. Ethanol is metabolized by two main enzymatic systems in the liver: alcohol dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1). ADH metabolizes ethanol at low serum concentrations, while CYP2E1 activity will take place with higher serum levels. Both enzymatic systems metabolize ethanol to acetaldehyde, which is then converted to acetate by aldehyde dehydrogenase (ALDH). Acetaldehyde is the toxic metabolite responsible for the systemic effects of alcohol (headache, nausea, flush) and is also responsible for direct liver toxicity.

This metabolism of alcohol alters the normal hepatocyte lipid metabolism and leads to excessive storage of lipids in the hepatocyte (steatosis).

Fibrogenesis: while steatosis and inflammation are reversible when alcohol is stopped, the formation of severe fibrosis (cirrhosis) is generally irreversible. The

Table 8.6 Pure alcohol content by type of beverage

Drink	Alcohol level	Usual glass volume	Quantity of pure alcohol	Maximal daily safe intake[a]	
				Men	Women
Beer	5%	350 mL	13.8 g	3–6 glasses	1.5–3 glasses
Wine	12%	120 mL	10.7 g	4–8 glasses	2–4 glasses
Alcohol	40%	45 mL	13.4 g	3–6 glasses	1.5–3 glasses

[a]40–80 g/day of pure alcohol for men and 20–40 g/day for women for 10 years

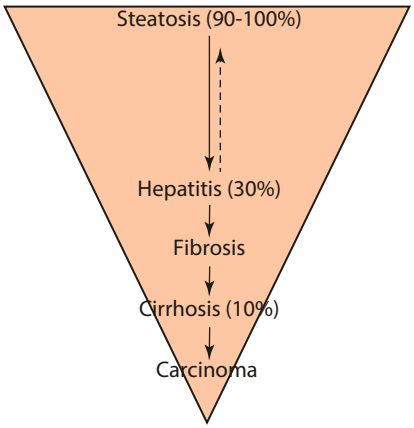


Fig. 8.22 Histologic progression of alcoholic liver disease

activation of hepatic stellate cells by certain cytokines and by alcohol itself is responsible for the production of collagen, leading to the deposition of fibrosis, which progress with years of alcohol aggression to micronodular cirrhosis (Fig. 8.22).

(a) Alcoholic steatosis Steatosis is defined by an accumulation of triglyceride vacuoles in the cytoplasm of hepatocytes. It is the initial lesion caused by chronic alcohol consumption and is almost universally present in individuals who consume more than 60 g of alcohol per day. It can also occur after an isolated episode of severe alcohol intoxication.

Steatosis is asymptomatic. Examination may reveal signs of chronic consumption of alcohol and hepatomegaly.

Liver tests can show a moderate rise in AST (AST > ALT), a rise in GGT, as well as biochemical anomalies caused by alcohol consumption (hypertriglyceridemia, hyperuricemia, macrocytosis, and thrombocytopenia, all being reversible after cessation of drinking). At this level, there is no evidence of liver failure.

Abdominal ultrasound, CT scan, and magnetic resonance scan show steatosis and possibly hepatomegaly.

This is a benign hepatic injury, which is completely reversible after cessation of alcohol consumption. It can progress to alcoholic cirrhosis if intoxication persists.

(b) Acute alcoholic hepatitis Acute alcoholic hepatitis occurs after repeated, sustained, and severe alcohol consumption (usually more than 120 g of pure alcohol per day), in a patient who is often cirrhotic, although it can also occur in the absence of cirrhosis.

New-onset jaundice is the usual mode of presentation. Moderate fever is common, even in the absence of infection. Patients can complain of fatigue, anorexia, weight loss, and dull right upper quadrant abdominal pain. Signs of liver failure are frequent (ascites, hepatic encephalopathy). Firm sometimes tender hepatomegaly, cirrhotic-type liver, and sometimes splenomegaly can be found on physical examination.

Biological tests show high bilirubin levels with moderate elevation in AST, generally less than 300 IU/L. AST is higher than ALT (AST/ALT >2). INR is elevated in severe cases.

Alcoholic hepatitis is defined histologically by the presence of hepatocyte lesions, such as ballooning, acidophilic necrosis, and Mallory bodies, with an inflammatory infiltrate containing numerous neutrophils and significant macrovacuolar steatosis. Fibrosis is often present to varying degrees and often predominates in the centrilobular zone (alcohol being metabolized in the centrilobular zone). These lesions are not specific to alcoholic hepatitis; they are also present in cases of non-alcoholic hepatic steatosis.

Treatment first consists in stopping alcohol consumption. In severe cases (as identified using the Maddrey score which is based on bilirubin and INR levels), treatment with prednisolone (40 mg per day for 28 days; prednisolone is preferred over prednisone, as the liver metabolism of prednisone to prednisolone may be impaired in case of hepatic failure) is beneficial and improves survival. Nutritional support is important, given the high prevalence of undernutrition. It involves oral supplementation with vitamins and minerals (thiamin, vitamin B6, B12, folate, zinc, selenium). The nutritional intake should be at least 35–40 kcal/kg/day, including 1.2 g/kg/day of protein. If the oral intake is less than 2000 kcal per day, enteral tube feeding (or even parenteral nutrition if necessary) must be implemented.

Prognosis depends on the severity of the hepatitis. In severe hepatitis, mortality is 35–45% at 30 days. Without treatment, the survival rate of severe acute alcoholic hepatitis is approximately 50% at 6 months.

(c) Alcoholic cirrhosis Alcoholic cirrhosis is typically micronodular. Patients who still actively consume alcohol show steatosis and signs of alcoholic hepatitis (Mallory bodies, hyaline necrosis).

8.6.2.3 Chronic Autoimmune Liver Diseases (AIH, PBC, Sclerosing Cholangitis)

Chronic autoimmune liver diseases include:

- Autoimmune hepatitis (AIH) where inflammation targets hepatocytes and results in cytolysis with elevated liver enzymes (serum ALT, AST) (Fig. 8.23)
- Primary biliary cholangitis (formerly called primary biliary cirrhosis) (PBC) where inflammation targets interlobular bile ducts and results in cholestasis (increased serum alkaline phosphatase) (Fig. 8.24)

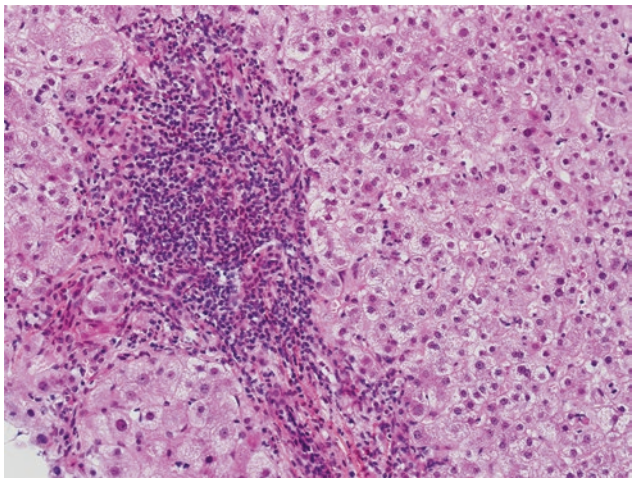


Fig. 8.23 Histology of a chronic hepatitis, with the portal space infiltrated with lymphocytes. Differential diagnosis includes chronic viral hepatitis B or C, autoimmune hepatitis, and even some drug-induced hepatitis. (Photo from C. Vincent)

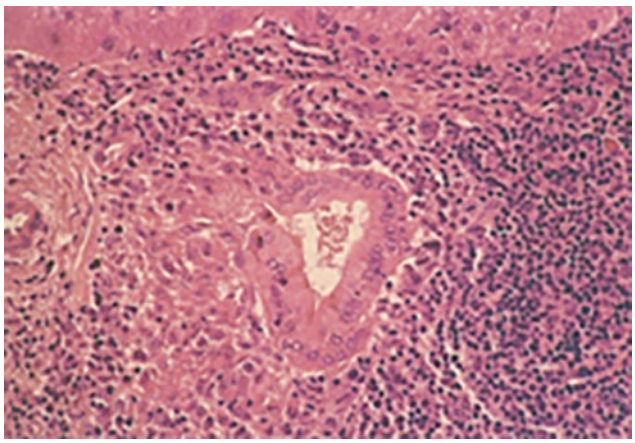


Fig. 8.24 Characteristic feature of primary biliary cholangitis: non-necrotizing granuloma near a bile duct infiltrated by lymphoplasmocytes. (Photo from C. Vincent)

- Primary sclerosing cholangitis (PSC) where inflammation targets the large intrahepatic and extrahepatic bile ducts and results in cholestasis

There are also overlapping syndromes or borderline forms where clinical, biochemical, and histological characteristics of two of these entities overlap. The most common overlap syndrome occurs between AIH and PBC or PSC. Patients can present with the overlapping criteria at the time of diagnosis or develop them over time. This is relevant to 10–15% of autoimmune liver diseases.

(a) Chronic autoimmune hepatitis Like the majority of autoimmune diseases, AIH mainly affects women (3:1 ratio). It is a rare disease with a prevalence of 1–20/200,000 people. It is a chronic disease.

Diagnosis is made by the presence of elevated AST/ALT with:

- Positive antinuclear, smooth muscle, liver-kidney microsome, or hepatic cytosol antibodies
- Hypergammaglobulinemia (IgG type)
- Interface hepatitis on liver biopsy with lymphoplasmacytic infiltration of the limiting plate of periportal hepatocytes

There are two types of AIH. Type 1 AIH is characterized by the presence of smooth muscle and antinuclear antibodies and is the most common form. It is diagnosed in all age groups. Type 2 AIH is characterized by anti-LKM (anti-liver-kidney microsome) antibodies and accounts for 30% of pediatric cases. Its initial presentation is often severe, acute, and with jaundice.

The mode of presentation of AIH is highly variable. Patients can present with:

- Asymptomatic chronic hepatic cytolysis or cytolysis with fatigue
- Established cirrhosis with or without liver failure
- Acute icteric or anicteric hepatitis (especially postpartum)
- Fulminant hepatitis

AIH can occur spontaneously or be triggered by drugs such as minocycline or statins.

Treatment is a combination of prednisone and azathioprine. In non-cirrhotic patients, budesonide can be used instead of prednisone, because it is of comparable or even superior efficacy and has fewer side effects (budesonide is a corticosteroid absorbed by the intestine and metabolized by the liver). Patients often require maintenance treatment with azathioprine, as relapse is very frequent (85%). When patients are diagnosed with liver failure, liver transplantation may be necessary.

(b) Primary biliary cholangitis PBC is an autoimmune disease that occurs in genetically predisposed people, mainly in women (ratio 9:1), between the ages of 45 and 55 years. The prevalence is estimated at 400 cases/million, but is probably underestimated.

Clinical picture is variable. Some patients are asymptomatic; typical symptoms are pruritus and fatigue, sometimes disabling. Advanced cases present with jaundice; in these cases, the prognosis is worse, and progression to liver failure is common. Some patients will show complications of portal hypertension (esophageal varices rupture).

Diagnosis of PBC is made in a patient with high alkaline phosphatase (>1.5 × normal) and positive antimitochondrial antibodies (>1/80). Liver biopsy is not required for diagnosis.

Treatment of PBC involves ursodeoxycholic acid, which is a water-soluble bile acid that reduces the harmful consequences of cholestasis. Inflammation around

the interlobular bile ducts leads to the accumulation of fat-soluble bile acids that are toxic to hepatocytes. Ursodeoxycholic acid decreases portal inflammation and accumulation of bile acids in hepatocytes. Patients where their alkaline phosphatase decreases to <1.5 times normal with normal bilirubin and transaminases have a prognosis comparable to the general population. On the other hand, nonresponders to ursodeoxycholic acid and patients with jaundice may progress to hepatic failure. It is therefore advisable to try a second-line treatment, either obeticholic acid or fibrates. Liver transplantation gives excellent results.

(c) Primary sclerosing cholangitis PSC is a progressive disease characterized by cholestasis secondary to inflammation and diffuse fibrosis of the biliary tree, both intra- and extrahepatic. The disease is more common in men (70% of cases). It is a rather rare disease; the prevalence is 1 per 100,000 populations in the United States. It is associated with inflammatory bowel disease in 80% of cases. New diagnosis of PSC requires a colonoscopy to look for the presence of an inflammatory bowel disease (ulcerative colitis or Crohn's disease), even if the patient has no symptoms.

The cause of PSC is unknown, but there is a familial tendency. Secondary forms of sclerosing cholangitis exist: cholangiopathy associated with hepatolithiasis or choledocholithiasis, HIV cholangiopathy, ischemic cholangiopathy (secondary to hepatic artery thrombosis/stenosis in the context of liver transplantation), biliary trauma, toxic cholangiopathy (5-fluorouracil), and IgG 4 cholangiopathy. IgG 4 cholangiopathy, a relatively newly described entity, is important to diagnose because it has a better prognosis as it can often be treated effectively. It causes stenosis and dilation of the biliary tree similar to PSC radiologically. It is associated with autoimmune pancreatitis, affects mostly men, and is not associated with an increased incidence of inflammatory bowel disease. It is diagnosed by high IgG 4 serum levels and/or a liver biopsy that shows IgG 4-labeled lymphocytes in the portal inflammatory infiltrate. Prednisone treatment often leads to resolution of macroscopic stenoses. When treatment is stopped, the disease tends to recur.

Symptoms of PSC gradually develop and progress over time, with pruritus, fatigue, weight loss, and eventually jaundice. PSC is sometimes discovered fortuitously during the assessment of inflammatory bowel diseases. Patients may progress to liver failure or develop complications of portal hypertension. Patients are at risk of repeated episodes of cholangitis. Lipid maldigestion can occur and is manifested by steatorrhea or fat-soluble vitamin deficiencies (A, D, E, and K). The most serious complication of PSC is cholangiocarcinoma, which affects 15% of patients. Increases in serum CA 19–9 at concentrations to >100 IU/mL are strongly suggestive of cholangiocarcinoma in patients with no active cholangitis. Indeed, CA 19-9 levels can be markedly increased during acute infectious cholangitis and will normally decrease with antibiotic treatment. The identification of a dominant bile duct stricture on imaging raises concern about the presence of cholangiocarcinoma. In such cases, endobiliary brushing cytology of the dominant stenosis is imperative.

The diagnosis of PSC is made in individuals with elevated serum alkaline phosphatase levels and radiologic findings of intra- and/or extrahepatic bile duct stenoses and dilatations on magnetic resonance imaging of the bile ducts (MRI cholangiography) or, more rarely now, by endoscopic retrograde cholangiography (Fig. 8.25). Liver biopsy is not necessary for diagnosis, but can help establish the stage of fibrosis. Concentric

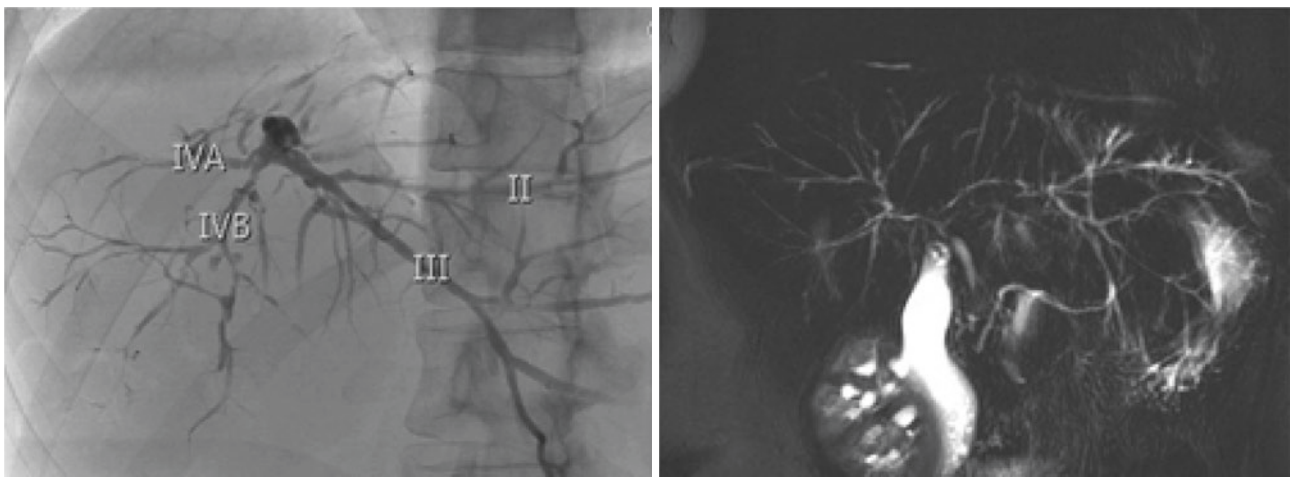


Fig. 8.25 Biliary tract imaging in sclerosing cholangitis. Left: ERCP cholangiography showing strictures and dilatations of the bile ducts in segments IVa and IVb (while the dominant bile duct in segment III appears more normal). Right: MRI cholangiography showing strictured and irregular bile ducts. (Photos from C. Vincent)

fibrosis surrounding bile ducts (onion-skin appearance) is the characteristic histological lesion.

A *treatment* that can modify the evolution of PSC is still to be discovered. High-dose ursodeoxycholic acid (30 mg/kg) is potentially harmful, and the efficacy of lower doses (15 mg/kg) remains controversial. In presence of a dominant stenosis of the extrahepatic bile ducts, diagnostic cytologic brushing with dilatation of the stricture should be performed and, if necessary, a biliary stent be inserted. The only curative treatment is liver transplantation with Roux-en-Y hepaticojejunostomy with bile duct resection in order to avoid the development of cholangiocarcinoma in the remaining bile ducts. Unfortunately, recurrence of the disease occurs in 20–25% cases after transplantation.

8.6.2.4 Metabolic Liver Diseases (NAFLD, Hemochromatosis, Wilson's)

(a) Non-alcoholic fatty liver disease (NAFLD)

NAFLD is the term used for conditions characterized by the accumulation of fat in the liver, which, as indicated by its name, is not due to alcohol intake. It includes two entities – simple steatosis and non-alcoholic steatohepatitis:

- Simple steatosis (SS) refers to the accumulation of fat in hepatocytes that is not associated with liver injury. It is most often found on liver imaging (ultrasound, CT scan). It is asymptomatic and is frequently found in overweight and type 2 diabetes individuals. Liver enzymes are most often within normal limits.
- Non-alcoholic steatohepatitis (NASH) is an important condition that affects 3–5% of Western population and is becoming the leading cause of cirrhosis (about 15% of NASH patients) and transplantation in the United States.

The difference between SS and NASH is not always easy to establish on clinical grounds. Generally, the presence of abnormal liver enzymes, of signs of advanced liver disease (stigmata), and of abnormal liver contours on imaging requires more thorough investigation such as liver elastography or even liver biopsy that remains the gold standard to differentiate between the two conditions.

Pathology Steatosis refers to the accumulation of lipids in hepatocytes. The histologic image (Fig. 8.26) in NASH is similar to that observed in alcoholic steatohepatitis (explaining the fact that many patients were once wrongly suspected, or even accused, of unavowed or hidden alcohol consumption).

Physiopathology of fatty liver The amount of liver lipids increases with increased intake of fatty acids either from the diet (15% of liver fatty acids), or from liver synthesis arising from carbohydrates (26%), or, mainly (59%), from endogenous visceral fat. Liver fat can also increase during a reduction in their breakdown (which normally occurs by oxidation into ketone bodies or transformation into triglycerides and export by VLDL) (Fig. 8.27). Several clinical conditions, involving mainly an increased fat input or sometimes a reduced catabolism or excretion, are associated with lipid overload and steatosis; fasting, malnutrition, obesity, excessive caloric intake, alcohol abuse, corticosteroid use, and diabetes are the most frequent causes.

Insulin resistance and hyperinsulinism play a central role in NASH by promoting the transformation of dietary carbohydrates into fatty acids, the synthesis of fatty acids into triglycerides, and, above all, the release, by adipocytes of visceral fat, of fatty acids that will reach the hepatocytes.

Abdominal obesity and metabolic syndrome are the hallmarks of NASH. Abdominal (or visceral) obesity is associated with adipocyte dysfunction leading to an increase in circulating fatty acids, insulin resistance with hyperinsulinism, and release of inflammatory cytokines. Steatosis can evolve, under the toxic influence of oxidative stress and free radicals, to steatohepatitis and ultimately cirrhosis.

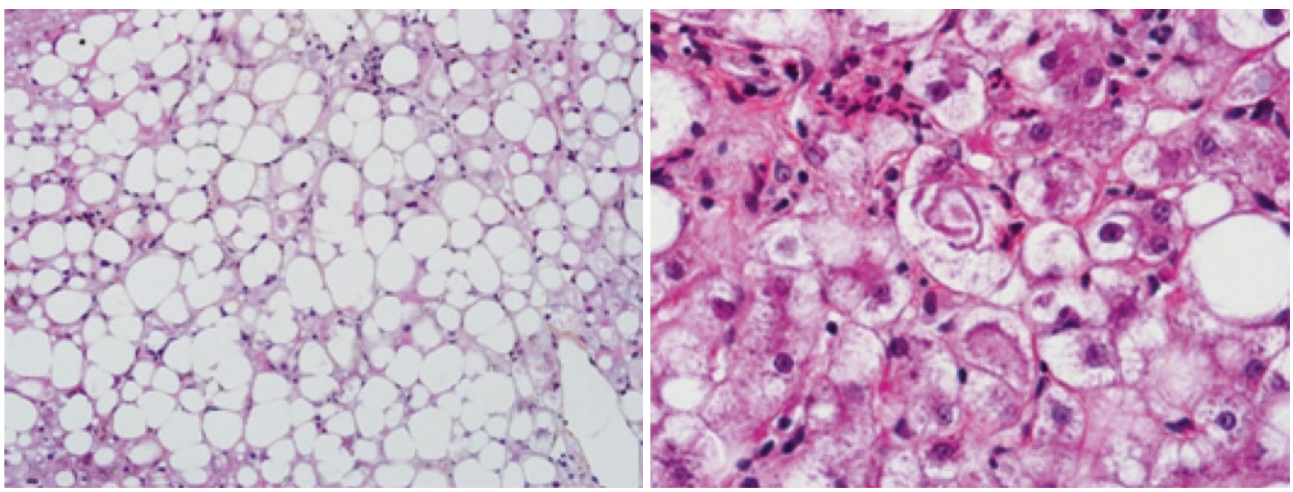


Fig. 8.26 Steatosis (hepatocytes swollen with lipid droplets): on the right, Mallory acidophilic bodies, typical of steatohepatitis

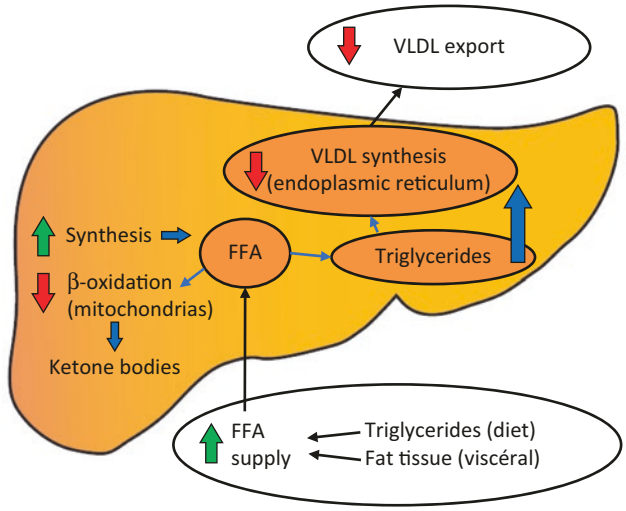


Fig. 8.27 Schematic representation of the mechanisms of liver fat accumulation (FFA free fatty acids; VLDL very-low-density lipoproteins)

Clinical presentation The patient is most often middle-aged and obese. Clinical characteristics include hepatomegaly, slightly elevated serum liver enzymes, and steatosis on ultrasound. Sometimes, the patient already has cirrhosis.

In pediatrics, NASH is the most frequent diagnosis found in children with abnormal transaminases.

The diagnosis of NAFLD is most often made in presence of liver steatosis in an individual with no significant alcohol intake (>20 g/d), with a high BMI, and without other causes of liver disease.

The difference between SS and NASH can be difficult to establish. In practice, if liver enzymes always remain normal and no signs of cirrhosis are found on the physical exam and on imaging studies, NASH is probably not a concern. However, in patients with SS, careful follow-up and reinforcement of the message to keep weight within normal BMI range will need to be applied since the risk of developing NASH is significant (according to three different studies, 25%, 44%, or 64% of patients with SS would, respectively, develop NASH overtime).

The treatment is aimed at correcting the factors that promote liver steatosis (obesity, diabetes). Abstinence from alcohol is recommended. A loss of 3–5% of the initial weight can usually improve steatosis, and a loss of 7–10% is needed to reverse inflammation and fibrosis. In the presence of steatohepatitis, a more aggressive therapeutic approach is recommended. Treatments are mainly aimed at improving insulin sensitivity (weight loss, bariatric surgery, GLP-1 analogues), reducing liver inflammation (vitamin E), or protecting the liver (antioxidants, polyunsaturated fatty acids). However, at the present time, effective pharmacological treatments against NASH are yet to be developed.

Once cirrhosis is established, its treatment is the same as for other cirrhosis (including liver transplantation, screening for hepatocarcinoma, etc., as discussed later).

(b) Hemosiderosis/hemochromatosis

Definition and epidemiology Hemosiderosis is the overload of hemosiderin (iron-containing degradation product of hemoglobin) in various tissues. It is characterized by a progressive accumulation of iron which eventually, if left untreated, leads to functional impairment of several target organs, including the liver, pancreas, heart, etc. Hemosiderosis can be acquired or hereditary:

- It can be acquired by exogenous iron overload (repeated transfusions) or endogenous iron overload (increased destruction of hemoglobin in hemolytic anemia, major thalassemia, etc.).
- It may be related to a hereditary condition (such as hemochromatosis) affecting iron metabolism. Hemochromatosis is due, in a very large majority of cases, to a mutation of the HFE gene located on chromosome 6. Genetic mutations affecting other proteins of the iron metabolism (hemojuvelin, hepcidin, ferroportin) are much rarer.

In this chapter, we will focus on hereditary hemochromatosis related to the HFE gene regulating hepcidin synthesis. Eighty-five to ninety percent of the affected patients are homozygous for the C282Y mutation (Cys 282→Tyr). In the Caucasian population of Northern European descent, approximately 1 in 250 people is homozygous for the hemochromatosis gene (C282Y); however, penetrance is highly variable. Only 70% of people who are homozygous for C282Y have elevated ferritin levels, and only a minority of them show clinical consequences of iron overload.

Iron metabolism and pathogenesis The average daily intake of iron in the diet is 10–20 mg of iron, of which only 1–2 mg is absorbed. The amount that is absorbed depends on body stores: with low iron stores, absorption increases, and vice versa.

The control of iron absorption is of primary importance to maintain iron hemostasis. Dietary iron is absorbed from duodenal and proximal jejunum enterocytes (see ► Chap. 3). Enterocytes adapt to absorb more or less iron according to the needs of the body. Hepcidin,

discovered by a French team in 2002, is a small protein of 25 amino acids considered to be the main regulator of iron absorption. This hormone is produced by hepatocytes (under regulation by HFE gene) and is released into circulation to bind to ferroportin, found on the basolateral surface of enterocytes. Ferroportin, as its name suggests, is a carrier of iron from the inside to the outside of cells. When hepcidin binds to ferroportin, ferroportin is internalized and degraded, so that iron transfer from inside the cell to plasma stops. Hepcidin therefore acts as an inhibitor of intestinal iron absorption. Its expression is decreased in the presence of anemia, inefficient erythropoiesis, or hypoxemia, resulting in increased iron absorption.

In individuals carrying the hemochromatosis HFE gene, hepcidin expression is decreased, and ferroportin levels are elevated, resulting in increased and uncontrolled iron absorption. Excess iron is intercalated with ferritin. When ferritin is saturated with iron, unbound iron causes hepatocyte injury. As iron accumulation progresses, iron accumulates in other tissues including the pancreas, pituitary gland, heart, etc.

Clinical presentation of hemochromatosis Nowadays, the vast majority of patients are diagnosed before becoming symptomatic, after discovery of abnormal routine iron tests or following screening of family members.

The accumulation of iron is progressive, which means a long asymptomatic phase before the appearance of clinical signs and symptoms. It is during this period that treatment can be initiated and thus prevent the onset of complications of iron overload in the target organs.

If undetected, hemochromatosis can become clinically apparent between 40 and 60 years of age in men. The disease is typically 10 times more common in men than in women, because women are "protected" from iron excess because of blood loss from menstruation and pregnancy.

Classically referred to as "bronze diabetes," hemochromatosis can affect a variety of organs:

- The skin can show a brownish-bronze discoloration maximal in areas of the body exposed to the sun, as well as on genitals and old scars.
- The liver is often enlarged. Eventually, and relatively late, signs and symptoms of cirrhosis can develop. Fifteen to thirty percent of patients with cirrhosis will develop a hepatocellular carcinoma, and this may be the mode of presentation.
- Endocrine problems may occur: diabetes (selective iron deposition in pancreatic beta cells), hypogonadism (with loss of libido, erectile dysfunction, testicular atrophy in 30–35% of men, and amenorrhea in about 15% of women), pituitary insufficiency with hypothyroidism, and adrenal insufficiency.
- Joints are often affected (up to 2/3 of patients) and show degenerative changes with an atypical pattern of distribution (involving mainly the hands) and crystal arthropathy (CPPD).
- The heart can be damaged by accumulation of iron in the myocardium leading to conduction system anomalies with EKG changes in 35% arrhythmias and, more rarely, by heart failure secondary to dilated cardiomyopathy.

Diagnosis of hemochromatosis Serum iron is elevated, transferrin is hypersaturated (>45%), and serum ferritin, which is an index of iron stores, is increased (these parameters can be elevated in other circumstances, especially in a context of inflammation and alcohol use disorder, and therefore are not necessarily indicative of iron overload). The diagnosis is confirmed by genetic testing for the C282Y mutation.

Once an individual has been diagnosed, screening of first-degree relatives is required. Iron tests including ferritin are requested, as well as genetic testing for hemochromatosis (HFE). In children of a probant case, it is recommended to wait until adulthood before performing genetic testing.

Liver biopsy is no longer necessary to diagnose hemochromatosis, given the genetic tests now available.

It is important to remember that the diagnosis of hemochromatosis, because of its frequency, should be sought in every patient with cirrhosis, even if another etiology has been identified.

Treatment and follow-up of hemochromatosis Therapeutic phlebotomy is the cornerstone, frontline treatment. Each phlebotomy removes 500 mL of blood, equivalent to one unit of packed red blood cells, which corresponds to approximately 200–250 mg of iron. Phlebotomies are initiated once a week, if tolerated (while ensuring not more than a 20% decrease in hemoglobin compared to the previous value). Patients may have accumulated significant excess iron stores of up to 30 g or more. Therefore, 2–3 years of regular phlebotomies may be required before normalization of serum ferritin levels. The frequency of maintenance phlebotomies varies greatly from person to person: some individuals need to maintain monthly phlebotomies, while others only need one to two phlebotomies annually. The explanation for this variation in the rate of iron accumulation is not known.

Since not everyone with the HFE gene mutation will develop significant iron overload, annual follow-up with iron tests is recommended. Those with high ferritin levels will start treatment with phlebotomies, or make regular blood donations, to prevent complications of iron overload.

Phlebotomies can improve general well-being, energy levels, and hyperpigmentation and help with heart and liver function. The benefit of treatment is less obvious when diabetes is present and absent in cases of testicular atrophy and arthropathy.

(c) Wilson's disease

Definition and pathology Progressive lenticular degeneration described in 1912 by Wilson is a rare hereditary disease characterized by excess copper levels in the liver and the brain.

The gene responsible for Wilson's disease, ATP7B, is found on chromosome 13 and codes for a copper transporter ATPase. When the ATP7B protein is absent or dysfunctional, there is a reduction in the biliary excretion of copper, as well as the incapacity to incorporate copper into ceruloplasmin, the major plasma copper transporter.

Copper accumulates in the liver and causes liver damage. Eventually, copper overflows into the circulation, with additional damage to other target organs, particularly the brain, cornea, and kidneys.

Clinical presentation The clinical consequences of copper overload are predominantly hepatic and neuropsychiatric, with a predominance of one or the other depending on age at presentation. Copper begins to accumulate from birth, and diagnosis is made on average between the ages of 5 and 35 years, but as early as 3 years, and even as late as 70 years.

Liver manifestations are variable: asymptomatic abnormal liver tests, acute or even fulminant hepatitis, chronic hepatitis (8–10% of cases of chronic active hepatitis in young people), or even cirrhosis (sometimes presenting with end-stage liver failure requiring urgent transplantation).

Neurological manifestations include gait, movement, and speech disorders (dystonic, ataxic, and Parkinsonian syndromes). Cognitive, psychiatric, or behavioral disorders can also be observed.

On ophthalmic examination (slit lamp), Kayser-Fleischer (KF) rings, made of copper deposits in Descemet's membrane of the cornea, can be found. These rings are found in 44–62% of patients with liver presentation but in 95% of individuals with neurological presentation.

Diagnosis of Wilson's disease KF rings, decreased ceruloplasmin, and increased 24-hour urinary copper confirm the diagnosis. Genetic testing can also be performed when diagnosis remains uncertain.

Treatment of Wilson's disease Copper overload must be treated to prevent liver and neurological complications. Copper chelating agents such as penicillamine or trientine are used to reduce the amount of excess tissue copper. Liver transplantation may be required in cases of severe liver failure.

(d) Alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin (A1AT) is a 394AA protein encoded by the SERPINA gene located on chromosome 14 that inhibits several tissue proteases such as trypsin (as the name suggests) but mainly elastase. A1AT is synthesized in hepatocytes and released into the circulation and diffuses in pulmonary alveoli to inactivate neutrophil elastase (the main protease responsible for alveolar destruction and activated with continuous exposure to inhaled pathogens). The loss of the lung protective effect of A1AT can lead to the early development of emphysema.

Pathophysiology and epidemiology The genetic mutations responsible for A1AT deficiency are multiple (>100) and may affect the synthesis, the hepatocyte secretion, or the functioning of the molecule itself.

The variant designated Pi Z is the consequence of a substitution mutation of glutamic acid for lysine at position 342. The resulting unstable polypeptide undergoes polymerization within the endoplasmic reticulum where it remains trapped, unable to be released into the circulation. As a result, serum A1AT levels are decreased. On liver biopsy [following PAS (periodic acid-Schiff) staining], the abnormal accumulation of A1AT can be observed as diastase-resistant red globules inside the hepatocytes.

Only A1AT mutations leading to the inability to secrete the protein outside hepatocytes are associated with liver damage. With certain mutations, subjects produce no A1AT and develop emphysema very early (100% before the age of 30 years), but they do not accumulate A1AT inside the liver cells and therefore do not develop liver disease.

Clinical presentation Hepatic manifestations of A1AT Pi ZZ deficiency can occur in the neonate (hepatitis, neonatal jaundice), in childhood, or even in adults (with cirrhosis, liver failure, etc.).

Diagnosis A1AT blood levels are low. Liver biopsy reveals typical diastase-resistant PAS-positive globules inside hepatocytes. Genetic testing can also identify the mutated gene.

Treatment In presence of cirrhosis, management is the same as in any other cases. When the liver disease progresses to decompensated cirrhosis with liver failure, the only treatment remains transplantation. The recipient acquires the A1AT phenotype from the donor: A1AT blood levels are normalized, and the disease does not recur.

The infusion of purified human A1AT is used in people with lung disease, but is ineffective in cases of liver disease.

8.6.3 Cirrhosis

Liver cirrhosis is a diffuse involvement of the liver that is caused by various pathological processes and is diagnosed with varying degrees of severity depending on the stage of the disease.

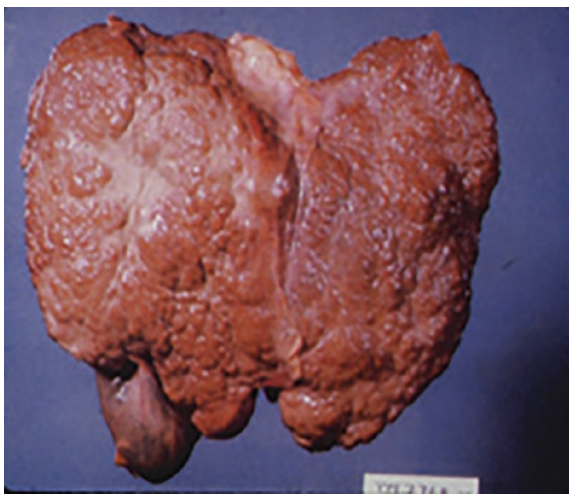
8.6.3.1 Pathology

Macroscopically, the cirrhotic liver is irregular and hard with the presence of nodules of variable size (◘ Fig. 8.28). Sometimes, the liver can look almost normal, but has a harder consistency.

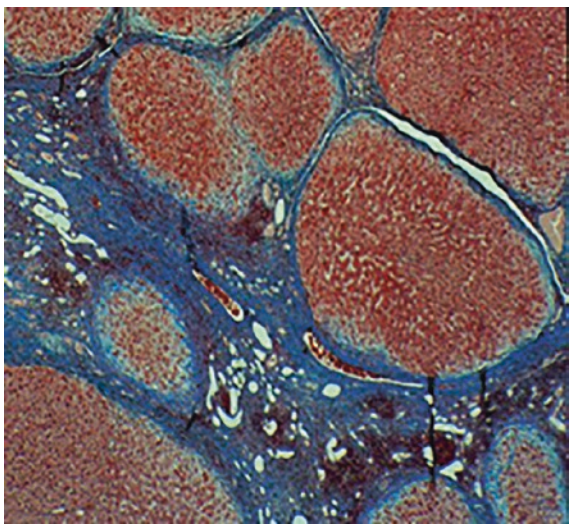
On histological examination, cirrhosis is defined as a loss of normal liver architecture (see ► Sect. 8.2) due to fibrous septa that separate regenerative nodules (double-cell hepatocyte plates) (◘ Fig. 8.29). Cirrhosis is often referred to as being micronodular (nodules <3 mm, typical of alcoholic cirrhosis), macronodular (nodules >3 mm, often encountered in post-necrotic cirrhosis associated with viruses B, C, etc.), or mixed.

In addition to these basic lesions, one can find histological lesions that are more or less specific for an underlying etiology: portal inflammatory infiltrate; lobular or cellular necrosis; centrilobular congestion; deposits of bile, iron, copper, alpha-1 antitrypsin globules; presence of granulomas, bile duct lesions, etc.

Liver biopsy remains the most useful test to determine the underlying etiology of cirrhosis: furthermore, our understanding of the pathological process rests on the description of the injury described on histology. The liver biopsy is nowadays often replaced by noninvasive methods, especially for the determination of the stage of fibrosis (e.g., FibroScan® elastography).



◘ **Fig. 8.28** The cirrhotic liver: here with increased volume, having lost its regular contours and with widespread irregular nodules. (Photo from G. Pomier)



◘ **Fig. 8.29** Hepatocytes (in red) are arranged in nodules surrounded by bands of fibrosis (in blue). (Photo from G. Pomier)

8.6.3.2 Etiology of Cirrhosis

Possible causes of cirrhosis are listed in ◘ Table 8.7. Each etiology has been discussed in previous sections. The most frequent causes of cirrhosis are chronic alcohol abuse, chronic viral hepatitis B and C, and NASH (non-alcoholic steatohepatitis, the incidence of which is rapidly increasing worldwide).

Table 8.7 Causes of cirrhosis

Alcohol
Virus
Hepatitis B, C, or D
Metabolic disorders
Non-alcoholic steatohepatitis
Hemochromatosis
Wilson's disease
α1-Antitrypsin deficiency
Galactosemia
Glycogenosis type 4
Tyrosinemia
Fructosemia
Cholestasis
Sclerosing cholangitis
Chronic obstruction of bile ducts
Primary biliary cholangitis
Cystic fibrosis
Autoimmune diseases
Drug induced
Vascular diseases
Veno-occlusive disease
Budd-Chiari syndrome
Cardiac cirrhosis
Cryptogenic cirrhosis

8.6.3.3 Clinical Manifestations of Cirrhosis

When diagnosed, cirrhosis can be asymptomatic (compensated) or complicated by evidence of liver failure (decompensated).

Each complication has its pathophysiology explanation and will be discussed separately.

(a) Compensated cirrhosis The disease can be suspected or revealed by the fortuitous discovery of clinical, biochemical, imaging, or endoscopic abnormalities.

Clinically, hepatomegaly, stigmata of chronic liver disease (spider naevi, palmar erythema, white Terry's nails) (Fig. 8.30), portal hypertension (abdominal wall collateral circulation, splenomegaly), or signs specific to each etiology can be found (Table 8.8).

Laboratory tests can show abnormal liver tests (total and conjugated bilirubin, transaminases, alkaline phosphatase) and signs of alteration in liver function (low albumin and/or increased INR and bilirubin levels) or in the blood count (thrombocytopenia being the most frequent).

The frequent use of imaging tests (ultrasound, tomodensitometry, magnetic resonance) prescribed for non-hepatic reasons has led to more and more patients being diagnosed fortuitously with liver disorders. A dysmor-

Table 8.8 Clinical signs suggestive of cirrhosis

Hepatomegaly
Signs of portal hypertension
Abdominal wall collateral circulation
Splenomegaly
Ascites
Signs of chronic liver disease
Jaundice
Palmar erythema
Spider naevi
White nails
Loss of body hair
Gynecomastia
Clubbing
Signs suggestive of a specific etiology
Xanthelasma (cholestasis)
Dupuytren's disease (chronic alcoholism)
Kayser-Fleischer ring (Wilson's disease)

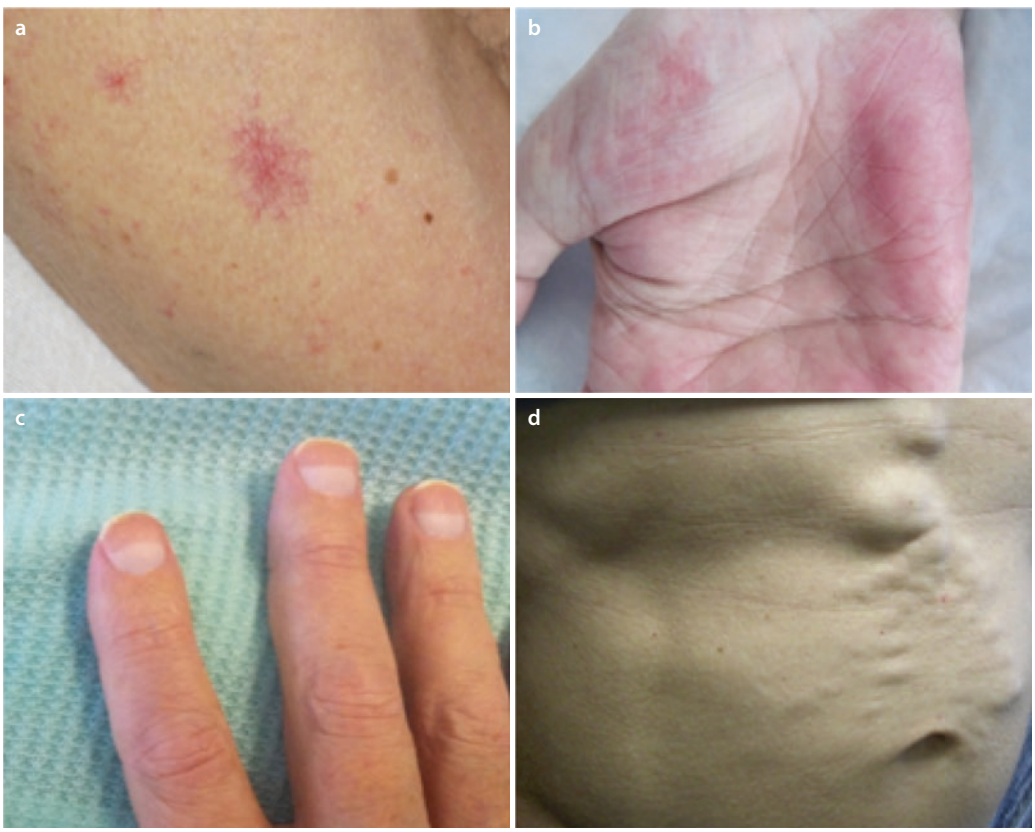


Fig. 8.30 Stigmata of chronic liver disease: **a** spider naevi, **b** palmar erythema, **c** white Terry's nails, **d** abdominal venous circulation. (Photos from G. Pomier)

phic liver, atrophic or hypertrophic, and/or signs of portal hypertension (splenomegaly, subclinical ascites, collateral circulation) raise concern of the presence of cirrhosis.

Upper gastrointestinal endoscopy can reveal cirrhosis when esophageal or gastric varices, portal hypertensive gastropathy (fish-like appearance of the gastric mucosa), and GAVE (gastric antral vascular ectasia, striated hyperemia of the antrum) are found (Fig. 8.31).

The prognosis of compensated cirrhosis is highly variable. The diagnosis of cirrhosis is an important warning signal, and regular follow-up should be instituted to identify complications and enhance patient management.

The major complications of cirrhosis are related to portal hypertension, liver failure, or the development of a hepatocellular carcinoma.

(b) Portal hypertension In portal hypertension (PHT), the pressure inside the portal vein is more than 5 mmHg

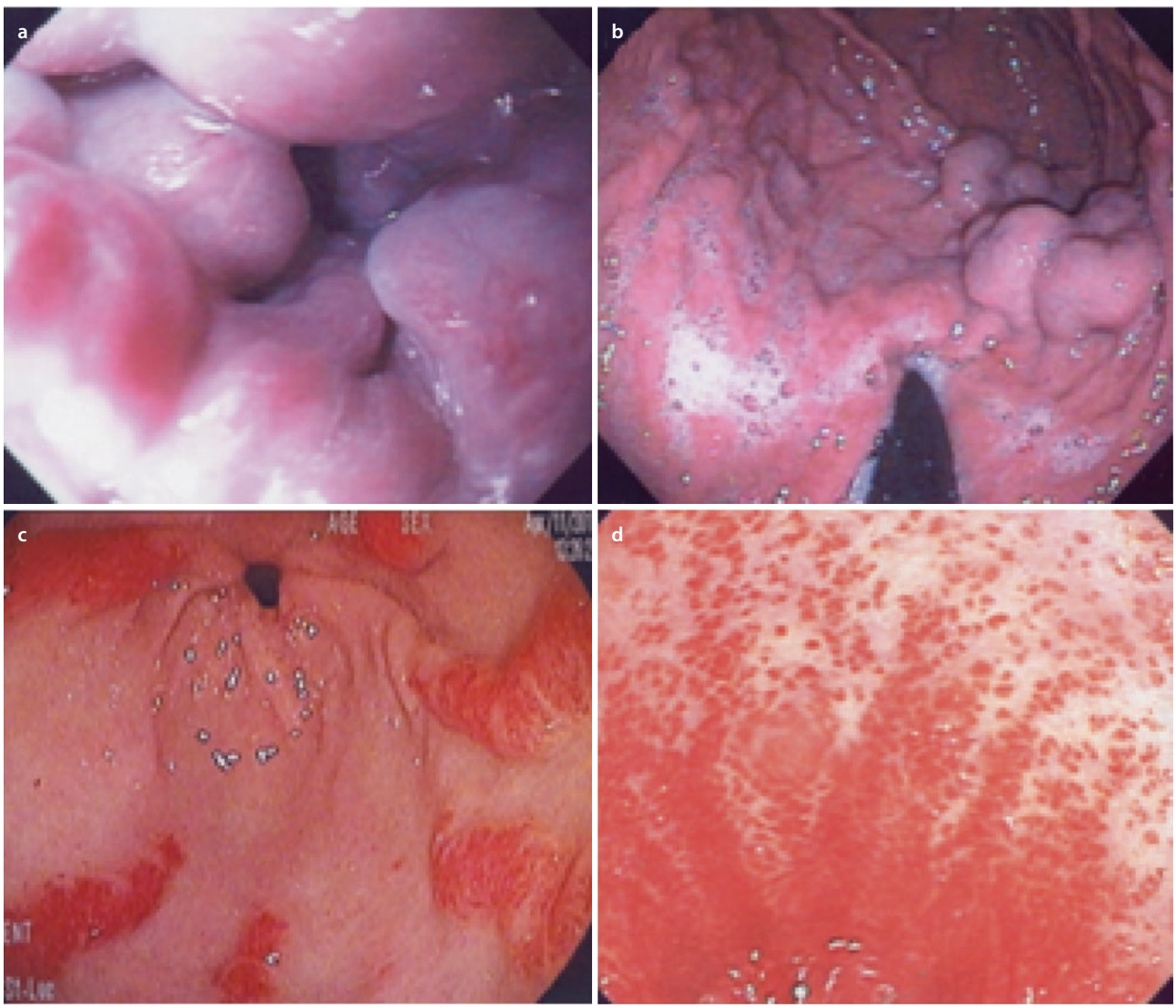


Fig. 8.31 Endoscopic findings associated with cirrhosis: **a** esophageal varices, **b** gastric (fundal) varices, **c** GAVE with watermelon appearance, **d** diffuse GAVE. (Photos by P. Poitras)

Table 8.9 Classification of portal hypertension

Pre-sinusoidal
Extrahepatic (portal vein thrombosis, stenosis, or obstruction)
Intrahepatic (granulomatosis)
Sinusoidal (cirrhosis)
Post-sinusoidal
Intrahepatic (veno-occlusive disease)
Extrahepatic (Budd-Chiari syndrome, constrictive pericarditis, right heart failure)

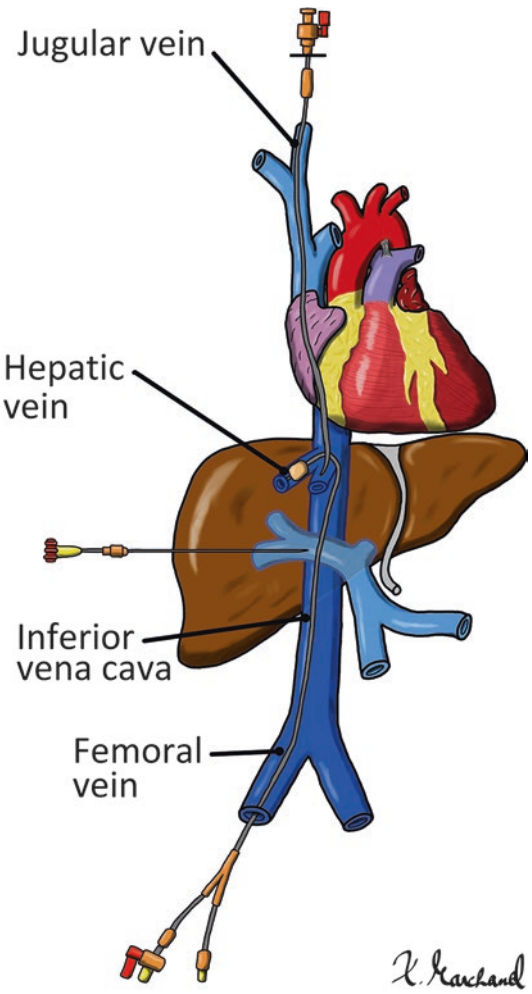


Fig. 8.32 Measurement of portal pressure by various approaches: (1) transhepatic route directly into the portal vein; (2) by venous route via the jugular vein, or (3) the femoral vein to reach a hepatic vein (by obstructing the vein with a small balloon, the recorded pressure recorded corresponds, in the majority of cases, to the upstream venous pressure, i.e., that of the portal vein)

bove the pressure in the vena cava. PHT can develop from pathology at the pre-sinusoidal, sinusoidal, or post-sinusoidal level (Table 8.9) causing an increased resistance to portal blood flow between its entry into the liver and its exit in the inferior vena cava.

Portal pressure can be measured by highly specialized techniques, either directly with a needle inserted into the portal vein through a percutaneous transhepatic approach or, more safely, with a needle inserted into the jugular vein, brought through the right atrium and the inferior vena cava to the hepatic veins, and then pushed through the liver to the portal vein. The portal pressure can also be assessed by an indirect method where the pressure within the hepatic vein is measured with the pressure sensing catheter (inserted through a jugular or femoral vein) being free within the vein and after wedging in the liver parenchyma or while obstructing the vein with a small balloon: the difference between the free and the wedged or blocked pressures gives the hepatic venous pressure gradient which reflects the portal pressure in the majority of cases (Fig. 8.32).

Liver fibrosis developing along the sinusoids can block portal blood flow as it travels from the portal space to the terminal hepatic vein to reach the hepatic veins and the systemic circulation. This obstacle to portal flow is responsible for portal hypertension. When this develops, new blood channels will develop and lead to the formation of collateral veins that enable the portal blood to reach the systemic circulation by bypassing the liver. Such collaterals are formed from the portal vein to the thoracic veins of the lower esophagus (esophageal varices) or the upper stomach (gastric varices), to the superior rectal veins (rectal varices or hemorrhoids), or to the umbilical vein and abdominal wall (caput medusae in Cruveilhier-Baumgarten abdominal varices) (Fig. 8.33).

Therefore, cirrhosis can be complicated, in response to portal hypertension, by the development of collateral veins of which esophageal (EV) and gastric varices are the most clinically dangerous. Gastrointestinal (GI) bleeding secondary to EV rupture is a frequent complication of portal hypertension; the risk of recurrence after a first episode is high (70% at 1 year in the absence of treatment). Each hemorrhagic episode is associated with a significant risk of mortality (10–20% at 6 weeks) especially in individuals with liver failure. This is why systematic screening for EV is performed in cirrhotic patients, especially since treatments have been shown to be efficient in preventing the first episode of GI bleeding in these patients.

Treatment methods for esophageal varices are summarized in Table 8.10.

Prophylactic treatment of EV rupture is effective in preventing bleeding, either by lowering portal pressure

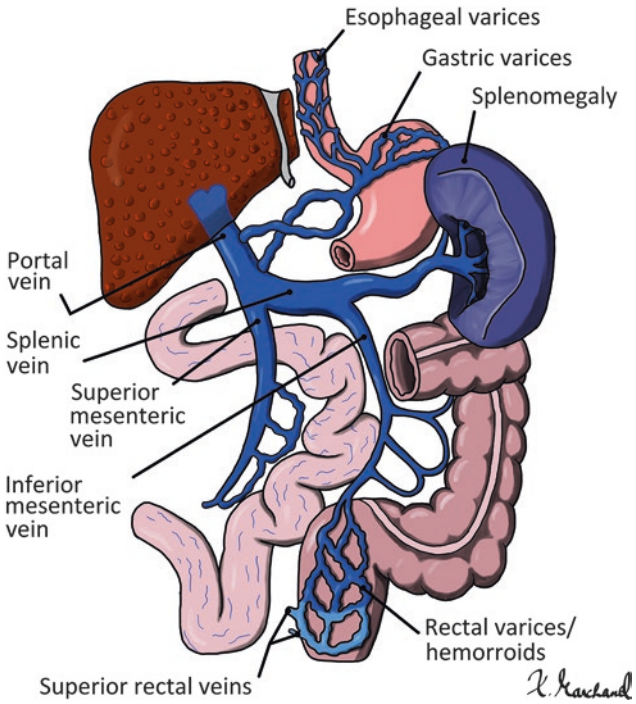


Fig. 8.33 Portal venous hypertension leads to the development of venous collaterals in the upstream vascular territory, resulting in esophageal (via the left gastric vein), gastric (via the left gastric vein and/or the short gastric veins from the splenic vein), rectal (via the inferior mesenteric vein), or even intestinal (via the superior mesenteric vein) varices. Increase in splenic vein pressure causes splenomegaly observed in that setting

Table 8.10 Treatment of variceal bleeding in cirrhotic patients

1. Primary prophylaxis (before EV rupture)
Beta-blockers (carvedilol 12.5–25 mg/day or nadolol 20–80 mg/day)
Endoscopic variceal ligation
2. Treatment of GI bleed secondary to EV rupture
Pharmacological (octreotide 50 ug/h IV for 2–5 days)
Endoscopic: esophageal varices ligation
Gastric varices obliteration with biologic glue
Others: Blakemore tube, TIPS
3. Secondary prophylaxis (to prevent recurrence of bleeding)
Beta-blockers
Endoscopic variceal ligation
TIPS
Liver transplant

(with beta-blockers) or by eradicating EV by endoscopic variceal ligation (EVL, to be repeated 3 or 4 times, at 4-week intervals until the varices are eradicated).

In the case of acute bleeding, the bleeding can be stopped by lowering portal pressure pharmacologically. Octreotide, a somatostatin derivative, is widely used for this purpose, as is terlipressin (a vasopressin derivative not currently available in Canada). EVL is the most effective way to stop EV bleeding. When these approaches fail (10–20% of cases), bleeding can be stopped by tamponade of the EV with a balloon catheter (Blakemore tube, ◘ Fig. 8.34, left) or by radiologically creating a channel inside the liver between the portal vein and the hepatic vein (TIPS (transjugular intrahepatic portosystemic shunt), ◘ Fig. 8.34, right). The management of upper GI bleeding is discussed in ▶ Chap. 11.

Treatment of portal hypertension, and its complications, has long relied on the premise of bypassing the liver (creating an obstacle responsible for PHT) with blood from the portal circulation being derived directly into the systemic circulation. For many years, a surgical portocaval shunt, by which the portal vein is anastomosed to the inferior vena cava, was used for this purpose. A delicate operation, often carrying a high morbidity risk (since it was performed in unstable patients with decompensated cirrhosis, hemorrhage from ruptured EV, etc.), the portocaval shunt was effective in reducing portal pressure but was often complicated by hepatic encephalopathy (portal blood now derived from the liver is then not filtered to extract toxic

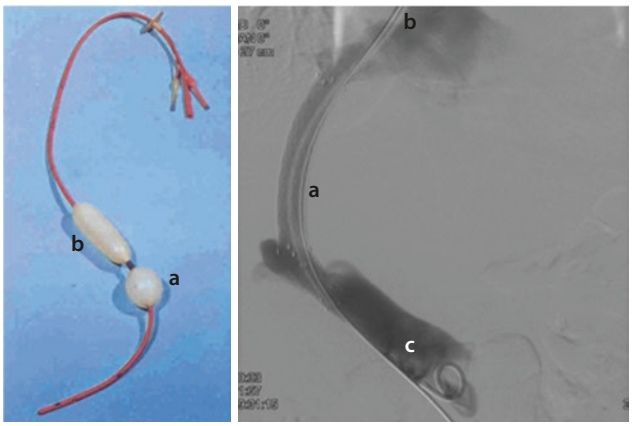
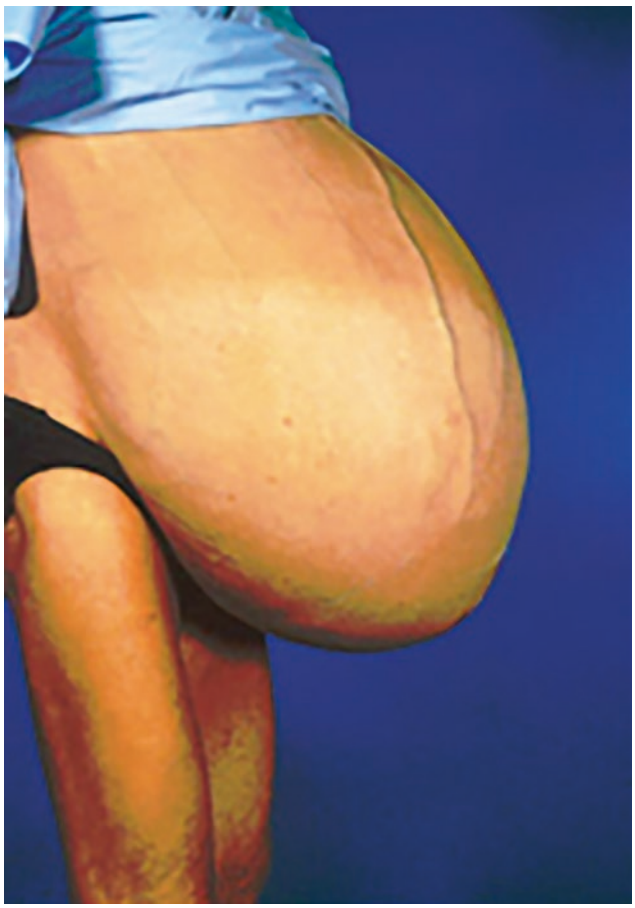


Fig. 8.34 Left: Blakemore tube, inserted nasally or orally, includes a lower balloon (a) that will be inflated in the gastric fundus to compress gastric varices and an esophageal balloon (b) to compress esophageal varices. Right: TIPS – under fluoroscopic guidance, a vascular stent (a) is introduced via a hepatic vein (b) through the liver parenchyma into the portal vein (c), thus decompressing it by restoring a direct flow from the portal vein to the inferior vena cava

substances such as ammonia). Today, TIPS (transjugular intrahepatic portosystemic shunt) is the method of choice to decompress the portal vein and reduce portal pressures. It is performed by inserting, through a jugular vein approach and under radiological guidance, a vascular stent to be positioned in the liver to bridge between the hepatic and portal veins. Simpler and safer than a surgical shunt, this procedure is also reversible and does not jeopardize a future liver transplant if necessary.

(c) Ascites Ascites is defined as an accumulation of fluid in the abdominal cavity. The etiology includes multiple causes; its differential diagnosis is discussed in ▶ Chap. 28. In the setting of cirrhosis, the formation of ascites is triggered by portal hypertension combined with hypoalbuminemia [which promotes the passage of fluids from the intravascular space to the extravascular space (here, the peritoneal cavity due to PHT)].

Clinically, ascites is manifested by an increase in abdominal girth (◘ Fig. 8.35) associated with signs of portal hypertension (collateral circulation, splenomegaly, ◘ Table 8.8). The development of an umbilical and/or inguinal hernia is common. Abdominal collateral circulation may be localized in the periumbilical region (caput medusae of Cruveilhier-Baumgarten syndrome). Edema of the lower limbs is often present (promoted by the decrease in oncotic pressure due to hypoalbuminemia and an increase in pressure of the lower limb veins due to compression of the intra-abdominal vena cava by ascites).



◘ **Fig. 8.35** Ascites: distension (here "monstrous") of the abdomen by fluid accumulated in the peritoneal cavity. (Photo from G. Pomier)

Abdominal paracentesis of ascitic fluid in portal hypertension reveals a low albumin fluid (serum albumin *minus* ascites albumin ≥11 g/L) and few white blood cells (<250 neutrophils/mm^3). When neutrophils are ≥250 elements/mm^3, an ascites infection must be assumed; this is confirmed by a positive culture in about half of the cases.

Ascites infection (called spontaneous bacterial peritonitis (SBP)) is common and caused by bacterial translocation promoted by splanchnic vasodilatation and increased permeability of the digestive barrier. It tends to recur after a first episode. SBP should be suspected in the presence of abdominal pain, fever, and any unexplained deterioration in clinical status or liver function in a cirrhotic patient. SBP needs to be treated promptly with broad-spectrum antibiotics; adjustment can be made once a bacterium has been identified. Prevention of relapse of infection is indicated by using quinolones on a chronic basis (e.g., ciprofloxacin 500 mg daily).

Treatment of ascites (◘ Table 8.11) consists primarily of a low-salt diet (2–4 g NaCl per day) sometimes associated with water restriction in case of severe hyponatremia. The addition of diuretics is often necessary

Table 8.11 Treatment of ascites

1. Non-infected ascites
Low-salt diet (NaCl 2–4 g/d)
Water restriction (if hyponatremia is present)
Diuretics: furosemide (20–160 mg/d) + spironolactone (100–400 mg/d)
2. Refractory ascites
Regular paracentesis + albumin infusions
TIPS
Liver transplant
3. Ascites with bacterial spontaneous peritonitis
Treatment of the episode: antibiotic (according to the most likely bacteria) + albumin infusions (to prevent acute renal failure)
Prophylactic treatment of recurrence: daily quinolone
4. Hepatorenal syndrome
Albumin infusions + midodrine + octreotide (or terlipressin if available)
Liver transplant

and leads to increased sodium loss. Spironolactone and furosemide are most often combined at increasing doses to achieve a weight loss of no more than 1 kg per day in the absence of peripheral edema. The recommended initial dose is spironolactone 100–200 mg/d and furosemide 20–40 mg/d, with maximum doses of 400 mg/d and 160 mg/d, respectively. Exceptionally, a low dose of metolazone (2.5 mg 3 times/week) can be used in combination with these two diuretics.

In case of refractory ascites, two options are available: repeated large-volume paracentesis combined with albumin infusions and TIPS. A liver transplant is the definitive solution given the poor prognosis of refractory ascites.

The development of ascites marks a turning point in the clinical picture of a cirrhotic patient and is indicative of significant degree of hepatic failure. At that point, cirrhosis is considered decompensated. Even if at the beginning ascites can be easily controlled with a low-salt diet and diuretics, it will become resistant to medical treatment in 5–10% of cases.

The onset of ascites is associated with a poor mid-term prognosis.

(d) Extra-digestive complications Decompensated cirrhosis can also be complicated by kidney or lung disorders:

- *Hepatorenal syndrome*. Hepatorenal syndrome is defined as an increase in the level of serum creatinine, low urinary sodium, and increased urinary Osmolarity in the absence of hypovolemia and organic kidney disease.

  Ascites is associated with a series of hemodynamic disturbances with splanchnic vasodilatation followed by sequestration of blood in the splanchnic region; systemic hypovolemia then develops which triggers a compensatory increase in vasoconstrictor systems (renin-angiotensin, catecholamines) resulting in renal cortical vasoconstriction responsible for sodium retention which perpetuates ascites. When the renal hemodynamic changes are significant, the hepatorenal syndrome can appear (Fig. 8.36).

  Hepatorenal syndrome most often occurs in the setting of severe liver failure. It is treated with vasoconstrictors such as intravenous norepinephrine (or terlipressin when available) and albumin infusions. The combination of octreotide (50 µg/hour) and midodrine (2.5–10 mg 3 times daily according to tolerance) is another therapeutic option. Efficacy is most often transient, and liver transplantation is the only definitive treatment.
- *Hepatopulmonary syndrome* is characterized by dyspnea and hypoxemia that manifests while the patient is in the standing position and which improves in the supine position. It is caused by marked vasodilatation of the pulmonary capillary bed and resolves after liver transplantation.

  It is to be differentiated from porto-pulmonary hypertension, which is defined as pulmonary arterial hypertension without identifiable cause in a patient with portal hypertension. Vasoactive treatments are used with variable success (beta-blockers and TIPS should be avoided). Severe porto-pulmonary hypertension is a contraindication to liver transplantation due to the high risk of perioperative mortality.

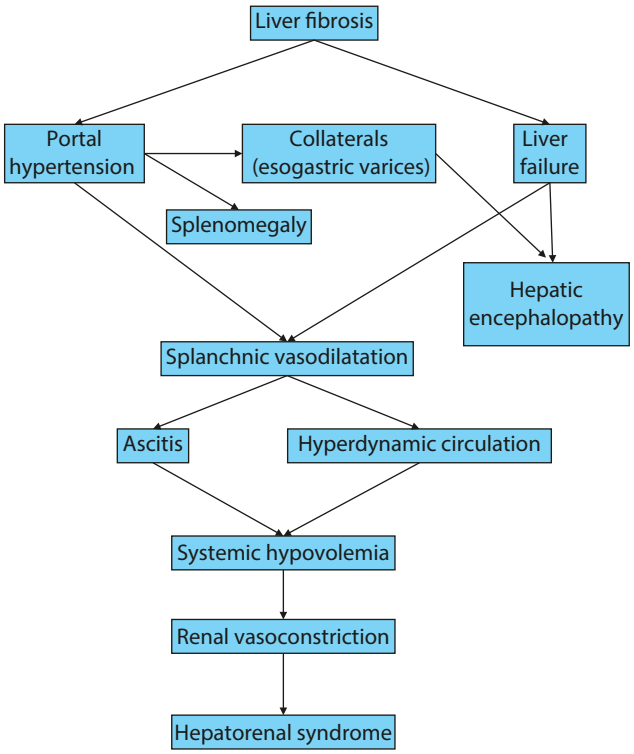


Fig. 8.36 Hepatorenal syndrome

(e) Hepatic encephalopathy Hepatic encephalopathy (HE) results from reversible neurotoxicity of one or more substances [among which ammonia (NH_3) plays an important role] not eliminated by the liver due to (a) liver failure (mainly by a decrease in the number of hepatocytes) and (b) bypassing of blood from the liver through venous collaterals (e.g., esophageal varices) developed with PHT and draining blood from the splanchnic territory directly into the systemic circulation.

NH_3 is not the sole cause of hepatic encephalopathy (other mediators are probably involved), but it is a commonly implicated etiologic factor. It is a product of the degradation of proteins by colonic bacteria. NH_3 is absorbed in the colon, reaches the portal circulation,

and is normally rapidly extracted during its first pass through the liver where it is metabolized in the urea cycle in hepatocytes. In case of hepatic failure, or bypass of the liver by portosystemic collaterals, high concentrations of NH_3 accumulate in the circulation and reach the brain. Most therapeutic strategies for HE (see below) will aim at reducing ammonia levels by reducing its production or absorption (antibiotics against colonic flora, acceleration of colonic transit, etc.) or by facilitating its excretion (sodium benzoate).

Clinically, HE is manifest by the presence of a flapping tremor with or without other alterations in neurological function. There are four different clinical stages of increasing severity as shown in ◘ Table 8.12.

When a cirrhotic patient develops neurological symptoms, one must first exclude other causes (toxic-metabolic, cerebral hemorrhage, meningitis, etc.). HE can be spontaneous or triggered by precipitating factors (infections, GI bleed, constipation, electrolyte imbalance, drugs, etc.).

On laboratory testing, there are usually signs of severe liver damage: high total bilirubin (usually mixed direct and indirect); variable increase, depending on the etiology, in transaminases and alkaline phosphatase; low albumin; and coagulation factors (increased INR, etc.). Kidney function (as measured by plasma creatinine) is variably impaired. Increased ammonia is often present in HE, but is not a diagnostic criterion (as it may be elevated in the absence of encephalopathy); its level does not correlate with the severity of the stage of hepatic encephalopathy and should not be routinely measured.

Treatment of HE is aimed at (1) correcting the triggering factor (infection, electrolyte imbalance, dehydration, constipation, GI bleed, use of neuroactive drugs such as opioids or sleeping pills); (2) decreasing neurotoxins involved in HE pathophysiology (primarily ammonia, either by increasing its elimination or decreasing its synthesis) (◘ Table 8.13).

Lactulose acts by acidifying the feces and transforming ammonia (NH_3) into non-absorbable ammonium ion (NH_4^+).

The antibiotic rifaximin decreases the anaerobic colonic flora, an important source of ammonia. It has replaced neomycin and metronidazole, which are too toxic.

Sodium (or potassium) benzoate eliminates ammonia in the urine in the form of hippuric acid.

Low-protein diet is no longer recommended on a chronic basis, as it leads to loss of muscle mass.

(f) Hepatocellular carcinoma Hepatocellular carcinoma can develop in the setting of cirrhosis, regardless of its etiology.

8.6.3.4 Prognosis of Cirrhosis

The prognosis of cirrhosis strongly depends on the degree of liver failure, which can be assessed (in adults) using the clinical-biological scores of Child-Pugh (◘ Table 8.14)

◘ **Table 8.12** Stages of hepatic encephalopathy (West Haven classification)

Stage	Mental state	Asterixis
1	Euphoria or depression	±
	Mild confusion	
	Slow speech	
	Sleep disturbances	
2	Lethargy	+
	Moderate confusion	
	Minimal disorientation	
	Inappropriate behavior	
3	Severe confusion	+
	Inconsistent speech	
	Sleepy but arousable	
	Gross disorientation	
4	Coma	–

Table 8.13 Treatment of hepatic encephalopathy

1. Eliminate another cause of encephalopathy
Brain injury (hematoma, stroke, etc.)
Meningitis
Metabolic (hypo-/hyperglycemia, uremia, etc.)
2. Correct precipitating factor(s)
Infection (ascites, pneumonia, urinary tract infection, etc.)
GI bleed (blood in the intestine leading to protein overload)
Medications (opiates, anxiolytics, etc.)
Electrolytic imbalance (diuretics, hypokalemia, etc.)
Constipation (promotes NH_3 absorption)
Portocaval shunt (TIPS, etc.)
3. Reduce ammonia
Lactulose (30 mL 2–4 times/day to obtain 2–4 stools/day; reduces NH_3 absorption by accelerating transit and acidifying stools)
Antibiotics: rifaximin (reduces colonic flora producing NH_3)
Benzoate of Na^+ (3 g TID; enhances urinary excretion of NH_3)

Table 8.14 Child-Pugh index

Measurements	1 point	2 points	3 points
Total bilirubin, µmol/L	<34	34–50	>50
Serum albumin, g/L	>35	28–35	<28
INR	<1.7	1.71–2.30	>2.30
Ascites	Absent	Mild	Moderate to severe
Encephalopathy	0	Grades I–II	Grades III–IV

Child-Pugh score is obtained by adding the points of the five measures (max: 15 points) and is used as a prognostic tool

Points	Class	1-year survival
5–6	A	100%
7–9	B	81%
10–15	C	45%

Table 8.15 MELD (Model for End-Stage Liver Disease) score

MELD score uses the patient's values for serum bilirubin, creatinine, and INR
Results are then incorporated in the following formula: MELD score = 3.78 [Ln bilirubin (mg/dL)] + 11.2 [Ln INR] + 9.57 [Ln creatinine (mg/dL)] + 6.43

Score	3-month mortality
40 or more	71.3%
30–39	52.6
20–29	19.6
10–19	6.0
<9	1.9

and MELD (Model for End-Stage Liver Disease) score (Table 8.15). This information is crucial in determining the 3-month risk of death and postoperative or post-TIPS complications and is used worldwide to decide if a patient should be referred for transplantation.

8.7 Tumor Disorders

8.7.1 Primary Neoplasms

(a) Hepatocellular carcinoma Hepatocellular carcinoma (HCC or hepatoma) is the fifth most common cancer in men and the seventh most common in women. Macroscopic and microscopic appearances of HCC are shown in Fig. 8.37.

Risk factors In the vast majority of cases (90%), HCC is found in a patient with underlying cirrhosis, with an annual incidence of 1–8%. But it can also occur in absence of cirrhosis. The main risk factors for hepatocellular carcinoma are infection with HBV and HCV, chronic heavy alcohol consumption, and non-alcoholic steatohepatitis. HBV is responsible for nearly 50% of cases of HCC worldwide. HBV is highly carcinogenic and can lead to the development of HCC in the absence of cirrhosis. In patients with HCV, the risk of hepatocellular carcinoma is increased 15-fold as compared to uninfected persons; in this setting, cancer occurs in patients with severe fibrosis or cirrhosis.

Other risk factors include male sex (approximately 2:1), diabetes, obesity, and dietary exposure to aflatoxin. The risk increases when several risk factors are present. For example, chronic heavy alcohol consumption (from 40 grams of pure alcohol per day) doubles the risk of cancer in patients with the C virus.

Clinical manifestations The symptomatology depends on the stage at which the cancer is diagnosed. It can be asymptomatic in the case of a small nodule or present with right upper quadrant pain, weight loss, and signs of liver failure in the case of a large tumor mass. Outside the context of screening, it is often diagnosed late.

HCC screening The recognition that HCC was more frequent in individuals with risk factors has led to the implementation of screening programs. This allows for the diagnosis of HCC at an earlier stage with the goal of achieving an improved overall survival. The groups in which screening is currently recommended are (1) any cirrhotic patient in whom anticancer treatment can be considered (i.e., this excludes Child C patients who are not candidates for liver transplantation) and (2) non-cirrhotic patients such as Asian HBV carriers (men over the age of 40 years and women over the age of 50 years), HBV carriers with a family history of HCC, and black HBV carriers.

Screening is based on abdominal ultrasound at 6-month intervals in order to detect suspect nodules. These nodules are usually hypoechoic. The sensitivity of ultrasound is 60–80% and specificity more than 90%.

Alpha-fetoprotein is a fetal glycoprotein, in which serum levels can be elevated in cases of hepatocellular carcinoma. It has a low specificity.

Diagnosis The diagnosis of hepatocellular carcinoma in cirrhosis can be made noninvasively according to well-defined radiological criteria by CT scan or MRI. When

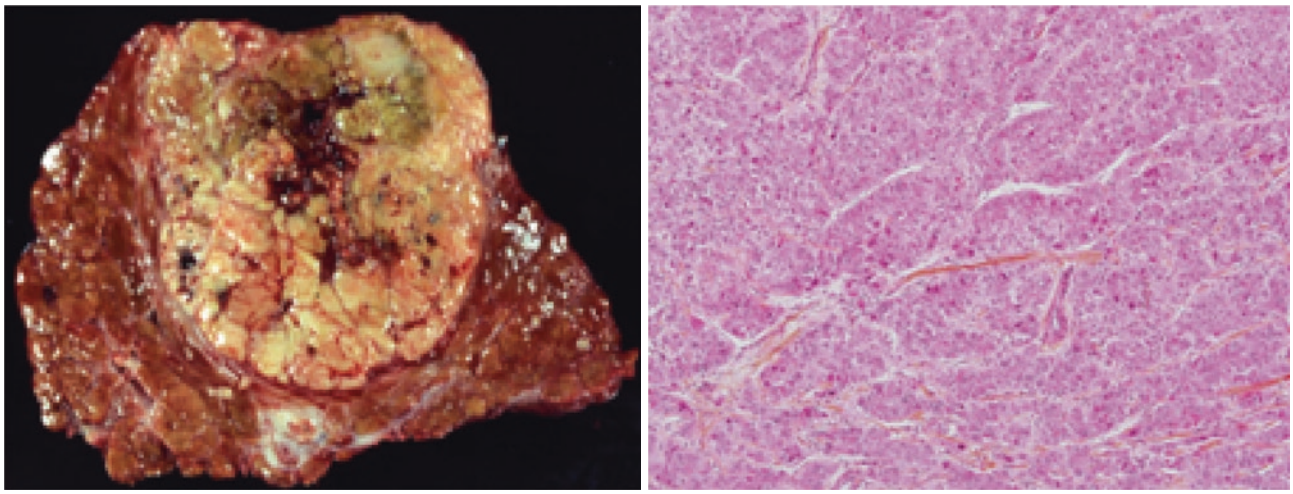


Fig. 8.37 Left: hepatocellular carcinoma (HCC) arising in a cirrhotic liver. Right: microscopic appearance – anarchic proliferation of hepatocytes that are disorganized (more than two-plate thick and portal spaces that are unrecognizable, instead of simple hepatocytic trabeculae distributed around portal spaces as seen in the normal liver). (Photos from G. Pomier)

these are not present, confirmation by liver biopsy may be required.

Treatment of hepatoma Liver transplantation is indicated in patients with hepatocellular carcinoma and underlying cirrhosis: it then treats the cancer and the underlying disease. Patients with a single tumor of less than 5 centimeters or nodules of less than 3 centimeters are eligible for transplantation. Survival at 5 years is between 60% and 80%, and recurrences are of the order of 4–20% at 5 years.

Liver resection is possible in cases of a single nodule; the overall survival at 5 years is 50% with a recurrence-free survival of 30%.

Local therapy by radiofrequency ablation (with high-frequency electrical current) is an alternative to surgery. It offers destruction of the tumor by a transcutaneous approach with one or more probes inserted in the liver under radiological guidance (ultrasound or abdominal CT). Best results are obtained for small lesions <3 cm; long-term survival is similar to that of resection. Alternatives to radiofrequency ablation are alcohol injection, cryoablation, or targeted radiotherapy.

Transarterial chemoembolization (TACE) is a treatment used where a chemotherapeutic agent coupled with embolizing material is injected into the feeder arteries of the tumor. It is offered to patients with multiple nodules limited to the liver or a single large lesion, in the absence of liver failure. It is not curative but has been shown to improve survival.

Systemic treatment with cell kinase inhibitors or with immunotherapy (anti-PDI) can be considered with tumors that cannot be resected by surgery/transplantation or local treatment.

(b) Cholangiocarcinoma Intrahepatic cholangiocarcinoma is a malignant tumor arising from the biliary epithelium. Cholangiocarcinoma can be found at different locations of the biliary tree, from the secondary intrahepatic bile ducts to the Hering duct. It is considered a primary liver tumor, just like hepatocellular carcinoma (unlike extrahepatic cholangiocarcinoma, e.g., hilar cholangiocarcinoma, discussed in ▶ Chap. 6).

Epidemiology and risk factors Intrahepatic cholangiocarcinoma accounts for 15% of all liver cancers and is less frequent than cholangiocarcinoma of the extrahepatic biliary tree. It occurs at an average age of 70 years. Its incidence is about 1 per 100,000 inhabitants in North America. In Southeast Asia, the main risk factor is chronic infection of the bile ducts by parasites endemic to these regions (*Opisthorchis viverrini*, *Clonorchis sinensis*). The infection is acquired through the ingestion of raw fish, and the adult parasite completes its cycle in the intrahepatic bile ducts where it lays its eggs. It is the chronic inflammatory reaction that initiates the process of carcinogenesis.

Primary sclerosing cholangitis is associated with an increased risk of developing cholangiocarcinoma (1.5% per year). Polycystic liver diseases, Caroli's disease, congenital liver fibrosis, and some bile duct cysts are also associated with an increased risk of cholangiocarcinoma. Other potential risk factors include intrahepatic gallstones, carcinogens such as thorium dioxide (Thorotrast), diabetes, and smoking. Recent data suggest that the hepatitis C virus is associated with an increased risk of intrahepatic cholangiocarcinoma (with a fivefold increase in risk).

Clinical manifestations The symptomatology is often not very informative, except in the case of large tumors. Abdominal pain is possible in the case of large tumors, as well as asthenia, anorexia, nausea, or weight loss.

Diagnosis of cholangiocarcinoma Tumor markers are of limited diagnostic value due to their low sensitivity and specificity. Serum CA19-9 levels are between 100 and 1000 IU/ml in 25% of patients and above 1000 IU/ml in 30% of patients, but this marker is uninterpretable when cholestasis is present. It can also be elevated in cases of gastric, colorectal, or pancreatic cancer.

Radiological diagnosis: Imaging (abdominal CT scan with contrast-enhancing agent or abdominal magnetic resonance scan with gadolinium or PET scan) is suggestive of the diagnosis. The main differential diagnosis is liver metastasis (often from colon or breast cancer). Definitive diagnosis requires biopsy of the lesion.

Endoscopic retrograde cholangiopancreatography is generally useful for perihilar or extrahepatic cholangiocarcinomas. The examination can allow brushing for cytological exam.

Treatment of cholangiocarcinoma Liver resection is the only potentially curative treatment. After optimal surgical treatment (free resection margins), the 5-year survival rate can be as high as 35%.

Systemic chemotherapy (gemcitabine, cisplatin) can achieve modest response rates of 10–20%.

Biliary drainage (preferably endoscopic rather than percutaneous) is indicated in cases of biliary obstruction.

Prognosis Cholangiocarcinoma has a very poor prognosis due to its often late diagnosis. Survival at 1 year is 28% and at 5 years less than 5%.

In children, hepatoblastoma is the most common primary malignant tumor of the liver (about 1% of all pediatric tumors). The average age at diagnosis is between 18 and 24 months; the majority of cases are detected before the age of 3. Clinically, it presents as a palpable liver mass. Treatment combines chemotherapy and surgery to remove the tumor; when this is not possible, in the absence of metastasis, liver transplantation may be indicated.

8.7.2 Secondary Neoplasms

Liver metastases are a frequent manifestation of vascular dissemination of neoplastic cells. They are observed in a number of neoplasms, especially gastrointestinal adenocarcinomas drained by the portal vein (colon, pancreas, stomach), but also lung cancers (especially small cell lung cancer), breast cancers, and melanoma. Metastases of neuroendocrine tumors, especially carcinoid, as well as liver localizations of certain lymphomas can also be observed.

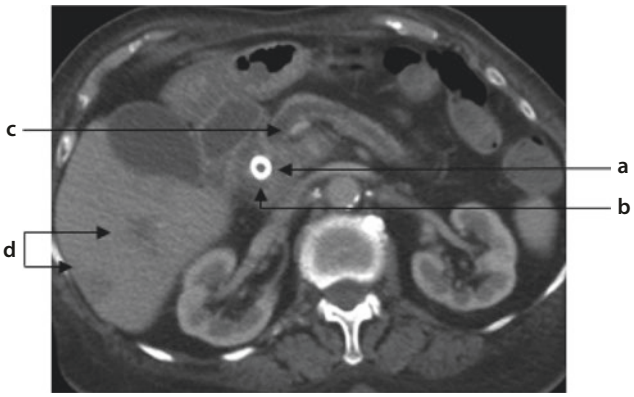


Fig. 8.38 Liver metastases in a case of pancreatic adenocarcinoma on CT scan: (a) the head of the pancreas is replaced by a mass; (b) a biliary stent is in place here to decompress the bile ducts; (c) the Wirsung duct is dilated ahead of the cephalic obstacle; (d) metastases are present in the liver. (Photo by R. Déry)

The clinical picture is variable. In general, metastatic tumors appear in the follow-up of a known tumor and are associated with alteration of the general condition with anorexia and pain in the right hypochondrium. Some rapidly evolving metastatic tumors may present as jaundice, anorexia, or even progressive liver failure (even fulminant hepatitis). Sometimes the patient is completely asymptomatic, and metastases are discovered on physical examination (the liver is enlarged, hard, irregular, sensitive) or on abdominal ultrasound or other imaging modalities.

Ultrasound, CT scan (Fig. 8.38), or MR images are most often very typical (especially if there is a known history of cancer). In some cases, guided biopsy will be required to confirm the diagnosis and guide patient management.

The presence of liver metastases is associated with a poor prognosis. In some digestive cancers, prolonged survival may be obtained after resection of the primary tumor and of isolated metastases. Depending on the histological type, chemotherapy can be administered, usually with palliative intent.

8.7.3 Benign Tumors

Benign liver tumors are most often found incidentally on an imaging exam.

(a) Hemangioma

Epidemiology Hemangioma is the most common liver tumor, found in 2–5% of the adult population. Its size

varies from a few millimeters to more than 20 cm. It is called giant hemangioma if the diameter exceeds 5 cm. It is three times more frequent in women than in men. It is multiple in 40% of cases and can be found in both liver lobes.

Pathology Macroscopically, a hemangioma appears red-brown in color and spongy on palpation. Histologically, it consists of a proliferation of vessels of venous origin, creating cavernous vascular spaces separated by fibrous septa. They are lined with endothelial cells and filled with blood.

Clinical picture Hemangioma is generally asymptomatic. It is discovered incidentally on imaging, most often on ultrasound, in adults between 30 and 50 years of age, although it is present early in life. It is a very slow-growing tumor in around 40% of cases: in others, its diameter is fixed. Hemangiomas can sometimes become painful. Exceptionally, rupture of a hemangioma can be observed, either spontaneous or in the context of trauma; this leads to hemoperitoneum. An acute painful picture with fever and cytolysis can accompany acute thrombosis of the hemangioma. In these exceptional cases, surgical resection is required.

In children, giant hemangioma can be associated with high-flow heart failure and hypothyroidism, the pathophysiology of which is the conversion of T4 and T3 into inactive residues by a deiodinase produced by the hemangioma.

Diagnosis Ultrasonography of liver hemangioma is usually typical. It shows a well-defined hyperechoic round lesion. In some cases, contrast ultrasound (which consists of intravenous injection of a liquid containing microbubbles during the ultrasound), CT scan, magnetic resonance, and labeled red blood cell scan (there is an accumulation of the marker within the lesion) are used to characterize a less typical lesion.

Treatment Since hemangiomas are non-evolving lesions, small hemangiomas (<2 cm) do not require imaging control. No treatment is necessary. In some cases, the size of a hemangioma grows slowly, and it is recommended to monitor lesions larger than 5 cm.

(b) Adenoma

Epidemiology Liver cell adenoma is a rare tumor (prevalence 1/20,000). Measuring from a few mm to 20–30 cm, it is mostly found in adult women between 20 and 40 years of age. It is promoted by oral contraceptives and increases in volume during pregnancy. It can also be caused by the use of anabolic steroids and androgens used for body building and in transgender people. It is also associated with type 1 and 3 glycogenosis (see ► Sect. 8.8).

Pathology Adenoma is unique in 70–80% of cases and located mainly in the right lobe. Histologically, the adenoma is a monoclonal proliferation of normal hepatocytes that are more than two-plate thick, with occasional glycogen and lipid inclusions. Characteristically, there is no portal space and, in general, no Kupffer cells. The vascular supply depends solely on the hepatic artery. The tumor does not usually have a fibrous capsule, hence the significant risk of hemorrhage. Macroscopically, liver cell adenoma is soft and regular in consistency, beige in color, and covered with vessels on its surface.

Three subtypes of liver cell adenomas have been described according to molecular alterations detected in the tumors. Tumors harboring mutations of the hepatocyte nuclear factor 1 alpha are the most common. Mutations of the beta-catenin gene are associated with a high risk of neoplastic transformation of adenoma into hepatocellular carcinoma. The third subtype is called inflammatory adenoma.

Clinical picture The majority of adenomas occur in young women using oral contraceptives. Small adenomas are asymptomatic. When the tumor increases in size, during prolonged use of oral contraceptives and anabolic steroids or during pregnancy, it can be associated with abdominal pain in the epigastrium or right hypochondrium. It is rarely palpable. Acute onset of pain should raise concern about the possibility of intratumoral hemorrhage or necrosis. Some patients present with hemoperitoneum and require emergency surgery or radiological arterial embolization, especially if this occurs during pregnancy.

Diagnosis The diagnosis of liver cell adenoma is complex and requires several imaging modalities (ultrasound, CT, MRI). The differential diagnosis is between adenoma, focal nodular hyperplasia (a benign lesion), and a malignant lesion such as hepatocellular carcinoma, fibrolamellar hepatoma, or metastases. Sometimes the diagnosis can only be made by examining the surgical specimen.

Liver scintigraphy with technetium sulfide can be used to aid diagnosis. The radionuclide marker is taken up by Kupffer cells which are present in the normal liver but absent in adenomas: in case of an adenoma, this results in a blind spot in the region of the lesion.

Biopsy of the adenoma is not recommended because of the risk of hemorrhage. Histological examination of a surgical resection specimen requires high attention because of the difficulty in making the difference between adenoma, normal liver parenchyma, focal nod-

ular hyperplasia, and well-differentiated hepatocellular carcinoma.

Treatment Since liver cell adenomas are estrogen-dependent tumors, oral contraceptives must be discontinued, which may allow the lesions to stabilize or even slowly regress. Anabolic steroids and androgens must be stopped.

Adenomas can bleed and cause hemoperitoneum, especially during pregnancy; prophylactic surgical resection is therefore recommended in women who wish to become pregnant. Removal is also recommended in cases of large, subcapsular lesions and in symptomatic lesions. Adenomas related to anabolic steroids or glycogenosis present a high risk of neoplastic transformation into hepatocellular carcinoma; this is also an indication for resection.

■ (c) Focal nodular hyperplasia (FNH)

Epidemiology Focal nodular hyperplasia is a benign liver tumor which is more common than liver cell adenoma (prevalence 1/2000). It accounts for approximately 20% of benign liver tumors and more than 80% of non-angiomatous lesions. It is observed more frequently in women than in men (8:1), especially between the ages of 20 and 50 years. The role of oral contraceptives in the pathogenesis of this lesion remains controversial. In 25% of cases, it is associated with hemangiomas or liver cell adenomas, which renders diagnosis complex.

Pathology On microscopic examination, FNH appears as a localized nodule of cirrhotic tissue (it is also known as "focal cirrhosis"). It is a single lesion in 70% of cases; multiple (two to four) nodules are sometimes observed. These nodules contain normal hepatocytes distributed in single or double layers, and partially or totally surrounded by fibrous septa containing corkscrew arteries and ductular proliferation. Interlobular bile ducts are absent. Hepatocytes are often steatotic. The fibrous tissue can be inflammatory. Characteristically, the lesion includes a large central scar (which can contain an artery) from which fibrovascular and ductular septa radiate to the periphery (spoke-wheel pattern). This aspect is not identifiable in small lesions (<2 cm).

The pathophysiology of FNH remains poorly understood but seems to depend on a localized higher arterial supply in face of poor portal flow. At the molecular level, dysregulation in the angiogenesis-controlling pathways has been described.

Clinical picture FNH is usually asymptomatic and is discovered incidentally on imaging exams. Sometimes, patients may complain of right upper quadrant pain. The tumor is exceptionally palpable.

Diagnosis FNH is typically found on ultrasound. It can be further characterized by Doppler examination (which highlights the vessels and may find a central artery with spoke-wheel vessels), CT scan, and especially MRI (which will often show the central scar). Technetium hepatic scintigraphy shows a more intense uptake of the tumor than the surrounding hepatic parenchyma, due to the presence of Kupffer cells. This characteristic makes it possible to differentiate focal nodular hyperplasia from liver cell adenoma, when the presentation is typical.

Treatment FNH is a non-evolving tumor that does not require surgical intervention. Neoplastic transformation does not occur.

8.7.4 Other Lesions (Cysts, Abscesses)

(a) Cysts Congenital liver cysts are common, asymptomatic, and harmless. Usually less than 5 cm, they can be solitary or present in small numbers.

Polycystic liver disease is a hereditary disease often associated with polycystic kidney disease. The cysts are multiple and can vary from a few mm to more than 10 cm. Often asymptomatic, cysts can sometimes cause discomfort due to their size, can rupture, or can compress the bile ducts (jaundice) or main portal vessels (portal hypertension).

Hydatid cysts are caused by the parasite *Echinococcus*, which is found mainly in sheep and cattle and is most often transmitted to humans by dogs. If required, treatment is mainly surgical, but great care is taken to avoid the spilling of the cystic contents into the peritoneal cavity, which can lead to severe allergic reactions (anaphylactic shock, etc.).

(b) Abscess Pyogenic abscesses are the consequence of bacteremia (most often multi-germ such as *E. coli*, *Klebsiella*, *Pseudomonas*, etc.) resulting from an infection most often in the abdominal cavity; appendicitis is a classic cause, but diverticulitis, cholangitis, etc. are also causes of liver abscesses. Treatment involves antibiotics, often drainage (radiological or surgical), and the management of the initial condition.

Amoebic abscess is rare in the West, but common in tropical or subtropical countries. The patient experiences right upper quadrant pain with, almost invariably, high fever. The abscess contains a typical red-brown material ("anchovy paste" or "chocolate sauce"). It needs to be drained only in exceptional cases. Treatment is provided by antibiotics (metronidazole 750 mg tid × 10 days).

(c) Granuloma Granulomas are microscopic lesions. Tuberculosis (granuloma with caseating necrosis), sarcoidosis, and other infections such as *Mycobacterium avium* intracellulare, brucellosis, rickettsiae, leprosy, parasites (*Schistosoma*), and viruses (mononucleosis, CMV, etc.) can cause granulomatous inflammatory reaction. Granulomatous epithelial reactions can be caused by toxic substances such as beryllium, drugs (sulfamides, methotrexate, allopurinol, etc.), or certain diseases (Crohn's disease, primary biliary cholangitis, Hodgkin's disease, etc.).

8.8 Function Disorders

Some diseases are due to liver nonstructural disorders, i.e., non-related to inflammatory or tumoral lesions of the liver. They don't express the usual signs of liver dysfunction, and liver imaging (ultrasound, CT scan, MRI, nuclear medicine, elastography, etc.), as well as microscopic (histology) appearance, is normal.

These diseases are due to a defect, often congenital, in specific liver enzymatic systems. Several organs can be affected. The liver can appear completely normal (e.g., in porphyria, abnormalities of the urea cycle) or can sometimes be affected if hepatotoxic metabolites accumulate (such as with tyrosinemia and galactosemia).

These illnesses often manifest themselves at a pediatric age.

The following diseases are examples of functional abnormalities of the liver.

8.8.1 Porphyria

Porphyrias are due to a metabolic disorder affecting the synthesis of heme (20% of which occurs in the liver and 80% in the marrow). Enzyme deficiency can occur at eight different steps in the metabolic pathway (five in the liver, two in the liver and marrow, and one in the marrow) resulting in eight different subtypes of porphyria (acute intermittent porphyria, late porphyria, etc.). The accumulated toxic products most often affect the nervous system (neurogenic abdominal pain, paresthesias, neuropsychiatric symptoms); these are caused by toxic metabolites – 5-aminolevulinic acid and porphobilinogen – resembling the GABA neurotransmitter. Skin disorders are caused by excess porphyrins accumulated in the dermis (which, when activated in the presence of light, become toxic). Medical treatment mainly includes the prevention of promoting factors; liver transplantation is curative in some rare cases.

8.8.2 Disorders of the Urea Cycle

Five enzymes, each expressed in the liver, are used to convert ammonia (obtained from the catabolism of amino acids) into urea. Defects in each of these five enzymes have been described. Hyperammonia, often triggered by protein ingestion, leads to symptoms of irritability, lethargy, and even coma. In some severely affected individuals, liver transplantation is curative.

8.8.3 Glycogen Storage Diseases

Glycogen metabolism occurs mainly in the muscles and liver. More than ten enzymatic disorders can affect glycogen metabolism. The most common condition is glucose-6-phosphatase deficiency, which prevents the formation of glucose from glycogen. Clinical manifestations include hypoglycemia (somnolence, coma), liver glycogen, and fatty acid overload with ensuing hepatomegaly and liver cell adenoma (before the age of 15) and even carcinoma. Treatment mainly relies on dietary modifications; liver transplantation, if necessary, is effective in correcting the enzymatic deficiency and its consequences.

8.8.4 Tyrosinemia

Enzyme deficiencies in tyrosine catabolism can lead to four diseases, including alkaptonuria and other hereditary tyrosinemias. Hereditary tyrosinemia type 1 is particularly frequent in Quebec (1/1800 births in the Saguenay region vs. 1/100,000 in the world) due to a "founder effect." The accumulation of toxic products causes liver injury that is often rapidly progressive in the first months of life. Other forms of the disease include renal and, sometimes, neurological disorders.

Neonatal screening for tyrosinemia is now routinely performed. This allows early diagnosis and initiation of treatment with nitisinone that inhibits degradation of tyrosine and prevents accumulation of toxic metabolites. Since this treatment has been in use, the natural history of the disease has changed dramatically with no evidence of children requiring liver transplant (which used to be performed to restore the genetic defect and control the complications of the disease).

8.8.5 Galactosemia and Fructosemia

Galactosemia and hereditary fructose intolerance are two hereditary diseases caused by enzyme deficiencies that prevent the formation of glucose from galactose and fructose (from, respectively, the galactose-1-phosphate uridyltransferase and the fructose 1-phosphate aldolase). In both cases, the accumulation of sugars in the liver causes fatal liver disease. Galactose accumulation occurs when lactose is introduced into the diet (from breast milk or other sources) and is prevented by its complete elimination from the diet. Fructose intolerance occurs when fructose is introduced into the child's diet (usually in the form of fruit juice) and is controlled by the complete and definitive elimination of fructose and sucrose from the diet.

8.8.6 α1-Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency, normally synthetized by hepatocytes, can affect the lungs or liver (as discussed previously in the ► Sect. 8.6.2.4).

Function liver disorders are most always caused by a genetic anomaly with associated enzymatic dysfunction. Gene therapy aimed at correcting these defective genes obviously represents a promising therapeutic avenue. Currently, the replacement of the dysfunctional liver with a normal one allows, in several cases, to restore normal enzyme function and cure the patient.

8.9 Miscellaneous

8.9.1 Liver Transplantation

Liver transplantation, popularized since the 1980s, has become a standard treatment for both adult and pediatric patients with end-stage liver disease or hepatocellular carcinoma that is now performed at hundreds of centers around the world. In orthotopic liver transplantation, the native organ is removed, and the donor liver is inserted in the same anatomical location. Most often, transplantation is offered to patients with a chronic liver disease (mainly decompensated cirrhosis). Patients with fulminant liver failure (<10%) occurring in a person with a healthy liver and some patients with hepatocellular carcinoma (HCC) (≈20%) are other potential candidates for this procedure.

The success of transplantation, as measured by the 1-year survival rate of the patient and the graft, is approximately 90% nowadays.

Table 8.16 Contraindications to hepatic transplantation

Absolute
Uncontrolled extrahepatic infection (bacterial or fungal)
Advanced cardiovascular or pulmonary disease
Metastatic liver neoplasia
Misuse of alcohol or drugs (active)
Relative
Portal vein thrombosis
Previous extensive hepatobiliary surgery
Past history of cancer (including melanoma, but excluding other skin neoplasia)
Severe obesity
Severe pulmonary hypertension
Non-compliance to medical directives
Unstable psychiatric condition
Age >70 years old

Contraindications to transplantation need to be taken into consideration and need to be excluded: some are absolute and others considered relative as shown in Table 8.16.

(a) Indications for liver transplantation Indications for liver transplantation are listed in Table 8.17. In adults, alcoholic cirrhosis, hepatocellular carcinoma, and NASH cirrhosis are the most frequent indications. In children, biliary atresia is the most common indication; other indications include genetic or hereditary metabolic disorders.

In cases of alcoholic cirrhosis, the candidate must meet strict criteria to ensure long-term abstinence to prevent recurrence of alcoholic liver disease. Despite this, recurrence of alcohol misuse is found in ≈10% of individuals.

Cirrhosis due to hepatitis C virus is now a less frequent indication for liver transplantation since the advent of highly effective treatments against the virus. If eliminated prior to transplantation, the virus does not reappear in the transplanted liver. In the case of chronic hepatitis B virus, the combination of hyperimmune B virus immunoglobulin (HBIG) and antiviral agents prevents graft re-infection.

Autoimmune hepatitis has a graft survival that is comparable to other causes of cirrhosis, but it recurs in around 25% of cases. Among chronic cholestatic diseases, pri-

Table 8.17 Liver transplant indications

Children
Bile duct atresia
Genetic or hereditary disorders
Tyrosinemia
Wilson's disease
Glycogenosis
Crigler-Najjar type 1
Primary hyperoxaluria
α1-Antitrypsin deficiency
Alagille syndrome
Congenital hepatic fibrosis
Byler's disease
Non-resectable hepatoblastoma
Adults
Cirrhosis secondary to chronic viral hepatitis (HCV and HBV)
Alcoholic cirrhosis
NASH cirrhosis
Primary biliary cholangitis
Autoimmune cirrhosis
Primary sclerosing cholangitis
Cryptogenic cirrhosis
Hepatocellular carcinoma
Fulminant hepatitis
Thrombosis of hepatic veins (Budd-Chiari)
Familial amyloidosis

mary biliary cholangitis is associated with an excellent 5-year survival (>90% and a 5% recurrence rate).

Hepatocellular carcinoma (HCC), usually in cirrhotic liver, represents the second most frequent indication (>25%) for liver transplantation. Patients with hepatocellular carcinoma (HCC) with good tumor biology and characteristics will show 5-year survival rates comparable to those observed with non-neoplastic indications (70% recurrence-free survival at 5 years).

(b) Technical considerations *Brain-dead donors*. The majority of liver transplant donors are cadaveric: with livers being obtained after brain or cardiac deaths. There is no age limit to donation: however, the ideal donor has the following characteristics: age ≤60 years, stable hemodynamics, adequate oxygenation, absence of bacterial or fungal infection, absence of liver dysfunction, and negative serology for B, C, and HIV viruses. Cardiovascular and pulmonary functions are maintained in the intensive care unit until the organ is removed in the operating room (multiorgan sampling is usually performed).

ABO blood group compatibility is required. HLA (human leukocyte antigen) match is not required. The harvested liver is stored in a cooled (4 °C) electrolyte solution on ice for up to 12 hours, allowing the organ to travel to the transplant center.

In Canada, potential organs are screened and distributed through organ procurement organizations that cover a predefined geographic region. Livers are allocated to a precise recipient depending on his/her blood type and rank on the waiting list. This rank is determined depending on MELD score (see above) which corresponds to a 3-month risk of death while on the waiting list. In individuals who are listed for other indications than liver failure and in children, predefined MELD exceptions are accorded.

Living donors. The annual rate of cadaveric donors in Canada is around 20 per million inhabitants. Around 10–15% of recipients will die while on the waiting list. The transplantation of a part of a living donor's liver was born out of this lack of organs to meet the demand, since there is no alternative treatment for liver failure. Transplantation with the left lobe is performed in children, adolescents, or low-weight adults. In adult-to-adult transplantation, the right lobe of the donor is transplanted. The living donor is subject to certain morbidity (an average of 10 weeks of postoperative recovery, with ≈5% of significant postoperative complications and a mortality risk between 0.2% and 0.4%).

Surgical technique. Hepatectomy of the recipient is often technically difficult due to portal hypertension and coagulopathy. Dissection of the portal vein, the supra- and infrahepatic vena cava, the hepatic artery, and the main bile duct allows the removal of the native liver with or without the vena cava; the anastomosis of the graft is then performed in the same order. A termino-terminal biliary anastomosis is performed between the donor and the recipient; biliary reconstruction with a Roux-en-Y hepaticojejunostomy is performed in patients with primary sclerosing cholangitis.

(c) Immunosuppression and rejection control The long-term success of liver transplantation has been made possible, in the early 1980s, with the discovery of cyclosporine (CSA), a powerful immunosuppressive agent. CSA is a calcineurin inhibitor which blocks T-cell activation by inhibiting interleukin-2 production and thus antigen rec-

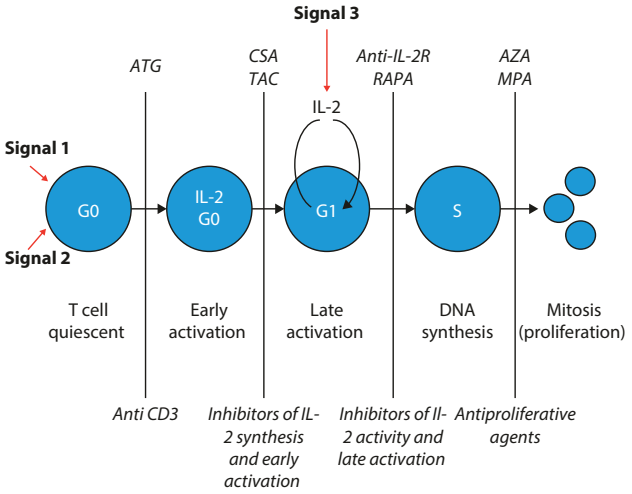


Fig. 8.39 T-cell activation and mechanisms of action of anti-rejection drugs

ognition by the T-cell receptor (Fig. 8.39). Nephrotoxicity is the most important adverse effect of CSA which causes dose-dependent tubular damage. Treatment with CSA can also induce arterial hypertension, hyperkalemia, tremor, dyslipidemia, glucose intolerance, hirsutism, and gingival hyperplasia.

Tacrolimus (TAC) has the same mechanism of action as CSA but is more than 10–100 times powerful. Its ease of use has rapidly made it the immunosuppressant of choice in most liver transplant centers since 1995. The nephrotoxicity of TAC is similar to that of CSA; its neurotoxicity can be more severe (tremors, convulsions, hallucinations, psychoses).

TAC and CSA are metabolized in the liver by cytochrome P4503A. Medications that induce this system will thus lower their blood levels (e.g., carbamazepine, rifampin, phenytoin), and those that inhibit this cytochrome increase their blood levels (e.g., fluconazole, ketoconazole, itraconazole). CSA and TAC are associated with a ≈ 1% risk of post-transplant lymphoma (referred to as PTLD "post-transplant lymphoproliferative disorders").

Azathioprine (AZA), an antimetabolite, was used from the beginning of the liver transplant in combination with glucocorticoids. Since the 2000s, mycophenolic acid (MPA), which has a similar mechanism of action to AZA, is often used instead of AZA. Rapamycin (RAPA), also known as sirolimus, is another immunosuppressive agent sometimes used.

Glucocorticosteroids are still used early on after transplant (induction period) but are usually withdrawn in the majority of patients between the 3rd and 9th month after transplantation.

Biological immunosuppressants such as anti-lymphocyte globulins (ATG, anti-thymocyte globulin) and antibodies against interleukin-2 receptors (basiliximab) are used in the induction period to delay the introduction of calcineurin inhibitors in patients with renal impairment.

The art of immunosuppression is to maintain a balance between preventing rejection and maintaining immunological competence against infections and cancer.

The incidence of rejection at 1 year is less than 20% nowadays and is almost always reversible with drug adjustments. The current trend is to reduce the dose of tacrolimus or CSA with the administration of bioactive agents (basiliximab or TGA) at the beginning of the induction phase and to add mycophenolic acid (or AZA) during the maintenance period to prevent side effects such as nephrotoxicity.

Complications of immunosuppression include B-cell lymphomas (PTLD) and, in the longer term, a higher incidence of neoplasia (all types of cancer, but particularly basal and squamous cell skin tumors).

8.9.2 Pregnancy and Liver

(a) Physiological modifications of the liver during pregnancy During pregnancy, the liver is displaced upward by the fetus and is impalpable; thus, a palpable liver is an abnormal finding during pregnancy. The majority of liver biochemical tests remain within normal limits during pregnancy. However, albumin is often slightly decreased (increase in plasma volume); alkaline phosphatase (placental production) and alpha-fetoprotein can increase.

(b) Liver disorders during pregnancy In any pregnant woman with abnormal liver tests, a non-pregnancy-related liver disorder such as viral hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, etc. should first be ruled out.

Pregnant women are at greater risk of developing fulminant hepatitis when they are infected with the hepatitis E or herpes viruses (HSV-1 and HSV-2). These infections should therefore be part of the differential diagnosis of a pregnant woman with severe hepatitis.

First trimester liver conditions Hyperemesis gravidarum (severe vomiting) can be accompanied by a slight increase (up to 3 × normal, but sometimes up to 1000 U/L) in liver enzymes (ALT > AST). Disturbances in liver function tests are usually proportional to the severity of symptoms and normalize with resolution of vomiting.

Last trimester liver conditions:

(a) *Intrahepatic cholestasis of pregnancy* presents as a disabling pruritus, mainly in the palms and soles, worsening at night. Bile salt levels are typically very high, while the routine cholestatic tests (alkaline phosphatase, bilirubin levels) are usually non-diagnostic. Liver enzymes (AST and ALT) can be very elevated (> 1000 U/L); 10% of patients will develop jaundice.

This disorder is caused by a genetic abnormality of the canalicular secretion of bile salts (or phospholipids). It affects up to 0.5% of pregnancies (higher risk in women of Scandinavian or Chilean origins). Treatment is with ursodeoxycholic acid, which helps relieve pruritus and improve liver tests. Cholestyramine can also be used.

Intrahepatic cholestasis of pregnancy is associated with an increased risk of prematurity, meconium aspiration, hyaline membrane disease, and fatal fetal arrhythmias. The risk of fetal loss is estimated at 1–1.5%. It is generally recommended to induce delivery after the 36th week of pregnancy. Recurrence occurs in 2/3 subsequent pregnancies.

(b) *HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome* is a potentially life-threatening disorder that's usually associated with preeclampsia. It is characterized by the presence of hemolysis (often associated with microangiopathy), increased liver enzymes (mainly AST and ALT), and thrombocytopenia. It complicates 1% of pregnancies and is considered a severe form of preeclampsia (10–20% of severe preeclampsia and eclampsia). The diagnosis is typically made in the third trimester, but can also be made after delivery.

Clinically, women can have nausea, vomiting, and right upper quadrant pain. High blood pressure and proteinuria are present. LDH and bilirubin levels (especially the indirect form) are elevated because of hemolysis; anemia is usually mild with schistocytes. Up to 20% of HELLP syndromes will develop disseminated intravascular coagulation. Placental abruption and subcapsular or intraparenchymal liver hematoma with rupture of the liver capsule are serious complications of this condition.

The first step in the management of HELLP syndrome is to stabilize maternal and fetal conditions. Anti-hypertensive drugs and magnesium are administered to treat preeclampsia. The definitive treatment for HELLP syndrome is delivery of the baby.

It is recommended to induce labor when the gestational age is 34 weeks, when there is fetal distress, or if maternal complications are identified (disseminated intravascular coagulation, liver hematoma, etc.). Recurrence occurs in around 7% of subsequent pregnancies.

(c) *Acute fatty liver of pregnancy* is the most serious liver injury during pregnancy as it can lead to fulminant liver failure. The most frequent symptoms are nausea, vomiting, epigastric pain, jaundice, and hepatic encephalopathy. Liver tests are modestly elevated (often less than 500 U/L), but INR and ammonia levels are increased, and hypoglycemia can occur. There can be considerable clinical overlap between HELLP syndrome and acute fatty liver of pregnancy: the presence of encephalopathy is more supportive of the latter diagnosis.

Acute fatty liver of pregnancy is secondary to an inherited defect in mitochondrial fatty acid beta-oxidation (LCHAD deficiency) in the child causing accumulation of microvesicular fat in maternal hepatocytes. It is a rare disease, with an approximate incidence of 1/20,000 pregnancies. Although the disease is always present before childbirth, the diagnosis is sometimes made after delivery.

Diagnosis must be made quickly (on a clinical basis, usually without the need for a liver biopsy), and management requires close monitoring, usually in liver-specialized intensive care unit. Immediate delivery is the treatment, regardless of the gestational age. Correction of hypoglycemia and coagulopathy is essential. Liver function improves within 24 hours and normalizes about 7 days after delivery. When diagnosed early and managed optimally, maternal mortality is about 2–4%. The disease may recur in subsequent pregnancies; genetic counseling is recommended.

PS: For complementary readings on the liver, see ► Chaps. 11, 26, 27, 28, and 29.

Digestive Symptoms, Signs and Other

Contents

Esophageal Symptoms: Heartburn, Dysphagia, and Chest Pain

P. Poitras and M. Bouin

Contents

P. Poitras (ed.), *The Digestive System: From Basic Sciences to Clinical Practice*,
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Diseases of the esophagus are revealed by *digestive* or *extra-digestive* symptoms.

9.1 Digestive Symptoms

Digestive symptoms of esophageal disease (see Fig. 9.1) include the following sensations:

- Heartburn and regurgitation (reflux)
- Pain on swallowing (odynophagia)
- Swallowing blockage (dysphagia)

9.1.1 Heartburns

Sensations of thoracic or retrosternal burning are usually due to the reflux of acidic material from the stomach into the esophagus. It can sometimes indicate a duodenal or gastric ulcer.

Pyrosis refers to a burning sensation rising up along the esophagus, secondary to reflux ascending from the stomach into the esophagus.

Regurgitation describes the esophageal reflux of gastric contents which can be perceived as a chest discomfort (distension?), a return of food or a bitter taste (due to bile or acid) in the mouth, or a spontaneous and effortless exteriorization of gastric material.

Vomiting (which needs to be differentiated from regurgitation) is a forced and abrupt expulsion of gastric material and is often accompanied by nausea.

Rumination describes regurgitation into the oral cavity of food, which is then re-chewed and re-swallowed.

Symptoms of heartburn, pyrosis, and regurgitation are often increased in the supine position or on bending the trunk. They are typical of gastroesophageal reflux disease (GERD).

GERD, depending on the extent and type of symptoms, may require an endoscopy (if symptoms are severe, chronic, or with alarm signs), to eliminate reflux esophagitis and complications such as Barrett's esophagitis. The presence of esophagitis (present at endoscopy in 30% of patients with reflux symptoms) most often signs a long-term continuous PPI therapy (to keep the patient symptom-free and avoid peptic complications); in absence of esophagitis, NERD (non-erosive reflux disease) management can rely on symptomatic treatment (with antacids prn etc.). Barrett's esophagitis, a premalignant condition, imposes in most cases a follow-up surveillance to detect early cancers (Fig. 9.2).

9.1.2 Odynophagia

Odynophagia refers to an esophageal pain perceived at the passage of food. It usually suggests esophagitis whose origin (Fig. 9.1) will be clarified by endoscopy of the esophagus.

9.1.3 Dysphagia

Dysphagia describes the sensation of blockage when food passes down the esophagus. It is an alarm symptom (since it can indicate cancer) that requires diagnostic intervention. Clinical questionnaire is used to determine the site and nature of the blockage:

- The site of food blockade felt by the patient is most often indicative of the anatomical site of blockage. However, an upper site of dysphagia may be misled-

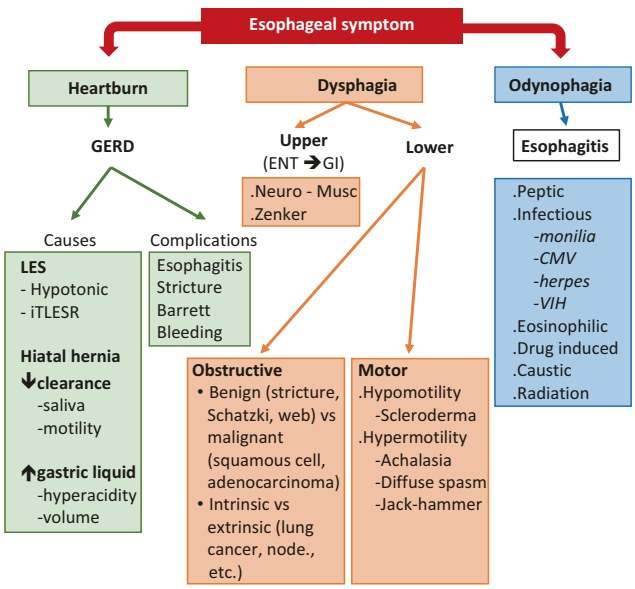


Fig. 9.1 Esophageal symptoms

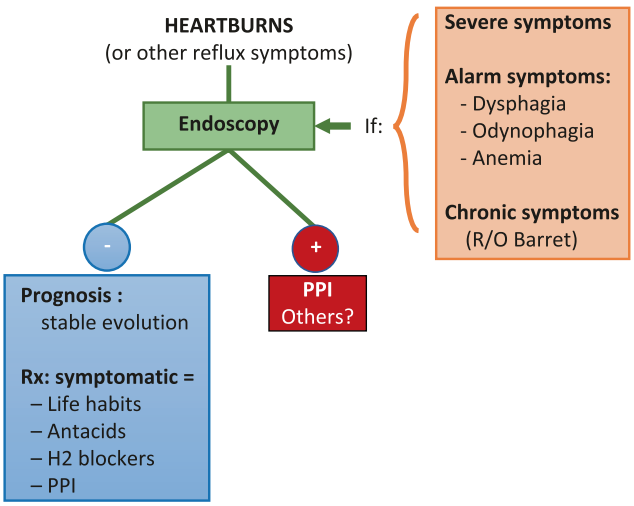


Fig. 9.2 Heartburn and reflux

ing, since a sensation of upper dysphagia may, sometimes, be due to a distal obstruction. On the opposite, lower dysphagia can never be explained by a proximal lesion.

- Progressive dysphagia related to the size of solid foods characterizes esophageal (malignant or benign) stricture. Dysphagia reported preferentially with liquids suggests motor disorders (such as achalasia).

Upper (oropharyngeal or proximal or transfer) dysphagia is often accompanied by false "routes" to the upper (nose) or lower (lungs) respiratory tract. Clinical examination may indicate an impairment of the 12th cranial nerve with an asymmetry or dysmotility of the soft palate.

Radiological study of barium swallowing is the examination of choice to reveal oropharyngeal neuromuscular dysmotility or Zenker's diverticulum. Complementary endoscopy will eliminate an obstructive lesion of the esophagus (◘ Fig. 9.3).

Lower (esophageal or distal or transport) dysphagia involves an abnormality in the upper, middle, or lower esophagus. Obstructive dysphagia will be differentiated from motor dysphagia by the patient's difficulty in ingesting fluids. In obstructive dysphagia, whether due to a benign or malignant stricture, while fluid ingestion is maintained, solid foods will become progressively more and more difficult to swallow due to the progressive narrowing of the esophageal lumen. In case of motor dysphagia (achalasia, etc.), swallowing of liquids is often compromised early in the course of the disease.

Endoscopy (as shown in ◘ Fig. 9.4) is the examination of choice to visualize and characterize an intraluminal obstructive lesion (peptic stenosis, squamous cell carcinoma or adenocarcinoma, etc.). X-ray with barium swallowing may detect diverticula, hernias, or extrinsic lesions (periesophageal lymph node, lung mass, etc.) that are difficult to detect endoscopically, may determine the length of a stenosis (if not passed by the endoscope), or may reveal abnormal contractions.

Esophageal manometry is used to characterize motor disorders of the esophagus (achalasia, scleroderma, etc.).

9.2 Extra-digestive Symptoms

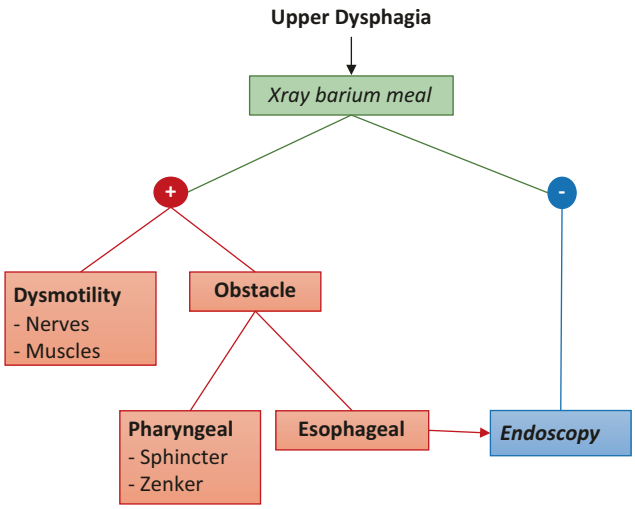
Extra-digestive symptoms can accompany esophageal disease.

9.2.1 "Respiratory" Symptoms

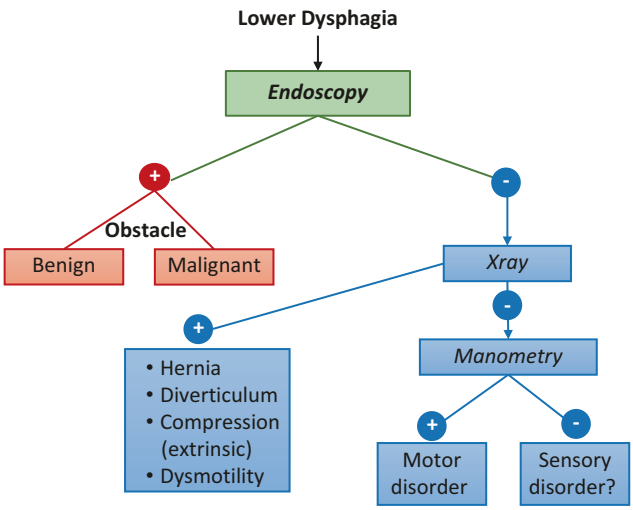
Hoarse voice and cough may be due to posterior laryngitis, while asthma symptoms (cough, dyspnea) may be triggered or aggravated by GERD. Therapeutic trial with a double-dose PPI for 2–6 months to resolve these extra-digestive symptoms is the most practical way to verify the contribution of acid reflux in the genesis of these symptoms; in face of a negative trial, i.e., no improvement in extra-digestive symptoms while on PPI treatment, the involvement of GERD remains highly uncertain.

9.2.2 "Cardiac" Symptoms

Chest pain mimicking angor pectoris may be due to esophageal pathology. The most important point in acute chest pain is to conduct a cardiac investigation



◘ **Fig. 9.3** Upper dysphagia: investigation plan



◘ **Fig. 9.4** Esophageal dysphagia: investigation plan

to rule out heart disease (that could potentially be lethal). Clinical examination will exclude a musculoskeletal cause, and, depending on the context, a pulmonary cause (pulmonary embolism, etc.) may have to be ruled out.

Esophageal spasms are often considered responsible for non-cardiac chest pains, but they are rarely identified due to their episodic, intermittent, and unpredictable nature. Esophageal investigation of non-cardiac chest pain is summarized in Fig. 9.5. Gastroesophageal reflux can induce esophageal spasm; endoscopy, esophageal pH-metry, or PPI trial therapy may be useful to establish the diagnosis of acid reflux (non-acid GERD may be detected by impedancemetry in some patients).

Esophageal manometry will detect motor disorders (achalasia, diffuse spasm, jackhammer esophagus, etc.) that could induce painful episodes. Esophageal sensitivity tests may, in some patients, reveal visceral hypersensitivity explaining increased pain perception.

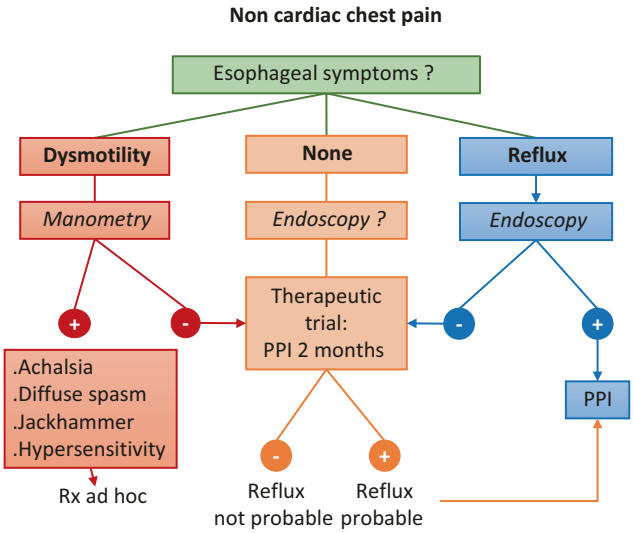


Fig. 9.5 Chest pain of non-cardiac origin: investigation plan

Nausea and Vomiting

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Contents

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10.1 Definition

Nausea is an unpleasant sensation of feeling like vomiting. Vomiting refers to the sudden and forceful oral expulsion of the stomach content (and possibly including material from the duodenum or the more distal intestine with bilious or fecal vomiting) due to antiperistaltic digestive movements accompanied by contractions of abdominal and diaphragmatic muscles. Vomiting is different from regurgitation, which is an effortless reflux of gastric contents into the esophagus (that can even reach the mouth).

10.2 Physiology

Nausea and vomiting are controlled by the vomiting center located in the brain stem medulla. This vomiting center can be stimulated by various factors, including vagal or spinal sensory afferents that detect abnormalities in the digestive system (occlusion, irritation, etc), neurological stimulation of the labyrinth or brain (e.g., intracranial hypertension), or by signals coming from the chemoreceptor trigger zone located outside the blood-brain membrane (under the floor of the fourth ventricle) and activated by numerous medications (e.g., chemotherapeutic agents), toxins, emotions, etc.

10.3 Causes

The causes for nausea and/or vomiting are numerous and can involve digestive and extra-digestive conditions (see ◘ Table 10.1). Digestive causes include any condition that prevents the forward movement of the digestive luminal content (e.g., pyloric obstruction, intestinal blockade, ileus with dysmotility), which leads to retrograde movements of these materials and their expulsion by vomiting. Nausea is also a common non-specific reaction to any "irritative" stimulus affecting the stomach or other digestive organs (e.g., gastritis, appendicitis, etc.).

Table 10.1 Nausea/vomiting: causes

(a) Digestive
Obstruction of the digestive tract
Lesional (e.g., pyloric ulcer, duodenal tumor, etc.)
Functional (e.g. paralytic ileus in peritonitis)
Visceral "irritation"
Gastric specific: "gastritis" (ROH, virus, etc.)
Non-specific: any pathological GI condition (infectious diarrhea, appendicitis, etc.)
(b) Central
Intracranial hypertension (tumor, etc.)
Labyrinth disorders (infection, motion sickness, etc.).
(c) Drug-induced
Opioids
Chemotherapy agents
Cannabis
Others
(d) Others
Pregnancy
Migraine
Postoperative [combination of a) and c)]
Psychogenic

10.4 Complications

- The loss of large amounts of fluids during vomiting (and impaired oral feeding) may be severe enough to induce dehydration, renal failure, etc.
- The loss of H^+ ions during vomiting of acidic gastric fluids can generate metabolic alkalosis (and hypokalemia due to the secondary entry of K^+ into the cells).
- The abrupt movements of the esophagogastric junction during vomiting efforts can result in a mucosal

tear of the cardia (Mallory-Weiss laceration; see ▶ Chap. 1). It manifests by bleeding with hematemesis or melena.

- The aspiration of refluxed gastric liquids into the bronchi and lungs can cause a "chemical" pneumonia. This occurs in the presence of an altered state of consciousness (e.g., by alcohol, drugs, trauma, etc.) that prevents the coughing/expulsion reflex that is normally evoked in response to a bronchial aspiration of foreign material.
- The rise in esophageal pressure during vomiting can be massive enough to provoke a rupture of the esophageal wall, which is a rare and serious condition (Boerhaave syndrome; see ▶ Chap. 1).

10.5 Treatment

Eliminating the factor(s) causing nausea and vomiting (e.g., withdrawal of opioid drugs, correction of pyloric stenosis, etc.) should be the main therapeutic target.

Various medications can be used to relieve nausea, as mentioned in ◘ Table 10.2.

◘ **Table 10.2** Nausea: pharmacological treatment

Classes	Generic name (commercial)	Precautions
Natural products	Ginger (Gravol® ginger)	
Antihistamines	Dimenhydrinate (Gravol®)	Central/anticholinergic effects
	Meclizine (Bonamine®) α	
Antidopaminergics	Domperidone (Motilium®) β	QT elongation, arrhythmias (predisposing factors)
	Metoclopramide (Reglan®, Maxeran®) β	Extrapyramidal reactions (EPR), tardive dyskinesia (rare)
	Prochlorperazine (Stemetil®)	Anticholinergic effects, EPR
	Haloperidol (Haldol®) δ	QT elongation, arrhythmias, central effects, EPR, tardive dyskinesia
Anticholinergics	Scopolamine (Transderm-V®) α	Anticholinergic effects (drowsiness, dry mouth)
Cannabinoids	Nabilone (Cesamet®) δ	Drowsiness, dizziness, psychiatric effects
5HT3 antagonists	Ondansetron (Zofran®) δ	
	Granisetron (Kytril®) δ	
NK-1 antagonists	Aprepitant (Emend®) δ	
Corticoids	Dexamethasone (Decadron®) δ	

Main indications of certain anti-nausea drugs: *α* motion sickness, *β* prokinetic effect useful if gastroparesis, *δ* N/V cancer chemotherapy

Upper Gastrointestinal Bleeding (UGIB)

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Contents

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11.1 Definition

Upper gastrointestinal bleeding (UGIB) results from the rupture of a blood vessel in the upper GI tract proximal to the ligament of Treitz.

11.2 Clinical Presentation

Blood loss Patients with UGIB present with hematemesis {vomiting of red blood or coffee-ground material (in less active bleeding)}, melena (black, tarry stools corresponding to blood digested along the digestive tract), or sometimes hematochezia (red- or maroon-colored stools coming out of the anus or a stoma, a condition occurring with massive bleeding and rapid intestinal transit without digestion of blood and formation of melenic stools).

Hemodynamic stability Loss of blood decreases the circulating vascular volume, and signs of hemodynamic instability will progressively appear. Initially, orthostatic hypotension (i.e., blood pressure drops by more than 20 (systolic)/10 (diastolic) mmHg when moving from a lying to a standing position; dizziness, vertigo, or even loss of consciousness when changing position may occur) takes place. When the circulating blood volume is reduced by 20%, the heart rate will accelerate (tachycardia to maintain blood supply to the body's organs) before the arterial pressure starts to drop (if further reduction in the vascular volume occurs). Finally, if more than 40% of the circulating blood volume is lost, severe hypotension (blood pressure less than 80 mmHg) and hypovolemic shock (with pallor, sweating, cold extremities, altered state of consciousness, etc.) will ensue.

Laboratory data After bleeding, the blood hemoglobin (Hb) concentration will progressively decrease (resulting in anemia). The reduction in the intravascular volume generates fluid shifts from the extravascular to the intravascular compartment (diluting Hb concentration) in order to correct the intravascular hypovolemia and maintain an adequate arterial pressure for organ perfusion; in the early stage of bleeding, the Hb concentration may remain normal for some time until the physiologic response of fluid transfer to the intravascular compartment occurs or until medical resuscitation (administration of saline solutions, etc.) is performed (see below).

Blood urea frequently rises after the absorption from the intestinal lumen of proteins from blood spilled in the GI tract.

Complications Ischemia, secondary to vascular hypovolemia and hypoperfusion, can affect various organs such as the brain (stroke), the kidneys (acute renal failure), the heart (myocardial infarction), etc. Mortality due to GI bleeding reaches 5–10%. Death is rarely due to exsanguination, but is rather due to the ischemic consequences on vital organs. Elderly subjects or those with comorbidities such as arteriosclerosis, diabetes, high blood pressure, kidney disease, etc. are therefore at greater risk.

Table 11.1 Causes of upper GI bleeding

Gastroduodenal peptic ulcer	30–50% of cases
Mucosal erosions	20–40%
Esophageal varices	12–14%
Vascular malformations	5–6%
Mallory-Weiss	5%
Tumors	5%
Dieulafoy	1%
Others	10%

11.3 Causes of UGIB

Any vessel in the GI wall can be eroded by any lesion and provoke digestive bleeding. Various lesions can erode the digestive vessels, as summarized in Table 11.1.

Two types of bleeds can be observed:

- *Variceal hemorrhage*, i.e., secondary to the rupture of an esophageal or gastric varicose vein related to portal hypertension and liver disease
- *Nonvariceal hemorrhage*, i.e., due to the erosion of a vessel of the gastroduodenal mucosa most often by an ulcer lesion

This differentiation is necessary considering the specific therapeutic strategies that differ for each condition. Variceal hemorrhage is less common (10–15% of UGIB), but it is often more abundant and clinically more severe.

11.4 Treatment of UGIB

The treatment steps are shown schematically in Fig. 11.1.

- ***Step 1: Minimize ischemia and restore perfusion supply***
  (a) Oxygen supplementation: increase inspired O_2 by nasal cannula or Venti-Mask.
  (b) Intravenous access: access one vein (two is better) with a relatively large-volume catheter (e.g., #16).

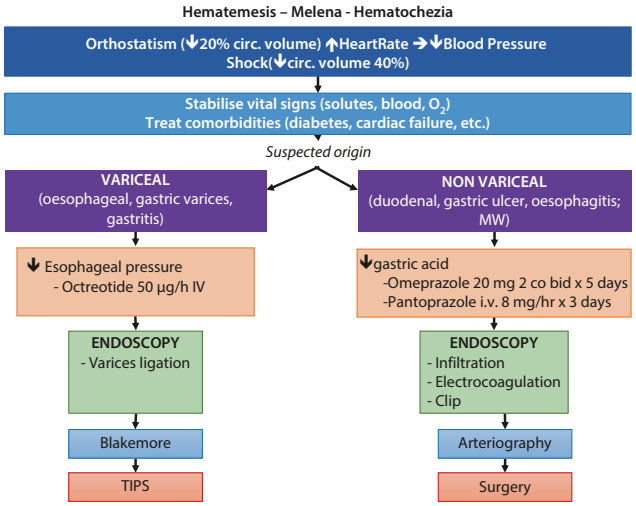

Fig. 11.1 Therapeutic strategy for UGIB

(c) Fluid resuscitation: infuse an iso-osmolar solution such as NaCl 0.9% (normal saline) or lactated Ringer's solution.
The amount of fluid to be replaced can be estimated based on vital signs:
- Orthostatic hypotension = 20% circulatory loss, i.e., about 1 liter of fluid required.
- Tachycardia and hypotension correspond to a loss of about 30%, i.e., 1.5 liters.
- Shock = loss of more than 40%, i.e., 2 liters.

This amount of fluid replacement is usually administered over 1–2 hours to restore the hemodynamic state. The speed of fluid administration, however, will be adjusted according to the severity of the bleeding and hemodynamic instability (may require faster correction if shock is present) vs. the patient ability to receive a large and sudden fluid load (with risk of vascular overload if heart failure, kidney failure, etc.).

(d) Transfusion: red blood cell transfusions may be required.
Transfusional thresholds of 70 or 80 g/L are suggested. Excessive elevation of hemoglobin may unnecessarily increase vascular volume and/or pressure and precipitate worsening of the bleeding; however, patients with diseases that compromise blood supply to vital organs (e.g., coronary artery disease, etc.) may benefit from a hemoglobin maintained at 90–100 g/L.

Step 2: Clinical and biological evaluation of the patient

(a) The evaluation of vital signs is necessary to assess the severity of the bleeding and to adjust the initial vascular repletion therapy.

(b) The clinical history and examination will subsequently make it possible to evaluate (1) the general health status and comorbidities that require immediate and short- or medium-term management (e.g., decompensated diabetes, etc.) and (2) the cause of the UGIB and thus to orient specific treatment for a variceal or nonvariceal source of bleeding.
Risk factors for variceal bleeding include:
- A known or suspected liver disease (e.g., history of alcohol abuse, etc.)
- Clinical signs suggesting liver disease such as jaundice, ascites, peripheral edema, spider angiomas, collateral abdominal circulation, hepatosplenomegaly, etc.

Risk factors for nonvariceal bleeding include:
- A known acido-peptic disease or symptoms of ulcer dyspepsia
- Use of aspirin or non-steroidal anti-inflammatory drugs
- Use of anticoagulants or antiplatelet drugs

(c) Nasogastric lavage: the insertion of a nasogastric tube (Levin or Salem tube) with drainage of the stomach to evacuate blood clots, and even with ice lavage of the stomach to control the bleeding, was once a must in the management of UGIB. However, it is uncomfortable for the patient and is no longer routinely recommended. It can be useful to:
- Identify the presence of blood in the stomach in a patient with melena but without hematemesis, suggesting UGIB. However, 10% of duodenal ulcer bleedings may present with an absence of blood detectable at gastric lavage.
- Empty the stomach to relieve some discomforts such as nausea, etc. or to reduce the risk of bronchial aspiration (if disturbed consciousness).
- Empty the stomach of blood clots to facilitate endoscopy and reduce the risk of aspiration during the examination procedure (usually performed under sedation). However, the stomach can also be emptied with a prokinetic drug such as erythromycin (1–3 mg/kg IV given 1 hour before endoscopy).

(d) Laboratory examinations: complete blood count (Hb, WBC, plt), INR, renal (urea, creatinine, electrolytes) and liver (bilirubin, ALT, AST, alkaline phosphatase) tests, and blood glucose are obtained at the arrival of the patient and repeated every 6–12 hours.

(e) Correction of the comorbidities identified by the clinical and/or biological examinations: insulin

therapy if high glucose, coagulation correction (administration of vit. K, fresh plasma, platelets, etc.) if required, etc.

- ***Step 3: Specific drug therapy***
  (a) *Variceal bleeding* can be managed by lowering the pressure in the esophageal varicose veins. Somatostatin analogue octreotide administration (50 µg IV bolus followed by a 50 µg/h infusion) allows the pooling of circulating blood in the splanchnic and mesenteric vascular circulations resulting in decreased blood flow to the esophageal or gastric varicose veins and, often, in cessation of GI bleeding.
  (b) *Nonvariceal bleeding* is treated according to the principle that the suppression of gastric pH promotes the stabilization of the coagulation clot and platelet plug forming on the vessel erosion. Intravenous pantoprazole (80 mg bolus followed by an 8 mg/h infusion for 3 days) is the classic approach but may be limited by cost. Its use is suggested if UGIB is severe and/or occurs in a patient with comorbidities or if the patient is already on proton pump inhibitor (PPI) therapy. Otherwise, most patients can be treated with an orally administered PPI (usually given at a double BID dose, i.e., omeprazole equivalent of 20 mg 2 CO BID, × 5 days).

These pharmacological treatments are started empirically depending on the suspected cause of UGIB (variceal or nonvariceal) at initial evaluation and can be re-evaluated based on the endoscopic findings.

- ***Step 4: Endoscopy***

Endoscopy is the examination of choice for the diagnosis and treatment of UGIB. Endoscopy is usually performed after the patient has been stabilized and the medical treatment described above has begun. It is performed as soon as possible during the first 24 hours after the patient presents to the hospital. Endoscopy, however, does require medical expertise, which may vary from one setting to another. The cause of the UGIB (see ◘ Table 11.1 and ◘ Fig. 11.2) will be established in more than 90% of cases by endoscopy.

Endoscopy will also allow the performance of therapeutic maneuvers (variceal banding ligation, ulcer coagulation, etc.) to stop the bleeding.

- ***Step 5: In case of failure***

The pharmacological and endoscopic maneuvers described above control 90% of UGIB. In case of persistent bleeding, various therapeutic strategies are possible:

Variceal bleeding

- Repeated endoscopy for a second attempt at variceal ligations, or more rarely sclerotherapy (intra-variceal injection of a sclerosing agent such as ethanolamine), of esophageal varices.
- Tamponade tubes: Linton or Blakemore tubes, introduced nasally or orally into the esophagus, are equipped with a round balloon inflated at the gastric fundus (to compromise the venous flow from the splanchnic circulation to the esophageal varices, Linton-Nachlas tube) or a longitudinal balloon inflated into the esophagus (to apply pressure on the varices, Sengstaken-Blakemore tube). See ▶ Chap. 8.
- Portosystemic shunt: Portal hypertension can be reduced by diverting the portal flow into the inferior vena cava. A surgical anastomosis is no longer necessary, and it is now usually performed percutaneously by a TIPS (transjugular intrahepatic portosystemic shunt). This procedure uses a catheter inserted through the jugular vein and introduced, under fluoroscopic guidance, successively via the superior vena cava, the right atrium, the inferior vena cava, and the hepatic veins through the liver into the portal vein to install an intrahepatic vascular prosthesis (stent) diverting the portal flow directly into the hepatic veins and to the inferior vena cava (thus bypassing the hepatic obstacle that generated increased portal pressure and led to the formation and rupture of esophageal varices).

Nonvariceal bleeding

- Repeated endoscopy for additional endoscopic hemostatic maneuvers
- Angiography with embolization of the bleeding vessel
- Laparotomy with surgical suture of the hemorrhagic vessel

Management steps for UGIB are summarized in ◘ Table 11.2.

Table 11.2 UGIB: initial clinical assessment and emergency management

A. Vital signs: heart rate, blood pressure
→ Guiding initial emergency resuscitation [type (blood?) and rate of resuscitation fluids]
B. Medical history: comorbidities (cardiac, pulmonary, etc.)
→ Adjust resuscitation (O_2, insulin, etc.)
C. Gastrointestinal history: suspected causal lesion?
→ Variceal vs. nonvariceal bleeding?
D. Initial empiric treatment
→ ↓ Variceal pressure (somatostatin) vs. ↓ gastric acid (PPI)
E. Upper digestive endoscopy
→ Variceal ligation vs. ulcer hemostatic therapy (thermocoagulation, clip, etc.)

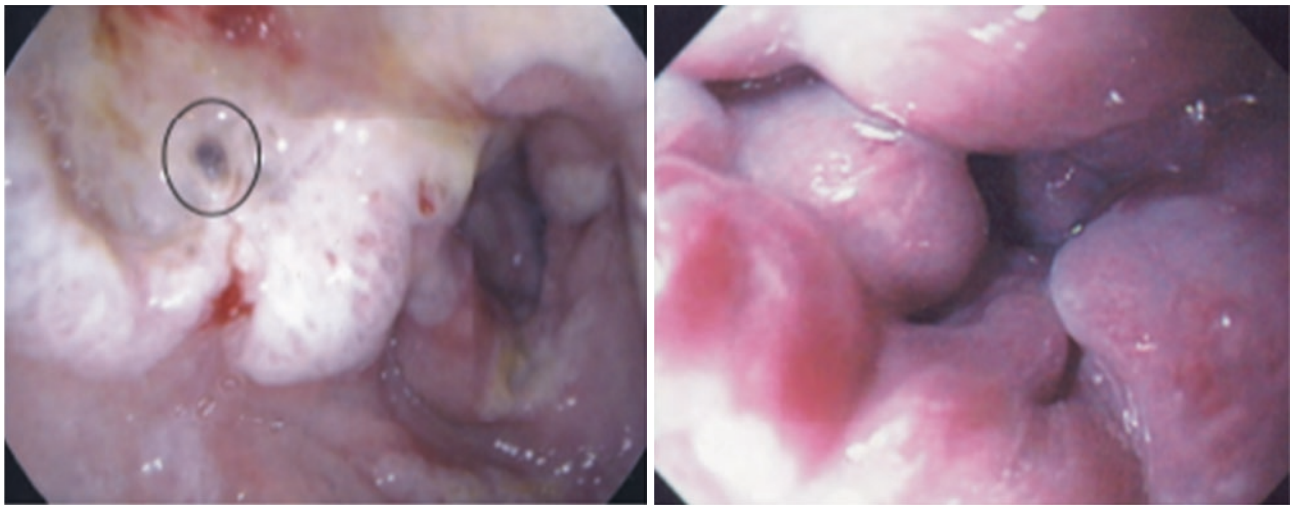

Fig. 11.2 Endoscopy revealing bleeding lesions that will be treated by endoscopy. Left: duodenal ulcer with a visible vessel (blue circle) that will be treated by an injection of saline solution around the hemorrhagic vessel (edema compression) prior to its obliteration by electrocoagulation or application of endoscopic clips. Right: esophageal varices which will be ligated using elastic bands

11.5 Special Topic: GI Bleeding and Altered Coagulation

The patient presenting with a GI bleeding while on anticoagulant or antiplatelet treatment constitutes a therapeutic challenge. These antithrombotic drugs increase the risk of GI bleeding and can limit the efficacy of hemostatic procedures.

The decision to interrupt or reverse the antithrombotic treatment is difficult. Potential benefits of reducing the bleeding process vs. the risk of inducing thrombotic complications must be weighed when modifying the antithrombotic therapy. As a general rule, interruption or reversal of the antithrombotic treatment must be limited to patients with severe, life-threatening, and uncontrollable hemorrhage.

- The vitamin K antagonist warfarin has a half-life of 40 h, and its therapeutic effect lasts 2–5 days. Antagonists include:
  1. Prothrombin complex concentrates (PCC), such as Octaplex®, Beriplex®, and Kcentra®, are produced by chromatography purification of large plasma pools and contain coagulation factors II, VII, IX, and X, as well as proteins C and S. They can induce rapid INR reduction.
  2. Fresh (frozen) plasma are easily available and 10× less expensive than PCC (although probably less potent).
  3. Vitamin K 2.5 mg PO or IV, a very cheap alternative, slowly reverses the anticoagulation effect in 24–28 h.
- Direct oral anticoagulants (DOACs) have a shorter effect. The half-life of dabigatran (Pradaxa®), a thrombin inhibitor, and apixaban (Eliquis®) and rivaroxaban (Xarelto®), inhibitors of factor X (that promotes the transformation of prothrombin to thrombin), are 12–17 h, 12 h, and 8–9 h, respectively.

  Specific antagonists are available for dabigatran [idarucizumab (Praxbind®), a monoclonal antibody binding and inhibiting dabigatran], as well as for apixaban and rivaroxaban [andexanet alfa (Andexxa®), an inactivated factor X that will attract factor X inhibitors], but they are very expensive.

  PCC can possibly help to restore coagulation in some patients on DOACs.
- Antiplatelet agents, such as ASA and P2Y12 platelet receptor inhibitors [clopidogrel (Plavix®), prasugrel (Efient®), ticagrelor (Ticlid®)], block platelet function for a prolonged period (up to 10 days).

  Platelet transfusions to reverse the drug effect have been associated with an increased mortality risk in patients with normal platelet count, and this therapeutic approach needs to be reconsidered.

Dyspepsia

P. Poitras

Contents

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12

12.1 Definition

The word "dyspepsia," from the ancient Greek for bad digestion, refers to symptoms of discomfort or pain all over the epigastric region, related (increased or decreased) to meals or food and believed to originate from the upper digestive tract (most often the stomach).

Functional dyspepsia (FD) refers to a function GI disorder with chronic dyspeptic symptoms (over 3 months) attributed to the stomach and occurring in the absence of structural abnormalities that can be identified by standard tests such as X-rays, gastroscopy, biopsies, etc. (as discussed in ▶ Chap. 2).

12.2 Symptoms

Acute episodes of dyspepsia (upset stomach) can occur in many people in connection with food poisoning, enteric (often viral) infection, drug intolerance, stress, etc. Self-medication with antacids, natural products, etc. is frequent. More severe or acute conditions of epigastric pain that may lead to an urgent medical consultation will be discussed in ▶ Chap. 16. Chronic dyspepsia (e.g., more than 3 months) affects about 25% of the population and is a frequent reason for medical consultation.

Retrosternal or thoracic discomforts, such as burns, pyrosis, and regurgitation, indicate gastroesophageal reflux, which we will personally differentiate from dyspepsia, although many authors include gastroesophageal reflux in dyspepsia conditions.

Although debatable, the Rome IV classification of FD identifies the epigastric pain syndrome (EPS, previously referred to as painful, or ulcer-type, or non-ulcer dyspepsia) and the postprandial distress syndrome (PDS, motor- or dysmotility-type dyspepsia). It is usefull to describe the main symptoms of dyspepsia in patients (◘ Table 12.1) and guide their treatment.

◘ **Table 12.1** Functional dyspepsia: classification

Epigastric pain syndrome (ulcer-like)	Postprandial distress syndrome (motor type)
Epigastric pain (burning, cramping, etc.) increased or decreased by food	Sensation of "difficult/slow digestion"
	Early satiety
	Postprandial fullness
	Distension upper abdomen
	Belching
	Nausea/vomiting

Epigastric pain, often in the form of a burning sensation or gastric cramps, which is triggered by meals or, on the contrary, relieved by meals (as in duodenal ulcer), identifies EPS.

Symptoms of PDS include sensation of "difficult/slow digestion," early satiety, postprandial fullness, upper abdominal distension, belching, nausea, and vomiting.

12.3 Differential Diagnosis

The differential diagnosis of conditions responsible for dyspepsia is shown in ◘ Fig. 12.1.

In more than half of the cases, the investigation of chronic dyspepsia symptoms will not reveal normal diagnostic tests (blood tests, esophagogastroduodenoscopy, radiological examinations such as barium meal, ultrasound, abdominal CT, etc.) This is known as functional dyspepsia. The physiopathology of FD involves abnormal gastric relaxation and/or visceral sensitivity as discussed in ▶ Chap. 2. As shown in ◘ Table 12.2, some clinical elements can help to differentiate lesional (or organic) dyspepsia from functional dyspepsia.

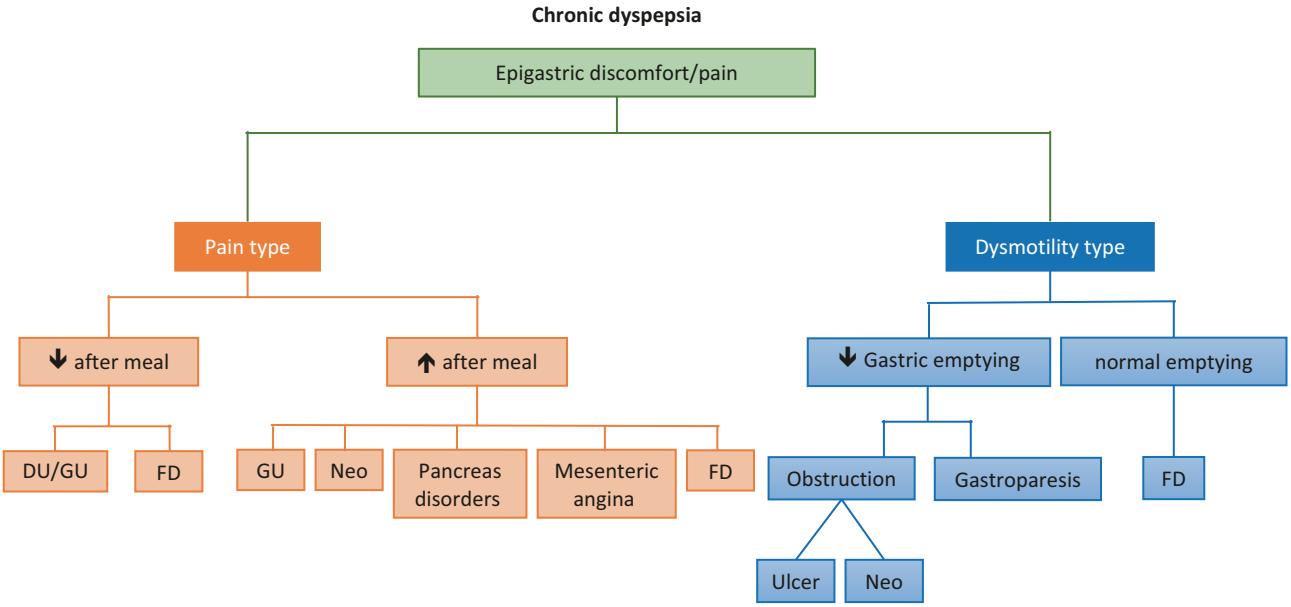
The discovery of gallstones on ultrasound in a dyspepsia patient must be approached with great care. Symptoms of gallbladder lithiasis include biliary colic (acute epigastric/right hypochondrium pain), migration accident (with pancreatitis and/or jaundice), acute cholecystitis, etc. (as presented in ▶ Chap. 6). Gallstones do not cause symptoms of chronic dyspepsia, and cholecystectomy does not improve symptoms of chronic dyspepsia.

12.4 Investigation

When to investigate? FD is the most common condition for chronic dyspepsia symptoms. Its diagnosis is established by history and clinical examination and, if necessary, by exclusion of digestive lesions. The suspicion of an organic lesion (which may have a vital impact and/or require specific treatment) is the first cause of medical investigation. The intensity of the symptoms (severe symptoms draw attention) or the expectations of the patients (worried about more severe conditions) are the other reasons for a more or less extensive investigation.

How to investigate? Upper gastrointestinal endoscopy is the main examination that will be used to document duodenal or gastric ulcer disease, as well as neoplastic lesions responsible for painful or motor dyspepsia.

Abdominal ultrasound is an easy, noninvasive, inexpensive examination to detect gross pancreatic abnormalities or stenosis of abdominal arteries (if performed with Doppler technology).



NB: gallstone does not cause chronic dyspepsia

Fig. 12.1 Differential diagnosis of chronic dyspepsia symptoms (EPS and PDS types). FD functional dyspepsia, DU duodenal ulcer, GU gastric ulcer, Neo neoplasm

Table 12.2 Structural/organic vs functional dyspepsia

Structural/organic	Functional
New symptoms or recent onset	Chronic evolution
Age > 50 years old	Associated with other functional GI disorders (IBS, proctalgia fugax, globus, etc.)
Weight loss	Associated with other functional disorders (migraine, fibromyalgia, hypoglycemia, etc.)
Impaired health condition	Associated with psychological comorbidities (related to stress, anxiety, etc.)
Abnormal physical examination (abdominal mass, lymph nodes, etc.)	
Blood test abnormalities (anemia, liver or pancreas tests)	

Abdominal CT scan (or CT angiography if mesenteric angina is suspected) may be required in some individuals to detect abnormalities (pancreatic or others).

Echo-endoscopy (endoscopic ultrasound, EUS) is an ultra-specialized, highly sensitive examination to identify abnormalities (pancreatic or others) and can be performed in certain cases (depending on its availability).

Gastric emptying can be evaluated by nuclear medicine examination. Reserved for certain severe cases, it is the test of choice to document gastroparesis.

Tests for visceral sensitivity or gastric distension are useful to understand the pathophysiology of FD (see ▶ Chap. 2). In practice, their diagnostic use is limited to exceptional cases and is accessible only in certain ultra-specialized investigation units. Moreover, the sensitivity/specificity of the tests is poorly established in clinical practice.

12.5 Treatment

The identification of an organic or lesional lesion responsible for dyspepsia will of course impose the treatment of this condition by the appropriate method. The management of FD has been presented in ▶ Chap. 2.

Diarrhea

P. Poitras

Contents

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13.1 Definition

Diarrhea, in medico-scientific language, refers to a condition where the weight of stools is greater than 200 g per day. In clinical practice, the term "diarrhea" is used by patients (and physicians) to describe stools that are too abundant, or too frequent (normal stools, 1–3 times/day), or too soft (or liquid), or urgent, or difficult to retain (incontinence).

13.2 Simplified Pathophysiology

The digestive tract absorbs (i.e., passage from the intestinal lumen to the body) nutrients and substrates essential for life, but it also secretes (i.e., passage from the body to the digestive tract) solutions used for this vital digestion/absorption process (e.g., 1 L of saliva, 2 L of gastric secretions, 2 L of pancreatic secretions, 1 L of biliary secretions, 1 L of intestinal secretions, etc.). Expelled stools are made of materials unabsorbed by the intestine and are therefore the net result of the secretory and absorptive functions of the digestive tract. The increase in stools, diarrhea, may involve the small intestine and/or the colon. In a simplified way, we can understand the physiopathology of diarrhea by using the complementary notions of the horizontal and vertical concepts.

Horizontal concept The intestine can be seen as a horizontal tube where absorption and secretion phenomena take place (Fig. 13.1). The intraluminal content of this pipe rises when there is a decrease in the absorption movements or an increase in secretion flow. This simple concept, where diarrhea occurs when the intestine either does not absorb enough or either secretes too much, makes it possible to understand all diarrhea conditions (since all diarrhea can be classified, generally speaking, as osmotic or secretory diarrhea).

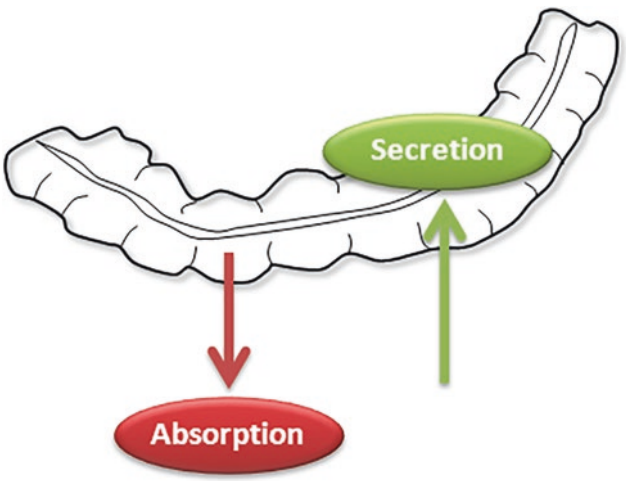

Fig. 13.1 Horizontal concept: The intestine is a tube able to absorb and secrete. The intraluminal content is the result of the balance between absorption and secretion activities. During diarrhea, the increase in intraluminal content may be due to a reduced absorption or to an increased secretion

Vertical concept The digestive tract can be seen as a long tube with a proximal entry side and a distal exit, extending from top to bottom (from the mouth to anus) (Fig. 13.2). It is made of successive segments (horizontal segments described above) following each other from top to bottom and where absorptive and secretory fluxes take place – distal segments adapting their response to the incoming material from the more proximal ones.

To understand the relationship going on between the horizontal and the vertical concepts, numerous examples can be looked at from the clinical world: during the hypersecretion of the stomach by oversecreted gastrin in Zollinger-Ellison syndrome, the small bowel will increase its absorption rate; diarrhea will appear only when the volume of gastric secretions overcomes the reabsorption

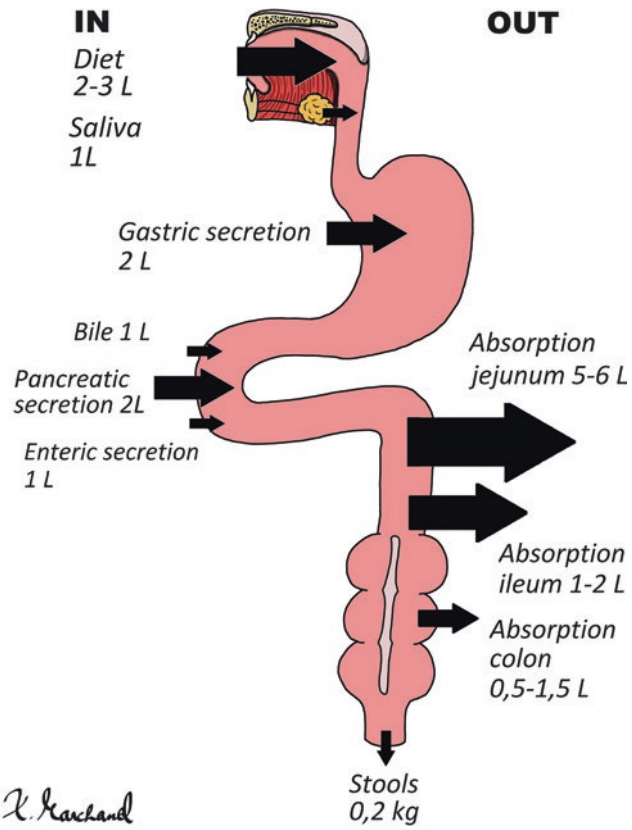

Fig. 13.2 Vertical concept: Absorption and secretion occur at all stages of the digestive tract. The amount of stools produced (normally 0.2 kg/d) results from a balance throughout the digestive tract between the substances exiting the digestive tract since absorbed (normally 5–6 L in the jejunum, 1–2 L in the ileum, 1–1.5 L in the colon) and those entering the digestive tract when secreted (7 L of endogenous secretions from saliva, stomach, bile, pancreas, and intestine) or ingested (2–3 L of dietary fluids)

capacity of the more distal gut. Similarly, when an exaggerated quantity of liquids (more than the usual 1.5 L/day) reaches the ileocecal valve (e.g., during infectious enteritis), the colon will be able to increase its absorption capacity up to 4–5 L/day; this explains why, after colectomy, patients with an ileostomy are highly susceptible to dehydration during infectious enteritis. Villous adenoma of the colon can secrete daily up to 300 mL of liquid; if located in the cecum, the polyp can stay asymptomatic since these secretions can be all reabsorbed by the more distal colon, while it may cause incapacitating diarrhea if growing in the rectum where chances for reabsorption are greatly decreased. A 10-cm-long Crohn's disease inflammation in the ileum is unlikely to increase stools, whereas a similar 10-cm-long Crohn's disease located in the rectum can be responsible for several bowel movements.

13.3 Differential Diagnosis

Acute vs. Chronic diarrhea *Acute diarrhea* must first suggest an infectious origin, either viral (usually lasting less than 2–3 days), bacterial (often more than 3 days), or parasitic (to be suspected if diarrhea is present for more than a week).

Chronic diarrhea (more than 2–3 weeks) is one of the most difficult diagnostic challenges in medicine due to the very large number of possible causes. To facilitate the clinical approach, various classifications based on pathophysiological mechanisms are used. ◘ Table 13.1 summarizes one of the most common classifications used to attempt to classify the type and origin of diarrhea in order to guide the diagnostic algorithm. Based on this pathophysiological classification, the diagnostic approach can be oriented for a better management of the patient.

The various diseases involved in diarrhea most often affect the small intestine and/or colon and are presented in their respective sections of this manual (▶ Chaps. 3 and 4, etc.).

Laboratory In some cases, the cause of the diarrhea can only be determined after specialized investigations; but in most cases, the tests described in ◘ Table 13.2 will have identified the diagnosis.

◘ **Table 13.1** Chronic diarrhea: clinical classification to guide the diagnosis

Osmotic diarrhea	*Secretory*	*Inflammatory*	*Motor*
. ↓ absorption . Stops with fasting . Stool: osmotic gap present	. ↑ secretion . Persists while fasting . Stools: osmotic gap absent	.Stool: Leukocytes +, Calprotectin ↑	.Postprandial diarrhea (mostly colic)
Causes 1) Malassimilation of nutrients Maldigestion -Pancreas: enzymes ↓ -Intestine: disaccharidase ↓ Malabsorption - Enterocytes ↓ 2) Nonabsorbable substances (Mg, lactulose, sorbitol, etc)	**Causes** -Toxins (Cholera, Shigella) - Villous adenoma colon - Hormones (VIP, 5HT, gastrin) - Bile salts - Ingested products (prostaglandins, senna)	**Causes** -Infections bacteria, parasites -Inflammation Crohn's disease, ulcerative colitis microscopic colitis	**Causes** - Functional (IBS) - Hormones (5HT, TCT, T4) - Nerves (post-vagotomy, diabetes) - Intestinal occlusion (colon cancer, fecal impaction)
Tests 1) Fecal fat dosage Maldigestion -Pancreas: .imaging .elastase Malabsorption -Small bowel: ·imaging ·biopsy 2) Lactose test	**Tests** - Colonoscopy - CTscan - Octreoscan - Hormone dosage (Gastrin, 5HIAA, VIP)	**Tests** -Stools: culture, parasites -Small bowel: X-ray, endoscopy -Colon: colonoscopy, biopsy	**Tests** Rule out lesions: - Obstruction - Inflammation - Etc.

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Table 13.2 Diarrhea: diagnostic tests

Stool examinations
Bacterial culture + parasite research: possible false negatives
Daily stool weight (if <200 g: no real diarrhea or abnormal defecation due to incontinence or rectitis)
Fasting test:
Diarrhea persists: secretory diarrhea
Diarrhea stops: osmotic diarrhea
Fecal calprotectin (or WBC): Elevated if infection or inflammation
Fecal fat dosage (collection over 48–72 h): "gold standard" to document steatorrhea; but often neglected because "tedious"
Fecal electrolytes:
Cations (Na^++ K^+) + anions (Cl^- + HCO_3^-) = osmolarity
In practice = (conc Na^+ + conc K^+) × 2 = ≈ 300
If (Na + K) × 2 = 300: secretory diarrhea
If (Na + K) × 2 < 250: osmotic diarrhea [osmotic gap (of >50) created by unabsorbed sugars, prot, Mg^+, etc.]
Small bowel investigation
Radiology: small bowel X-ray (barium contrast ingestion)/ EnteroScan/MR enterography
Endoscopy + duodenal biopsies
Enteroscopy via endoscopy or video capsule
Colon investigation
Colonoscopy + colonic biopsies
Pancreas investigation
Imaging (CT scan, MRI, ultrasound)
Functional tests [HCO_3^- secretion (rarely performed)/fecal elastase]
Therapeutic trial (pancreatic enzymes)
Blood tests
General:
Inflammation: HB ↓, Sed ↑, CRP ↑, platelets ↑, iron ↓, transferrin ↓, ferritin N or ↑
Malabsorption: Ca ↓,PTH ↑, INR ↑, Hb ↓, iron ↓, transferrin ↑, ferritin ↓, folate ↓, B12 ↓
Specific:
Anti-transglutaminase serum antibodies
Serum gastrin (VIP, TCT rare)
5HIAA urinary

13.4 Treatment

Acute treatment: hydration Loss of water and electrolytes with dehydration (leading to kidney failure, etc.) is the main consequence of diarrhea. Rehydration with water and electrolytes will therefore be the primary step in the treatment of diarrhea. This can be achieved by:

- Intravenous solutions (NaCl 0.9 ± KCl) allow to quickly replace fluids and ions but obviously require a hospital setup.
- Oral intake can be used to compensate for losses, but water, juices, or other clear drinks are unfortunately not sufficient for electrolyte intake (Table 13.3). The addition of glucose facilitates the absorption of Na^+ and secondarily of H_2O; WHO-type solutions, Pedialyte®, at worst "sports drinks" such as Gatorade™, are preferred. Various diets are traditionally used in episodes of diarrhea: chicken broth, soda cookies, boiled potatoes/vegetables, or a diet made of bananas, rice, applesauce, and toast (BRAT diet). Oral intake may increase diarrhea (which patients often want to avoid), but the therapeutic principle to manage dehydration is simple: ingesta > excreta.

Causal treatment Identify the cause (e.g., infection, inflammation, etc.) and treat it.

Symptomatic treatment Stool evacuation can be reduced by decreasing the intestinal transit (and thus promoting absorption) with opioids such as loperamide (Imodium®) 1–2 co qid prn (or Lomotil®, codeine, etc.). Diarrhea, however, can be seen as a defense mechanism of the body

Table 13.3 Preparation used for the oral rehydration of patients with diarrhea

Solution	Sodium (mmol/L)	Potassium (mmol/L)	Glucose (g/L)
WHO Solution	90	20	20
Pedialyte®	45	20	25
Gatorade™	23.5	<1	40
Coca-Cola™	1.6	<1	100
Apple juice	<1	25	120
Tea	0	0	0
Chicken broth	250	8	0

to evacuate harmful toxins and therefore does not necessarily need to be abolished. Aggravation or prolongation of the infectious state has been reported with the use of transit inhibitors in patients with bacterial enteritis (*Shigella*, etc.). Loperamide has been shown safe to use in benign travellers' diarrhea, but it should be avoided if the patient presents with fever or dysentery (bloody stools) or other signs suggestive of bacterial diarrhea. In severe colitis (inflammatory as well as infectious), the administration of loperamide is not recommended since transit inhibitors (including morphine or other opioids for pain control) have been associated with megacolon development.

Empirical treatment Most cases of acute diarrhea resolve spontaneously within a few days, and our treatment will concentrate on avoiding dehydration. If diarrhea persists for more than 3 days, a bacterial cause may be suspected, and stool cultures may be requested to identify the causal germ and treat it specifically. However, the results of stool cultures may take 3–4 days, and the patient's condition (fever, severe diarrhea, general illness, etc.) may require rapid treatment. A broad-spectrum antibiotic such as ciprofloxacin (500 mg bid po) is traditionally used; however, resistance to this antibiotic (e.g., campylobacter) has led to the increasing use of azithromycin (500 mg die). Depending on the context (post-antibiotic diarrhea, suspicion of parasites, etc.), metronidazole (500 mg tid) can be used.

13.5 Summary

- **Acute diarrhea**
  - Infectious origin until proven otherwise.
  - Treatment: maintain fluid-electrolyte balance [po (see Table 13.3) or iv].
  - Symptomatic treatment = transit inhibitors (loperamide), if needed and if benign disease;
  - If >3–4 days: stool culture? Antibiotics? (depending on culture or empirical).

- **Chronic diarrhea**
  - Origin can be complex (given the number of possible causes).
  - Pathophysiological classification (Table 13.1) helps to target differential diagnosis.
  - Investigation according to differential diagnosis (Tables 13.1 and 13.2).
  - Specific treatment: according to diagnosis.
  - Symptomatic treatment: slowing intestinal transit (opioids – chronic use?).

Abdominal Distension and Bloating

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Contents

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Distension and bloating of the abdomen are common complaints. Distension refers to an objective increase in the abdominal girth [that usually can be objectively identified (e.g., by measuring the abdomen circumference, visualizing large air content on abdominal X-rays, etc.)]. Bloating refers to a subjective sensation of abdominal distension or fullness (often without measurable increase in the abdominal volume).

14.1 Abdominal Distension

Distension of the abdomen may be due to air, liquids, or solids that cause the abdomen to expand (Table 14.1). On physical examination, digital percussion will help differentiate air distension (percussion with resonant sounds) from other causes (percussion with dull sounds). Palpation of the abdomen may reveal more or less circumscribed liquid or solid masses. In radiological examinations, air will be easily visualized on a simple plain X-ray of the abdomen; liquid or solid components will be identified by ultrasound or CT scan.

Distension by solids is slowly progressive. Pregnancy is the most obvious example of solid distension (although not limited to the fetus, but also including a liquid component considering the amniotic fluid). Fat in obese people can be located outside the abdominal cavity in the subcutaneous tissues (the abdominal adipose panicle, which can be easily palpated), but it can also be distributed intra-abdominally as a mesenteric infiltrate increasing the volume of the abdomen (the famous "beer belly"). Tumoral masses (benign or malignant) as well as organomegaly (e.g., liver, spleen) can sometimes grow large enough to increase the abdominal volume.

Fluid distension can be diffuse (ascites from liver disease or others) or localized (pseudocyst of the pancreas, gastric distension by pyloric occlusion, etc.).

Air distension is found during a mechanical (by obstruction) or paralytic ileus (reflex to an intra-abdominal pathology, postoperatively, drug induced, etc.) (Fig. 14.1). It is also common in patients suffering from pseudo-obstruction with severe dysmotility.

In many cases, the abdominal expansion or protrusion cannot be attributed to an abnormal accumulation of solid, liquid, or air material. This "pseudo-distension" can sometimes be related to an increased curvature of the lumbar spine (lumbar lordosis) or, as recently described (see later), to an abdomino-phrenic dyssynergia amplifying the frontal projection of the abdomen.

Table 14.1 Abdominal distension: causes

Distension by solids
Pregnancy
Obesity
Visceromegaly (liver, spleen)
Tumoral mass
Distension by liquids
Diffuse: ascites
Localized: cyst, pseudocyst, visceral distension (stomach)
Distension by air
Acute
Mechanical ileus
Paralytic ileus
Chronic
Intestinal pseudo-obstruction (myopathic or neurogenic)
Bloating syndrome

14.2 Abdominal Bloating

Abdominal bloating is a very frequent cause of consultation. Patients feel full, tight, swollen, and having an inflated balloon in the abdomen. It is chronic, usually variable over time (even during a single day, often appearing in the evening or after a meal), causing a sensation of tight garments (that need to be loosed), sometimes accompanied by flatulence, and attributed by many patients to excessive gas. However, bloating, even with an apparent abdominal expansion, is not always associated with a measurable abdominal distension or an exaggerated accumulation of gas (here identified as functional bloating). It is often associated with irritable bowel syndrome (IBS) or constipation.

Physiology of intestinal air

Quantitative or qualitative analysis of the intestinal air is not easy and could only be obtained through often complex research methodologies. Based on radiographic images, it can be estimated that the digestive system normally contains 100–1000 cc of air. Digestive air can be mobilized along the intestine, and a normal daily airflow of 200–1500 mL divided into 13 ± 7 evacuations (farts)

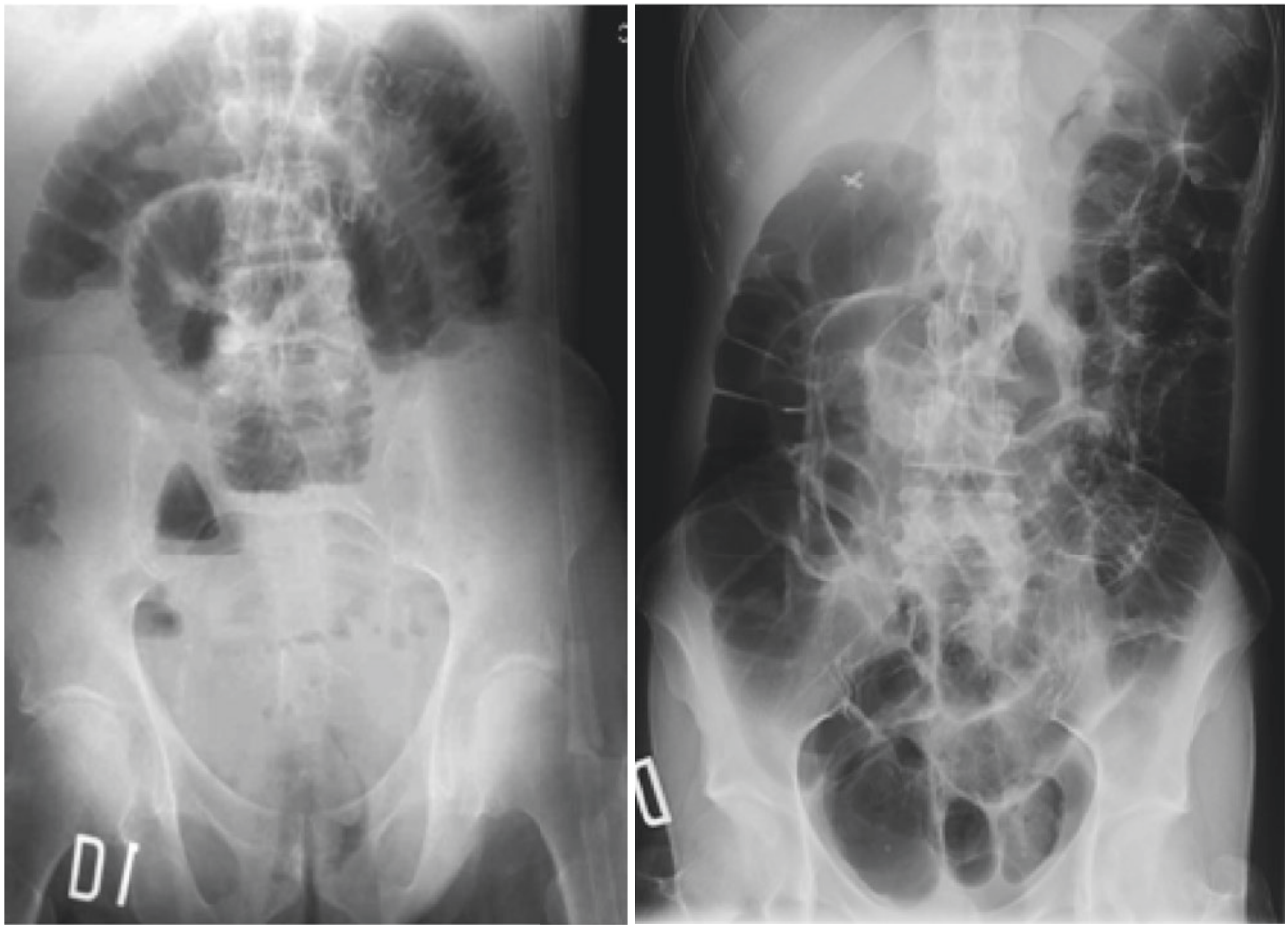

Fig. 14.1 **Left**. X-ray of the abdomen (plain X-ray) showing a mechanical ileus during an intestinal obstruction by an adhesion: the small intestinal loops are distended, filled with air and fluids, upstream of the obstruction site; downstream, the normal intestinal tract is not visible (air remaining upstream of the obstruction). **Right**. Paralytic ileus: the small intestine and the colon (air is present in the rectum) are diffusely distended, since the ileus involves the entire GI tract

has been documented in normal subjects. Air in the digestive system consists of swallowed gases (N_2 and O_2 present in the upper digestive tract) or those produced in the intestine (CO_2, H_2, and CH_4 found in the distal digestive tract).

Swallowed air: several cc of atmospheric air are normally aspirated with each swallow. Exaggerated aerophagia usually results in exacerbated belching or in gastric distension. Aerophagia appears to be promoted by various factors such as greedy swallows, chewing gum, smoking, carbonated drinks (soft drinks, beer, etc.), and especially anxiety.

Produced air: it is due to the fermentation by intestinal (mostly colonic) bacteria of ingested nutrients. Gases such as CO_2, H_2, and CH_4 are normally produced in the intestine and can actually have significant caloric benefits. An exaggerated production of gas occurs under the following circumstances:

- Generalized malabsorption with exaggerated quantities of protein, lipid, or carbohydrate nutrients arriving in the colon during, for example, pancreatic insufficiency or celiac disease
- Poorly absorbed disaccharides in case of lactase or sucrase deficiency from the enterocyte brush border
- Ingestion of sugars (e.g., raffinose, stachyose, starch, etc.) poorly assimilated by the human intestine as contained in bran, corn, many vegetables (beans, Jerusalem artichokes, etc.), "diet" products (sorbitol, etc.), laxatives (lactulose), etc.

Abnormalities in abdominal bloating

Increased quantity of intestinal air: cause of bloating? Bloating is a common symptom, often associated with IBS or constipation, and, according to many patients,

related to accumulated intestinal gases. However, all studies aiming to measure the amount of air contained in the intestine (even when using fancy technologies such as 3D imaging with MRI, isotopic plethysmography, etc.) failed to detect a significantly higher quantity of intestinal air in patients with functional bloating than in normal subjects.

Abnormal airflow? The transit of gas seems to be slow in patients with functional bloating. This probably explains the effectiveness of 5HT4 agonists (tegaserod, prucalopride), which are used as prokinetic agents for the treatment of constipation, to improve symptoms of bloating in constipated patients.

Colon anatomy probably explains the localized pain felt by some patients in the subcostal regions and relieved by rectal gas evacuation. The "hepatic flexure syndrome" as well as the "splenic flexure syndrome" could be explained by a localized accumulation and trapping of air in these sharply angled areas.

The instillation of air into the intestine of patients suffering from functional bloating causes, in experimental conditions, greater discomfort than in normal subjects. This may be related to the visceral hypersensitivity frequently encountered in patients with functional GI disorders. Therefore, reducing the amount of air present in the intestine could be an indirect but logical method to reduce the intestinal bloating discomfort. Gas absorbents such as simethicone or activated charcoal are used by many patients to relieve their bloating symptoms (although none of them have been scientifically proven to be effective).

Pseudo-distension and abnormal abdominal wall relaxation? Bloating is frequently associated with a visible abdominal distension that remains unexplained. Recently identified by researchers in Barcelona, the abdomino-phrenic reflex is an interesting concept to understand the pseudo-distension of the abdomen occurring in these patients. When gas is present into the intestine, the normal subject (as well as patients with intestinal pseudo-obstruction) will react by contracting the abdominal wall (to restrain abdominal expansion) and relaxing the diaphragm (which rises to enlarge the abdominal cavity); in patients with functional bloating, the abdominal wall relaxes while the diaphragm contracts and flattens, allowing the abdomen to extrude forward (without real distension) (see Fig. 14.2). This abdomino-phrenic dyssynergia probably explains the pseudo-distension of the abdomen found in many patients. Biofeedback therapy has been used in these patients.

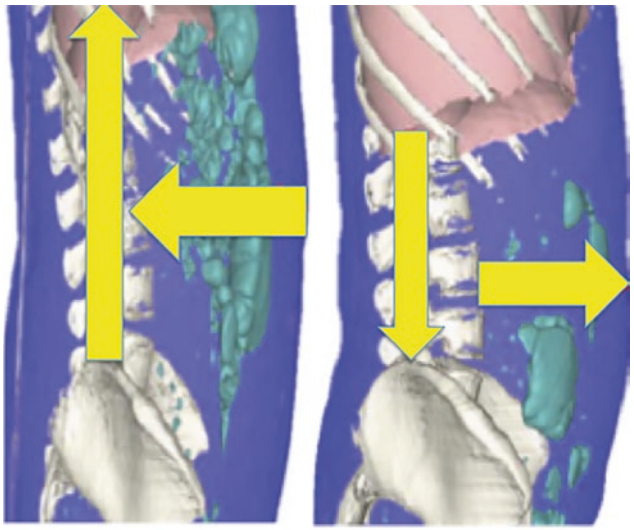

Fig. 14.2 Schematic illustration of abdomino-phrenic dyssynergia. When gas is present into the intestine, the normal subject (on the left) will react by contracting the abdominal wall (to restrain abdominal expansion) and relaxing the diaphragm (which rises to enlarge the abdominal cavity); in patients with functional bloating (on the right), the abdominal wall relaxes while the diaphragm contracts and flattens, which leads the abdomen to extrude forward. (Adapted from Accarino A et al. *Gastroenterology* (2009))

14.3 Treatment

Treatment of intestinal gases is summarized in Table 14.2.

Table 14.2 Treatment of intestinal gases

(A) Aerophagia
"Behavioral" approach = avoid favoring factors:
Gulping (eat slowly, chew well, no straw)
Carbonated drinks
Chewing gum
Smoking
Anxiety
(B) Abdominal bloating/flatulence
(a) Reduce ingestion of gas-producing nutrients:
Unabsorbed "medicinal" sugars (lactulose, sorbitol, etc.)
Malabsorbed disaccharides (if lactose or sucrose intolerant)
Poorly assimilable food sugars: bran, fermentable vegetables (cabbage, beans, corn, etc.), candied fruits, etc.
FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols)
(b) Reduce gas production
Lactaid® (if lactose intolerance): lactase to digest lactose into simple sugars
Beano®: alpha-galactosidase for digestion of sugars from vegetables (effectiveness, however, not demonstrated)
Antibiotics (if bacterial overgrowth) to reduce gas-generating bacteria
Probiotics to modify the intestinal flora (effectiveness still to be demonstrated)
(c) Reduce intraluminal gases
Gas "neutralizers": simethicone, activated carbon (widely used, but no proof of their effectiveness)
Accelerate gas transit (5HT4 agonists, laxatives?)
(d) Reduce painful response to gas distension
Promote relaxation of the intestinal wall [antispasmodic Rx (such as pinaverium, trimebutine, dicyclomine, etc.)
Intestinal "analgesics" (tricyclics, etc.)

Constipation

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Contents

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15.1 Definition

Constipation, in the medical community, is often identified as a condition where the daily stools are low in number (the "normal" daily frequency being estimated as 1 ± 3 bowel movements/day) and/or weight (the "normal" weight of stools being approximately 200 g/day).

For the patients, constipation often relates to a feeling of an inadequate and/or unsatisfying evacuation of stools that are rare (not as frequent as they expect), usually of small volume and hard texture, and difficult to evacuate (with straining, etc.).

Rome IV classification of functional GI disorders recognizes that a patient is constipated if he/she presents at least two of the following items:

1. Straining during more than 1/4 of defecations
2. Lumpy or hard stools more than 1/4 of defecations
3. Sensation of incomplete evacuation more than 1/4 of defecations
4. Sensation of anorectal obstruction/blockage more than 1/4 of defecations
5. Manual maneuvers to facilitate more than 1/4 of defecations
6. Fewer than three bowel movements per week

Normal defecation is a vague concept. Most "normal" people report a frequency varying from one stool every 3 days to three stools per day. However, some people can tolerate a bowel movement once a week easily, while others report constipation with two or three bowel movements per day. The patient often associates various digestive symptoms (e.g., abdominal pain, bloating, flatulence, nausea, etc.) and even extradigestive symptoms (headache, fatigue, etc.) with constipation.

Constipation, in popular belief, is often perceived as a harmful phenomenon that may lead to the accumulation of toxins that are not evacuated and impair the health condition. However, there is no scientific evidence to support this concept in the general population.

15.2 Pathophysiology

Constipation involves the distal digestive organs, i.e., the colon and the anorectum. Stools are formed imperceptibly and involuntarily in the colon (► Chap. 4) and are expelled during a voluntary action involving the anorectal motility (► Chap. 7).

Colon transit The colon transit lasts, normally, 1–3 days. A rapid transit compromises the liquid absorption and leads to liquid frequent stools, whereas a slow transit will allow more time for the absorption process and cause dry, hard, and rare stools. Any condition slowing down the colon transit (e.g., opiate drugs, colonic inertia) will result in constipation.

Colon absorption The colon works to complete the nutrient and fluid absorption done upstream in the small bowel by reabsorbing daily more than 1 liter of water and electrolytes that have escaped the intestinal absorption.

Stools (about 200 g/day), normally, contain 75% water and 20% of non-absorbable matter such as dietary fibers. The colon thus absorbs nearly 90% of the liquids that are entering it in order to concentrate and solidify the colonic content into a feces material to be excreted in a way that is physiologically and socially useful and acceptable.

An impaired colon absorption will result in stools of increased quantity and decreased consistency (diarrhea), while an enhanced absorption will result in stools of reduced quantity and firmer consistency (constipation). Colon absorption may be increased by slow colon transit (e.g., opiate use, hypothyroidism) and, probably, in large colonic surfaces (e.g., dolichocolon).

Anorectal sensory perception Propelled by colon contractions, the colonic material will reach the rectum. The rectal distention will send a signal to the brain and will be perceived as a need to defecate. Failure to perceive this signal (e.g., in patients with spinal cord injury, brain lesions, or megarectum) may cause prolonged stagnation of colonic contents, leading to an increased fluid reabsorption and constipation.

Anorectal motility When distended by stools, the rectal walls first relax and accommodate, while the individual can voluntarily contract the anal sphincter to contain the fecal material until defecation is possible.

To defecate, abdomino-diaphragmatic wall (voluntary) contractions will increase the intra-abdominal pressure and push forward the intestinal content, while the puborectalis muscle relaxes to open the anorectal angle, and the anal sphincters open to allow the passage of stools. Any perturbation in these coordinate actions (e.g., unsufficient abdomino-diaphragmatic contraction, obstruction (by rectocele, non-opened sphincters, etc.) to stool passage) may cause constipation.

The expulsion of stools, therefore, is linked to the transit of the colonic contents and to the defecatory action. The anorectum allows this evacuation that is regulated by autonomic physiological events, controlled by

voluntary movements and dependent upon sociocultural needs and obligations (accessibility to the toilet, etc.).

As shown in ◘ Table 15.1, constipation can be caused by several phenomena:

- Lack of fiber or calorie intake reduces the solid fecal material (and high-fiber diet is a logical step in the treatment of constipation). Fasting is an obvious cause of absent stools (no ingesta, no excreta!).
- An obstruction in the distal colon or anorectal region can interfere with the stool transit and evacuation. The obstruction may be due to a lesion (a malignant or inflammatory stricture, etc.) or to a functional disorder (anorectal dyssynergia, rectocele, etc.).
- A slow colon transit, due to a disease (e.g., hypothyroidism) or medication (e.g., opioids), results in an exaggerated absorption of colonic fluids and therefore reduces the fecal bolus.
- An impaired defecation, caused either by an unperceived need to evacuate (e.g., spinal cord injury, quadriplegia, or idiopathic), by an obstruction (prolapsus, anorectal dyssynergia, etc.), or by a voluntary repression of defecation (e.g., due to a "difficult" access to the toilet, anal pain, encopresis, etc.), increases the colon transit time, therefore reducing the fecal bolus.
- Idiopathic: often left without any causal explanation, chronic constipation is then declared as idiopathic (70% of cases). Since the transit time is normal in this case, one could hypothesize that the colon has, here, an enhanced reabsorption capacity.

Acute vs. chronic constipation Constipation can be acute and is then most often related to a brief and reversible condition such as a temporary fasting, the use of medications that slow down the colon transit (e.g., opiate analgesics), or acute psychosocial conditions (stress, travel, etc.). Chronic constipation is most often idiopathic. It may be part of the irritable bowel syndrome (IBS-C) if accompanied by abdominal pain (see ► Chap. 4).

Proximal versus distal constipation The paradigm of constipation must consider not only the functions of colon transit and absorption but also the anorectal defecation process. The anorectal defecation is a voluntary gesture and can be compromised by an obstruction (e.g., Hirschsprung's disease, anorectal dyssynergia, rectocele, etc.) but also by psychosocial conditions (e.g., discomfort to defecate while travelling, at the office, etc.). These two phenomena (colon and anorectum motility) are linked: restrained defecation leads to slowdown of the colon transit.

◘ **Table 15.1** Constipation: most common causes

General mechanism	Diagnostic tests
(A) Deficient dietary intake	
General (fasting)	
Fiber	
(B) Obstruction	
Lesional	Endoscopic or X-ray imaging
Cancer	
Inflammatory stricture	
Functional	Anorectal manometry, defecography
Hirschsprung	
Anorectal dyssynergia	
Dyschezia (anal lesions, rectocele, prolapse)	
Voluntary repression	
(C) Slow transit	
Diseases	
Hypothyroidism	Blood tests
Metabolic disorders (Ca^+, K^+, Mg^+)	
Neurological conditions (diabetes, MS, Parkinson)	Neuro exams
Colonic inertia	Marker transit
Medications	
Opioids	
Anticholinergics (including TCAs, SSRIs)	
Calcium antagonists	
5HT-3 antagonists	
Iron, calcium, and aluminum supplements	
(D) Impaired rectal sensitivity	
Megarectum	Imaging
Rectal hyposensitivity	Rectal manometry, barostat
Neurological disorder	
Central	Imaging [MRI]
Peripheral (spinal cord, quadriplegia, etc.)	Imaging (fMRI, EMG)
(E) Idiopathic	
Functional constipation	
IBS-C	

15.3 Investigation

The investigation of constipation is based on the history and physical examination.

Favoring factors [such as low fiber intake, certain drugs (opiates, etc.), psychosocial conditions, stress, etc.] should be identified.

Alarm symptoms (recent onset, older age, rectal bleeding, anemia, impairment of the general health condition, abnormal physical exam) are indications for a medical investigation (mostly to rule out colon cancer).

A defecation disorder may be suspected in the presence of exaggerated straining, sensation of incomplete evacuation, sensation of anal blockage, or digital maneuvers (e.g., vaginal or perineal pressure) to facilitate stool expulsion.

Constipation is most often a condition that affects the quality of life of patients but is medically benign (i.e., without repercussions on the patient physical health). It is most often idiopathic, and, after an adequate questionnaire and medical examination, it can be managed by a stepwise treatment as described below. Biological investigation will not be necessary in all cases. Who, why, and how to investigate are described in Table 15.2.

Table 15.2 Biological investigation of constipation

Who to investigate	Why	How
Infant/child	R/O Hirschsprung	Anorectal manometry
Alarm signs	R/O colon lesion	Colonoscopy, X-ray imaging
Recent onset		
Rectal bleeding		
Impaired health condition		
Dyschezia symptoms	R/O rectocele, prolapse, dyssynergia	Anorectal manometry, defecography
Straining		
Digital maneuvers		
Severe symptoms	R/O colonic inertia	Marker transit (X-ray)

15.4 Treatment

The management of constipation is based on the following general principles:

- Reassurance and education: constipation is not harmful to the individual's physical health, and it has no real biological consequences (however, the impact on the patient's quality of life should not be minimized).
- The general treatment, according to the author's experience, should look for regular bowel movements and avoid extreme situations where the colon will be alternately overfilled with fecal residues in the absence of (effective) treatment or empty after taking too much laxatives.
- Optimizing defecation: synchronize the need to defecate and the defecation. The function of defecation is a voluntary act based on complex biological mechanisms (described in ▶ Chap. 7) but also governed by psychosocial conditions and conventions. The colonic motility, usually increased after meals, is "awakened" when waking up in the morning, which explains why a morning defecation is present in many people. Defecation cannot ignore the voluntary gesture (abdomino-diaphragmatic contraction with anal sphincter relaxation) which can be easily repressed (leading to slowdown of the colon transit), and unfavorable situations (embarrassment in a non-personal environment such as the office, cleanliness of public toilets, hectic pace of life, etc.) should be avoided to ensure satisfying stool evacuation.
- The therapeutic strategy may be progressive or stepwise as described in Fig. 15.1.

Education Patients often fear that constipation will have adverse effects on their health, leading to nonspecific symptoms such as migraine, fatigue, etc., or that it may induce serious complications, such as cancer. However, they should be reassured that there is no evidence to suggest that constipation should be treated to control systemic or future complications.

Lifestyle habits In subjects with insufficient fiber intake, diet adjustments can help. However, as a general treatment, many studies have shown that supplement dietary fibers will increase stool volume but will have no beneficial effects on the symptoms of constipation. Bloating, especially associated with insoluble fibers (bran, etc.) and fermentable foods (cabbage, onion, legumes), is a common consequence of an excessive fiber diet.

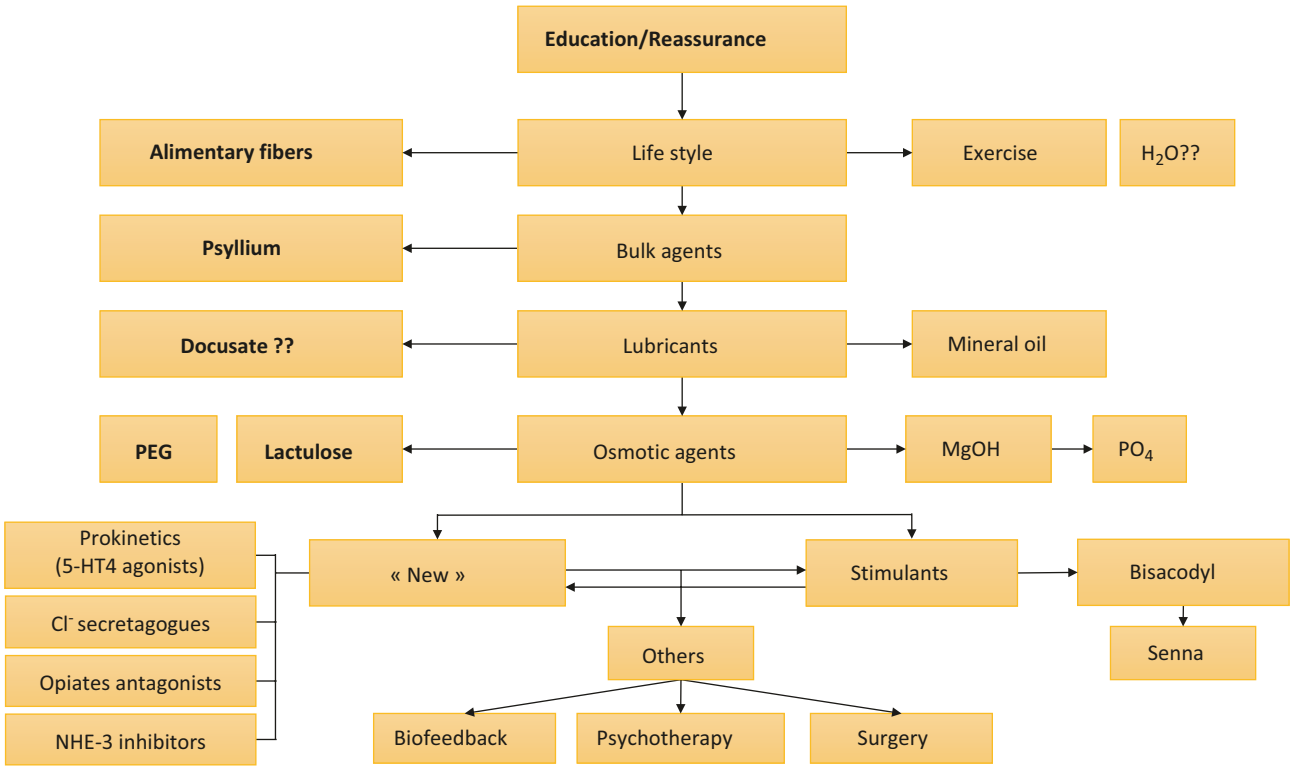

Fig. 15.1 Constipation: progressive step-up therapy

Physical exercise can improve constipation (intense exercise, such as marathon running, can even cause diarrhea!). It is also recognized that bed rest or immobilization in the hospitalized or bedridden patient is a cause of constipation (fecal rectal impaction is feared in these patients).

Increased water intake has no impact on the fecal bolus and constipation since these ingested fluids will be absorbed in the small bowel before reaching the colon and will therefore only influence the urine volume.

Bulking agents Bulk agents such as psyllium (Metamucil®, etc.) are effective in the treatment of constipation both to increase the fecal bolus and to decrease the symptoms related to constipation.

Lubricants (emollients) Docusate (Colace®) is widely used in clinical practice. It has the advantage of being easy to use (small, tasteless tablet) and has no significant side effects, but its effectiveness has been denied in all the studies available in the literature.

Mineral oil is used in children, but not much in adults. Malabsorption of fat-soluble vitamins (although this has been denied) and bronchial aspiration complicated by lipoid pneumonia are feared. To avoid this risk of bronchial aspiration, it should not be given to patients with swallowing disorders (and risks of a false route) or taken before bedtime (because of the supine position, which favors gastric reflux and possible bronchial aspiration).

Osmotic agents Osmotic agents (unabsorbed substances holding water into the small bowel or colon lumen) come in several forms. Polyethylene glycol 3350 solutions (Lax-A-Day®, MiraLAX®, RestoraLAX®, 17 g 1–2 times per day) are useful for normalizing stool frequency and consistency. PEG solutions with additional salts (Colyte®, PegLyte®, Klean Prep®, etc.) were developed for colonoscopy preparation (4 L ingested in 4 h for colon irrigation cleansing); they can also be used (250–500 mL daily) for the treatment of chronic constipation, but their taste is often not appreciated.

Lactulose is a non-absorbed sugar that improves stool frequency and consistency. However, the gas production from the sugars metabolized by the colonic bacteria is a source of bloating that is often uncomfortable for the patient.

Magnesium solutions (milk of magnesia) are well known clinically for their laxative effect. However, magnesium overload is to be feared in subjects with renal insufficiency.

Phosphate and/or sulfate solutions (e.g., Pico-Salax®, Fleet Phospho-Soda®) are powerful laxatives used mainly in acute conditions, such as preparations for

colonoscopy. There is little data on their chronic use in smaller quantities for the management of constipation.

Stimulant laxatives Stimulant (or irritant) laxatives have long been banned by medical authorities. However, bisacodyl appears to be effective and safe. Senna and its derivatives (natural products such as herbal teas, malva, etc.) have been used since centuries by constipated patients all over the world.

Senna (anthraquinone) derivatives are well known to induce a black coloration of the colon (an asymptomatic condition known as melanosis coli; see ► Chap. 4). They were also suspected to induce the "laxative (or cathartic) colon," a condition associated with laxative abuse and characterized by an atonic, often aganglionic, colon and progressively refractory to any laxative treatment. However, we now recognize the colonic inertia syndrome linked to a lack of colon neural ganglions and characterized by severe constipation requiring the use of powerful laxatives, such as senna; it is therefore possible that the colonic motor abnormality (cathartic colon) that has been attributed to senna abuse was, in fact, not a consequence of the high-dose laxative treatment, but was rather its cause!

Stimulant laxatives should not be used as a first-line treatment, but neither should they be banned from the therapeutic arsenal for constipated patients.

New drugs Various medications have been developed recently for the treatment of constipation. These drugs offer the advantages of having a better elucidated mode of action than the classic laxatives that have been empirically used for centuries and a therapeutic efficacy which has been validated by modern scientific investigations. However, many of them require a systemic route of action (with possible systemic side effects) and, as new drugs, have a long-term safety profile that is still poorly known. Their cost is also a limiting factor, and their place in the therapeutic arsenal (e.g., to be used before or after stimulant laxatives?) is still a matter of debate.

Prokinetics, such as 5-HT4 agonists, are known to be effective in the treatment of constipation and bloating since the earlier studies with tegaserod (now withdrawn from the market because of cardiovascular side effects). Prucalopride (suggested dose for treatment of chronic constipation, 2 mg die) is a 5-HT4 agonist marketed in Canada in 2012.

Chloride secretion activators act on the small bowel enterocyte to induce Cl^- and (secondary) H_20 secretion (and a secondary motility response). Lubiprostone, acting on the chloride channel 2, has been available in the USA since 2009. Misoprostol, a synthetic prostaglandin used for the treatment of peptic ulcers, is known to have a laxative effect; given its prostaglandin nature like lubiprostone, a similar mode of action is presumed. Linaclotide, a guanylin agonist activating cyclic GMP and Cl^- secretion from the enterocyte, is available in Canada since 2014 (plecanatide is also now available).

A sodium-hydrogen NHE-3 exchanger inhibitor, tenapanor, is available since 2019 to treat constipated IBS patients.

Peripheral opioid receptor antagonists such as methylnaltrexone, naloxegol, or alvimopan (available in the USA) may have a prokinetic effect by blocking the peripheral motor inhibition of opioids such as morphine, codeine, etc. [or even of endogenous opiates (endorphins)]. They are used in opioid users to block the drug-induced constipation.

Specific treatments for specific patients Biofeedback is used mainly in cases of anorectal dyssynergia where, during the defecation thrust, the patient contracts its external anal sphincter (rather than relaxing it), thus impeding the stool passage. Biofeedback therapy can correct this behavioral motor disorder.

Psychotherapy can improve certain conditions associated with constipation or irritable bowel syndrome. Anecdotally, it has also been found effective in some cases of colonic inertia or pelvic dyssynergia.

Surgery can be useful in certain selected cases. Defecation disorders linked to a rectocele, an intussusception, or a prolapse can be corrected by surgery. Some patients with a colonic inertia syndrome, with exclusive colonic involvement and without a generalized intestinal pseudo-obstruction disorder, can be improved after colectomy (and, most often, an ileorectal anastomosis).

15.5 Miscellaneous

Glycerin suppositories are used to stimulate the defecation in individuals with rectal hyposensitivity (e.g., spinal cord injury). Rectal enemas are useful in acute conditions (acute constipation, preparation for colonic examinations); they can also be used chronically in selected patients (neurological constipation, severe constipation, etc.).

15.6 Constipation in Children

Some guidelines for children:

- In full-term children, the first bowel movement occurs within the first 36 hours of life.
- At 4 years of age, a "normal" child has between three bowel movements/day and three bowel movements/week.
- Over 4 years of age, 97% of children have 0.5–3 stools daily.

Definition of constipation:

- In infants: breastfed, <2 stools/day; on cow's milk or "varied" diet, <3 stools per week.
- -In older children: <2 stools per week.

Hirschsprung's disease can sometimes be difficult to distinguish from functional constipation (see Table 15.3).

Table 15.3 Functional constipation vs. Hirschsprung's disease in infants

	Hirschsprung	Functional constipation
Age of onset	<2 months	>1 year
Meconium	Delayed >24 hours	Normal
Encopresis/ incontinence	Absent	Possible
Growth	Delayed	Normal
Abdominal pain	Rare	Frequent
Stool volume	Small	Large
Retention behavior	Absent	Present
Abdomen	Distended	Not distended
Rectal examination	Empty rectum	Stool

Abdominal Pain

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Contents

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16.1 General Considerations

Pain is defined as "an unpleasant sensory and affective experience associated with tissue damage…." Pain is a subjective sensation, variable according to individuals, time, etc.

The pathophysiology of pain involves (a) a "lesion" of a peripheral tissue, (b) activating a neurological signal afferent from the periphery to the brain, (c) where it generates a sensation of pain. Different steps are therefore involved (as summarized in Fig. 16.1).

1. **Pain transduction**. The transduction of a tissue "lesion" (e.g., distended gut) to a sensory nerve is the first step in the pain pathway where a physical phenomenon (e.g., mechanical, thermal, chemical "trauma," etc.) is converted into a sensory neurological transmission. Various mediators are involved here: the "traumatized" tissue produces prostaglandins, leukotrienes, protons, etc.; circulating anti-inflammatory agents such as platelets or leukocytes secrete bradykinin, histamine, interleukin, etc.; and in nerve endings, substance P is activated. Transduction is a step that can be modulated by certain drugs such as NSAIDs, corticoids, local anesthetics, etc., acting on these mediators.

At the intestinal level, the cutting or burning of the organ is painless (which allows, among other things, the therapeutic gestures of fulguration, electrocoagulation, etc. performed in digestive endoscopy and not perceived by the patient). The distension of the organ, the traction of its mesenteric attachments, the muscle contraction, and the tissue necrosis are sources of pain transduction.

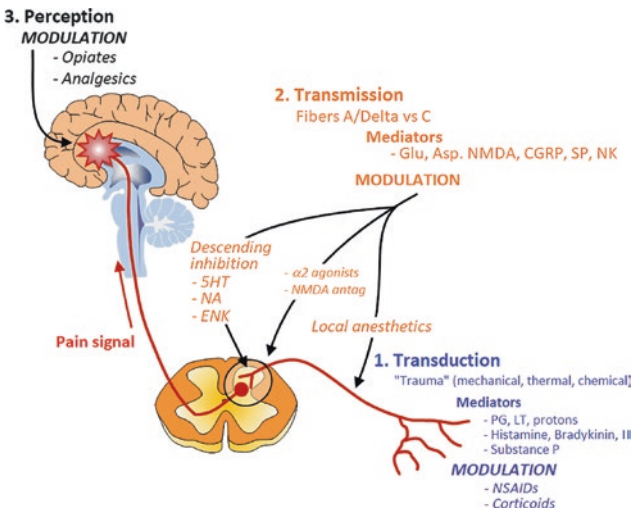

Fig. 16.1 Pain transmission from the peripheral organ to the brain in three steps: (1) transduction, (2) transmission, and (3) perception of the pain signal

2. **Pain transmission.** The transmission of the painful process from the "traumatized" organ to the brain takes place via nerve impulses, mainly from the sympathetic system. The primary nerve (also called first-order or first-class nerve) travels from the organ to the spinal cord through the celiac or mesenteric ganglia in the abdomen; at the level of the spinal cord, in the posterior horn, it meets a second-order neuron which will join the spinothalamic bundle (thermo-algesic sensibility) on its way to the brain.

The neurological fibers transmitting the afferent influx are of two types:

- The A/Delta fibers are myelinated, densely distributed on the organ, and capable of rapid influx transmission. The A/Delta fibers are involved in the somatic pain process (e.g., from the skin, musculoskeletal apparatus, etc.); they allow a precise perception of pain (e.g., a sensation of stinging can be differentiated from a sensation of burning and localized to a very precise site on the body). In the abdomen, A/Delta fibers are rare and limited to the parietal peritoneum and to the capsule of solid abdominal organs.
- The C fibers are non-myelinated, are distributed in limited quantities over their innervated organs, and provide slow impulse transmission. Pain sensation mediated by C fibers is often vague and poorly localized. C fibers are predominant in the abdomen and are responsible for the innervation of the digestive viscera. This explains why visceral pain, as opposed to somatic pain, is often vague and imprecise. For example, in appendicitis (see ▶ Chap. 4), the initial inflammation occurring in the viscera and its immediate vicinity is transmitted by the C fibers to often generate a rather vague, dull discomfort, felt in the periumbilical region before the inflammation ultimately reaches the parietal peritoneum to then activate the A/Delta sensory fibers allowing the precise localization of the pain in the right iliac fossa. The physiology of visceral pain explains the difficulty for patients to report their symptoms and the difficulty for physicians to diagnose them.

Abdominal pain afferents travel mainly with sympathetic fibers (the esophagus and pelvic organs are innervated by vagal or sacral parasympathetic fibers). While the somatic afferents (from the skin, muscles, etc.) give rise to well-established innervation segments that can be recognized according to the dermatomes (Fig. 16.2), the visceral afferents have a much less precise distribution. Afferents from the stomach, liver, and pancreas pass through the celiac ganglion before entering the spinal cord via the paraspinal ganglia located from T5 to

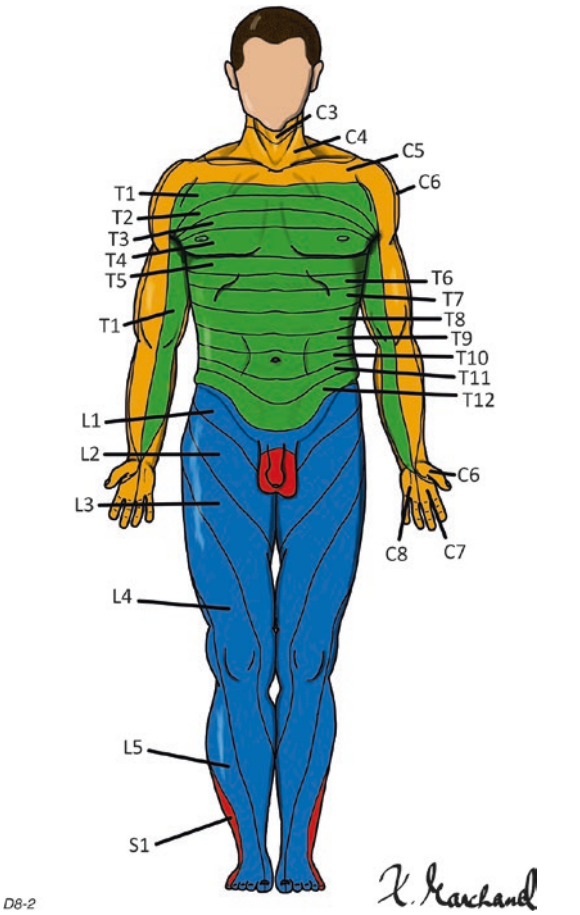

Fig. 16.2 Somatic pain is felt in specific territories corresponding to the dermatomes shown here. Visceral pain is less precise

T9; afferents from the intestine and colon are travelling via the celiac, superior mesenteric, or inferior mesenteric ganglia to the T10 to L2 spinal segments; the distal colon and pelvic organs may use parasympathetic fibers from S2 to S4. The extensive, overlapping segmentation of visceral afferents between different segments explains the relatively unclear parietal localization of a digestive pain. Broadly speaking, the travel of an abdominal pain follows the embryological development of the viscera, and pain originating from the "foregut" organs (stomach, bile ducts, pancreas) is felt in the epigastric region, that from the "midgut" viscera (small intestine) in the periumbilical region, and that from the "hindgut" organs (distal colon) in the hypogastrium.

Visceral pain can be *referred* to the corresponding somatic territory. Thus, the visceral C fibers innervating the diaphragm are found in spinal segments C3, C4, and C5 where the somatic A/Delta fibers innervating the shoulder converge; this explains the shoulder pain experienced during diaphragmatic irritation (e.g., by a suprahepatic abscess, post-laparoscopy air, etc.).

Visceral pain can be *radiating*, i.e., spread to other areas, such as pancreatitis, which causes epigastric pain radiating to the back, or renal colic, which causes pain in the flank or back and radiates to the genitals.

The neurological transmission of a pain impulse involves various neurochemical mediators including glutamate (Glu), aspartate (Asp), NMDA (N-methyl-D aspartate), CGRP (calcitonin gene-related peptide), somatostatin, substance P (SP), neurokinins (NK), etc. The transmission of peripheral nerve impulses can be blocked by local anesthetics (administered to the nerves, plexuses, epidural space, or subarachnoid space). This nerve transmission can also be modulated by pharmacological agents such as alpha-2 agonists (e.g., clonidine) and NMDA antagonists (ketamine) or by descending inhibitory fibers coming from the brain and releasing enkephalins, serotonin, noradrenaline, etc.

3. **Pain perception** takes place in the brain. This perception can be modulated by opiate drugs (morphine, etc.), general anesthetics, etc. The spinothalamic network, on its way to the brain, receives messages from the thalamic and limbic systems, and thus pain perception is also influenced by anxiety, emotions, painful memories, etc.

16.2 Clinical Approach to Abdominal Pain

The diagnosis of abdominal pain is difficult due to the visceral neurological system that is less efficient than the somatic system to express pain conditions as discussed above and due to the multiple conditions that need to be considered in the differential diagnosis. A detailed and focused history as well as a careful abdominal examination is essential.

1. ***Location of pain.*** The location of the pain is a primary diagnostic clue to be obtained. Figure 16.3 schematically describes the causes to be considered according to the location of the pain reported by the patient.
2. ***Radiation of pain*** may correspond to classic patterns described in Table 16.1.
3. ***Type of pain***: Burning pain is often caused by an acid peptic lesion (stomach/duodenum ulcer, etc.). Cramps are felt when intestinal or colonic muscle contractions are increased to overcome an obstacle (e.g., intestinal obstruction) or are stimulated by an "irritation" (e.g., viral gastroenteritis). Sudden, explosive pain suggests an abdominal emergency such as a visceral perforation, acute intestinal ischemia, etc. Pain of increasing intensity over 1–2 hours is common in cholecystitis, pancreatitis, or intestinal

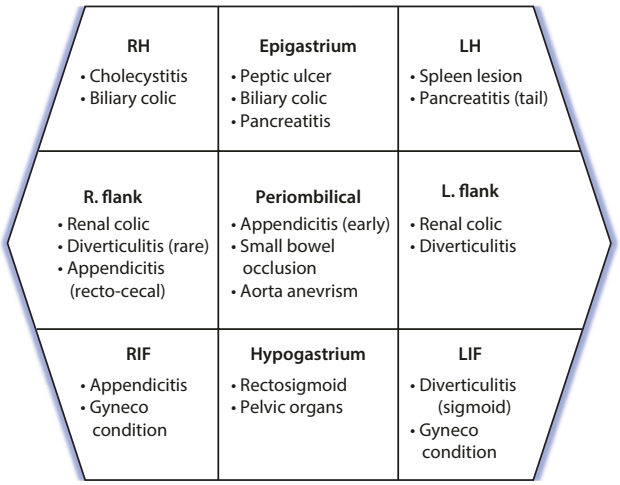

Fig. 16.3 Origin of abdominal pain according to its location in the right hypochondrium (RH), left hypochondrium (LH), right iliac fossa (RIF), etc.

Table 16.1 Radiating/referred pain

Pain	Radiation	Origin to be suspected
Epigastrium	Transfixing to the back	Pancreas
Epigastrium	Right hypochondrium	Gallbladder
Epigastrium	Left hypochondrium	Caudal pancreas
Flank	Groin, genitals	Renal colic
Right hypochondrium	Right shoulder	Subdiaphragm (abscess, air)

obstruction; vague, dull, progressive pain over a few hours is often found in appendicitis, incarcerated hernia, and diverticulitis.

4. ***Associated phenomena*** should be sought. Failure to pass stools and gas is a sign of intestinal ileus (by mechanical obstruction or reflex intestinal paralysis). Relief by bending over in a curled up position is common in pancreatitis. While the patient suffering from peritonitis is usually calm and prostrate, the subject with a renal colic may be rather agitated and inclined to walk.
5. ***Examination*** of the abdomen is a critical step in the assessment of abdominal pain. As described in Table 16.2, examination of the abdomen is based on visual inspection, auscultation, percussion, and palpation of the abdomen.

Table 16.2 Abdominal examination: important signs

Inspection	↑ abdominal volume: fluid = ascites; air = bowel obstruction
	Hernia (wall/inguinal areas) = potential incarceration site
	Surgical scar = potential intestinal occlusion by adhesions
Auscultation	Bowel sounds ↑ = bowel obstruction
	Bowel sounds ↓ = paralytic ileus (peritonitis, etc.)
Percussion	Tympanic = air (bowel obstruction) vs dull = fluid (ascites)
	Liver dullness absent = pneumoperitoneum due to visceral perforation
Palpation	Abdominal guarding (abdominal wall contraction during palpation)
	Voluntary (protection against pain) vs involuntary rigidity (peritonitis)
	Localized (local inflammation) vs diffuse (generalized peritonitis)
	Rebound pain (pain evoked by sudden release of abdominal palpation) = peritonitis
	Localized (Blumberg's sign) or at distance (Rovsing's sign)
	Specific pain sites
	McBurney's point (right lower quadrant = appendicitis)
	Murphy's sign (right upper quadrant: pain on inspiration) = cholecystitis
	Psoas sign (pain at thigh elevation) = psoas irritation (abscess, etc.)
	Obturator sign (pain during hip internal rotation) = obturator muscle irritation
	Rectal exam: pelvic pain = pelvic inflammation/abscess

16.3 Diagnostic Strategies in Abdominal Pain

The management of acute abdominal pain is primarily aimed at detecting severe conditions that require "urgent" surgical treatment.

1. **Laboratory tests**. In addition to the clinical examination, various laboratory tests (serum tests, X-rays, etc.) are obtained to guide the diagnosis. The blood count is used to check for a low hemoglobin (which could be due to internal bleeding) or elevated

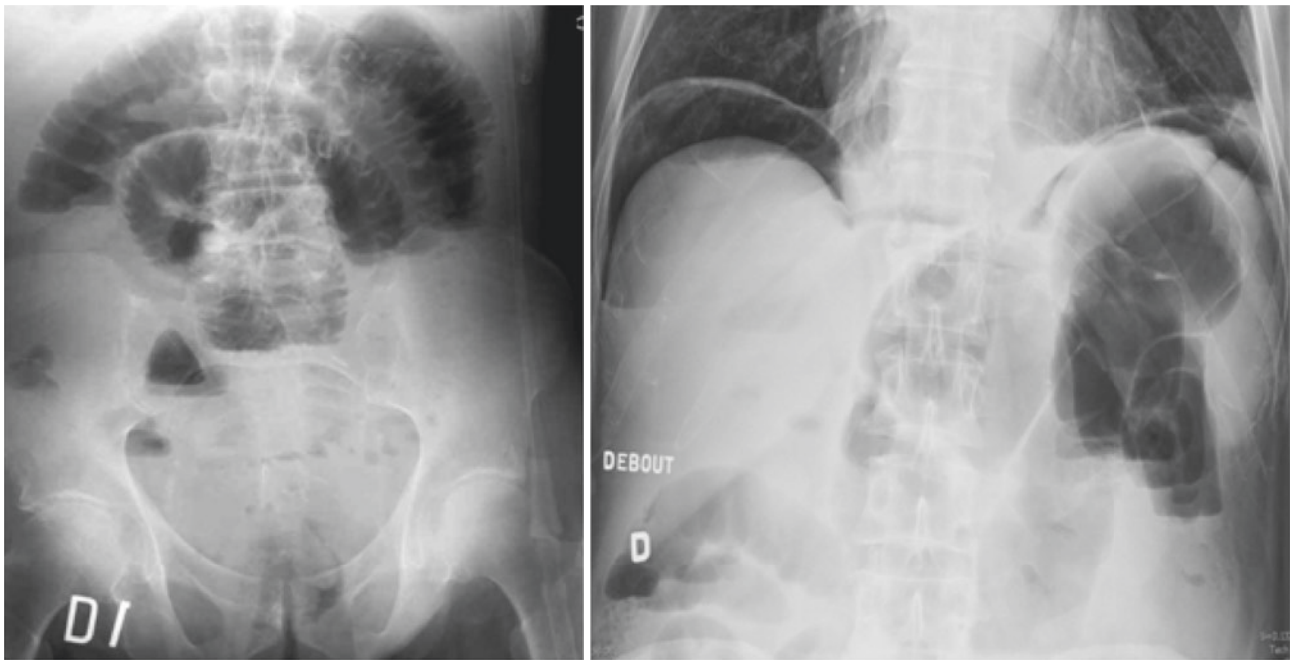

Fig. 16.4 Plain X-rays (flat plates) of the abdomen: Left: distension of small intestinal loops occluded by a scar adhesion. Right: free air under the diaphragm due to a perforated duodenal ulcer

leukocytes (suggestive of severe inflammation). Pancreatic enzymes (amylase, lipase) are elevated in pancreatitis (but also in other conditions). Hepatic enzymes (ALT, AST, alkaline phosphatases) are elevated in liver or biliary diseases. Lactic acid increases (unfortunately late) in the case of intestinal ischemia. A simple plain X-ray of the abdomen can reveal signs of visceral perforation (free air under the diaphragm) or intestinal obstruction (distended intestinal loops, gas-fluid levels, etc.; see Fig. 16.4).

2. **Surveillance**. Classically, the diagnostic strategy for acute unexplained abdominal pain was based on repeated clinical (and biological) evaluation (q 1–2 h) to monitor the evolution of the pain and the development of obvious or very significant signs for a precise diagnosis that would allow a specific therapeutic (often surgical) management. For example, appendicitis in its initial stage is most often manifested by a vague periumbilical discomfort (visceral pain mediated by C fibers) before the irritation of the parietal peritoneum (and activation of A/Delta fibers) allows the typical perception of pain in the right iliac fossa. Repeated physical examination allows early detection of signs of localized peritonitis and thus to decide on surgical intervention before more serious complications such as generalized fecal peritonitis may occur.
3. **Imaging.** In the last 20 years, however, abdominal imaging techniques have revolutionized the management of patients with acute abdominal pain. Ultrasound is crucial in gallbladder diseases and, depending on local expertise, may be very useful in other conditions such as appendicitis, diverticulitis, etc. CT scan is the most commonly used technique to elucidate abdominal pain investigated in the emergency room. It allows early identification of lesions that previously were, unfortunately, diagnosed only at an advanced (and complicated) stage of their evolution (e.g., ruptured appendix, intestinal ischemia with necrosis and perforation, etc.). It can also clarify the disease condition (e.g., extent of pancreatic damage, cause of intestinal obstruction, etc.) to guide the treatment procedures.

16.4 Therapeutic Strategies for Abdominal Pain

Specific treatment Treatment of the underlying cause of the abdominal pain (e.g., appendectomy if appendicitis, antibiotics if diverticulitis, etc.) will of course be undertaken as soon as possible.

General treatment will include:

- *Support treatment* to correct and maintain the vital parameters (O_2 saturation, hemodynamic stability, hydroelectrolytic equilibrium, etc.). Comorbidities (e.g., diabetes or coronary disease decompensated by stress, infection, blood loss, etc.) may need to be addressed.
- *Pain relief*: A nasogastric decompression tube can be installed in patients with vomiting and/or intestinal obstruction.

Analgesics such as morphine (5–15 mg sc, iv), hydromorphone (1–4 mg sc), or meperidine (50–75 mg im) are commonly administered. The use of analgesics in patients with acute abdominal pain was previously discouraged to avoid masking clinical signs (e.g., increasing pain and abdominal guarding in response to progressive peritoneal irritation) that could have justified an urgent surgical treatment; but this attitude now seems to be less important since, among other things, the diagnosis is now most often obtained earlier with radiological imaging. However, opiates can cause nausea, vomiting, and paralytic ileus, which can become confounding elements in the evaluation of an abdominal pain.

The most common urgent abdominal conditions are listed in Table 16.3.

Table 16.3 Most common abdominal emergencies

Disorders	Symptoms	Diagnostic tests	Treatment
Appendicitis	Pain periumbilical →RLQ	CT scan (ultrasound)	Cx: appendectomy urgent
Biliary colic	Pain epigastrium/RUQ (<4–6 h)	Ultrasound	Analgesia Cx: cholecystectomy elective
Cholecystitis	Pain RUQ Murphy +	Ultrasound	Analgesia/antibiotics? Cx: cholecystectomy < 24–48 h
Cholangitis	Pain RUQ Fever Jaundice	Ultrasound Blood cultures Serum liver tests	Antibiotics ERCP sphincterotomy 1–7 days
Pancreatitis	Pain epigastrium→back	Serum tests CT scan (non-urgent)	NPO, analgesia, hydration ICU (severe pancreatitis)
Visceral perforation	Pain periumbilical or diffuse Generalized peritonitis	X-ray (flat plate) (CT scan)	Cx: urgent Antibiotics
Intestinal occlusion	Cramp/colicky pain Abdomen distension	X-ray (flat plate) (CT scan)	Hydration, NG tube, analgesia? Cx: maximum wait 72 h
Intestinal ischemia	Pain periumbilical or diffuse	Serum lactate CT scan	Heparin? Vascular Cx/RX: urgent
Aortic aneurysm	Pain periumbilical	Ultrasound (CT scan)	Cx urgent
Ischemic colitis	"Colon" (flank, LLQ) pain Bloody stools	CT scan (Colonoscopy)	Hydration, analgesia, antibiotics?
Diverticulitis	Pain LLQ (most often) (Fever)	CT scan Blood WBC	Antibiotics vs NSAID+ analgesia Abscess drainage (RX/if >3 cm) (Surgery)
Ectopic pregnancy	Pain LLQ or RLQ	Ultrasound	Cx: urgent
Renal colic	Pain flank	CT scan	Hydration, Analgesia, tamsulosin [Stone extraction (ureteroscopy)]
"Solid" lesion (liver, spleen, intestine/tumor, abscess)	Pain at lesion site	CT scan	Rx of underlying condition

Abbreviations: *Cx* surgery; *ICU* intensive care unit; *LLQ* left lower quadrant (left iliac fossa); *LUQ* left upper quadrant (left hypochondrium); *NPO* nil per os (fasting); *NG tube* nasogastric tube; *RLQ* right lower quadrant; *RUQ* right upper quadrant; *Rx* treatment; *RX* radiology

16.5 Miscellaneous

Abdominal pain may be due to non-visceral, nonsurgical disorders as listed in ◘ Table 16.4.

Table 16.4 Non-visceral/nonsurgical abdominal pain

A. **Musculoskeletal disorders**
- Radiculopathy (from T6 to L2: disk herniation, diabetic neuritis, shingles, etc.)
- Parietal scar neuroma
- Psoas, rectus abdominis tendinopathy
- Xyphoiditis

B. **Radiating pain**
- Inferior wall myocardial infarction (epigastric pain)
- Inferior lobe pneumonia/pulmonary embolism (hypochondrium pain)

C. **Systemic or metabolic disorders**
- Porphyria
- Mediterranean fever
- Hemolytic crises (sickle cell anemia, malaria)
- Diabetic ketoacidosis
- Lead and arsenic poisoning
- Spider (black widow)/reptile bite
- Epilepsy/abdominal migraine
- Narcotic withdrawal
- Visceral hypersensitivity
- Somatization/anxiety

16.6 Abdominal Pain in Children

In children, some unique features are worth mentioning.

(a) ***Acute abdominal pain***
- In children, appendicitis is, by far, the most common cause of acute abdominal pain.
- In a child suffering from altered general condition, abdominal bloating, and bilious vomiting, an intestinal obstruction must be suspected; particularly, a volvulus secondary to an intestinal malrotation is to be feared since it can have catastrophic consequences if it is not recognized rapidly (short bowel syndrome, death).
- Intestinal intussusception occurs most often in children under 2 years of age. Typically, the child has a sudden abdominal pain, is crying loudly when lying down in a stooping position with the knees pulled to the chest, and presents red jelly-like ("currant jelly") stools. Most often located at the ileocolic junction, "telescoped" intestinal loops suffer from strangulation with venous stasis, parietal edema, and vascular compression; intestinal ischemia may lead to necrosis if the intussusception is not reduced rapidly. The diagnosis is made on ultrasound when the typical "donut" appearance is visualized. In the absence of contraindications (suspicion of perforation, hemodynamic instability, prolonged symptoms), a hydrostatic (or pneumatic) enema is attempted as a first-line treatment. In some cases, surgical reduction (or even intestinal resection) may be necessary. In children over 2 years of age, the possibility of a luminal process precipitating the intussusception, such as a Meckel's diverticulum, a polyp, or a small bowel tumor, should be considered.

(b) ***Chronic abdominal pain***

In 80% of cases, chronic abdominal pain in children is of functional origin. Other common causes are constipation and lactose intolerance.

Signs suggesting organicity include anorexia, weight loss, vomiting, diarrhea, nocturnal pain, and precise localization away from the periumbilical region.

Abdominal Hernias

R. Ratelle

Contents

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17.1 Definition

A hernia is a circumscribed mass formed by an organ emerging (partially or completely) from the cavity where it is normally contained, through a parietal (congenital or acquired) orifice.

The abdominal cavity is a hollow cylinder containing the digestive organs. It is bordered at the back by the lumbar spine and the spinal muscles and laterally by three superimposed large muscles: the transverse abdominis muscle (oriented horizontally), the internal oblique muscle (oriented upward), and the external oblique muscle (oriented on both sides downward). These three muscles, in the front, join together at the midline to enclose in an aponeurosis the two rectus abdominis muscles vertically elongated on either side of the linea alba (as seen on ◘ Fig. 17.2). The abdominal cavity is separated from the thoracic cavity by the diaphragm and extends below into the pelvic cavity.

The walls surrounding the abdominal cavity have natural areas of weakness, such as the esophageal hiatus at the diaphragm, the deep inguinal opening at the groin on both sides, or the umbilicus at the anterior wall of the abdomen, which may lead to the formation of hernias. Hernias can be congenital or acquired.

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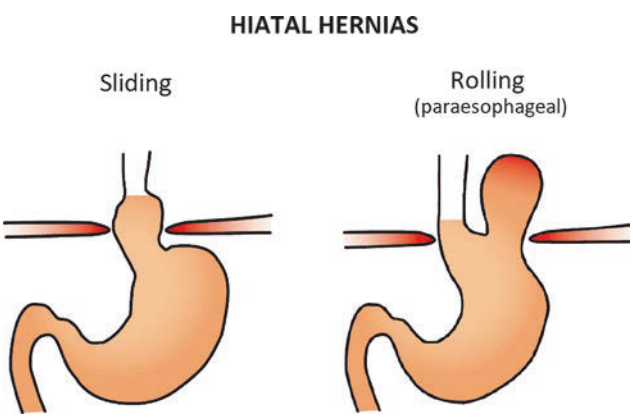
17.2 Diaphragmatic Hernias

Hiatal hernia occurs at the level of the esophageal hiatus from the stretching of the phreno-esophageal membrane formed by the fusion of the endothoracic and endoabdominal fascias to attach the esophagus to the diaphragm pillars. An increase in the abdominal pressure (during physical effort, vomiting, or swallowing) can cause this membrane to stretch, allowing part of the stomach to move in the mediastinum.



◘ **Fig. 17.1** Hiatal hernias

The most common type of hiatal hernia is the *sliding hernia*, where the cardia and a portion of the upper stomach slide upward into the thoracic cavity (see ◘ Fig. 17.1). In the *rolling (or paraesophageal) hernia*, the gastric fundus "rolls" along the esophagus into the mediastinum above the gastroesophageal junction (which most often remains positioned at the diaphragm). The sliding hernia may be associated with gastroesophageal reflux but only occasionally requires surgical correction. The paraesophageal hernia, responsible for chest pains and/or dysphagia, most often requires surgical treatment because of its risk of strangulation (and rupture with serious complications of mediastinitis). Hiatal hernias have been discussed in ▶ Chap. 1.

Other hernias of the diaphragm are much less common: the *Bochdalek hernia* at the side edge of the diaphragm due to an absence of a portion of the diaphragm (congenital or acquired following a trauma) and the *Morgagni hernia* occurring in the front of the diaphragm (at the junction between the internal mammary and the superior epigastric arteries) just below the xiphoid process.

17.3 Ventral Hernias

Ventral hernias are associated with a defect (most often of congenital origin) in the anterior abdominal wall (see ◘ Fig. 17.2).

- *Umbilical hernia* and *epigastric hernia* arise in the midline, in the region of the umbilicus and the epigastrium, respectively. They are often the result of a defective fusion of the rectus abdominis aponeurosis and result in the formation of a midline protrusion containing peritoneal fat or an intestinal loop. They may increase in volume under conditions that elevate the intra-abdominal pressure (such as pregnancy, ascites, and physical exercise). They are rarely symptomatic, but it is preferable to repair them, especially in young people (except for the umbilical hernia in newborns which may resolve spontaneously by the age of 2–3 years).
- *Spiegel's hernia* is an anatomical defect occurring at the point where the aponeurosis of the internal oblique muscle merges to the sheath of the rectus abdominis muscle. This transition (also known as the linea semilunaris) creates an area of weakness at the outer lateral border of the rectus abdominis, approximately 3 to 5 cm below the umbilicus. This condition is often difficult to diagnose clinically except for a typical subumbilical and paramedian pain. Surface ultrasonography or abdominal CT scan is used to establish the diagnosis before surgical treatment.

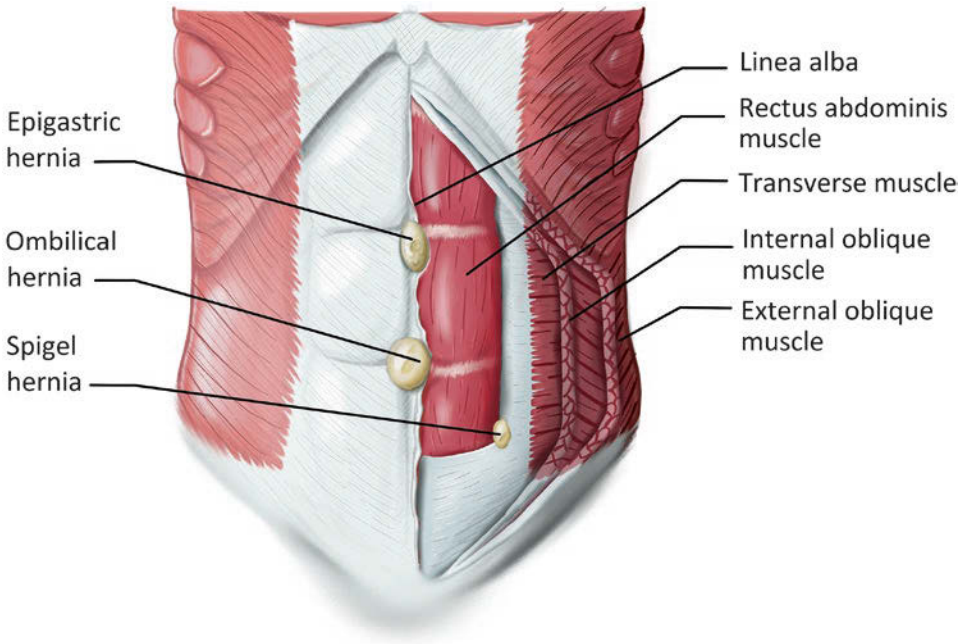


Fig. 17.2 Ventral (abdominal wall) hernia

- *Incisional hernias*, as the name suggests, occur at the site of an abdominal incision. It is the most common ventral hernia. It affects 10 to 15% of patients who have had an abdominal incision. The two most important etiological factors are smoking and postoperative wound infection. All types of incisions can present a hernia, but the most common are medial and supraumbilical incisions. The most important clinical manifestation is a bulge of the abdominal wall, more or less painful, increasing during effort. This type of hernia can be the site of an intestinal obstruction (from simple incarceration to strangulation and intestinal necrosis). It usually requires surgical repair, especially if it is of small caliber, as it is then at greater risk for incarceration.
- *Parastomal hernia* is a very specific incisional hernia developing in the presence of an ileostomy or colostomy. It occurs in 12–40% of patients with a permanent stoma, most often in the first few years after its creation. The consequences range from local pain to difficult fixing of ostomy bags or abdominal cramps but rarely to intestinal obstruction. Surgical repair is rarely indicated; it is reserved for acute complications or when there is a significant impairment of quality of life.

Clinical manifestations of ventral hernia Large hernias are associated with physical discomfort or cosmetic inconvenience but rarely with visceral incarceration since the intestinal loops are free to move without restriction on both sides of the hernial orifice. Small hernias present a greater risk of intestinal incarceration since the herniated intestinal loop may remain trapped by the narrow hernial collar, outside the abdominal cavity, and then suffer strangulation with ischemia (due to the compromised vascularization caused by the incarceration). Manual reduction of the hernia before ischemia occurs avoids complications (necrosis or perforation of the herniated bowel loop, etc.) and allows for simple surgical correction of the abdominal wall defect later.

17.4 Groin Hernias

Groin hernia is the third most common reason for consultation in general surgery and the most common surgical procedure performed. Its prevalence is estimated between 10 and 25% in men (8 times more often than in women), and its incidence increases with age.

- *Indirect inguinal hernia* is the most frequent (in both men and women) and corresponds to approximately 55% of groin hernias. It results from the outward passage of abdominal contents along the inguinal cord in men (spermatic vessels and vas deferens) or along the round ligament in women (see Figs. 17.3 and 17.4). An indirect inguinal hernia is due to the failure of the vaginal process to close during the descent of the testis (or round ligament) which normally occurs between the 12th week of gestation and birth. This descent is made thanks to the gubernacu-

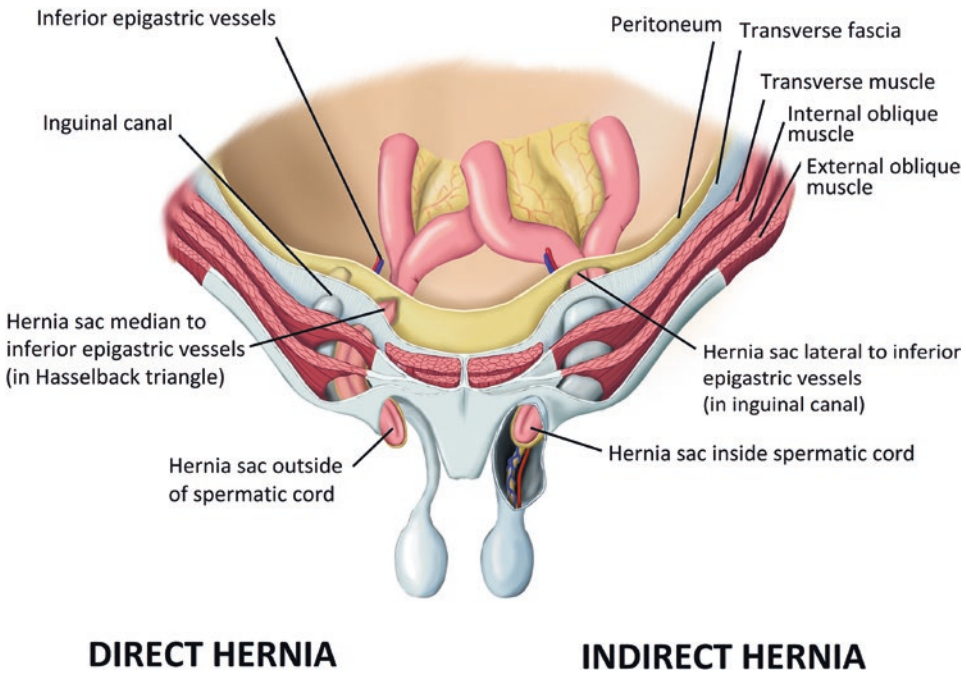


Fig. 17.3 Inguinal hernias : anterior view

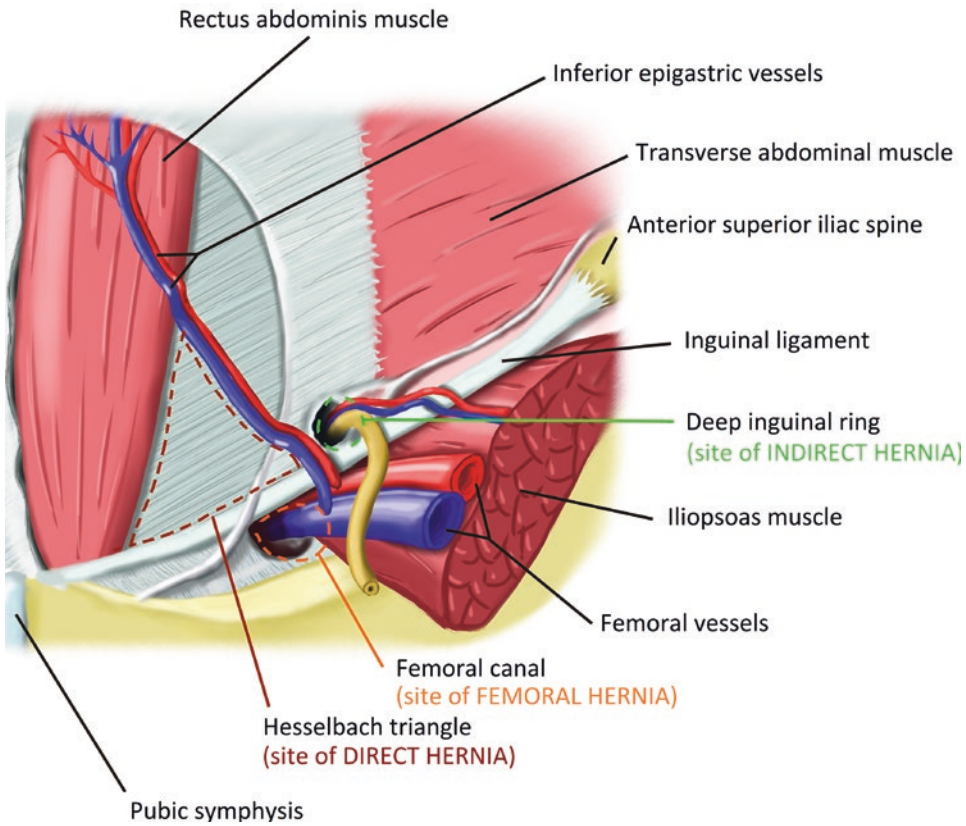


Fig. 17.4 Groin hernias: posterior view

lum testis which carries the testis and some peritoneum (vaginal process) toward the scrotum by passing through the three muscles constituting the abdominal wall, i.e., the transverse abdominal muscle and the internal oblique muscle, which delimit the internal (deep) orifice of the inguinal canal, and the external oblique muscle which forms the external (superficial) orifice of the canal.

- *Direct inguinal hernia* (see ◘ Figs. 17.3 and 17.4) accounts for 40% of hernias in men and 20% in women. It is most often due to a weakness or tearing of the floor of the inguinal canal, which on the internal side of the lower (or deep) epigastric vessels (originating from the external iliac artery) is supported only by the transversalis fascia and the aponeurosis of the transverse muscle. This area of weakness is therefore susceptible to deterioration with age or to tearing during an increase in intra-abdominal pressure. This area is defined as Hesselbach's triangle, which is bounded inferiorly by the inguinal ligament, laterally by the inferior epigastric vessels, and medially by the lateral border of the rectus abdominis muscle.
- *Femoral hernia* (◘ Fig. 17.4) accounts for 10% of groin hernias and is seen more frequently in women than in men (25% vs. 5%). It occurs at an older age and is complicated by incarceration in nearly 40% of cases. It is located under the inguinal ligament, medial to the femoral sheath and lateral to the lacunar ligament (of Gimbernat). The differential diagnosis of a mass in this region includes a lymphadenopathy (Cloquet's gland associated with anal or pelvic infection or metastasis).

Clinical manifestations of inguinal hernia Groin hernia results in an inguinal bulge, often accompanied by discomfort or a feeling of local heaviness. Acute or severe pain is rarely present; it should then raise the suspicion of an incarceration (manually irreducible inguinal hernia) or a strangulation (incarcerated hernia with clinical signs of intestinal ischemia, such as heat and local redness, and associated or not with intestinal obstruction).

The clinical examination allows in most cases to establish the diagnosis of groin hernia. An inguinal hernia can be seen in the standing position, easily reducible with local pressure, and completely reducible in the lying position. The hernia is most often on the right side and, in 15% of cases, can occur on both sides of the abdomen. In the case of a small hernia, the index finger can be inserted into the inguinal canal (thanks to the mobility of the scrotal skin) to feel a bulge in the inguinal canal during Valsalva maneuvers or coughing. The differentiation between a direct and an indirect inguinal hernia is often clinically difficult. During the surgical exploration, the position of the hernia outside (indirect hernia) or inside (direct hernia) the lower epigastric vessels serves as a diagnostic landmark.

The treatment of groin hernia is surgical and varies according to the patient's medical condition, age, and expectations.

17.5 Pelvic Hernias

- *Obturator hernia*, although rare, is the most common pelvic hernia. It most often (>90% of cases) presents as an intestinal obstruction and is diagnosed at laparotomy. It is most often encountered in women who had significant weight loss. This hernia occurs at the level of the obturator foramen (allowing the passage of the obturator nerve and covered by the internal obturator muscle and the obturator membrane). Clinically, patients complain of inguinal pain radiating along the inner thigh.
- *Ischiatic (sciatic) hernias* are rare. They occur either in the superior ischial notch, where the sciatic nerve passes over the piriformis muscle, or in the inferior ischial notch, where the pudendal artery and nerve pass.
- *Perineal hernia* occurs following a surgical procedure on the perineum and is similar to the incisional hernia of the abdominal wall.

17.6 Flank Hernias

These hernias occur on the sides or back of the abdominal wall, in the lumbar region. Two triangles are defined that can be the object of hernias. The upper lumbar triangle (Grynfeltt) is an inverted triangle bounded superiorly by the 12th rib and laterally by the erector spinae muscles of the lumbar spine and the internal abdominal oblique muscle. The lower lumbar triangle (Jean-Louis Petit) is a triangle based on the iliac crest and bounded on both sides by the latissimus dorsi and external abdominal oblique muscles, respectively. These hernias most often occur following urological surgery.

Fecal Incontinence

M. Bouin, R. Wassef, C. Faure, and P. Poitras

Contents

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18.1 General Considerations

Fecal incontinence is defined as an involuntary passage of gas or stool through the anus. It affects 5% of the active population and greatly impedes the quality of life of those affected – one-third of patients experiencing a reduction in social or professional activities and nine out of ten patients reporting that their quality of life has decreased. Anal incontinence is responsible for 2 weeks of work absenteeism per year and is the second leading cause of institutionalization among seniors – the cost of institutionalization reaches $100,000 annually per patient in Canada and is a very important social and medical problem. However, the physician is informed of this problem in only 15% of cases, as patients are reluctant to discuss this embarrassing symptom.

18.2 Physiology and Pathophysiology

Anal continence requires four conditions: (1) solid stool consistency, (2) an expandable rectal reservoir, (3) efficient sphincter muscles, and (4) efficient sphincter regulatory nerves.

Stool consistency Liquid stools are more difficult to retain than formed stools. The best sphincter apparatus in the world will struggle to contain liquid stools, especially if it is propelled by colonic contractions exaggerated by an infection (viral, bacterial, etc.) or an irritating factor (laxative, etc.). Voluntary sphincter contraction can only be maintained for about 60 seconds, after which the sphincter muscle becomes tired and weak. Any factor contributing to diarrhea or loose stools should be corrected. Hardening the stool consistency (with, e.g., loperamide) is the first pharmacological action to be taken to treat incontinence.

Rectum: reservoir The reservoir function of the rectum allows, thanks to its compliance, to postpone defecation. As the stool passes from the colon to the rectum (and one feels the desire to defecate), the rectum distends without significant increase in pressure and thus accommodates the fecal volume for a period of time. A decrease in rectal compliance leads to a "microrectum" which may be responsible for incontinence. Rectal compliance can be reduced in rectitis due to inflammatory bowel diseases (Crohn's disease, ulcerative colitis) or other conditions (e.g., post radiotherapy, infectious rectitis). Previous rectal surgery, the presence of stools (fecal impaction in the elderly or encopresis in children), a rectal or pelvic tumor, and rectal prolapse are other factors that may compromise the rectal reservoir function.

Sphincter muscles The sphincter muscles are essential for the tension of the sphincter barrier to provide fecal continence. Any muscle abnormality (anatomic disruption, myopathy, etc.) will compromise the continence function.

The primary cause of injury to the anal sphincter (internal and external) is childbirth; in an endoscopic ultrasound study, a postpartum sphincter injury was found in 27% of primiparous women.

Anal injury is also frequently related to an anorectal surgery procedure, even if there has been no voluntary sphincterotomy. Sphincter lesions can be observed after hemorrhoidal surgery, anal dilatation, or anal fistula treatment or, of course, after sphincterotomy for anal fissures.

Muscle function can also be compromised in certain muscle diseases, such as scleroderma.

Sphincter nerves Nerves control the muscular activity of the sphincter barrier. Any neurological damage can compromise the continence function.

- *Pudendal neuropathy*: the pudendal nerve originates from the last roots of the spinal cord to innervate the pelvic floor (anus, rectum, external genitalia, perineum, etc.). Pudendal neuropathy can affect the regulation of the sphincter muscles and is a common cause of anal incontinence; it is, however, poorly known and difficult to detect. Studies have shown that pushing efforts by the parturient can stretch and injure the pudendal nerve; the same type of lesions can occur in people suffering from chronic constipation associated with dyschezia, i.e., requiring increased pushing efforts to evacuate stools. More specifically, it is the descent of the pelvic floor that causes the pudendal nerve to be stretched. Long duration/repetition of the stretching traumas (number of deliveries, number of years of constipation, etc.) increases the risk of neuropathy.
- *Peripheral neuropathies* can also be caused by diabetes, alcoholism, nutritional deficiencies, etc.
- *Spinal cord injury* (traumatic transection, tumor, cauda equina syndrome, multiple sclerosis, etc.) may result in incontinence.
- *Central pathologies* (stroke, dementia, etc.) may also compromise the neurological regulation of continence.

18.3 Investigation

The questionnaire will guide the diagnostic approach and establish whether the patient suffers from (1) false incontinence with diarrhea or anal oozing, (2) an

Table 18.1 Diagnosis and management of fecal incontinence

	Stools consistency	Rectal reservoir	Deficient muscles	Nerve disorder
History/ Differential diagnosis	False incontinence? Chronic diarrhea Anal oozing	IBD signs? Diarrhea Blood/mucus Tenesmus	History Traumatic delivery (tearing) Anal/rectal surgery Anal trauma Muscle diseases (scleroderma, etc.)	History Difficult/multiple deliveries Constipation/dyschezia Pelvic static disorder Perineal descent Neural diseases Peripheral (diabetes/ ROH) Central
Physical examination	Anal examination Anus cancer? Fistula? Dermatitis? Pilonidal sinus? Prolapse? (hemorrhoidal/rectal)	DRE: Rectum cancer, fecal impaction	DRE: Hypotonic sphincter/ laceration?	Neuro exam (prn)
Diagnostic tests		Endoscopy Proctitis Cancer	Anorectal manometry Sphincter ultrasound MRI anus/pelvis	Anorectal manometry (+pudendal nerve conduction time) MRI spinal cord/brain (prn)
Treatment	Increase stool consistency (psyllium/loperamide)	Treatment of proctitis or other pathologies	Biofeedback Surgery Sphincter repair Sphincter reconstruction Colostomy	Biofeedback Sacral electrostimulation Colostomy

ineffective rectal reservoir, (3) deficient sphincter muscles, or (4) damage to the nerves regulating the continence function (Table 18.1).

Visual and digital examination of the anus and perineum can reveal causes of false incontinence or anal oozing. A DRE (digital rectal examination) is essential to eliminate a fecal impaction or a low rectal lesion; it also allows to evaluate, more or less precisely, the sphincter tone at rest as well as with effort.

Rectal endoscopy will detect proctitis or other rectal lesions that may compromise compliance.

Anorectal manometry evaluates the contractility of the external and internal sphincters. A highly specialized examination can measure the conduction velocity of the pudendal nerve.

Sphincter anatomy and the presence of a muscle laceration can probably be assessed digitally by some experts but will be revealed precisely by trans-anal ultrasonography or pelvic MRI.

In cases where a neurological damage is suspected, specialized examinations of the spinal cord or the central nervous system (usually by MRI) may be obtained.

Incontinence in children:

- Continence is acquired at the age of 4 years in 98% of children.
- The most frequent cause is functional and linked to chronic constipation that is not adequately treated (encopresis).
- "Organic" incontinence may be related to sequelae of anorectal malformations and surgical procedures for Hirschsprung's disease or spinal cord malformations (spina bifida).

18.4 Treatment

The treatment of fecal incontinence will depend on the underlying cause and can rely on various solutions (Table 18.2).

Increasing stool consistency is an essential strategy regardless of the cause of the incontinence. Psyllium and/or loperamide is helpful.

Counseling can be provided to the patients to improve their condition and quality of life. Wearing appropriate protective accessories or clothing can help,

especially when going out of the house. An empty rectum will decrease the likelihood of involuntary passage of feces; emptying the rectum can be done with glycerin suppositories or enemas (Microlax®, Fleet®, etc.) and may protect the patient from incontinence episodes for a few hours.

The help of expert specialists (gastroenterologist, colorectal surgeon, proctologist, etc.) may be required. Physical therapy and biofeedback exercises can strengthen the musculature and sphincter function. Sensory re-education to improve the rectal sensation and sensory delay may facilitate the early perception of a defecatory need and allow voluntary defecation before incontinence occurs.

Surgical correction of sphincter disruption may be necessary. Sphincter suture and plasty are usually performed, but sphincter reconstruction techniques including striated muscle grafting (taken from the thigh) may also be done. Implantable sphincter prostheses have also been developed, although they are still regarded as experimental.

If the pudendal nerve is affected, an electrostimulation of the sacral nerve roots can be performed with an implantable electrostimulator (similar to a cardiac pacemaker).

Colostomy may be necessary in some cases where incontinence is severe and cannot be controlled by any other method. In these severe cases, the disadvantage of the stoma is compensated by the improvement in quality of life obtained by avoiding fecal incontinence.

Table 18.2 Treatment of incontinent patients

- Increase stool consistency
  - (psyllium, cholestyramine, loperamide, etc.)
- Counseling
  - Empty the rectum
    - →glycerin suppository
    - →enema (microlax®, Fleet®, Peristeen)
  - Incontinence protection
    - →Pantiliners
    - →Incontinence briefs
- Biofeedback therapy
- Surgical correction of sphincter tears
  - Sphincteroplasty
  - Sphincter muscle reconstruction/transplant
  - Sphincter prosthesis
- Pudendal nerve stimulation
- Colostomy

Anorectal Pain

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Anorectal pain is the main reason for consultation in proctology. Thrombosed hemorrhoids, anal fissures, and perianal abscesses are the most common causes and are frequent reasons for consultation (Fig. 19.1).

19.1 Thrombosed Hemorrhoid

The pain from a thrombosed hemorrhoid appears rapidly and is continuous, and the patient generally describes the sensation of a sensitive mass of recent appearance near the anus.

The proctological examination generally confirms the diagnosis by showing a purplish tense formation located in the area of the external hemorrhoids, i.e., on the anal margin. Sometimes the thrombosis involves an internal hemorrhoid and will therefore not be visible without an anoscopic examination. The lump shows a palpable clot in the hemorrhoid with associated edema (more and more important if the consultation is delayed).

The natural evolution is spontaneous healing with a natural resorption of the clot over several days or even weeks. The aim of the treatment is essentially to relieve the pain and combine nonsteroidal anti-inflammatory drugs, analgesics such as acetaminophen, and the treatment of constipation if it is present.

An excision of the clot can be performed for rapid relief, if the patient present early in the episode; it can be done under local anesthesia, but it is contraindicated in cases of significant edema or multiple thromboses.

After spontaneous evolution with reduction of the thrombosis, a painless skin tag (skin growth) often remains in place of the thrombosed hemorrhoid.

19.2 Acute Anal Fissure

The characteristic pain evolves in three stages with an acute pain ("razor-sharp") at the time of defecation, sometimes followed by a painless period for a few minutes, before the reappearance of the pain which can last several hours and is accompanied by a sensation of contraction of the anal canal (also noted at the proctological examination). The presence of blood on the stool or on the wiping paper is frequent.

Constipation, with the passage of hard, large stools, is often a factor in the initial tear, as well as in maintaining and triggering the pain. Constipation is often increased by the patient's fear of triggering pain during defecation and his/her desire to avoid defecation.

The proctological examination may be difficult because of the sphincter contracture but allows to confirm the diagnosis by observing an effacement of the radial folds of the anus and visualizing, most often at the posterior pole of the anus, an ulcerated lesion in the shape of a racket. The sphincter contracture usually prevents digital rectal examination or anoscopy.

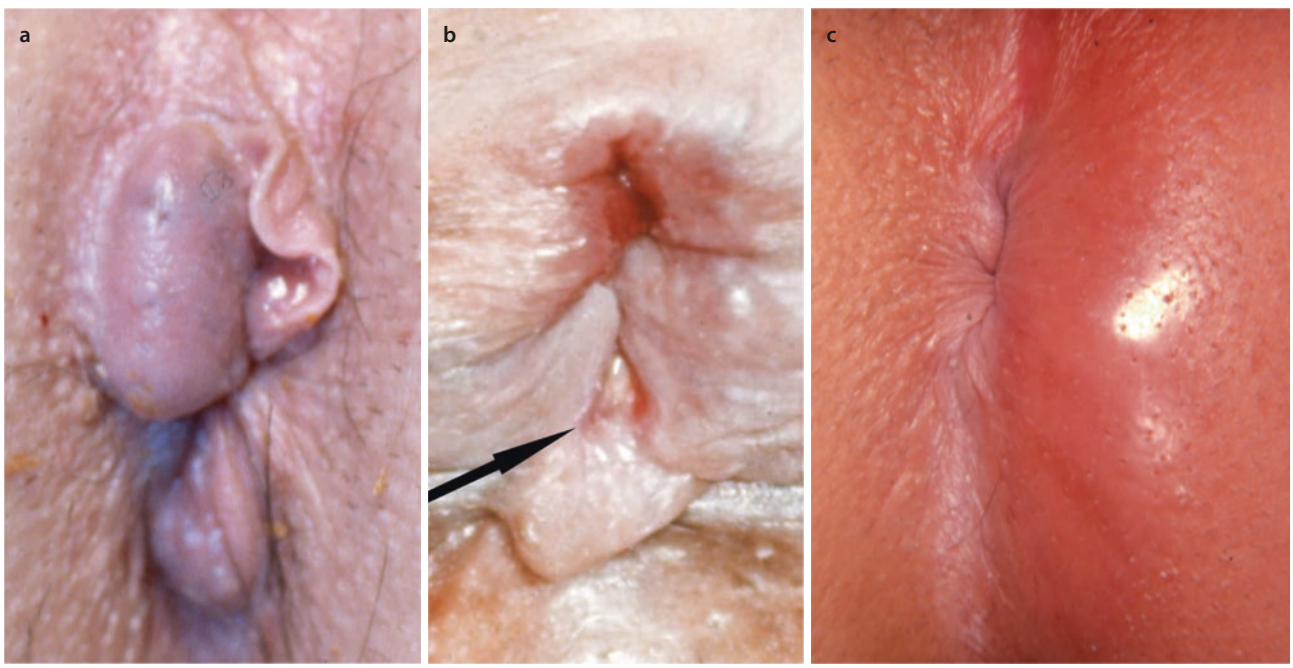

Fig. 19.1 **a** Thrombosed hemorrhoid, **b** anal fissure, **c** perianal abscess

Treatment in the acute phase aims to:

- Relax the sphincter with (a) sitz baths (2–4 times/day, warm water) and (b) local ointments such as diltiazem 2% or nifedipine 0.2% (or more rarely nitroglycerin 0.2%) bid for 4–8 weeks.
- Soften stools with dietary fibers or psyllium, mineral oil, or mild laxatives (e.g., PEG 3350).
- Relieve pain with the above tips, a local Xylocaine ointment, and acetaminophen or a nonsteroidal anti-inflammatory drug (beware of opiates and secondary constipation).

Chronic treatment, if the fissure persists, may require to relax the sphincter with a local injection of botulinum toxin or a surgical partial sphincterotomy.

19.3 Perianal Abscess

Pain accompanying a perianal abscess has specific characteristics with, in particular, a pulsatile, sleepless, continuous characteristic that is not dependent on defecation. General signs, such as fever, or signs of local repercussion, such as dysuria, may appear.

On clinical examination of the perineum, the abscess may be seen as an indurated, inflammatory mass (of various sizes), which may obscure the radial folds of the anus. Localization is more difficult when the abscess is deeper, but palpation of the surrounding tissues may reveal abnormal tension and a localized pain. Pus may be seen draining from the primary orifice on the examination of the anal margin. Digital rectal examination may reveal the same findings on palpation; anoscopy may be difficult because of pain.

A surgical drainage is classically required. Treatment with antibiotics (7–14 days, ciprofloxacin 500 mg bid/metronidazole 500 mg tid or amoxicillin-clavulanic acid 500 mg tid or 875 mg bid) may help to control the infection. A surgical drainage is classically required.

19.4 Proctalgia Fugax

It can be compared to a muscle cramp affecting the anal sphincter.

The pain typically occurs suddenly, without warning, and disappears after a few seconds or minutes (too briefly to allow a pharmacotherapeutic intervention). The attacks are often nocturnal and episodic (more than five attacks/year in 50% of cases).

Proctalgia fugax is very common, but many people are embarrassed to talk about it.

Reassuring the patient is essential. General relaxation (self-hypnosis, autogenic training, etc.) can probably help. Forcing sphincter relaxation with digital dilation (or suppository, etc.) is reported, by some patients, to be beneficial. Sublingual nitroglycerin (as for the treatment of coronary angina) may possibly help.

19.5 Levator Ani Syndrome

This syndrome is rare and not well known. The pain is often dull, in the form of a pelvic heaviness; it is often prolonged but may have acute periods of exacerbation.

This pain is linked to a contracture of the levator ani muscle, in particular the pubococcygeal fascicle. On examination, the digital palpation and posterior traction of the levator ani muscle are often painful.

A thorough pelvic investigation (MRI, endoscopy, etc.) may be necessary in some cases to rule out other painful disorders and confirm the diagnosis of the levator ani syndrome.

If reassurance and basic maneuvers are insufficient (Table 19.1), referral to a procedural specialist may be helpful even if there is no proven treatment for this condition. The muscle relaxant cyclobenzaprine maybe tried, as well as baclofen.

Table 19.1 Acute anal pain

	Thrombosed hemorrhoid	Anal fissure	Perianal abscess	Proctalgia fugax	Levator ani syndrome
Pain	– *Rapid onset* – *Continuous* – *Sensation of sensitive anal lump* – *Lasts 2–7 days*	*Three steps:* – *Acute ↑ by defecation* – *Brief dull* – *Anal contraction (hrs)* *(Bleeding possible)*	– *Progressive/ continuous* – *Pulsatile* – *Independent of defecation* *(Fever possible)*	– *Anus* – *Severe* – *Sudden* – *Crampy* – *Brief (sec to min)* – *Nocturnal (often)*	– *Anus + rectum* – *Vague, dull* – *Pressure form* – *↑ by sitting position* – *Lasts >20 min*
Exam	– *Bluish tense formation in hemorrhoidal area*	– *Anus: racket-like fissure (often posterior)* – *Sphincter contracture*	– *Inflamed, tender perianal swelling, visible/DRE*	– *Exam + DRE normal*	– *DRE: contracted, painful puborectalis muscle*
Treatment	– *Sitz baths (?)* – *Analgesics* • *Acetaminophen* • *NSAID* • *Opioid* – *Surgical incision if <48 hours and little edema*	– *Sitz baths* – *Soften stools:* • *Psyllium* • *Mineral oil* • *PEG 3350* – *Analgesia:* • *Xylocaine (local ointment)* • *Acetaminophen* • *NSAID* • *Opioid: avoid (constipation)* – *Relax sphincter:* • *Calcium blockers (local ointment)* • *Botulinum toxin (local injection)* – *Surgery (sphincterotomy)*	– *Antibiotics: cipro +metronidazole or amoxyll/clavulanic acid* – *Surgery (drainage)*	– *Reassurance* – *General relaxation (self-hypnosis, hot baths)* – *Sphincter relaxation [dilatation (finger, etc.), nitro]*	– *Pelvic muscle relaxation* • *Biofeedback* • *Muscle relaxants (diazepam, cyclobenzaprine)* • *Digital massage of the anus muscle* • *Sitz baths*

Rectal Bleeding

R. Wassef and P. Poitras

Contents

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Rectal bleeding usually occurs in small quantities, episodically and repeatedly (the frequency may vary, even being daily). Lower GI hemorrhage (discussed in ▶ Chap. 21) refers to an important, sometimes dramatic (with hemodynamic instability), isolated event, with the passage of a large quantity of blood through the rectum in a sudden and sustained manner.

Rectal bleeding is a common symptom; approximately 15% of the general population will, at one time or another, experience a passage of blood through the rectum. This symptom is often a sign of a benign pathology, which will only require a simple treatment, with explanations to reassure the patient. But it can also be a sign of a more serious disease, which deserves a rapid diagnosis and a more elaborate evaluation.

20.1 Common Causes of Chronic Intermittent Rectal Bleeding

Internal Hemorrhoids

- Bleeding is usually associated with the passage of stools and is seen as bright red blood ("like when you cut yourself") on the toilet paper or on the stool or dripping into the bowl ("like a faucet that is not properly closed") or staining one's underwear.
- It is usually without pain ("silent bleeding").
- It may be accompanied by a prolapsed mass (a hemorrhoid) in the anus that reduces spontaneously or requires manual reduction.
- External hemorrhoids are almost never the source of bleeding, which is more likely due to internal hemorrhoids. Unless the internal hemorrhoids are prolapsed, they are not visible on visual examination of the anus.
- The digital rectal exam (DRE), an essential step in almost all cases of rectal bleeding (we will name one exception below), cannot detect the presence of internal hemorrhoids since they are soft and have the same tactile consistency as the rectal mucosa. Only an endoscopy (anoscopy, rectoscopy, sigmoidoscopy, or colonoscopy) can confirm the presence of internal hemorrhoids.

Anal fissure

- It is the most common cause of anorectal bleeding in children.
- In adults who suffer from it, pain when passing stool is the predominant symptom and often described as a tear. This pain can be of variable intensity, usually of short duration (a few minutes, rarely a few hours).
- The blood is usually of small quantity, with a bright red color, and present on the wiping paper or on the surface of the stool.
- Once the diagnosis is suspected by the history, it can almost always be confirmed by a careful examination of the anal area. It is important to position the patient well (the author prefers lateral decubitus with the knees bent over the abdomen), to have a good light source, to reassure the patient, to explain each step of the examination, and to proceed gently. By spreading the buttocks and waiting a few moments to allow the patient to relax, it is possible in the vast majority of cases to visualize the fissure. In the majority of cases, it is located on the posterior midline and more rarely (15% of cases) on the anterior midline. A lateral fissure is considered atypical and deserves a careful differential diagnosis (trauma, Crohn's, HIV infection, squamous cell carcinoma, etc.). The rectal examination is almost always painful, reproducing a pain that the patient recognizes. It should be avoided if the diagnosis is obvious and/or the patient is very sore. A therapeutic trial can be undertaken to treat the fissure and the physical examination completed with a DRE when the pain is resolved. However, if the diagnosis is not clear, it can be done gently and with topical Xylocaine analgesia. In some cases, an examination under anesthesia may be required.

Polyps

- If the polyp is large enough and distally located, a stool may be stained with red blood as it passes (as for hemorrhoid or fissure).
- The blood may be contained in the stool (mixed with the feces).

Colorectal cancer

- Blood may appear as a trace of blood on the stools or be mixed with the feces.
- Bowel movements may be accompanied by other symptoms, such as changes in the size, shape, frequency, and consistency of the stools, or by symptoms associated with the presence of a mass in the rectal ampulla (false urges, urges, feeling of incomplete evacuation, incontinence, passage of mucus).
- Unfortunately, sometimes systemic symptoms, such as weight loss, nocturnal sweating, fatigue, and loss of appetite, may indicate more advanced cases.
- The rectal examination is the most important initial examination.

Proctitis

- Rectal bleeding is often accompanied by other rectal symptoms: increased frequency of defecation, false urges, passage of mucus (itself sometimes tinged with blood), and generally softer stools.

- It is due to an inflammatory bowel disease (ulcerative colitis or Crohn's disease), an infection (most often sexually transmitted), or a radiation therapy (prostate, ovarian, or anal cancer).
- Endoscopy is necessary to establish the diagnosis.

20.2 Investigation

- A careful and detailed history is essential.
- The physical examination is crucial to evaluate the patient's overall appearance, to detect signs of advanced disease, but especially to assess the anorectal area (mainly by visual inspection and digital rectal examination).
- An anoscopy (or rectoscopy) should be considered for any patient presenting with intermittent rectal bleeding. This simple procedure, which requires no patient preparation in the case of anoscopy and no specialized personnel or equipment {other than disposable anoscopes or rectoscopes and a light source}, will, in the vast majority of cases, confirm (or rule out) the presence of internal hemorrhoids or other rectal pathologies.

When and how to investigate?

The main question for the clinician facing a patient with chronic intermittent rectal bleeding is whether to simply treat the clinically suspected cause or to request further investigation. The dilemma is that most of these cases of chronic intermittent rectal bleeding are caused by common benign conditions, but a significant number may have a more serious condition. The history can guide the clinician, but does not give a definitive answer. It is also quite possible for one patient to have both a benign cause (e.g., hemorrhoids) and a more serious one (e.g., colorectal polyp or cancer). How can the clinician decide which case to investigate, knowing that access to investigations is limited and that tests considered for further investigation (e.g., colonoscopy) may be associated with some morbidity (not to mention patient apprehension)?

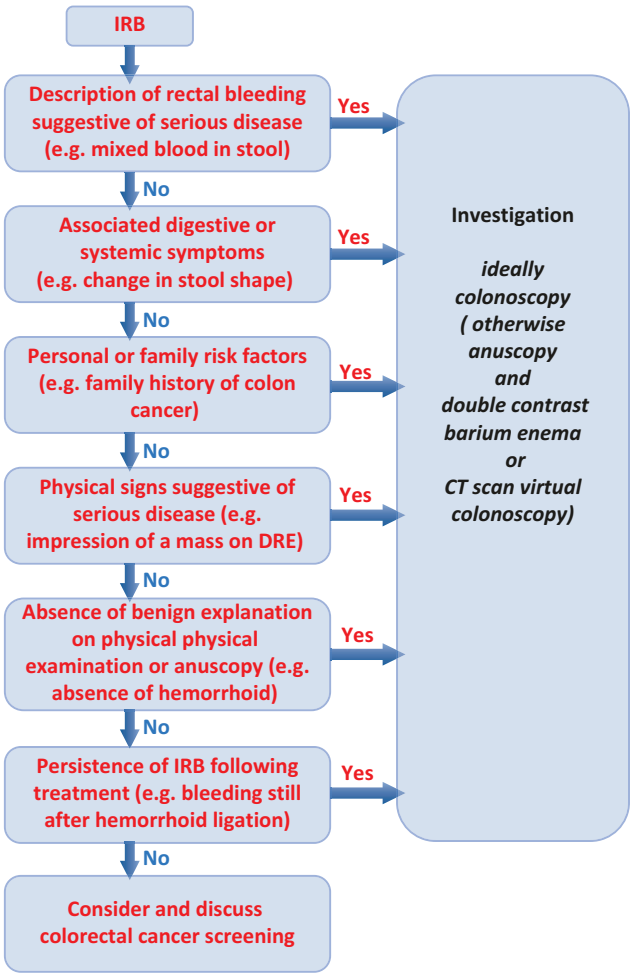

Fig. 20.1 Intermittent rectal bleeding (IRB): diagnostic management

The attached algorithm (Fig. 20.1) is presented to guide the clinician in selecting the cases deserving investigation of chronic intermittent rectal bleeding. Radiological examination by barium enema (now frequently replaced by CT scan virtual colonoscopy) is certainly less efficient than endoscopy for mucosal inflammatory lesions or rectal lesions but remains often more accessible than colonoscopy.

Lower GI Bleeding

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Contents

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Lower GI bleeding (LGIB), or hemorrhage, refers to a significant, sometimes dramatic, event marked by the passage of large amounts of blood [hematochezia (blood with stools) or rectorrhagia (blood without stools)] through the rectum in a sudden and sustained fashion.

The passage of copious blood through the rectum is a less frequent presentation than upper GI hemorrhage (20–27 per 100,000 vs. 50–150 per 100,000). It is associated with lower morbidity and mortality (4% vs. 6–13%). The majority of lower GI bleeds will cease spontaneously. However, patients with continuous bleeding over the initial 24 hours, altered vital signs (tachycardia and/or hypotension), or significant comorbidities are at greater risk for morbidity and mortality.

As in any bleeding case, the initial priority should be a comprehensive assessment of the patient and an aggressive reanimation. The unstable patient should not be moved for radiological or endoscopic examinations until his/her vital signs have been corrected and his/her condition has stabilized.

21.1 Step One

- **Minimize ischemia and restore perfusion supply**
  - (a) Oxygen supplementation: increase inspired O2 by nasal cannula or mask ventilator.
  - (b) Intravenous access: open a vein (two is better) with a large enough catheter (#16 or #18).
  - (c) Fluid resuscitation: infuse an iso-osmolar solution such as 0.9 NaCl (normal saline) or lactated Ringer's solution.

The amount of fluid to be replaced can be estimated based on vital signs:

- Orthostatic hypotension = 20% circulatory loss, i.e., about 1 liter of fluid required.
- Tachycardia or hypotension corresponds to a loss of about 30%, i.e., 1.5 liters.
- Shock = loss of more than 40%, i.e., 2 liters.

This amount of replacement fluid is usually administered over 1–2 hours to restore the hemodynamic state. The speed of administration, however, will be adjusted according to the severity of the instability (may require faster correction if shock) vs. the patient's ability to receive a large and sudden fluid load (with risk of vascular overload if heart or kidney failure, etc.).

- (d) Red blood cell transfusions may be required. The usual goal is to maintain hemoglobin at 80 g/liter; however, patients with diseases that compromise blood supply to vital organs (e.g., coronary artery disease) may benefit from a hemoglobin maintained at 90 g/liter.

21.2 Step Two

- **Clinical and biological assessment of the patient**
  - (a) The evaluation of vital signs is necessary to assess the severity of the bleeding and to adjust the initial vascular repletion therapy.
  - (b) The clinical history and examination will subsequently make it possible to evaluate (1) the general health status and comorbidities that require immediate and short- or medium-term management (e.g., decompensated diabetes, etc.) and (2) the cause of the LGIB and thus to orient specific treatment.
  - (c) Biological examinations: complete blood count (Hb, WBC, plt), INR, renal (urea, creatinine, electrolytes) and liver (bilirubin, ALT, AST, alkaline phosphatase) tests, and blood glucose are obtained at the arrival of the patient and repeated every 6–12 hours.
  - (d) Correction of the comorbidities revealed in the clinical and/or biological examinations: insulin therapy if high glucose, coagulation correction (administration of vit. K, fresh plasma, platelets, etc.) if required, etc.

21.3 Step Three

- **Lower or upper GI bleeding?**

The generally accepted definition of LGIB is bleeding from the GI tract distal to Treitz's angle; it is, however, important to remember that a significant number of patients (10–15%) presenting with the passage of a large amount of blood through the rectum are actually bleeding from an upper GI lesion (UGIB; see ▶ Chap. 11). This condition is seen with severe bleedings and should be suspected in patients with hemodynamic instability and dark/maroon hematochezia (patients with less severe UGIB have melenic stools).

One of the first diagnostic procedures in the patient suspected of UGIB is to insert a nasogastric tube to check for the presence of blood that would indicate a gastric or duodenal lesion (that would need appropriate treatment as discussed in ▶ Chap. 11). If the tube brings back bile without blood, an upper source is virtually eliminated; in the absence of blood and bile, a duodenal lesion remains sometimes possible (10% of these cases).

In patients suspected of an UGIB, an upper GI endoscopy should be performed promptly. It can be

realized rapidly (in comparison with colonoscopy that requires laxative preparation, etc.) to give a definitive answer on the presence or absence of an upper lesion and provide a specific and effective therapy for the UGIB lesion.

21.4 Step Four

Causes of LGIB

Once a proximal source of bleeding has been eliminated, the differential diagnosis of LGIB will primarily include the following clinical entities (see Table 21.1):

Colon diverticulum

- It is the most common cause of LGIB, causing between 20% and 55% of them. It rarely occurs before the age of 40 years, and the incidence increases with age.
- The pathogenesis of a diverticular bleeding is attributed to an erosion (probably by a fecalith) of vasa recta on the edge of a diverticulum.
- Originating from an eroded arterial vessel, the bleeding is frequently acute and with large quantities of red blood. In most cases, the bleeding will stop spontaneously, but it may recur.

Ischemic colitis

- It is the most common form of intestinal ischemia.
- It is usually transient and reversible.
- The areas most susceptible to ischemia are the splenic angle, the rectosigmoid junction, and the right colon.
- The bleeding is usually accompanied by diarrhea.

Table 21.1 Causes of LGIB in various series in the literature

Colon diverticulum	10–40% of cases
Colitis	
Ischemic	5–20%
Infectious	3–30%
Inflammatory	2–4%
Radiation	1–3%
Neoplasm or polyp	3–10%
Vascular lesions/angiodysplasias	3–30%
Anorectal lesions (hemorrhoid, fissure, etc.)	5–15%

- It may occur without identifiable cause, but the usual setting is an elderly patient with a cardiac or vascular disease.
- The diagnosis is usually confirmed on colonoscopy and/or suspected on abdominal CT.
- The majority of patients will show a spontaneous and complete resolution. Some may progress to intestinal necrosis and will require an emergency intervention; the risk of mortality for these patients is significant.

Hemorrhoidal bleeding (and those associated with other anorectal sources)

- The bleeding is usually chronic and intermittent, but it may occasionally be profuse and may be designated as LGIB.
- The diagnosis can be made easily at anoscopy or rectoscopy, hence the importance of one of these procedures early in the investigation of a LGIB.

Gastrointestinal angiodysplasia (or vascular ectasia)

- They are commonly associated with occult bleeding and iron deficiency anemia, but occasionally, they may cause LGIB.
- They are more common in the elderly, being secondary to the degeneration of the venules in the submucosa.
- They are often associated with other conditions such as valvular heart disease or renal failure.
- The lesions are often multiple, but usually in the right colon.
- The recurrence rate is high (up to 80%) after spontaneous cessation of bleeding.
- Endoscopic treatment is effective.

Inflammatory, infectious, and radiation colitis

- They can cause bloody diarrhea.
- They are rarely a cause of LGIB.

Colorectal polyps and cancers

- They may cause occult or visible blood loss.
- In a small percentage of cases, they can cause LGIB.

Post-polypectomy bleeding

- Bleeding in the days following endoscopic removal of a polyp occurs in 1 to 6% of cases.
- Typically, bleeding can occur rapidly following polypectomy (same day) or 7–10 days later when the scab falls off.
- The majority of these cases can be treated conservatively or by endoscopic hemostasis of the polypectomy site.

Small bowel bleeding

- They may be secondary to vascular lesions (e.g., angiodysplasias, Dieulafoy's lesion), Meckel's diverticulum, ulcers, Crohn's disease, etc.
- They represent a small percentage of the causes of LGIB (2% to 15%).
- Meckel's diverticulum bleeding is a common cause of LGIB in children.

21.5 Step Five

Investigation

Once the patient is stabilized and an upper GI or anorectal source has been ruled out, the investigation of the etiology of the LGIB will usually continue with colonoscopy.

Colonoscopy is the test of choice to identify the colonic cause of LGIB. However, it has many disadvantages: it requires a laxative preparation (e.g., Colyte 4 liters in 4 hours) that takes time (and "patience") and may not be totally effective in cases of severe and/or persistent bleeding; it is a procedure whose preparation (induced diarrhea) as well as its realization may be difficult to tolerate (particularly in a fragile, elderly, or unstable patient); it may, in the case of active hemorrhage, be difficult to perform and/or interpret, given the difficulty of visualizing the colonic walls that are not perfectly clean; and it certainly allows therapeutic measures to control the bleeding lesion, but its therapeutic impact is less obvious than for the upper endoscopy in UGIB.

When colonoscopy is not feasible (most often because of active bleeding that compromises the patient's hemodynamic balance or does not allow an effective "colonic lavage"), the following alternatives may be used:

- Labeled red blood cell scintigraphy in nuclear medicine is a noninvasive test and does not require intestinal preparation. However, it is more useful for localizing the site of a bleeding than for a precise diagnosis, and the investigation will generally have to be completed by an endoscopy or another procedure. The technique consists of labeling (by an in vivo or in vitro technique) the patient's red blood cells with a radiotracer followed by dynamic image acquisition over the following hours. The accumulation of the radiotracer signals the site of bleeding. This imaging technique is sensitive since it can detect a bleeding of 0.5 mL/min.
- CT angioscan is increasingly used to detect a bleeding site that would give extravasation of blood into the GI lumen. Its sensitivity is not well known, but CT is usually easier and faster to perform than the scintigraphy described above or the arteriography (see below).
- Angiography necessitates technical expertise that may not be available in all centers. It is an invasive examination but does not require bowel preparation and can detect bleeding of the order of 1 mL/min. Its diagnostic performance is limited by the fact that the bleeding has to be active at the precise and limited time when the exam takes place (the same comment applies for the CT angioscan described above). Arteriography allows therapeutic procedures (arterial embolization to occlude the bleeding vessel). Arteriography and its therapeutic procedures can lead to complications, sometimes serious (intestinal ischemia of the embolized segment).

When the small intestine is the cause of LGIB, it can be investigated with an EnteroScan or video enteroscopy. Push enteroscopy or double-balloon enteroscopy (via the oral or anal route) may also be used.

21.6 Step Six

Treatment

The stabilization of the patient is the priority of treatment in the initial phase. In addition to fluid replacement, an assessment of the patient's comorbidities must be made for the overall management of the patient. If required, the patient should be transferred to the intensive care unit for active monitoring.

The treatment strategy (see ◘ Fig. 21.1) will depend on two factors: (1) the cause of the bleeding and (2) the continuation or stopping of the bleeding. In the majority of cases, the bleeding will cease spontaneously; the investigation will then be primarily endoscopic, and the treatment will depend on the findings during this examination.

In cases of persistent or significant bleeding with hemodynamic repercussions, the immediate goal of treatment will be to stop the bleeding. The therapeutic options should be specific and are multiple: pharmacological, endoscopic, angio-radiological, and surgical.

Diverticular bleeding that has stopped will generally not require treatment if it is a first episode. If the

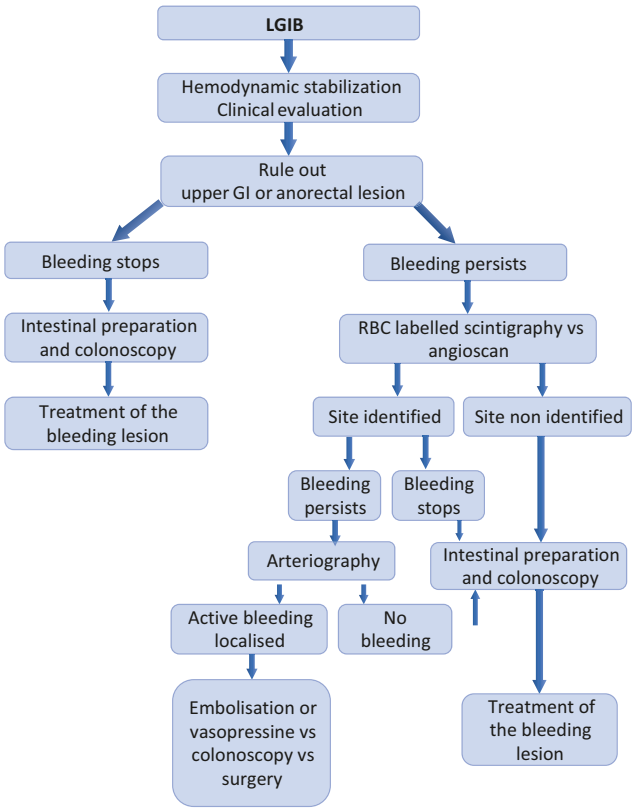

Fig. 21.1 Algorithm for the management of LGIB

bleeding is still active and the responsible diverticulum is clearly identified, per colonoscopy therapeutic maneuvers (sclerotherapy, etc.) can be attempted.

Angiodysplasia identified at colonoscopy can be treated by a variety of endoscopic techniques (electrocoagulation, injection, argon coagulation). If identified on arteriography, intra-arterial vasopressin infusion or selective embolization may be used.

A hemorrhoidal bleeding is usually easily treated once the cause is identified. Elastic ligation (Barron's technique) is most commonly used in North America. Specific cases, such as the cirrhotic patient bleeding from rectal varices and/or hemorrhoids, may be more complicated.

Ischemic colitis usually requires supportive treatment with fluid replacement, antibiotics (possibly), and correction of precipitating factors. A surgical resection may be necessary if the ischemia progresses to transmural necrosis.

Ideally, the surgical treatment should be directed to the specific cause of the LGIB. Investigative techniques now make it possible to avoid the unfortunate circumstance where the patient with an uncontrollable bleeding is taken to the operating room without localization of the bleeding site (and will be submitted to a blind partial or total colectomy).

21.7 Special Topic: GI Bleeding and Altered Coagulation

The patient presenting with a GI bleeding while on anticoagulant or antiplatelet treatment constitutes a therapeutic challenge. These antithrombotic drugs increase the risk of GI bleeding and can limit the efficacy of hemostatic procedures.

The decision to interrupt or reverse the antithrombotic treatment is difficult. Potential benefits of reducing the bleeding process vs. the risk of inducing thrombotic complications must be weighed when modifying the antithrombotic therapy. As a general rule, interruption or reversal of the antithrombotic treatment must be limited to patients with severe, life-threatening, and uncontrollable hemorrhage.

- The vitamin K antagonist warfarin has a half-life of 40 h, and its therapeutic effect lasts 2–5 days. Antagonists include:
  1. Prothrombin complex concentrates (PCC), such as Octaplex®, Beriplex®, and Kcentra®, are produced by chromatography purification of large plasma pools and contain coagulation factors II, VII, IX, and X, as well as proteins C and S. They can induce rapid INR reduction.
  2. Fresh (frozen) plasma are easily available and 10x less expensive than PCC (although probably less potent).
  3. Vitamin K 2.5 mg p.o. or i.v., a very cheap alternative, slowly reverses the anticoagulation effect in 24–28 h.
- Direct oral anticoagulants (DOACs) have a shorter effect. The half-life of dabigatran (Pradaxa®), a thrombin inhibitor, and apixaban (Eliquis®) and rivaroxaban (Xarelto®), inhibitors of factor X (that promotes the transformation of prothrombin to thrombin), are 12–17 h, 12 h, and 8–9 h, respectively.

  Specific antagonists are available for dabigatran [idarucizumab (Praxbind®), a monoclonal antibody binding and inhibiting dabigatran], as well as for apixaban and rivaroxaban [andexanet alfa (Andexxa®), an inactivated factor X that will attract factor X inhibitors], but they are very expensive.

  PCC can possibly help to restore coagulation in some patients on DOACs.
- Antiplatelet agents, such as ASA and P2Y12 platelet receptor inhibitors [clopidogrel (Plavix®), prasugrel (Efient®), ticagrelor (Ticlid®)], block platelet function for a prolonged period (up to 10 days).

  Platelet transfusions to reverse the drug effect have been associated with an increased mortality risk in patients with normal platelet count, and this therapeutic approach needs to be reconsidered.

Food Allergies

E. Drouin

Contents

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Food allergy refers to an immune response caused by the ingestion of food. It is often wrongly invoked by patients to explain digestive discomforts that do not necessarily involve an immunological reaction (e.g., symptoms of lactose intolerance) or that have no causal link with the suspected offending food (e.g., digestive intolerances of irritable bowel syndrome). In adults, true food allergy is relatively rare (and most often easily identifiable); in children, however, it is an essential condition to recognize.

In pediatrics, clinical manifestations associated with food constitute a frequent reason for medical consultation and parental concern. Approximately 30% of parents report symptoms related to food (milk, fruit, etc.) in their children below 2 years old. These reactions are usually short-lived and disappear within 6 months in the majority of cases. The probable explanation for this rapid symptoms resolution lies in the non-immunogenic nature of most of these reactions.

Allergic food reactions often begin in the first 2 years of life and affect 6–8% of children. The prevalence of food allergy seems to have increased over the last 20 years in North America. Several hypotheses have been proposed to explain this phenomenon, including an "excessive" hygiene (which would prevent the constitution of "natural" defenses); an abnormal intestinal microbiota; a diet low in omega-3 fatty acids, antioxidants, or vitamin D; as well as the ingestion of processed foods that may contain some protein alterations.

Food allergic reactions are mediated either by IgE specifically directed against certain foods and activating mast cells and basophils to release their histamine or bradykinin content or through non-IgE-mediated process involving eosinophils or T lymphocytes; mixed IgE- and non-IgE-mediated reactions are also possible.

22.1 IgE-Mediated Manifestations

IgE-type allergic manifestations begin rapidly, typically from a few minutes to 2 h after ingestion of the offending food (in order of frequency: cow's milk, soy, peanuts, eggs, seafood, fish, nuts, wheat, kiwi, sesame). The clinical signs and symptoms (described below) of these reactions are caused by the release of mediators (histamine, etc.) from tissue mast cells and circulating basophils.

- ***Urticaria*** is the most common cutaneous manifestation of IgE-type allergic reactions, appearing within minutes after the allergen ingestion. Food allergies are involved in 20% of acute urticaria cases but are rarely associated with chronic urticaria. Food allergies can also occur de novo in adults (seafood allergy is the most common).
- ***Oral allergic syndrome*** is an allergic contact reaction manifested by oral or ENT symptoms (tingling of the throat, mild edema of the lips, tongue, and throat) of limited duration. It is frequently found in children with allergic rhinitis to pollen. Various proteins (not resistant to cooking, hence the problem exists only with raw food) present in certain fruits and vegetables can cause a cross-reaction with the allergenic proteins present in pollen.
- ***Respiratory and ocular symptoms*** may occur in association with more systemic manifestations. Isolated conditions such as asthma or rhinoconjunctivitis are unlikely to be caused by food allergies.
- ***Gastrointestinal manifestations*** (nausea, vomiting, diarrhea, abdominal pain) in association with IgE-type allergic reactions are usually associated with other clinical manifestations and angioedema.

Angioedema is characterized by a tissue swelling due to an infiltration by vascular fluid. Mast cell mediators (histamine, etc.) are involved in laryngeal, bronchiolar, etc. edema of severe allergic reactions (and are treated by antihistamines). At the intestinal level, edema may also involve bradykinin, which production may be increased in C1 esterase inhibitor deficiency; this enzyme deficiency may be acquired (e.g., due to angiotensin-converting enzyme inhibiting drugs) or inherited. *Hereditary angioedema* may manifest in children (or in adults) by, among other things, episodes of abdominal pain, which may or may not be associated with systemic allergic reactions, characterized by radiologically identifiable intestinal edema. These attacks may last for several hours and may suggest an acute surgical abdomen (see ► Chap. 16); they are often resistant to antihistamines and may require treatment with bradykinin inhibitors.

Anaphylaxis is a severe systemic allergic reaction and can cause hypotension, hypoxemia, and death. This reaction may be biphasic and may recur within hours after the initial symptoms have been resolved.

Diagnosis In front of a possible IgE-type allergic reaction, the food history is the key diagnostic procedure. Once a food is strongly suspected by the history, allergists perform skin testing by scarification with food extracts. The search for specific IgE antibodies (e.g., milk, soy, eggs, etc.) may be complementary. An oral provocation test under medical supervision may be indicated.

Treatment of IgE-type manifestations includes stabilization of the acute reaction with antihistamines and, if necessary, epinephrine, corticosteroids, and hemodynamic stabilization. Food avoidance of the identified

allergen will be essential. Allergic sensitivity should be reassessed every 6–12 months (follow-up can be done by skin tests or by checking the specific IgE antibodies' serum levels). These children should wear an epinephrine autoinjector at all times and must be instructed to seek medical attention after use of this device due to the reported biphasic anaphylactic reactions. Food allergies will most often resolve by school age, with the exception of peanut and nut allergies, which have a spontaneous resolution rate of only 20%. Desensitization methods are currently being studied for children with persistent food allergies.

22.2 Non-IgE-Mediated Manifestations

Some digestive allergic reactions occur without involving IgE and affect the rectosigmoid, the small intestine, or simultaneously the small and large intestines. Cow's milk proteins are usually implicated, but other food proteins may be involved.

- ***Protein-induced proctitis/proctocolitis*** (***"allergic colitis"***) is present in infants between 2 and 8 weeks of age who is usually minimally symptomatic and with soft, mucoid stools with trails of blood. It is found in infants fed with formulas based on milk or soy proteins, or to a lesser degree in breast-fed infants. Ingestion of the allergenic proteins induces a tissue inflammatory response with an eosinophilic infiltration limited to the rectum or sigmoid colon. In breastfeeding mothers, the foods most frequently incriminated for their harmful effect on the infant are milk (65%), eggs (19%), corn (6%), and soy (3%). This is the most common cause of rectal bleeding in young infants in good health condition. It has been reported occasionally in older children when bovine milk proteins were introduced into the diet. Proctosigmoidoscopy is rarely required since empirical treatment is usually initiated based on the characteristic history.
- ***Food protein-induced enteropathy*** (***"bovine protein allergy" or "cow's milk protein allergy"***) is characterized by an infant presenting in the first year of life with diarrhea, occasional non-bilious vomiting, delayed weight, iron deficiency anemia, and hypoalbuminemia. The majority of these children are fed with milk protein-based formulas, and cow's milk is the most frequently incriminated allergen. However, soy-based formulas can induce the same type of enteropathy. An intestinal biopsy may be necessary to rule out celiac disease.
- ***Dietary protein-induced enterocolitis*** may present as an acute severe form in the neonatal period or as a less severe chronic form. In the acute form, typically, young infants under 6 months of age will present (most often in the emergency room), within 2–6 h after ingesting an allergen, vomiting, profuse diarrhea, lethargy, and dehydration. The main culprit allergens are milk, soy, and rice, but the diagnosis can include multiple food allergens. The chronic form occurs with the same foods, but the symptoms are less severe. Depending on the severity of the clinical symptoms and the response to dietary treatments, investigations to rule out celiac disease or inflammatory bowel disease may be required.

Diagnosis The diagnostic tests used for IgE-type reactions (skin tests, serum Ag, etc.) are of little help for non-IgE-mediated diseases. The best diagnostic method here remains a 2- to 4-week trial of withdrawal of a suspected allergen, possibly followed by an oral challenge (preferably blinded, which can be done at home or in a clinical setting if there is any doubt about an IgE-type reaction).

Treatment of the non-IgE allergies consists in the avoidance of the allergenic food(s) with oral rechallenge, usually after 1 year of age. The majority of these reactions will resolve by school age (as will IgE reactions). Avoidance of offending allergens is recommended for breastfeeding mothers of infants with allergic proctitis. Follow-up with a specialized nutritionist is recommended because of the severity of the avoidance diet and to prevent nutritional deficiencies in both mother and child. For formula-fed children, casein hydrolysate formulas (e.g., Nutramigen A+, Alimentum) are generally recommended and well tolerated. Occasionally, amino acid-based formulas (e.g., Neocate, PurAmino) must be used. For older children with enteropathy, an avoidance diet with oral challenge every 6–12 months is also recommended to verify the development of tolerance.

- ***Celiac disease*** (see ▶ Chap. 3) involves an immunological reaction of the intestine to gluten proteins (gliadin).

Non-celiac gluten intolerance, where patients, for reasons that are still unclear, seem to benefit from a gluten-free diet even in the absence of criteria for celiac disease, is an example where the concept of food allergy seems to be wrongly invoked.

22.3 Mixed, IgE- and Non-IgE-Mediated Manifestations

- ***Atopic dermatitis*** may be exacerbated by a food reaction in a child with severe eczema. The occurrence of pruritus and eczematous lesions in the minutes to hours after food ingestion suggests this entity. Avoidance of the offending allergen is recommended.

- ***Gastrointestinal eosinophilic diseases*** are characterized by digestive symptoms associated with an eosinophilic infiltration of various segments of the GI tract. Many children diagnosed with these diseases will have allergic reactions to various foods or environmental allergens.

Eosinophilic esophagitis is characterized by esophageal symptoms associated with an eosinophilic infiltration of the esophageal mucosa. It is more common in boys (70–75%) and in young adult men. Allergic diseases (eczema, asthma, rhinitis, food allergies, etc.) are common in these subjects. The mode of presentation varies with age: infants under 2 years of age usually present with various feeding difficulties, including refusal of solid foods, difficulty in the progression of textured foods, or regurgitations that may suggest gastroesophageal reflux; preschool and school-age children will tend to have postprandial vomiting or abdominal pain; adolescents, like adults, will usually show up with dysphagia to solid foods, or food blockage. Eosinophilic esophagitis was discussed in ► Chap. 1.

Eosinophilic gastroenteritis is characterized by chronic digestive symptoms (abdominal pain, vomiting, diarrhea, etc.) associated with an eosinophilic infiltration of various segments of the GI tract, including the antrum and duodenum. When the small intestinal mucosa is affected, diarrhea, abdominal pain, and failure to thrive may be present. The disease, in children, can, sometimes, be relatively benign and be similar to irritable bowel syndrome (IBS); in adults, the eosinophilic gastroenteritis is most often diagnosed in patients with severe digestive symptoms suggestive of inflammatory bowel disease (IBD). A plasma eosinophilia may be present and suggest the diagnosis of eosinophilic gastroenteritis.

Diagnosis of eosinophilic diseases is confirmed on GI biopsies with tissue infiltration by eosinophils.

Treatment The role of food allergy in these eosinophilic disorders is not well established, but the symptom improvement following exclusion diets clearly suggests a contribution of food into the pathogenesis of these diseases.

Skin allergy tests and specific IgE testing are rarely helpful in identifying a specific causative factor for these diseases. The nutritional therapy approach consists of either eliminating the six main food allergens (in order of importance: milk, wheat, soy, fish, eggs, nuts/peanuts) or administering an elemental diet (amino acids such as Neocate), orally or via a nasogastric tube, for a period of 6–8 weeks; the success rate of these methods is about 70%. The pharmacological approach includes the use of corticosteroids (preferably topical in case of eosinophilic esophagitis) in patients with severe disease or refractory to other modalities.

Undernutrition and Nutritional Support

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Contents

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23

Undernutrition occurs when the body's energy needs are not fulfilled by the nutritional intake.

Undernutrition has many consequences. It leads to a decrease in the muscle mass, affecting the functional capacity (respiratory, motor, etc.) and quality of life. It increases the risk of infection by inducing immunodepression and delays wound healing.

23.1 Types of Undernutrition

There are three forms of protein-energy undernutrition: *marasmus* caused by energy (calorie) deficiency, *kwashiorkor* secondary to pure protein deficiency, and *marasmic kwashiorkor* resulting from both protein and energy deficiency (see Table 23.1).

Several conditions can lead to undernutrition (Fig. 23.1). In developing countries, an inadequate caloric intake is frequently the cause. In developed countries, it is more often related to caloric malassimilation due to digestive diseases (pancreatic disease, Crohn's disease, etc.) or to an abnormally increased body metabolism (e.g., during cancer, chronic kidney failure, heart failure, liver cirrhosis, prolonged hospitalization, etc.).

23.2 Pathophysiology of Fasting

During a fast, the primary action of the body is to preserve the energy necessary for the functioning of the brain and vital organs.

- In the first 12–24 h, the *early fasting phase*, the glycogen stored in the liver is mobilized to produce glucose.
- Between days 2 and 4, the *short-term fasting phase*, once the liver reserves of glycogen are depleted, gluconeogenesis is increased, mainly from amino acids produced by the hydrolysis of muscle proteins and, to a lesser degree, from fatty acids in adipose tissue.
- Around the fifth day, the *long-term fasting phase*, in order to minimize the degradation and utilization of muscle proteins, ketone bodies (from fatty acids of the adipose tissue) will be synthesized by the liver and become the main source of energy for the brain and the muscles. This phenomenon of protein saving can be maintained until only 20% of the adipose reserves remain. A healthy adult weighing 70 kg and measuring 1.70 m will be able to endure 40 days of fasting.
- When the state of undernourishment is prolonged, the organism enters the *terminal phase* of fasting. The basal metabolism diminishes, and the organism will use the protein reserves (reduction of up to 30% of the protein mass), resulting in hypoalbuminemia (and edema), immunodeficiency (and infections), and muscular dysfunction (respiratory, motor, etc.). The adipose mass can decrease down to 5% of the body weight; the residual fat is paradoxically stored in the liver (hepatic steatosis).

Table 23.1 Forms of undernutrition

	Kwashiorkor	Marasmus
Deficiency	Proteins	Calories
Subcutaneous fat	Decreased	Absent
Edema	Important	Little
Liver steatosis	Present	Absent
Anemia	May be severe	Moderate

23.3 Nutritional Assessment

Nutritional assessment is based on clinical, anthropometric, and biochemical assessments (Table 23.2):

- *Clinical.* Poor nutritional intakes for more than 7 days or weight loss of more than 10% in 6 months are strongly suggestive of undernutrition. The physical examination looks for signs of undernutrition that includes loss of adipose tissue, muscle wasting, edema, as well as signs of micronutrient deficiencies.

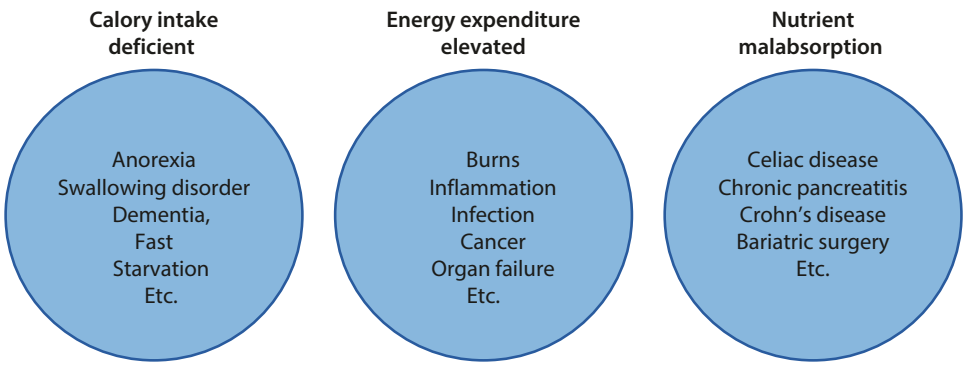


Fig. 23.1 Etiologies of undernutrition

- *Anthropometric*. Weight and height (BMI <20 kg/m^2) are part of this evaluation. The measurement of skin folds and brachial circumference assesses fat content and muscle reserves, respectively.
- *Biochemical*. Albumin, pre-albumin, and transferrin may be used as indicators of the nutritional status. However, they are also influenced by non-nutritional factors such as inflammation, or by the patient's condition (e.g., in cirrhosis, low concentrations of these parameters may reflect a decrease in liver synthesis rather than a poor nutritional status). Albumin, because of its long half-life (21 days), may show normal serum concentrations for a long time even in the presence of established undernutrition.

These parameters of nutritional evaluation are imperfect and are influenced by a certain degree of subjectivity. Their relative sensitivity and specificity can also be affected by the patient's condition.

Clinical signs of micronutrient deficiencies are shown in ◘ Fig. 23.2 (and have also been discussed in ▶ Chap. 3).

Criteria for defining malnutrition have been proposed by the GLIM (Global Leadership Initiative on Malnutrition) expert group in 2018 (see ◘ Table 23.8).

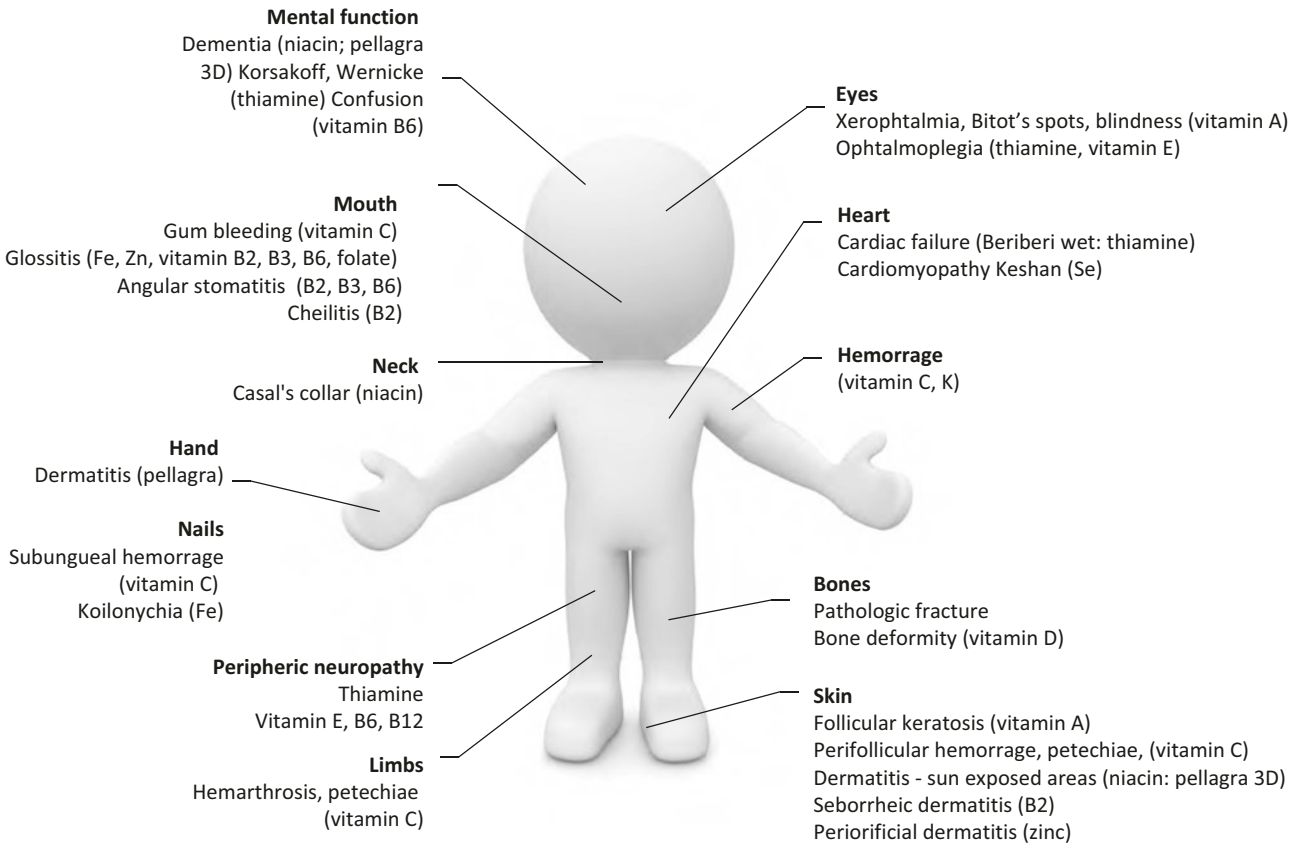
Table 23.2 Nutritional assessment: clues to look for

- Poor nutritional intake for more than 7 days
- Weight loss (unintentional) >5% over the past 6 months
- BMI <20 kg/m^2
- Loss of body fat (triceps, anterior chest, intercostal area)
- Loss of muscle mass (in order of appearance: temporal, interossei, scapular, deltoid, biceps, triceps, quadriceps)
- Edema (peripheral, presacral, ascites).
- Lowered serum tests: albumin, pre-albumin, transferrin

23.4 Indications for Nutritional Support

Nutritional support includes the use of oral nutrition supplementation or enteral or parenteral nutrition depending on the function of the gastrointestinal tract and the ability to take food and liquids orally.

Nutritional support is clearly indicated in undernourished patients (weight loss, muscle wasting, etc.) who are unable to meet 60% or more of their energy



◘ **Fig. 23.2** Clinical signs of micronutrient deficiencies

requirements as a result of a poor oral intake, malabsorption, losses, or other causes of intestinal failure in the context of non-terminal diseases (reasonable life expectancy and disease prognosis).

Providing nutritional support to patients at nutritional risk or to those with mild or suspected undernutrition is also necessary in situations of "stress" such as critical illness, major surgery or medical/surgical complications, and sepsis. In addition, undernourished patients should be considered for nutritional support for a minimum of 7–10 days prior to a major surgery to reduce postoperative complications.

Nutritional support should be considered, as a preventive measure, in any subject who will not be able to meet his nutritional needs through oral nutrition for more than 7 days (e.g., hospitalization for severe pancreatitis). A 7-day fasting, even if not accompanied by florid signs of undernutrition, has a negative influence on the immune system, wound healing, etc., and must be prevented.

23.5 Assessment of Energy and Protein Needs

Daily energy expenditure depends on the basal metabolism (amount of energy required in a resting individual) and the metabolism associated with physical activity and stress (such as illness). It can be estimated by various relatively complex formulas (such as the Harris-Benedict's formula that takes into account the weight, height, and age) or by precise measurements (such as indirect calorimetry). In practice, a simple formula, although imperfect, allows the estimation of energy and protein requirements according to the level of physiological stress (see ◘ Table 23.3).

◘ **Table 23.3** Caloric and protein requirements according to the degree of physiological stress (based on the patient's optimal weight)

Stress	Calories (kcal/kg/day)	Protein (g/kg/day)
Mild (uncomplicated operative phase)	25–28	0.8–1.0
Moderate (infection, acute pancreatitis, peritonitis, severe IBD)	28–32	1.0–1.5
Severe (polytrauma, severe burns)	32–35	1.5–2.0

23.6 Nutritional Support: Enteral Versus Parenteral

Normal oral nutrition should always be the preferred route to correct undernutrition. Nutritional counseling with the help of a dietician should be available. Psychological stimulation can be required to increase food intake in cases of dementia or anorexia, adapted soft food diet must be used if dysphagia, etc.

However, if normal oral nutrition is not possible, artificial nutrition can be used to fulfill the patient's nutritional needs either completely (during total fasting) or partially (if oral nutrition is present but unsatisfactory).

Artificial feeding can sometimes be used for specific therapeutic purposes (e.g., "immune hypostimulation" in the management of eosinophilic esophagitis or food allergies (see ► Chaps. 1 and 22), treatment of pediatric inflammatory bowel disease (► Chap. 4), "pancreatic rest" therapy during acute pancreatitis (► Chap. 5), etc.).

Two types of artificial nutrition are available: enteral (oral, gastric, or intestinal) or parenteral (intravenous). Based upon economical and medical arguments, the enteral nutrition should be the first choice in all patients and parenteral nutrition be reserved in cases where enteral nutrition is not possible.

23.7 Enteral Nutrition

The enteral approach will always be preferred if the digestive tract is functional. Compared to parenteral nutrition (discussed below), enteral nutrition is less expensive, preserves the integrity of the small intestinal mucosa (thus reducing the incidence of infection by translocation of intestinal bacteria through the digestive epithelium), and has a much lower risk of complications (septic, vascular, etc.).

Most liquid solutions for enteral nutrition are poorly tolerated when given orally (due in part to their palatability), and, most often, they are administered through a gastric or intestinal tube. The (naso)gastric route will be preferred in most cases, while the (naso)jejunal route (more complex to install and manage) will be chosen if the gastric administration is contraindicated (e.g., in the case of gastroparesis) or poorly tolerated (nausea, regurgitations, vomiting) (◘ Table 23.4). For chronic or prolonged enteral feeding, a percutaneous catheter may be inserted by endoscopy, radiology, or surgery.

Commercial solutions for enteral nutrition are designed to ensure a complete nutritional intake. They are available in a variety of forms: standard polymeric (non-digested nutrients, with or without fiber residues; the most commonly used preparation), special-pur-

pose polymeric (nutrient composition adapted for lung or kidney diseases, etc.), semi-elemental, or monomeric (or elemental, i.e., made of hydrolyzed nutrients such as amino acids instead of proteins) solutions. The characteristics of each are listed in Tables 23.5 and 23.6. The formulas provide 1–2.1 kcal/ml. The concentrated formulas are useful to limit fluid intake in sensitive patients (e.g., those with chronic renal or heart failure). Hyperosmolar solutions may be more difficult to tolerate.

Table 23.4 Gastric or jejunal tube feeding (?)

Favorable (+) and unfavorable (−) issues

Gastric feeding

(+) Easy to install
(nasogastric tube, percutaneous gastrostomy)
(+) Easy to administer by constant flow
(e.g., 100 ml/h × 15 h) or by bolus (e.g., 500 ml tid)
(−) Risk of gastroesophageal reflux vomiting, bronchial aspiration
(−) Gavage in the supine position to be avoided

Jejunal feeding

(−) Complex installation
(guidance by fluoroscopy, etc.)
(−) Rate-controlled administration by infusion pump
(−) Risk of diarrhea, dumping
(if rapid administration of hyperosmolar solution)
(+) Prevents esophageal reflux
(and bronchial aspirations)
(+) Possible with gastroparesis
(+) Secure in supine position

Table 23.6 Specific-use enteral nutrition formulas

Formulas	Special features	Indications
Boost® fruit-flavored drink	0.8 kcal/ml Very low fat Non-dairy taste	Well-tolerated oral supplement to complement other nutritional regimes
Nepro®	2 kcal/ml Reduced in Na, K, P, Mg	Renal failure
Pulmocare®	1.5 kcal/ml 20% MCT (medium-chain triglycerides)	Severe lung disease Difficult weaning from respiratory assistance Cystic fibrosis
Oxepa®	1.5 kcal/ml 55% lipids	Acute respiratory distress syndrome
Glucerna®	1 kcal/ml 33% fat	Diabetes
Nutrihep®	1.5 kcal/ml 50% branched chain AA 12% fat (66% MCT) Sodium limited	Hepatic encephalopathy
Impact AR®	Supplemented with arginine, omega-3, nucleotides	Preoperative period in malnourished patients

Table 23.5 Different classes of nutrient formulas

Composition	Specificity	Indications	Examples
Polymeric			
Polymers of macronutrients (proteins, lipids, non-predigested carbohydrates)	HN (high nitrogen) or VHP (very high protein) products provide up to 25% of energy as proteins	Patients with adequate absorption and digestion	Boost® Ensure® Isosource® Jevity® Nutren® Osmolite®
Semi-elemental			
Blend of intact and hydrolyzed macronutrients	Contains medium-chain triglycerides (MCT)	Impaired digestion or absorption (short bowel, proximal enterocutaneous fistula, pancreatic fistula)	Peptamen® Vital®
***Monomeric* (*elemental*)**			
Almost completely hydrolyzed	High carbohydrate and low fat content	Minimal digestion or absorption [short bowel, need to reduce pancreatic or intestinal secretions (fistula, chylous ascites)]	Vivonex®

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23.8 Parenteral Nutrition

Intravenous parenteral administration of nutrients will be used when the gastrointestinal tract cannot be used. Because of the high osmolarity of the nutritional solutions to be administered, a large central vein catheter (vena cava, jugular or subclavian vein) is required.

Parenteral solutions contain a mixture of dextrose and amino acids with a lipid emulsion, as well as electrolytes, vitamins, and trace elements.

- The required *protein* intake depends on the patient's clinical condition, nutritional status, and liver/kidney functions (see ◘ Table 23.7). Proteins provide 4 kcal/g as energy.
- *Lipids* are an important source of energy (9 kcal/g). Excess administration should be avoided because of the risk of hypertriglyceridemia and their theoretical immunosuppressive effect. In general, the maximum recommended dose is 1–1.5 g/kg body weight per day. Various lipid preparations are available, including the classic soy-derived preparation (Intralipid®), or those made from fish oils (Omegaven® with omega-3), or made of mixed oil emulsions (soy, medium chain triglycerides, olive oil, fish oil, such as SMOFlipid®) or with olive and soy oils (Clin-Oleic®).
- The *dextrose* intake is limited to 5 mg/kg/min or 7 g/kg/day in order to respect the oxidative capacity of the liver and avoid an increased hepatic lipogenesis that could induce liver steatosis. Hyperglycemia may occur if carbohydrate intake is excessive. Glucose is administered at a concentration of 5–20%, depending on the cases.
- The total caloric intake should be carefully evaluated (and monitored) according to the weight and condition of the patient (◘ Table 23.7). The old therapeutic strategy of "hyperalimentation" is now contraindicated, due to its liver complications (steatosis, possibly complicated by cirrhosis).

The composition of the solutions to be administered can be calculated as shown in ◘ Table 23.7. Nutrient solutions can be administered continuously over 24 h or can be infused cyclically, for example, at night to facilitate patient mobility during the day. In the case of cyclical nutrition, the interruption of the perfusion must be monitored for hypoglycemia. Glucose infusion induces insulin release, and its abrupt cessation may, in some patients, be followed by a transient hypoglycemia (due to the delay in the secretion of endogenous insulin to adapt to the sudden drop in blood glucose); a gradual reduction in glucose infusion may be required to allow adaptation of the insulin response.

Table 23.7 Parenteral nutrition: evaluation of nutrient solutions to be administered

Step 1: Define

(A) Optimal patient weight = _____ kg

(B) Patient's stress level (see ◘ Table 23.3) = _____

Step 2: Calculate daily caloric requirement (based on patient weight and stress)

(A) Total calories required:
25 kcal/kg pt (moderate stress, 30; severe, 35) = _____ kcal total/day

(B) Specific calories to be given:

- Proteins (4 kcal/g prot)
  1g/kg pt (moderate stress: 1.5. severe: 2.0 g/kg) = _____ kcal prot (= _____*vol prot*)
- Lipids (9 kcal/g lipid)
  1g/kg pt = _____kcal lipid (=_____*vol lipid*)
- Carbohydrates (3.4 kcal/g glucose)
  [___kcal total required] - [___kcal prot + ___ kcal lip] = ____ kcal glucose (= _____*vol glucose*)

Step 3: Calculate fluid requirements

(A) Total liquid volume required:
Baseline requirement (30 mL/kg pt) + losses = _____ mL/day

(B) 0.9 or 0.45 NaCl infusion:
[Total volume required: _____] - [volume of prot+ lipid+ glucose: _____] = _____ mL NaCl/day

Step 4: Additives

(A) Ca^{+}, $PO4^{-}$, K^{+}, Mg^{+}, and Na^{+} as needed by the patient

(B) Multivitamins, Vit K (sc route), trace elements (Cu, Zn, Se, Cr, Mn, etc.): according to standards

Delivery of the various nutrients will often require an infusion pump for each of the three to four nutrient solutions. Pre-mixed parenteral nutrition solutions in varying proportions of amino acids and dextrose are commercially available (e.g., AA 5%, glucose 5%, 10%, or 20%). They have the advantage of facilitating preparation in the pharmacy but offer little flexibility to meet the specific needs of a patient.

Vitamins, electrolytes, and trace elements (such as copper, zinc, chromium, manganese, selenium) can be added to the solutions in desired quantities.

Parenteral nutrition is generally administered in hospitals for a limited period of time. It requires close monitoring with frequent bloodwork and complex procedures that involve central catheter handling, infusion pumps,

and compounding of solutions by pharmacy. Some patients may require long-term parenteral nutrition due to chronic intestinal failure. This is then provided at home after a rigorous training and monitoring. Patients are then followed by a home parenteral nutrition program.

***General complications* of parenteral nutrition**, especially with long-term use, include:

(a) Catheter infection and secondary sepsis (which is fatal if left untreated). The catheter provides a wide open doorway for the direct introduction of bacterial or mycotic germs (cutaneous or other) into the bloodstream. Caregivers must be very careful in the sterile manipulation of catheters inserted in large central veins. Patients receive intensive training to learn how to aseptically handle their catheters.

(b) Venous thrombosis can occur in the catheterized veins perfused with hyperosmolar irritating substances. If it occurs repeatedly, it can compromise the essential venous access for parenteral nutrition and impose small bowel transplantation.

(c) Metabolic disorders, such as electrolyte imbalances (Na^+, K+, etc.), micronutrient deficiencies such as trace elements (Zn, Mn, Se, etc.), macronutrient overload (especially with glucose or lipid that can lead to hepatic steatosis), should be monitored with regular follow-up.

(d) Secondary liver damage (probably due to a misidentified toxic factor) to soy-derived lipid emulsions is of particular concern in long-term parenteral nutrition, as it may lead to liver diseases requiring liver (and possibly small bowel) transplantation. It can now be prevented (or even treated) with lipid emulsions derived from fish oils.

23.9 Re-feeding Syndrome

After severe dietary restriction, the nutritional recovery must be progressive to avoid the complications of the re-feeding syndrome (linked to a deficiency mainly in phosphorus but also in potassium, magnesium, and calcium, as well as in thiamine).

The re-feeding syndrome occurs following a glucose load leading to insulin secretion which triggers intense cellular activity in an organism that was affected by a reduced metabolism and with mineral and vitamin reserves compromised by malnutrition. The sudden and abrupt revival of metabolic cell activity (which had been "asleep" until then) induces a high energy expenditure and a great need for energy substrates (Fig. 23.3):

1. ATP, the main cell energy substrate, is then produced in large quantities, causing an increase in the use of phosphorus.
2. Potassium, magnesium, calcium, and thiamine are rapidly required as co-factors for the synthesis of glycogen, lipids, proteins, etc.
3. Phosphorus, potassium, calcium, magnesium, thiamine, etc. are then rapidly mobilized from the out-

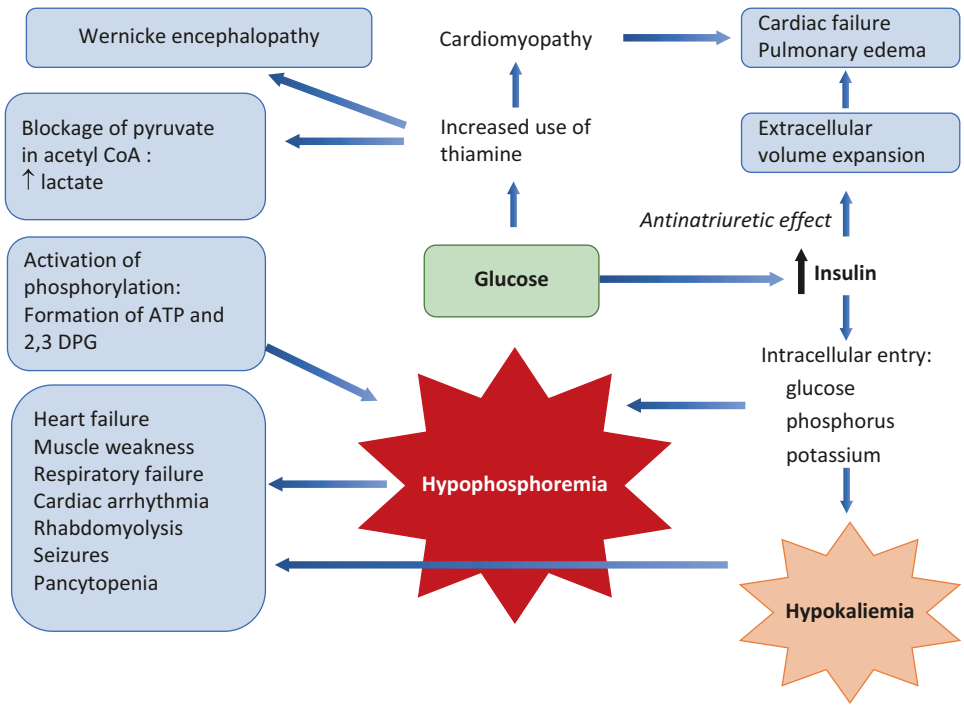

Fig. 23.3 Re-feeding syndrome

side to the inside of the cells, resulting in their serum depletion.

4. Organ functions such as cardiac (arrhythmias, cardiovascular insufficiency, volume overload, edema), respiratory (diaphragm, intercostal muscles), and peripheral muscles (muscle spasms, tetany, rhabdomyolysis) may be affected by these ionic deficits. Wernicke's neurological syndrome or beriberi heart disease may occur in response to the lack of thiamine.

The risks of developing a re-feeding syndrome are elevated in subjects with a BMI <18 and/or a compromised nutritional intake of 5–10-day durations. Serum levels of PO_4^-, K^+, Mg^+, and Ca+ should be monitored before and during re-feeding.

The treatment, apart from massive replacement of the incriminated agents, i.e., PO_4^-, K^+, Mg^+, Ca^+, and thiamine, includes progressive re-feeding (25, then 50, then 75% of caloric requirements) of subjects at risk.

23.10 Addendum

Criteria for defining malnutrition were published in 2018 by the Global Leadership Initiative on Malnutrition (GLIM) (see Table 23.8) and summarize our discussions well in this chapter.

Table 23.8 Criteria for defining malnutrition (according to GLIM 2018)

Phenotypic criteria	Etiological criteria
Involuntary weight loss >5% in <6 months >10% in >6 months	Insufficient nutritional intake <50% requirements >1 week Any reduction >2 weeks
Lowered BMI <20 if <70 years <22 if >70 years	GI condition that affects nutrient absorption Short bowel, celiac disease, Crohn's, chronic pancreatitis, etc.
Reduced muscle mass Estimated by objective measures or physical examination	Acute inflammation (increased energy expenditure) Major infection, serious burn, severe trauma, etc.
	Chronic disease Cancer, renal, cardiac, respiratory failure, etc.

Malnutrition is confirmed if the patient presents at least one phenotypic criteria and one etiological criteria

Obesity

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Contents

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In 1997, the World Health Organization (WHO) declared that obesity had reached the threshold of a worldwide epidemic. Obesity has become a major public health problem with significant economic implications. More than 6 million Canadians are obese, and more than 10% of children are overweight.

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24.1 Definition of Obesity

Obesity is an excessive accumulation of body fat. In adults, definitions of overweight and obesity are based on the body mass index (BMI), which is determined by dividing the subject weight in kilograms by its height in square meters. A BMI of 25–29.9 kg/m^2 corresponds to overweight, >30 kg/m^2 to obesity, and >40 kg/m^2 to morbid obesity. Complications increase with the degree of overweight. In children and adolescents, overweight is defined by a BMI >85th percentile for age and sex and obesity by a BMI >95th percentile.

The type of body fat distribution is important. Intra-abdominal or visceral fat accumulation is associated with a greater risk of metabolic disease and mortality compared to a peripheral, subcutaneous, or gluteofemoral fat accumulation. *Waist circumference* and *waist-to-hip ratio* correlate with intra-abdominal obesity and are better risk markers of chronic disease than the BMI (which is a reflection of overall adiposity). There is an increased risk of type 2 diabetes, hypertension, dyslipidemias, and coronary heart disease when the waist circumference exceeds 102 cm in men and 88 cm in women.

24.2 Complications of Obesity

Compared to a healthy weight population, an obese individual has a greater need of medical care and a shortened life expectancy (Tables 24.1 and 24.2).

Table 24.1 Risk of premature mortality from any cause according to BMI

Weight	BMI	Premature mortality
Healthy weight	18–24.9 (kg/m^2)	RR 1.00
Overweight	25–29.9	1.13
Obesity class I	30–34.9	1.44
Obesity class II	35–39.9	1.88
Obesity class III	40 and over	2.51

Table 24.2 Risk of premature mortality according to anthropometric measures in men and women

Parameter	Anthropometric measure	Premature mortality
Waist circumference		
Male	>102 cm	RR 2.05
Female	>88 cm	1.78
Waist to hip ratio		
Male	>1.0	1.68
Female	>0.85	1.51

Table 24.3 American Heart Association criteria for metabolic syndrome (three of the five conditions listed below must be met to make the diagnosis)

Waist circumference (cm)	>102 in men
	>88 in women
Triglycerides (mmol/L)	≥1.7
HDL (mmol/L)	≤1.03 in men
	≤1.3 in women
Blood pressure (mmHg)	≥130 systolic or
	≥85 diastolic
Fasting blood glucose (mmol/L)	≥5.6

Metabolic syndrome The metabolic syndrome encompasses several conditions including obesity, dyslipidemia, hypertension, and hyperglycemia (three of the five conditions listed in Table 24.3 must be met to make the diagnosis).

An individual suffering from the metabolic syndrome has a higher risk of having a heart attack or a stroke (3×), of dying from one of these pathologies (2×), and of developing diabetes (5×). Lifestyle changes can reduce the incidence of the metabolic syndrome and its complications.

The metabolic syndrome is due to insulin resistance, the severity of which is strongly correlated to the volume of intra-abdominal fat tissue. In obese individuals, fat cells increase in volume, decreasing the blood supply to the adipose tissue and creating a state of hypoxia and necrosis, with macrophage infiltration and possibly

overproduction of pro-inflammatory cytokines including TNFα and IL-6.

Non-alcoholic steatohepatitis Non-alcoholic steatohepatitis (NASH; see ▶ Chap. 8), which can progress to fibrosis and cirrhosis, is a complication of obesity. In Western industrialized countries, obesity is becoming the leading cause of cirrhosis.

Other complications Other complications such as sleep apnea or osteoarthritis of the knees, hips, and spine can affect the health of the obese subject.

Various conditions Various conditions (whose causal link with obesity is less obvious) are found more frequently in the obese population, such as certain cancers (breast, endometrium, ovary, esophagus, pancreas, colon, etc.) or Alzheimer's disease.

24.3 Etiology of Obesity

Obesity is a complex and multifactorial disease.

Genetics The role of genetics has been demonstrated in studies of twins, family members, and adopted children. Studies of twins have shown that the correlation of BMI is greater between monozygotic (0.74) than dizygotic (0.33) twins. There is also a strong correlation between the BMI of monozygotic twins raised in different environments, as well as between the BMI of adopted individuals and their biological parents and siblings.

Over 50 "obesogenic" genes have now been identified (some of them are known to cause monogenic obesity). The FTO (fat mass and obesity-associated protein) gene has been identified as a risk factor for obesity. The MC4R (melanocortin 4 receptor) gene can undergo mutations that are known to be responsible for monogenic forms of severe obesity (because of its involvement in the leptin-melanocortin pathway through the induction of satiety as discussed below). A mutation in the gene for the metabolism and release of adipocytokines (such as adiponectin) has also been implicated in the genesis of obesity.

Other genes such as SH2B1, NEGR1, BDNF, NRXN3, and PRL have been identified in the regulation of eating behavior. Obesity is most often polygenic as it results from the inheritance of several genes. In these cases, obesity will develop later in life. Only 7% of morbid obesity is "pure" and attributable to the mutation of a single gene; obesity in these cases is severe and develops from childhood. In the rare cases of isolated leptin deficiency, obesity is perfectly controlled by daily leptin injections.

It has also been noted that the propensity to be physically active is genetically determined, as is the body's response to regular physical activity. In addition, dietary preference for foods high in simple carbohydrates and fats is also partially genetically determined and may be almost three times more frequent in some genetically predisposed individuals.

Environment Environment has a decisive influence and it is not only genetics that intervenes in the development of obesity. An individual, despite his genetic predisposition, may not be overweight if he is not exposed to an obesogenic environment.

Studies on migrant populations have revealed that individuals with a common genetic heritage living in different environments develop obesity when exposed to an obesogenic environment. This phenomenon has been well documented among Japanese who migrated to the United States. The sharp increase in the incidence of obesity over the past 30 decades in the West is considered to be the result of a positive energy balance rather than the influence of genetics.

Energy balance and appetite regulation Positive energy imbalance resulting from excessive calorie intake and/or insufficient energy expenditure is most often responsible for obesity. Appetite dysregulation is therefore a major factor in obesity.

Appetite regulation involves a balance between orexigenic (appetite stimulating) and anorexigenic (appetite inhibiting) factors. The hypothalamus is the regulatory center of appetite. It contains both a satiety center (ventromedial nucleus, VMN) that is rich in leptin receptors and a hunger center (lateral hypothalamus area, LHA) rich in neuropeptide Y (NPY) receptors, both acting on the solitary tract nucleus (nucleus tractus solitarius, NTS) (◘ Fig. 24.1).

The *orexigenic pathway* includes first-order neurons that can be stimulated by ghrelin to secrete NPY and AgRP peptides influencing second-order neurons releasing MCH (melanin-concentrating hormone) and orexin to induce the sensation of hunger via NTS.

The *anorectic pathway* includes first-order neurons stimulated by leptin and other digestive hormones such as insulin, CCK, and PYY to secrete the peptides POMC (pro-opiomelanocortin, precursor of melanocortin) and CART (cocaine- and amphetamine-regulated transcripts) acting on second-order neurons releasing CRF (corticotropin-releasing factor) to induce satiety via the NTS.

The passage of nutrients through the digestive system triggers a succession of signals relayed to the hypothalamus and brainstem, both by the vagus nerve and by the secretion of hormones throughout the digestive tract (insulin, cholecystokinin, PYY, glucagon-like peptide-1

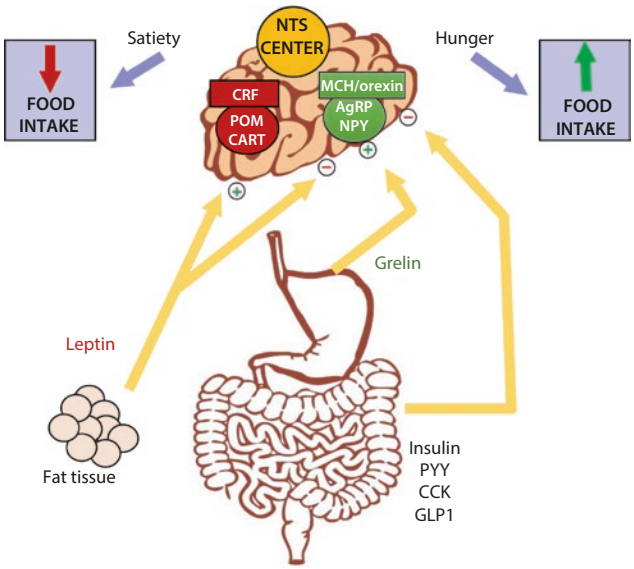

Fig. 24.1 Appetite regulation by orexigenic and anorexigenic factors. Appetite stimulatory and inhibitory pathways are identified, respectively, by green and red colors

(GLP-1), oxyntomodulin, etc.). The physiological importance of most of these peptides is not yet established, but the role of cholecystokinin, insulin, and PYY in triggering postprandial satiety is recognized.

Leptin inhibits hunger by activating hypothalamic anorexigenic pathways (POMC/CART) and by inhibiting orexigenic pathways (NPY/AgRP). In the rare cases of isolated leptin deficiency, obesity is perfectly controlled by daily injections of leptin. Ghrelin, mainly produced by the stomach, has the opposite effect of leptin, stimulating appetite by activating NPY neurons. Mutations in the melanocortin receptor gene or in the CART gene that prevent activation of the satiety pathway are known causes of familial obesity in humans. Attempts to treat obesity by reducing appetite with a stimulation blocker, such as an anti-ghrelin, or with an inhibition stimulant (e.g., CCK agonist), have never achieved the desired effects. It is clear that the control of appetite is based on complex mechanisms involving several regulatory agents, including central and peripheral, stimulatory and inhibitory factors.

The intestinal microbiota may possibly play a role. The human gut is home to more than 10^{13}–10^{14} microorganisms, and the microbiome of obese individuals is thought to have less bacteroids and more firmicutes than that of normal weight subjects. Modification of the microbiota by prebiotics seems to lead to weight loss, a decrease in food intake, an increase in GLP-1 and PYY, and a decrease in ghrelin. The exact nature of the link between prebiotics, probiotics, microflora, and factors regulating food intake remains to be clarified but constitutes a major research challenge.

Secondary obesity Obesity is most often primary, i.e., it results from a positive energy balance due to an excessive intake of calories and/or insufficient energy expenditure. Weight gain can also be secondary to certain medications (such as antidepressants, antipsychotics, antiepileptics, corticosteroids) or diseases (e.g., hypothyroidism, Cushing's).

24.4 Treatment of Obesity

(1) Nutritional treatment Decrease food intake or increase energy expenditure? To lose weight, one must aim for a *negative energy balance*, either by *reducing food intake* or by *increasing energy expenditure* or by combining the two. If a maximal loss of 0.5 kg (1 lb) per week is desired, a daily energy deficit of 500 kcal is required. However, the effort required to obtain a negative energy balance of 500 kcal per day will be less difficult by restricting food intake than by increasing energy expenditure. For example, an energy expenditure of 500 kcal corresponds to 1 hour of jogging at a pace of 5 km/h or 35 minutes of rope skipping. Conversely, skipping one piece of ice cream cake and one glass of wine in a day will reduce the number of calories consumed by 500 kcal.

Exercise, while having a modest effect on weight loss compared to dietary restriction, has the advantage of minimizing the loss of lean tissue (muscle) and limiting the decrease in basal metabolism associated with weight loss. Improved fitness per se is correlated with a lower risk of all-cause morbidity and cardiovascular mortality, and this occurs in obese individuals independent of weight loss. In addition to these beneficial effects, exercise has been shown to play an important role in the prevention of cardiovascular disease, cancer, and diabetes, in improving lipid profile and lowering blood pressure, and in glycemic control through improved insulin sensitivity. The benefits of physical activity do not necessarily have to be of vigorous intensity; an increase of 3000 steps per day for 12 weeks will contribute to a decrease in waist circumference even if the BMI remains unchanged. All forms of physical activity should be encouraged.

Weight loss in the vast majority of individuals will not be achieved without a reduction in the caloric intake.

Are all diets the same? The popular literature tends to praise one diet over another for promoting weight loss. *Low-carbohydrate diets* (such as the Atkins diet developed in 1972) do not seem to seem more effective than low-fat diets to induce weight loss. However, some authors have observed a superior benefit of this diet on lipid profile, particularly HDL and triglyceride levels. *Fat-restricted diets* may result in improved glycemic control and lowered risk of cardiovascular disease. *Low*

glycemic index diet (e.g., Montignac diet) promotes the intake of low glycemic index foods (pasta, fruits, legumes; rather than high glycemic index foods such as white bread, potatoes) to induce a more gradual secretion of insulin (which would increase appetite, promote anabolism of adipose tissue, and lead to weight gain). Studies have not shown that the low glycemic index diet is superior to other types of diets in inducing weight loss; however, it would be metabolically beneficial for type 2 diabetics. *High-protein diets* appear to be effective in reducing body fat and triglyceride levels, particularly in individuals with dyslipidemia or those at risk for type 2 diabetes. *Ketogenic* (low-carb/high fat) diet and intermittent (more or less prolonged) *fasting* are used to burn visceral fat, and both receive a lot of attention these days.

In summary, several dietary strategies can induce weight loss with no one strategy appearing to be superior. Caloric restriction, rather than macronutrient content of the diet, seems to be the most important element in achieving a healthy weight. The biggest challenge, however, once weight loss has been achieved, is to maintain that weight over the longer term by continuing to adhere to the dietary changes. Individual support from a nutritionist and/or physician or group support, or the addition of behavioral therapy, can be used to help maintain this goal.

(2) Pharmacological treatment According to NHLBI (National Heart, Lung, and Blood Institute) recommendations, adjuvant pharmacological treatment may be considered in individuals with a BMI greater than 30 kg/m^2. Despite these indications, prescription of anti-obesity medications remains infrequent due to limited efficacy, contraindications, side effects, cost, and limited coverage by insurance plans.

There are two categories of anti-obesity drugs: appetite suppressants that act on the central nervous system and those that inhibit nutrient caloric absorption.

(a) Appetite suppressants Drugs in this category act through norepinephrine, dopamine, or serotonin. In the 1930s, amphetamines were the first anorectics on the market, but because of the risk of dependence, they were replaced by sympathomimetics and other agents.

Sibutramine is a serotonin and norepinephrine reuptake inhibitor that resulted in a weight loss of 4.5 kg at 12 months of treatment. Since 2010, the drug has been withdrawn from the market due to an increased risk of cardiovascular events.

Diethylpropion and phentermine are sympathomimetics. They block the reuptake of norepinephrine. Increased blood pressure, dry mouth, constipation, and insomnia are among their side effects. Their use is only permitted for a short period of 12 weeks. A combination of phentermine and topiramate (Qsymia®) is available in the United States. A combination of bupropion and naltrexone (Contrave®, an adrenergic/dopaminergic agent that stimulates the POMC/CART pathways) is available in Canada.

A 5HT2C serotonin agonist, lorcaserin (Belviq®), was recently marketed in Canada.

GLP1 agonists (liraglutide: Victoza® for diabetes, Saxenda® and Ozempic® for obesity) reduce appetite (by indirectly inhibiting NPY/AgRP activity and directly stimulating POMC/CART).

Given the potential influence of certain gut "hormones" on appetite, CCK agonists, leptin agonists, or ghrelin antagonists have been tested but have not provided conclusive results, supporting the theory that appetite regulation is not due to a single substance but is rather provided by a complex mechanism requiring multiple regulatory agents acting in concert or in balance.

(b) Food absorption inhibitors Pancreatic and gastric lipase, necessary for the hydrolysis of dietary lipids into fatty acids and monoacylglycerol, can be blocked by orlistat, which inhibits 30% of lipid digestion. Its effect on weight loss is dose-dependent. Since the drug causes lipid maldigestion, side effects are mostly gastrointestinal, including steatorrhea, flatulence, and urgency of defecation. It may decrease the absorption of fat-soluble vitamins, so multivitamin supplementation may be necessary.

(3) Surgical treatment Bariatric surgery is the only treatment considered effective to counteract obesity and maintain weight loss in cases of severe obesity. It significantly improves several medical conditions associated with obesity, including type 2 diabetes, hypertension, sleep apnea, and dyslipidemia. Postoperative blood glucose levels improve even before significant weight loss is achieved.

As surgical treatments are not without risk, it is important to carefully select the candidates. Patients with severe obesity (BMI >35 kg/m^2) complicated by comorbidities or those with morbid obesity (BMI >40 kg/m^2) are considered for this type of treatment. Most bariatric surgical procedures are performed laparoscopically, because of fewer complications and shorter hospitalization time. Various surgical procedures are available as illustrated in ◘ Figs. 24.2 and 24.3.

(a) ***Restrictive surgeries*** (to limit the dietary intake) rely on various techniques:
- *Longitudinal sleeve gastrectomy* (◘ Fig. 24.2b) consists of a vertical resection of the stomach that follows the greater curvature. In addition to the reduction of gastric volume, resection of the gastric fundus containing ghrelin-secreting cells may exert additional effect on hunger signaling.

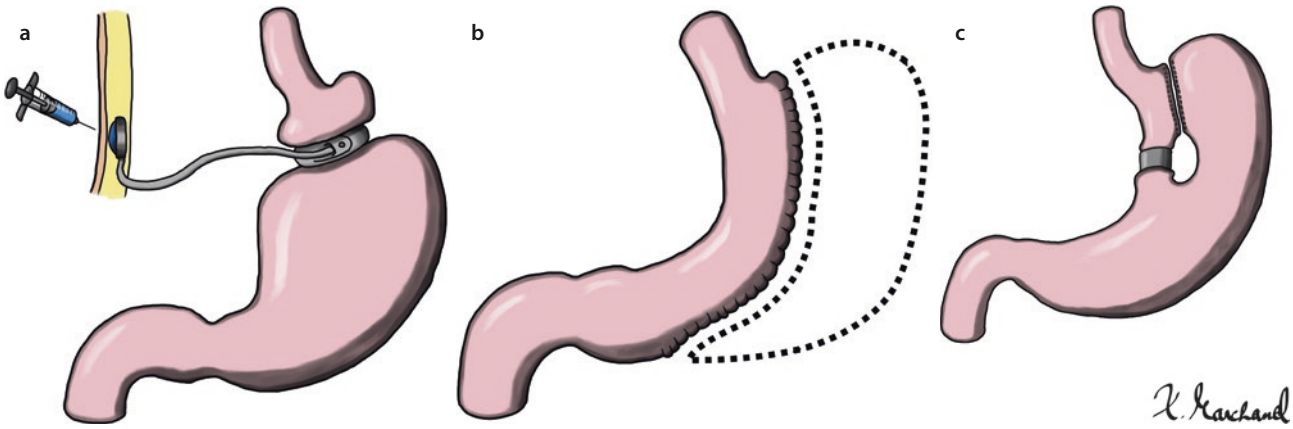

Fig. 24.2 Restrictive surgeries: **a** adjustable gastric band; **b** longitudinal sleeve gastrectomy (the most commonly used); **c** vertical banded gastroplasty (now an abandoned procedure)

The weight loss achieved with this method is between 40 and 50%. Since 2013, this procedure has been the most widely used worldwide.

- *Adjustable gastric banding* (Fig. 24.2a) involves placing a band at the proximal portion of the stomach below the gastroesophageal junction. A catheter connected to the band is then externalized and allows adjustment (with saline injections) of the band diameter and degree of opening (and secondary dysphagia). After the operation, the first adjustment is made at 6 weeks and then at intervals of 2–3 months until the desired level is reached. The expected weight loss is 40–60% of the excess weight. However, the use of this implant is decreasing, as the removal of the band sometimes becomes necessary in the long term.
- *Vertical banded gastroplasty* (Fig. 24.2c) creates a small gastric pouch with the use of a mechanical suture line, and a prosthetic band is needed to maintain the gastric pouch opening to a fixed size. Because of staple line failure over time, this procedure is no longer performed, but it stimulated the interest in gastric banding and surgical gastric volume reduction.

(b) ***Malabsorption surgeries*** (to decrease caloric digestion and absorption) involve the following procedures:

- *The Roux-en-Y gastric bypass* (Fig. 24.3a) is currently considered the safest and most effective bariatric surgery. (1) It involves a small gastric pouch of 15–20 mL created immediately below the gastroesophageal junction by stapling the stomach from the lesser curvature to the angle of His. (2) This gastric pouch empties directly to the jejunum via a jejunal loop (Roux-en-Y loop), mounted and anastomosed to the neo-stomach. (3) Gastroduodenal and the biliopancreatic secretions are thus short-circuited, and the free distal end of the biliopancreatic loop is anastomosed 75–150 cm past the loop of Roux. This surgery results in a 70–75% loss of excess weight in 5 years.
- *Biliopancreatic diversion with duodenal switch* (Fig. 24.3b) is the most severe malabsorptive bariatric surgical procedure. (1) A longitudinal gastrectomy is made, and (2) the duodenum is transected above the ampulla of Vater. (3) The small intestine is transected 250 cm from the ileocecal valve, and the distal loop of the small intestine is anastomosed to the proximal duodenum to drain the stomach; (4) the distal biliopancreatic loop is anastomosed in the distal ileum 50–100 cm from the ileocecal valve. Biliopancreatic diversion has important functional repercussions (due to short-circuiting of the proximal small intestine and poor mixing of biliopancreatic enzymes) including diarrhea and malabsorption with a risk of nutritional defi-

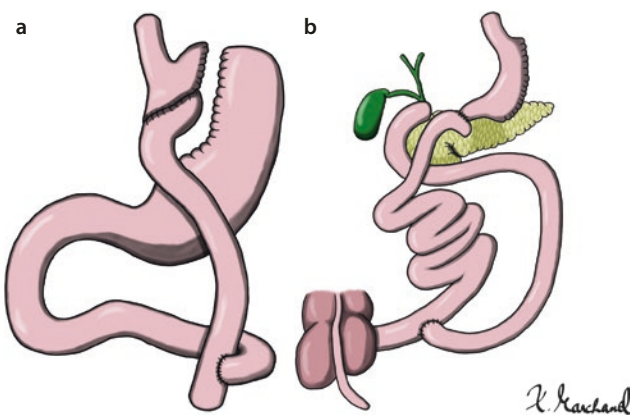

Fig. 24.3 Malabsorption surgeries: **a** gastric bypass with Roux-en-Y (gastric bypass); **b** biliopancreatic diversion with duodenal switch (and gastric restriction by longitudinal gastrectomy)

ciencies. It is reserved for patients with morbid obesity and requires life-long iron, calcium, and multiple vitamin supplementations and periodic monitoring. The average initial excess weight loss 1 year post-op is 50–90%, with the least risk of weight regain over the years.

(4) Endoscopic treatment Endoscopic methods are in development to reduce cost, avoid surgery, and improve accessibility.

- *Intragastric balloon*. During a gastroscopy, an intragastric balloon is placed in the stomach and inflated to reduce caloric ingesta by inducing early satiety during meals. This simple technique is used in various countries in the world.
- *Percutaneous gastrostomy* aspirating the gastric contents reducing the amount of food transferred to the intestine.
- *Endoluminal gastroplasty*: a sleeve-like restriction can be realized endoscopically with endoscopic suturing devices.
- *Endoluminal sleeve:* a gastric tube can be fixed to the esophagus to mimic a gastric sleeve, or a 60–100-cm-long flexible tube can be attached to the pylorus to cover the walls of the duodenum and jejunum and prevent the absorption of nutrients in the proximal small intestine and also prevent the nutrients from stimulating the secretion of secretin and cholecystokinin hormones.
- *Endoscopic fistulas*: endoscopic devices can be installed to create intestinal fistulas, short-circuiting the absorptive proximal gut.
- *Duodenal mucosal resurfacing*: thermal ablation of the duodenal mucosa may result in remodeling of the signaling pathway of duodenal neuroendocrine cells and of the appetite regulation process.

In pediatrics, a BMI greater than the 85th percentile defines overweight and a BMI greater than the 95th percentile defines obesity.

- In obese children under 7 years of age, the goal is to maintain weight while growing rather than lose weight. In obese children 8 years of age or older, therapeutic weight loss and a training program can be initiated.
- Pharmacological treatment is not recommended in pediatric age.
- Surgical treatments are now available for extremely obese children with serious comorbidities.

24.5 Summary

Obesity is the result of a chronic imbalance of energy regulation metabolism. The causes are genetic and environmental and involve multiple and various factors. The net effect is a multiplication of adipocytes that lead to the metabolic syndrome and other comorbidities. Many therapies against obesity were developed from our understanding of the physiological digestive process (see Table 24.4). Lifestyle changes and diets, pharmacological agents, and surgical and endoscopic procedures are not perfect but will continue to evolve.

Table 24.4 Obesity treatments according to the reported mechanism of action

Approach	Reduced caloric intake or increased energy expenditure	Reduced caloric absorption
Behavioral	Low-calorie diets (with individual or group support)	
	Physical exercise	
Pharmacological	Amphetamines (withdrawn from market)	Lipase inhibitor (orlistat)
	Sympathomimetics (phentermine, bupropion)	
	Serotoninergics (5-HT2C lorcaserin)	
	GLP-1 agonists (liraglutide)	
Endoscopic	Intragastric balloon	Intestinal sleeve
	Endoscopic suture (longitudinal sleeve, etc.)	
Surgical	Adjustable gastric band	
	Longitudinal sleeve gastrectomy	
	Gastric bypass (Roux-en-Y)	Gastric bypass (Roux-en-Y)
	Biliopancreatic diversion	Biliopancreatic diversion

Genes and Digestive Cancers

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Contents

P. Poitras (ed.), *The Digestive System: From Basic Sciences to Clinical Practice*,
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Hereditary digestive cancers represent a group of entities with a very high risk of cancer and are identifiable by genetic testing.

25.1 Clinical Approach to Families at Risk

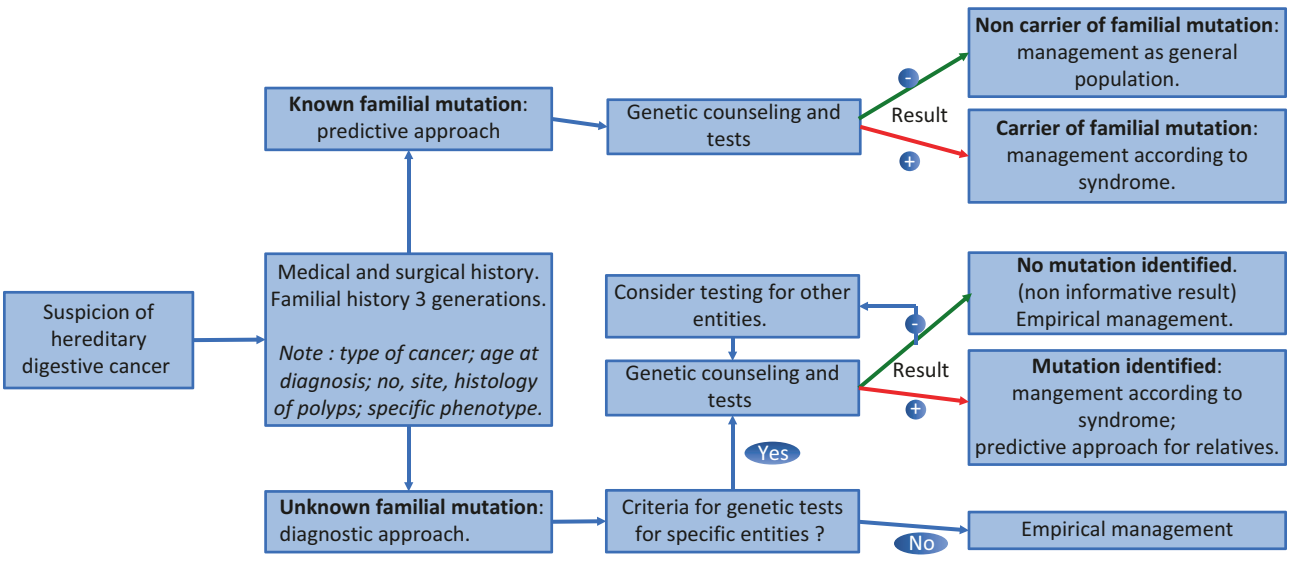
Genetic counseling, which is directed at both the family and the individual, encompasses the entire diagnostic process for genetic conditions that predispose to cancer. It includes the collection of family and personal information, the construction of a family tree covering at least three generations, the differential diagnosis of the condition at risk, the sharing of information with family members, the selection of individuals for genetic testing, the informed consent with its ethical and legal ramifications, the disclosure of test results and discussion of their implications, as well as the preventive management based on the genetic status. In the interdisciplinary team responsible for this process, the role of the geneticist and genetic counselor is to perform the actual counseling, while the role of the clinician is to initiate and complete the process. A general outline of the clinical approach is shown in ◘ Fig. 25.1.

In general, genetic predisposition syndromes for digestive cancers are autosomal dominant entities, affecting suppressor genes important in growth, differentiation, or genome integrity, and whose constitutive inactivation promotes tumor development.

25.2 Predisposition Syndromes to Colorectal Cancer

25.2.1 Lynch Syndrome

Among all the hereditary predispositions to colorectal cancer (CRC), Lynch syndrome is the most common. Formerly called HNPCC (hereditary non-polyposis colon cancer), it has been renamed after the person who originally described it (Dr. Henry Lynch died in 2019). It is a dominant predisposition with variable penetrance to colorectal and endometrial cancers as well as other cancers. The main genes involved are MLH1, MSH2, MSH6, and PMS2. The function of these genes is to repair DNA bases mismatch (MMR genes) occurring during DNA replication. Loss of this function results in errors, especially in areas of tandem sequence repeats called "microsatellites." These errors are uniformly present in cancers associated with the syndrome and result in a recognizable molecular tumor phenotype: microsatellite instability. The gain, or more often the loss, of the number of repeats, when it occurs in coding regions, leads to changes in the reading frame of the sequences involved. This leads to the inactivation of certain genes, including BAX and TGBFR2, which in turn promotes carcinogenesis. Since MMR gene products are nuclear proteins that disappear when mutated, the loss of protein expression revealed by immunohistochemistry correlates very closely with the microsatellite instability. Testing with an immunohistochemistry panel for these



◘ **Fig. 25.1** Clinical approach to hereditary digestive cancers

four proteins (MLH1, MSH2, MSH6, PMS2) has replaced in clinic the direct measurement of microsatellite instability since it is easier to obtain.

The tumors in Lynch syndrome are often undifferentiated and multiple, synchronous or metasynchronous. They are located mostly in the right colon and occur in young adults less than 50 years old. The flat adenoma is the typical precursor. Microsatellite instability occurs mostly in advanced adenomas, suggesting that the propensity for CRC in Lynch syndrome results from a late acceleration of carcinogenesis rather than a predisposition to develop adenomas. It is not uncommon for CRC to develop 1 or 2 years after a normal colonoscopy. CRC is associated with a better survival than in the sporadic setting. In addition, immunotherapy may be effective in CRC related to Lynch syndrome.

The cumulative risk of CRC varies according to the mutated gene, from 20% for PMS2 to over 50% for MLH1. The syndrome is associated with a risk of extracolonic cancers, mainly the endometrium (the cumulative risk varies from 20% to 60% depending on the gene involved). Other cancers, in decreasing order of risk relative to the general population, can affect the urinary tract, ovary, biliary tract, small intestine, and stomach. The association with glioblastoma is recognized as the Turcot syndrome and with sebaceous neoplasms as the Muir-Torre syndrome. The risks of breast and prostate cancer in individuals with Lynch syndrome are about twice those of the general population.

Diagnosis of Lynch syndrome

The Amsterdam II criteria (Table 25.1) identify families with a suspected diagnosis of Lynch syndrome, but they are neither sensitive nor specific. It is therefore preferable to evaluate resected tumors for the microsatellite instability phenotype (usually by immunohistochemistry) and then offer genetic testing in the presence of this phenotype. The Bethesda criteria were developed to select families for microsatellite testing; but they are now falling into disuse as most centers have replaced them with a universal approach of screening for microsatellite instability in colorectal cancers.

Management of Lynch syndrome

Surveillance colonoscopy, beginning at age 20–25 years, is performed annually or biennially, but typically annually after age 40. Endoscopic surveillance reduces the incidence and risk of death from CRC. In the event of CRC, total colectomy is recommended to reduce the risk of a second primary lesion.

For ovarian and endometrial cancers, annual surveillance is recommended, but the effectiveness of the available modalities is not documented. A hysterectomy with bilateral salpingo-oophorectomy is recommended when the family is complete.

Gastric cancer can be monitored by interval gastroscopies, with eradication of *Helicobacter pylori* when the bacteria is present.

Table 25.1 When to suspect lynch syndrome?

Amsterdam II criteria

Lynch syndrome is strongly suspected when a family meets the following criteria:

1. One cancer before age 50 (colorectal, endometrial, small bowel, or urethral)
2. Two successively affected generations
3. Three people with cancer who are first-degree relatives

Revised Bethesda criteria

A CRC must be tested for microsatellite instability if any of the following criteria are met:

1. Diagnosis before the age of 50 years
2. Two synchronous or metasynchronous Lynch syndrome-associated cancers[a] in the same person
3. Histology with ring cells, cribriform pattern, or dense lymphocyte infiltration before age 60
4. Family history of a first-degree relative with Lynch syndrome-associated cancer before age 50
5. Family history of two first- or second-degree relatives with Lynch syndrome-associated cancer

[a]Lynch syndrome-associated cancers: CRC, endometrial, stomach, small bowel, ovarian, pancreatic, urethral, renal, pelvic, bile duct, and brain, sebaceous skin tumors or keratoacanthoma

25.2.2 Hereditary Polyposis

Hereditary polyposes are divided into adenomatous polyposis and hamartomatous polyposis. Unlike Lynch syndrome, the individual phenotype is distinctive and often diagnostic. Genetic typing is useful to validate the diagnosis and guide the clinical management as well as to determine the carrier status of relatives. Some commercial laboratories offer detailed analysis of the genes associated with these entities.

25.2.2.1 *Familial Adenomatous Polyposis (FAP)*

FAP is an autosomal dominant syndrome of CRC predisposition due to a mutation in the APC (adenomatous polyposis coli) gene. Carrying a penetrance of almost 100%, a mutated gene is found in about 1/5000 persons in the general population. New mutations account for one-third of cases, and family history is not

always present. The APC gene product is a large protein with several domains that correspond to specific binding sites and distinct functions. It plays a role in cell proliferation, differentiation, and apoptosis. The APC protein participates in a protein complex that binds beta-catenin and inhibits the Wnt (for wingless/integrated) signaling pathway. Dysfunction of this gene is a general, and usually initial, mechanism in colonic carcinogenesis in general (not only in FAP).

Individuals with a classic FAP mutation gradually develop adenomas, usually starting at puberty, and the disease usually progresses to the point where, by adulthood, the colon is covered by hundreds to thousands of adenomas. A malignant transformation is inevitable (considering the numbers of polyps), and CRC is diagnosed at an average age of 45 years. The location is most often distal to the splenic angle. The rate of malignant transformation of individual adenomas is probably not increased, the syndrome being only a constitutive part of the first stage of colonic carcinogenesis.

Attenuated FAP can be seen in some patients with APC mutations (particularly those at the ends of the gene). The attenuated phenotype includes later-onset and fewer adenomas that tend to be located in the right colon, as well as a lower probability of developing cancer.

Digestive polyps in FAP can be found outside of the colon. Benign gastric glandular polyposis (polyps of the fundic glands) can progress to dysplasia, but rarely to gastric cancer. Duodenal adenomas are common, most often in adulthood and in the vicinity of the papilla; without resection, progression to adenocarcinoma occurs in one-third of cases, most often late in life. Adenomas of the small intestine occasionally arise, especially distally, particularly following colectomy.

Desmoid tumor is a benign but invasive proliferation of connective tissue which occurs most often in the abdominal cavity and can be caused by trauma such as surgery or childbirth. Its growth can lead to local complications, including obstruction of digestive or urinary structures. It is part of the clinical spectrum of Gardner's syndrome and is associated with mutations leading to a particularly florid polyposis.

Gardner's syndrome designates FAP who presents with extracolonic manifestations. The most common are osteomas, benign lesions often located on the skull and in the long bones, and desmoid tumors. Dental abnormalities (such as odontogenic cysts, supernumerary and impacted teeth) can occur, as well as benign skin lesions (including epidermoid cysts, lipomas, dermatofibromas, and pilomatrixomas). These manifestations have no diagnostic value, but their presence raises the possibility of FAP. Some mutations are associated with congenital hypertrophy of the retinal pigment epithelium (which can be detected on indirect ophthalmoscopy; the bilateral presence of half a dozen of these lesions strongly suggests the presence of FAP).

Extradigestive neoplasms, such as papillary thyroid and adrenal cancers, can occur in less than 5% of mutation carriers. The occurrence of a central nervous system tumor, most often a medulloblastoma during childhood or adolescence, is part of *Turcot syndrome.*

The diagnosis of FAP is most often clinical, with a cumulative number of more than 20 colonic adenomas constituting a working diagnosis and a number of 100 polyps constituting an almost certain diagnosis.

In some rare individuals, colonic polyposis can develop in the absence of APC mutations. Other genetically defined clinical entities can be involved:

- *Recessive polyposis*, which is the main one, is due to a biallelic mutation of the MUTYH gene (involved in the repair of oxidative DNA damage). It occurs in about 1/10,000 people. Similar to FAP, it can be associated with florid polyposis and sometimes has similar extracolonic manifestations, but the polyposis occurs later, is often associated with hyperplastic or serrated polyps, and has a lower risk of CRC
- *Polymerase proofreading polyposis,* with a phenotype similar to attenuated FAP, is caused by mutations in the POLE and POLD1 genes
- *Hereditary mixed polyposis* has serrated and hamartomatous lesions in addition to adenomas
- *Serrated polyposis,* previously known as hyperplastic polyposis, carries a high risk of CRC

The management of FAP includes surveillance colonoscopy and prophylactic colectomy. Genetic diagnosis of FAP allows targeting of individuals for colonic surveillance by an annual flexible sigmoidoscopy, most often starting at puberty. When adenomas appear, a full colonoscopy is performed annually. Colectomy is done when polyposis becomes florid, cancer is suspected, large lesions or high-grade dysplasia occur, or conditions for adequate surveillance are compromised. The procedure of choice is usually a total proctocolectomy with ileoanal anastomosis and ileal pouch. Without prophylactic colectomy, CRC occurs, inevitably, before age 45.

Management of duodenal polyposis is done in adulthood, usually after colectomy. Surveillance for thyroid cancer includes annual physical examination and ultrasound.

25.2.2.2 *Hamartomatous Polyposis*

- ***Peutz-Jeghers syndrome*** is an autosomal dominant entity due to a mutation in the STK11 gene. It is characterized by the combination of abnormal skin pigmentation (especially peri- and endo-oral lentiginous lesions) and hamartomatous gastrointestinal polyps with specific histology. The arborization of the muscularis mucosa within the polyps, associated with cystic dilatation of the mucous glands, confers a Christmas tree-like appearance. These non-dysplastic polyps that appear during childhood can cause bleeding, obstruction, or intussusception. The occurrence of cancer, sometimes due to neoplastic degeneration of the digestive polyps, is frequent from the age of 40. The organs affected are, in descending order, the colon, stomach, pancreas, and small intestine. The syndrome is also associated with an elevated risk of breast, ovarian, and testicular cancers, as well as with some increased risk of lung cancer. Surveillance to prevent benign complications and early detection of neoplastic lesions is done with specific imaging and endoscopies at regular intervals.
- ***Juvenile polyposis*** is an autosomal dominant hamartomatous polyposis syndrome in which a mutation in the SMAD4 or BMPR1A genes can be found in half of the cases. While sporadic juvenile polyps of the colon are common in childhood, the occurrence of a cumulative number of five such lesions in the colon, most often in childhood, establishes the diagnosis of juvenile polyposis. The hamartomatous nature of juvenile polyps is frequently obscured by a significant inflammatory component. These polyps may be complicated by hemorrhage (during self-amputation), obstruction or intussusception. In adulthood, affected individuals are at high risk for CRC, as well as stomach and, less often, small bowel cancers, especially for carriers of SMAD4 mutations who frequently present with manifestations of hereditary hemorrhagic telangiectasia. Endoscopy and/or imaging of the lower and upper GI tract is recommended.
- ***Hamartomatosis syndromes*** and PTEN-related tumors are divided into two distinct autosomal dominant entities: one pediatric and one adult, but they share common features. The pediatric Bannayan-Riley Ruvalcaba syndrome combines a variety of extradigestive manifestations, including macrocephaly, with extensive glycogenic acanthosis of the esophagus and digestive hamartomatous polyps. The latter manifestations are also found in the adult Cowden syndrome, which combines skin anomalies and a high risk of cancers, especially of the breast, endometrium, thyroid, kidney, and colon.

25.3 Predisposition to Other Digestive Cancers

25.3.1 Pancreatic Cancer

Familial pancreatic cancer, defined by the occurrence of this cancer in two first-degree relatives, represents 5–10% of cases of pancreatic cancer. The risk for relatives is nearly ten times that of the general population and increases with the number of affected relatives. In a minority of these cases, a genetic cause is identified: most often a mutation of the BRCA2 or BRCA1 gene. Sometimes mutations in the ATM or PALB2 genes, also linked to breast cancer, are found. Some families with hereditary melanoma have a high risk of pancreatic cancer due to mutations in the CDKN2A gene, whose somatic mutations are common in sporadic cancer. Other families carry mutations associated with Lynch or Peutz-Jeghers syndromes or FAP.

In addition, chronic pancreatitis is associated with an increased risk of pancreatic cancer. This disease, most often caused by alcohol, is sometimes due to a heterozygous mutation of the PRSS1 gene whose product is the cationic trypsinogen. Mutation carriers develop acute pancreatitis in childhood; in adulthood, the disease progresses to chronic calcifying pancreatitis with exocrine and endocrine insufficiency. The risk of pancreatic adenocarcinoma is about 50%. A similar clinical picture is sometimes the result of a mutation of the SPINK1 gene coding for a trypsin inhibitor, or a heterozygous mutation of the CFTR gene. As with chronic alcoholic pancreatitis, the progression of hereditary pancreatitis can be slowed by abstinence from alcohol and tobacco.

Management of the high risk of pancreatic cancer consists in annual surveillance with echo-endoscopy (EUS) or magnetic resonance imaging; however, the benefit of this approach is uncertain.

25.3.2 Hereditary Diffuse Gastric Cancer

Familial occurrence of gastric cancer is usually the result of *Helicobacter pylori* infection. In the general population, the risk of cancer is reduced when the bacterium is eradicated before the stage of intestinal metaplasia.

A few families with early diffuse gastric cancer and lobular breast cancer carry a mutation in the CDH1 gene, coding for adhesion protein E-cadherin. Because of the nearly 70% risk of gastric cancer and the ineffectiveness of endoscopic surveillance, this condition is the only one in gastroenterology where it is recommended to resect the organ at risk before detecting a lesion. Preventive total gastrectomy is associated with a mortality rate of less than 1%.

Jaundice

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Contents

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26.1 General Considerations

Jaundice (from *jaune*, the French name for yellow; also called icterus, from icteros (ιχτεροσ), the Greek name to designate a yellowish coloration of the skin) refers to a yellow color of the skin caused by a bilirubin accumulation due to excess bilirubin levels in the blood (hyperbilirubinemia).

The skin color looks yellowish and, in severe and prolonged hyperbilirubinemia, may take on a brownish or greenish hue. Icteric eye sclera may be seen at low bilirubin levels insufficient to cause jaundice on the skin.

Unconjugated bilirubin circulates bound to albumin and is therefore unfilterable by the kidneys. Bilirubin is conjugated in the liver and is excreted in the urine; conjugated bilirubin causes a dark coloration of the urine (coca-cola-like urine in the case of jaundice with hyperbilirubinuria). The absence of bilirubin excretion from the liver into the intestines causes the stools to lose their brownish color and become pale or clay-colored (acholic stools).

Bilirubin, a degradation product of hemoglobin, relies on a three-step metabolic process (see ◘ Fig. 26.1): (1) at the pre-hepatic level, hemoglobin is degraded to heme, biliverdin, and ultimately unconjugated bilirubin; (2) in the liver, unconjugated bilirubin is transformed into conjugated bilirubin; (3) at the post-hepatic level, conjugated bilirubin, mixed in bile, flows through the bile ducts into the duodenum for intestinal expulsion in the stools.

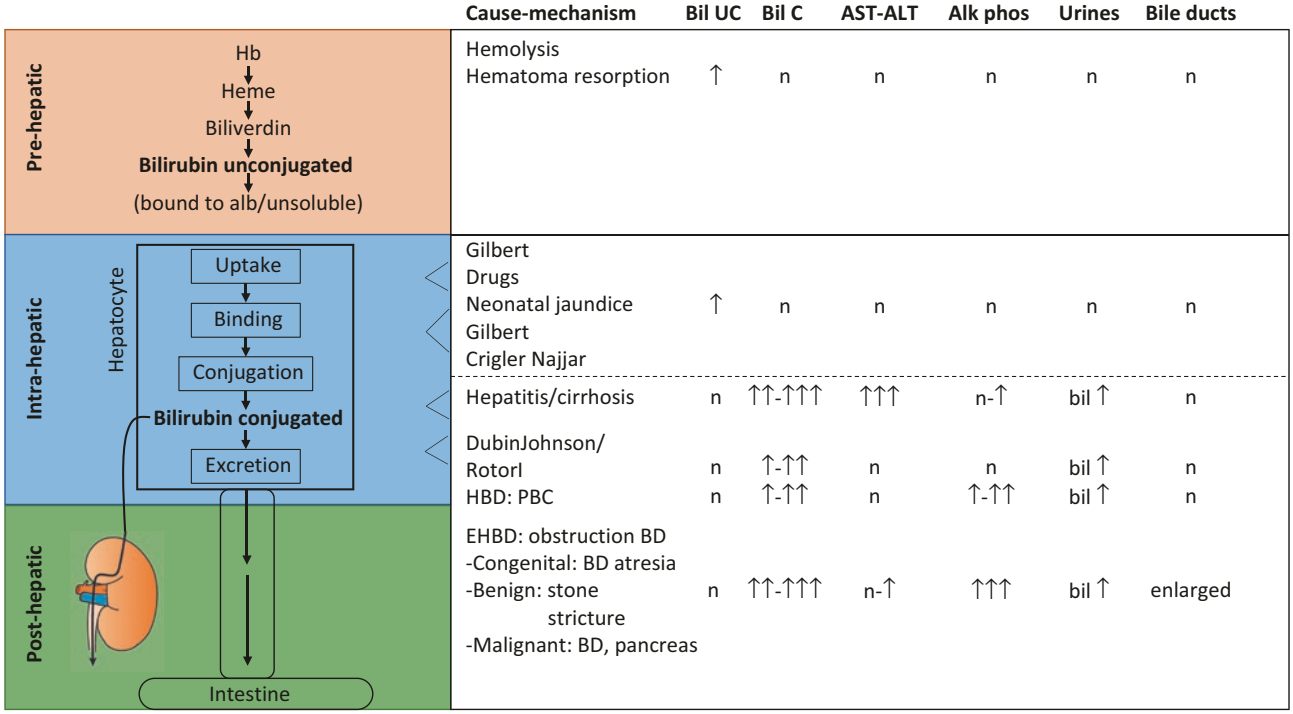
26.2 Differential Diagnosis

Many conditions can cause jaundice. In clinical practice, the following questions will help to guide the diagnosis and treatment of an icteric patient: (1) is the jaundice caused by disorders affecting preconjugation processes (leading to unconjugated hyperbilirubinemia) or (2) is the jaundice caused by a post-conjugation process (leading to conjugated hyperbilirubinemia) and then involving intra or extra-hepatic bile duct mechanisms?

26.2.1 First Question Asked: Is This a Pre-conjugation Disorder?

Unconjugated hyperbilirubinemia is then present. Jaundice is usually modest, and urine is of normal coloration (since unconjugated bilirubin is bound to albumin and not filtered by the kidneys).

Bilirubin is derived from the catabolism of hemoglobin. Intravascular hemolysis (e.g., hemoglobinopathy) or extravascular hemolysis (e.g., hematoma resorption) may result in an increased production of unconjugated bilirubin.



Cause-mechanism	Bil UC	Bil C	AST-ALT	Alk phos	Urines	Bile ducts
Hemolysis Hematoma resorption	↑	n	n	n	n	n
Gilbert Drugs Neonatal jaundice Gilbert Crigler Najjar	↑	n	n	n	n	n
Hepatitis/cirrhosis	n	↑↑-↑↑↑	↑↑↑	n-↑	bil ↑	n
DubinJohnson/ Rotorl	n	↑-↑↑	n	n	bil ↑	n
HBD: PBC	n	↑-↑↑	n	↑-↑↑	bil ↑	n
EHBD: obstruction BD -Congenital: BD atresia -Benign: stone stricture -Malignant: BD, pancreas	n	↑↑-↑↑↑	n-↑	↑↑↑	bil ↑	enlarged

◘ **Fig. 26.1** Bilirubin metabolism and pathophysiology of jaundice. Bil UC = unconjugated bilirubin; Bil C = conjugated bilirubin; BD = bile duct; IHBD = intrahepatic bile duct; EHBD = extrahepatic bile duct; n = normal; PBC = primary biliary cholangitis

Unconjugated bilirubin, at the hepatocyte, is taken up at the sinusoidal membrane and enters the cell; Gilbert's syndrome as well as certain drugs may interfere with this step of bilirubin transformation.

In the cytosol of the hepatocyte, unconjugated bilirubin binds to glutathione S-transferase before undergoing the glucuronyl transferase conjugation process. Glucuronyl transferase activity may be absent or minimal in the very rare Crigler-Najjar syndrome, may be reduced in the very common Gilbert's syndrome, may be impaired by certain drugs, or may be compromised in the neonatal jaundice of the immature newborn.

High levels of unconjugated bilirubin in the neonate can lead to deposition of insoluble bilirubin in the basal ganglia (kernicterus) and induce neurological toxicity. UV light therapy allows unconjugated bilirubin to become soluble (and excreted) and thus prevents its neurotoxic accumulation.

26.2.2 Second Question: Is the Post-conjugation Disorder Located at the Hepatic or Post-hepatic Level?

When conjugated bilirubin blood levels are elevated, jaundice can be very severe, urines are dark (due to bilirubinuria), and stools may be acholic (due to an absent bilirubin excretion in the intestine).

Elevated serum transaminases (ALT, AST) are indicative of liver damage. Cholestasis, assessed by elevated alkaline phosphatase or gamma-glutamyl-transferase serum levels (GGT is normal when alkaline phosphatases are elevated by bone conditions such as bone metastases, or bone growth in children), indicate hepatic or post-hepatic disorders.

Unconjugated bilirubin, after its uptake at the hepatocyte sinusoidal membrane and its binding to glutathione transferase, is converted in the endoplasmic reticulum by glucuronyl transferase to conjugated bilirubin, which is transported to the ductal membrane. Disturbance in the transport and excretion of conjugated bilirubin to the bile pole of the hepatocyte is the main mechanism of jaundice in viral hepatitis, alcoholic hepatitis, some drug-induced hepatitis, or cirrhosis.

Conjugated bilirubin, transported to the canalicular membrane, is excreted from the hepatocyte by the MRP2 carrier. The rare congenital Dubin-Johnson syndrome is due to a defect in MRP2 expression.

Outside the hepatocyte, bilirubin circulates in canaliculi. Primary biliary cholangitis is known to damage and obstruct these intrahepatic ductules.

Conjugated bilirubin then passes from the intrahepatic to the extrahepatic bile ducts and reaches the duodenum. Any obstruction of the extrahepatic bile ducts by a benign (stone, inflammatory stricture, etc.) or malignant (pancreas cancer, bile duct cancer, etc.) condition interrupting the excretory flow of bile will lead to the discharge of bilirubin into the bloodstream and provoke jaundice.

Apart from the esthetic disadvantage of skin coloration, jaundice is often accompanied by a severe, incapacitating itchiness (pruritus) which may be refractory to many medical treatments (antihistamines, etc.). Pruritus is usually relieved after cholestasis is reduced.

Retention in the liver of bile products not excreted by the biliary tract is toxic and, within a few weeks, may induce secondary biliary cirrhosis.

26.3 Treatment

Treatment of jaundice requires the treatment of the underlying condition. The diagnostic and therapeutic approach is summarized in ◘ Fig. 26.2. Complications of jaundice, either the deposition of unconjugated bilirubin in the basal ganglia in the neonate or the development of secondary biliary cirrhosis when bile excretion is impaired, are severe and warrant prompt intervention to correct the situation.

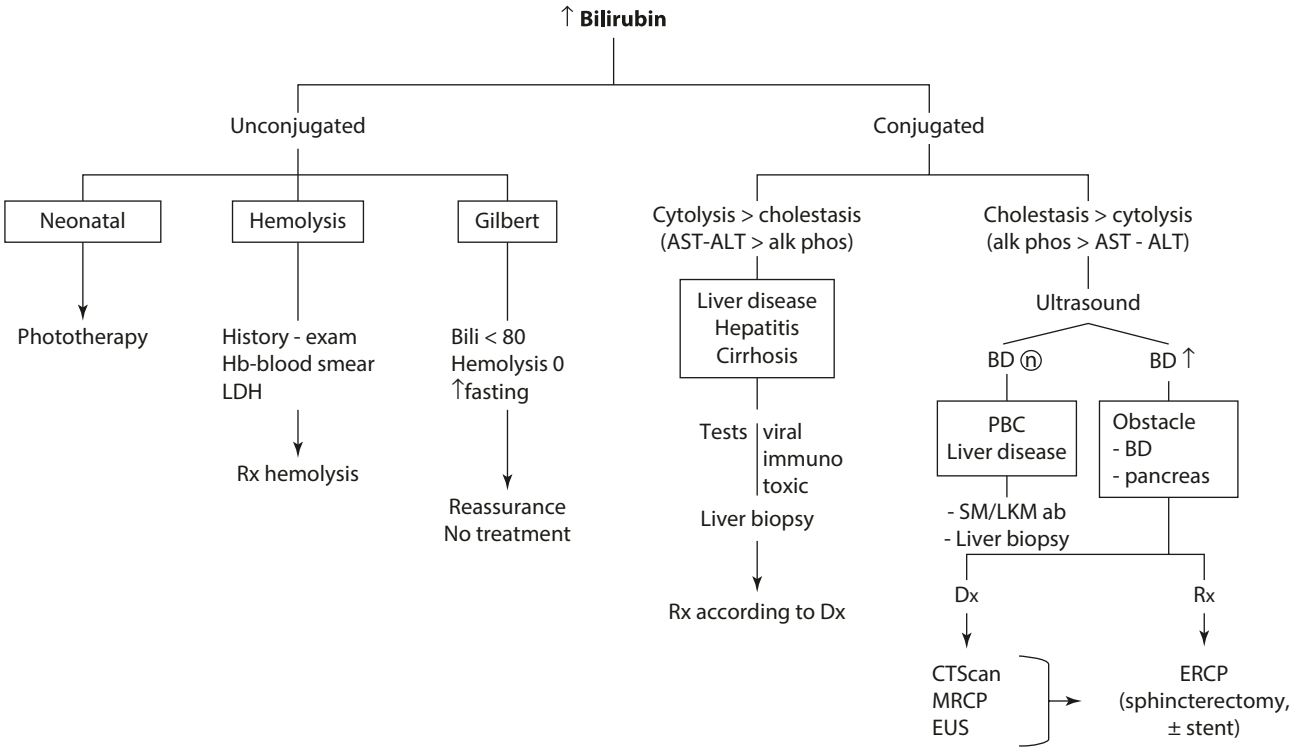


Fig. 26.2 Jaundice: diagnostic and therapeutic strategy. Alkphos = alkaline phosphatase; Bil = bilirubin; BD = bile duct; Dx = diagnosis; ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasound; LKM ab = liver-kidney microsomal antibody; MRCP = magnetic resonance cholangiopancreatography; PBC: primary biliary cholangitis; Rx = treatment; SM ab = smooth muscle antibody

Abnormal Liver Tests

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Contents

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Abnormal liver tests can be obtained (e.g., during a routine blood analysis for a non-liver condition) in subjects that look apparently healthy or free of liver disease and constitute a frequent reason for consultation.

27.1 Bilirubin Elevation

In case of increased serum bilirubin, levels of unconjugated or conjugated bilirubin must be determined. Elevated conjugated bilirubin is often associated with jaundice and significant liver disease.

Unconjugated bilirubin elevation is a common finding, most often due to Gilbert syndrome, a benign genetic condition (affecting 5–8% of the population, more prevalent in men (6M: 1F)) due to a deficient enzymatic transformation of unconjugated to conjugated bilirubin. Liver tests are then otherwise normal, and normal blood count eliminates red blood cell hemolysis.

27.2 Transaminase Elevation

Elevated serum transaminases (alanine aminotransferase ALT, aspartate aminotransferase AST) in an asymptomatic patient constitute a common problem. In most cases, the elevation is mild (<2 times the upper limit of normal) or moderate (2–10×). A more marked elevation (>10×) is more likely to indicate a diagnosis of acute hepatitis, and the patient is often symptomatic.

Transaminases are present in many body tissues (Fig. 27.1). Because of their very high concentration in the liver (5–10,000× blood concentration), transaminases are a sensitive indicator of hepatocellular damage.

The first step in evaluating elevated transaminases is to repeat the test; if abnormalities persist, the etiology should be investigated.

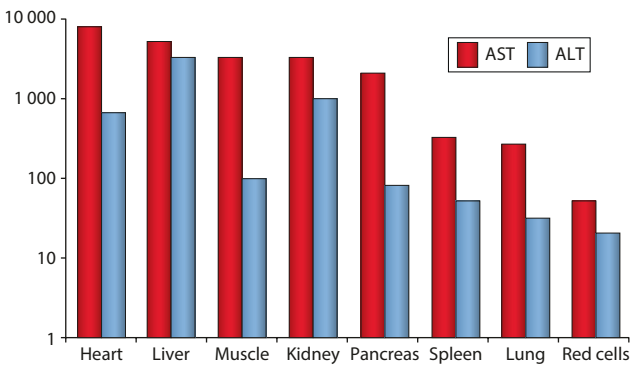

Fig. 27.1 Concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in various tissues relative to the serum concentration assigned a value of 1. The concentration gradient on the ordinate axis is on a logarithmic scale

Cell damage and cholestasis (leading to increased ALT, AST, and alkaline phosphatase (alkphos), respectively) are often co-existing in liver diseases. Elevation in transaminase is isolated or predominant (↑ALT, AST >>> alkphos) in cytolytic disorders and can be modest (↑ALT, ALT <<< alkphos) in cholestatic disorders. Many conditions must therefore be considered (see Table 27.1) and identified by an appropriate investigation (Table 27.2):

Chronic hepatitis C Chronic hepatitis C is one of the most common causes of transaminase elevation. The main risk factors are intravenous drug use and transfusions, but in individuals from certain countries (e.g., Italy, Egypt, Vietnam), the mode of acquisition is often unidentifiable. The initial test for hepatitis C is the HCV antibody test. If positive, it may indicate an active or an old infection (resolved hepatitis C). The diagnosis of active infection will be confirmed by measuring hepatitis C virus RNA.

Chronic hepatitis B The major risk factors for hepatitis B are unprotected sex, intravenous drug use, and mother-to-child transmission in countries where hepatitis B is endemic. Hepatitis B testing includes serum HBsAg, anti-HBs, and anti-HBc antibodies. The presence of anti-HBs

Table 27.1 Causes of abnormal blood liver tests in asymptomatic subjects

Cytolytic disorders: transaminase elevation

Common causes

- Chronic hepatitis C
- Chronic hepatitis B
- Alcoholic liver disease
- Non-alcoholic steatohepatitis
- Drugs, natural products, toxic products

Less frequent causes

- Autoimmune hepatitis
- Hemochromatosis
- a1-antitrypsin deficiency
- Wilson's disease
- Celiac disease
- Muscle diseases

Obstructive disorders: alkaline phosphatase elevation

- Partial obstruction of the bile ducts
- Hepatic tumor (primary or secondary)
- Medications
- Primary biliary cholangitis
- Autoimmune cholangitis
- Primary sclerosing cholangitis
- Sarcoidosis
- Granulomatous hepatitis
- Adult ductopenia

Table 27.2 Biological investigation of chronically elevated transaminases

Test	Investigation
Anti-HCV	The presence of anti-HCV suggests chronic hepatitis C. Confirm with hepatitis C RNA assay
HBsAg, anti-HBs and anti-HBc	Presence of HBsAg and anti-HBc indicates chronic hepatitis B. Confirm active hepatitis B by measuring HBeAg and hepatitis B virus DNA
Blood glucose, cholesterol, and triglycerides	Diabetes and hyperlipidemia are often associated with nonalcoholic steatohepatitis
Protein electrophoresis	A polyclonal increase in gamma globulin suggests autoimmune hepatitis. Confirm with antinuclear, anti-smooth muscle, and anti-LKM antibodies
	A significant decrease in a1-globulins suggests a1-antitrypsin deficiency. Confirm with a1-antitrypsin assay, followed by genetic analysis
Transferrin saturation, ferritin	Iron overload suggests hemochromatosis. Confirm with a search for mutations in the HFE gene
Ceruloplasmin	A low level suggests Wilson's disease, especially in a patient under 40 years of age
Anti-transglutaminase antibody	Suggest celiac disease
CK	Elevated levels suggest transaminases of muscle origin
Anti-mitochondrial antibodies	In the presence of cholestasis, this test is pathognomonic of primary biliary cirrhosis
Abdominal ultrasound	Useful in the presence of transaminitis with cholestasis

Abbreviations: *Anti-HCV* antibody to hepatitis C virus, *HBsAg* hepatitis B surface antigen, *Anti-HBs* antibody to hepatitis B virus surface antigen, *Anti-HBc* antibody to hepatitis B virus capsid antigen, *HBeAg* hepatitis B virus e antigen, *Anti-LKM* antibodies to liver and kidney microsomes, *CK* creatine kinase

and anti-HBc, without HBsAg, indicates resolved hepatitis B. The presence of HBsAg and anti-HBc confirms infection with the B virus. The presence of HBeAg and/or HBV-DNA indicates active hepatitis B virus replication.

Hepatitis A Hepatitis A never progresses to chronicity, so serology for hepatitis A is not useful in the workup of persistent elevated transaminases.

Alcoholic liver disease The diagnosis of alcoholic liver disease may be difficult to make if the patient does not admit alcohol abuse. The presence of hepatomegaly and an AST/ALT ratio > 2/1 should raise suspicion of this diagnosis.

Non-alcoholic steatohepatitis (NASH) NASH is a common cause of chronic transaminase elevation. The main risk factors are obesity, diabetes, and hypertriglyceridemia. The diagnosis is usually established by exclusion of other causes of transaminase elevation and by demonstration of a hyperechoic liver on ultrasound. In case of doubt, a liver biopsy will confirm the diagnosis.

In pediatrics, non-alcoholic steatohepatitis is currently the most common cause of consultation for increased transaminases in children.

Medications, natural products, and toxic products Many medications can cause liver injury, so it is important to obtain a comprehensive drug history. Non-steroidal anti-inflammatory drugs, antibiotics, anti-tuberculosis drugs, anticonvulsants, statins, and methotrexate are among the most common agents involved. To establish a causal relationship between a drug and transaminase elevation, three elements are considered: (a) a temporal relationship (introduction of the drug a few weeks or months before the transaminase elevation, and resolution of the abnormalities upon discontinuation of the medication); (b) the prior knowledge (in the literature, etc.) of cases of drug-induced hepatitis with the suspected drug; and (c) re-exposure to the drug (most of them accidental) with recurrence of transaminase elevation.

Natural products and drugs of abuse can also cause persistent transaminase elevation (Tables 27.3 and 27.4), so their use should be specifically sought on the questionnaire.

The LiverTox website (► https://livertox.nih.gov) is an excellent source of information for liver toxicity of drugs and natural products.

Autoimmune hepatitis This hepatitis occurs mostly in young and middle-aged women and is often accompanied by other autoimmune conditions, especially Hashimoto's thyroiditis. Autoimmune liver disease is characterized by polyclonal hypergammaglobulinemia and the presence of anti-smooth muscle, antinuclear, or, more rarely, anti-LKM (liver kidney microsomal antibodies) auto-antibodies. A liver biopsy is essential to confirm the diagnosis.

Genetic Hemochromatosis This disorder is suspected by elevated serum ferritin and transferrin saturation. However, both tests can be abnormal in any liver condition (especially alcoholic liver disease, non-alcoholic steato-

Table 27.3 Some natural products that can increase transaminases

Latin	English
Alchemilla	Lady's mantle
Atractylis gummifera L	White chameleon
Callilepis laureola	Ox-eye-daisy (Impila)
Cassia angustifolia	Senna
Chelidonium majus	Greater Celandine
Crotalaria	Rattlebox, rattleweed
Ferula asafoetida	Asafetida
Gentiana lutea	Gentian
Hedeoma pulegioides	American pennyroyal
Heliotropium	White heliotrope
Humulus lupulus	Hops
Larrea tridentata	Chapparal, creosote bush
Sassafras albidum	Sassafras
Scutellaria sp.	Skullcap
Senecio sp.	Groundsel, Jacob's weed, St. James' weed
Senecio vulgaris	Old man's beard, groundsel
Symphytum officinale	Comfrey, cow's tongue, donkey's ears
Teucrium chamaedrys	Germander
Valeriana officinalis	Valerian, St. George's herb
Viscus album	Mistletoe
	Chinese herbs
	Dai-Saiko-To
	Jin-Bu-Huan
	Ma-Huang (ephedra)
	Syo-Sailo-To
	Vitamin A
	Shark's cartilage

hepatitis, and chronic hepatitis C) with cytolysis and secondary release of iron into the circulation. The diagnosis of genetic hemochromatosis, previously based on liver biopsy, can now be established by searching for mutations in the HFE gene.

Wilson's disease It is a rare genetic disorder caused by an abnormality in copper excretion. A lowered ceruloplasmin level and/or the presence of Kayser-Fleischer rings on ophthalmic examination is characteristic of the disease.

Table 27.4 Some drugs and substances whose abuse can increase transaminases

Cocaine
Ecstasy (MDMA, 5-methoxy-3, 4-methylenedioxymethamphetamine)
Phencyclidine (PCP)
Anabolic steroids
Glues and solvents (toluene, trichloroethylene, chloroform)

a1-Antitrypsin deficiency This enzymatic deficiency can induce liver damage without lung involvement.

Celiac disease Gluten sprue may result in chronic and unexplained elevation of serum transaminases. The presence of anti-transglutaminase antibodies suggests this diagnosis, which will be confirmed by duodenal biopsy. Transaminases normalize following treatment by a gluten-free diet.

Muscle diseases Muscle diseases (e.g., congenital myopathy, polymyositis) or strenuous exercise may cause elevation of aminotransferases (especially AST), because of their high muscle concentration (Fig. 27.1). A significant elevation of creatine kinase (CK) will point to such a diagnosis.

Other Cushing's disease, Addison's disease, thyroid disease, or the presence of macro-enzymes are very rare causes of transaminase elevation.

If no cause of transaminase elevation can be identified despite an extensive etiological workup, a liver biopsy is recommended in patients with transaminase elevation >2× normal value. In the others, a simple follow-up appears reasonable.

Transaminase elevation is a marker of hepatocellular damage and is found in cytolytic disorders as discussed above. It can also be present (usually to a lesser degree) in cholestatic disorders (see Table 27.1), typically characterized by a predominant alkaline phosphatase elevation (as discussed below).

27.3 Alkaline Phosphatase Elevation

Alkaline phosphatase elevation may be of hepatic or bone origin (or placental in pregnant women); an elevated γ-GT serum level confirms the hepatic origin (and cholestasis).

Elevation in serum alkaline phosphatase indicates cholestasis, a condition present at variable degrees in various liver diseases. The elevation can be modest in

cytolytic disorders (↑alkphos <<< ALT, AST), as described above; or it can be marked and predominant (↑alkphos >>> ALT, AST) in various obstructive disorders (see Table 27.1) affecting the extra- (biliary) or intra-hepatic bile flow, as discussed below.

Extra-hepatic lesions are usually readily identified by imaging exams. Bile duct obstruction or the presence of a primary or metastatic liver tumor is sought by abdominal ultrasound.

The presence of anti-mitochondrial antibodies (AMA) is almost pathognomonic of primary biliary cholangitis (PBC). Autoimmune cholangitis is a variant of PBC characterized by the presence of antinuclear antibodies rather than AMA.

In presence of a significant (>2× normal) and unexplained increase in serum alkaline phosphatase, visualization of the bile ducts (by magnetic resonance imaging or endoscopic retrograde cholangiography) should be performed to establish the diagnosis of sclerosing cholangitis. If negative, a liver biopsy will be done to identify sarcoidosis, granulomatous hepatitis, or adult ductopenia (chronic cholestatic disease of unknown cause characterized by a progressive loss of interlobular bile ducts).

In the presence of a more discreet elevation of serum alkaline phosphatase in an asymptomatic patient with a normal abdominal ultrasound, a simple follow-up appears reasonable.

Ascites

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Contents

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Ascites is defined as the pathological accumulation of fluid (up to many liters) in the peritoneal cavity. It is often responsible for abdominal pain and/or dyspnea due to diaphragmatic compression.

The diagnosis of ascites is clinical with an increase in the abdominal volume: percussion evokes a shifting dullness in the flanks when the patient is turned on the side (and the intra-abdominal fluid moving to the dependant area); upon palpation, the liver can be felt as floating in the ascites (ice cube sign); and percussion of one side of the abdomen generates a fluid wave that can be felt on palpation of the opposite side (fluid thrill or wave). Umbilical hernias and/or inguinal hernias (with, sometimes, presence of ascites fluid in the scrotum) are common. When the amount of ascites is small, the diagnosis may only be possible with abdominal ultrasound, which can detect a small amount of fluid (about 200 ml).

Different clinical signs may be associated depending on the cause of the ascites: for example, signs of portal hypertension (collateral circulation), liver disease (jaundice, etc.), heart failure (distended jugular veins, heart murmur, pulsatile liver), infection (fever, etc.), cancer (cachexia, etc.).

28.1 Causes

The causes of ascites are multiple and are summarized in ◘ Table 28.1. Cirrhosis (80%) and cancer (10%) are the most common in Western countries; heart failure (3%), tuberculosis (2%), and pancreatic ascites (1%) are less common.

Table 28.1 Ascites: etiological diagnoses

Portal hypertension
Cirrhosis
Budd-Chiari
Others
Heart disease
Right heart failure
Constrictive pericarditis
Hypoalbuminemia
Severe malnutrition
Nephrotic syndrome
Exudative enteropathy
Inflammatory
Vasculitis
Rheumatoid arthritis
Amyloidosis
Sarcoidosis
Pancreatitis
Neoplastic
Digestive cancer with peritoneal carcinomatosis
Ovarian cancer
Mesothelioma
Meigs' syndrome
Infectious
Spontaneous bacterial peritonitis
Secondary peritonitis (digestive perforation)
Tuberculosis
Miscellaneous
Hypothyroidism
Postoperative or traumatic
Chylous ascites

28.2 Diagnosis

The etiological diagnosis of ascites is usually made by the clinical history and the analysis of the ascites fluid (obtained by direct transabdominal puncture according to clinical landmarks or under ultrasound guidance if the amount of ascites is minimal or if there is concern for iatrogenic organ perforation) as shown in ◘ Table 28.2.

The protein concentration in the ascites fluid classifies ascites as a transudate (protein < 25 g/l) or an exudate (protein > 25 g/l). The most frequent causes of transudation ascites are portal hypertension or heart failure (the fluid being shifted into the abdomen by transudation through the walls of the hepatic sinusoids due to an elevated capillary pressure, while proteins stay inside the vessels). Ascites found in infectious, inflammatory, or neoplastic pathologies is exudative with a high protein concentration due to an active inflammatory secretion by the local pathological process. However, the ascites classification as transudate/exudate according to the ascites protein concentration (< or >25 g/l) is imperfect since it is affected, among other things, by the hypoalbuminemia present in many patients, and today the albumin gradient (serum con-

Table 28.2 Ascites fluid analyses (to be performed according to the clinical context)

Cell count
Leukocytes (N < 500 × 10^9/l)
Neutrophils (N < 250 × 10^9/l)
Red blood cells (neoplasm; trauma)
Biochemistry
Proteins, albumin (transudate vs exudate)
Amylase (pancreatic ascites)
Triglycerides, cholesterol (chylous ascites)
Microbiology
Culture
Search for tuberculosis
Cytology (after centrifugation)

centration–ascites concentration) is preferred as a diagnostic criterion. A gradient >11 g/l is highly suggestive of portal hypertension (albumin concentration being low in ascites). Elevated leukocyte count and positive bacterial culture suggest an infectious etiology, whereas the presence of neoplastic cells or hemorrhagic fluid is secondary to a cancer. Amylase in ascites indicates a pancreatic etiology.

28.3 Treatment

The treatment is of course based on the cause of ascites. Treatment with diuretics is useful in cirrhosis (see ▶ Chap. 8) or heart failure but is rarely effective for neoplastic ascites. Evacuation of ascites by drainage with abdominal tap is often helpful in relieving abdominal pain and dyspnea. Rapid removal of large amounts (>5 l) of ascites may result in mobilization of intravascular fluid to the extravascular peritoneal cavity and secondary circulating hypovolemia (with potential consequences such as hypotension, prerenal kidney injury, etc.); intravenous administration of albumin (25 g per 3 l of removed ascites) can compensate for these losses and prevent hypovolemia.

For refractory ascites in cirrhosis, transjugular intrahepatic porto-systemic shunt (TIPS), or even liver transplantation, may be indicated.

Diets and Digestive Diseases

L. D'Aoust and P. Poitras

Contents

Note: * is used in this review to identify the level of proof for a diet indication in the management of a specific digestive disorder. Diet indication can be experimentally validated (EV*) by controlled studies, scientific analysis, etc. in line with the concepts of evidence-based medicine (e.g., FODMAP diet for IBS), or the indication can be clinically supported (CS*), i.e., based on clinical observation, long-time documentation of beneficial effects (e.g., gluten-free diet for celiac disease), or can be based on physio-pathological data (PB*) leading to potential diet therapy and often with some benefit reported by some patients and doctors (e.g., fat-free diet for functional dyspepsia).

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Diets and the digestive system are closely linked. We will review here the diet therapy available for various digestive diseases. However, the use of a diet regimen is not always well codified and is often based upon historic clinical observations as well as common sense or popular belief. The diet indication can be experimentally validated (EV*; see Note on page 417) or clinically supported (CS*) or rely on physiopathological bases (PB*).

29.1 Esophageal Disorders

29.1.1 Oropharyngeal Dysphagia

Oropharyngeal dysphagia, after a stoke, for example, is best managed by a soft-thickened food diet (CS*). A multidisciplinary approach involving a speech therapist and a nutritionist is essential. Modification of the consistency of solid **and** liquid foods is necessary to facilitate swallowing (big bites of food are difficult to swallow; hard-textured foods are difficult to masticate) and reduce the risk of tracheal aspiration (specially with liquids). Although clinical evidence is limited, the use of thickened nectar or honey-based liquids may be suggested.

The risk of dehydration associated with this nutritional intervention must be monitored; specific hydration protocols such as the Frazier water protocol may be required.

If oral nutrition is not safe and adequate, gastric or jejunal enteral nutrition can be used.

29.1.2 Obstructive Esophageal Dysphagia

In esophageal dysphagia (e.g., esophageal cancer), solids are poorly tolerated and, if the obstruction is not too severe, can be replaced by soft or liquid foods (CS*). Weight loss and malnutrition are common, and nutritional intervention will often be necessary to correct undernutrition. According to tolerance, chopped/minced and well-masticated foods, soft foods (blenderized, etc.), or liquid foods with high caloric content (including polymeric formulas as discussed in ▶ Chap. 23) can be used.

If food intake remains insufficient despite dietary advice, enteral feeding, via nasogastric tube or percutaneous gastrostomy, will be necessary (while monitoring the risk of refeeding syndrome). In case of contraindication to enteral nutrition, the parenteral route will be preferred.

After installation of an esophageal prosthesis, dietary recommendations include chewing the food appropriately and selecting soft and moistened foods (by adding sauce) with frequent intakes of liquids during meals to reduce the risk of food blockade inside the stent.

Preoperative care: regardless of the route used, a minimum of 10–14 days of nutrition to meet energy requirements is required in malnourished patients prior to any surgical procedure in order to reduce the risk of morbidity.

After esophagectomy, altered anatomy (gastric pull-up) may lead to symptoms of early satiety and regurgitation of fluids and/or food. The recommended nutritional approach is to eat several small meals a day (6 per day), as in most cases where gastric volume is limited.

29.1.3 Eosinophilic Esophagitis (EoE)

Various diets can be used to decrease the allergenic esophageal injury:

- Elemental diet (EV*): strict alimentation for 4 weeks with fully hydrolyzed macronutrients (amino acids, di-monosaccharides, and free fatty acids) that completely exclude potential allergens was shown to reduce eosinophilic inflammation, improve symptoms, and induce prolonged clinical remission in patients with EoE. Although this is theoretically the most effective therapeutic approach, compliance with this very restrictive (and poorly palatable) diet is often difficult in practice.
- Six-food elimination diet (CS*): six allergenic foods most often linked to IgE-mediated allergies, i.e., milk (and dairy products), wheat, egg, soy, nuts, and seafood/shellfish, are eliminated from the diet during a 6-week therapeutic trial followed by a progressive reintroduction of specific food elements. Empiric elimination diet offers moderate response rates but is often better tolerated than the elemental diet therapy.
- Four-food elimination diet: as above but four foods (milk, wheat, egg, soy) are eliminated.

To palliate symptoms of dysphagia, a soft/liquid diet can be used as in other cases of esophageal dysphagia.

29.1.4 Gastroesophageal Reflux Disease (GERD)

Obesity is a major risk factor for GERD, and, in obese persons or those with weight gain associated reflux, weight loss is probably one of the few factors that can improve GERD.

Food susceptible to decrease the lower esophageal sphincter function (alcohol, chocolate, mint, fat) or to increase gastric acid secretion and decrease esophageal sensitivity (lemon, spices, tomatoes, coffee, tea, soft

drinks) can be limited hoping to reduce GERD symptoms (PB*); it is sometimes useful to patients with mild symptoms not requiring pharmacological antacid treatments.

In the case of nighttime reflux, it is advisable to eat the last meal or snack more than 2 h before bedtime (PB*).

29.2 Gastric Disorders

29.2.1 Gastroparesis

Dietary modifications (PB*) are part of the initial management of patients with gastroparesis:

- Several small meals per day (4–6), divided throughout the day
- Low fat content (slowing down gastric emptying)
- Low insoluble fibers (difficult to empty and susceptible to bezoar formation)
- Solid food of small size (minced, chopped) and soft texture (noodles rather than steak) are easier to empty
- Liquids will be better tolerated
- Avoid medication slowing down gastric emptying (including opiates)

In cases of severe gastroparesis, jejunal enteral nutrition (bypassing the stomach) may be necessary.

29.2.2 Dyspepsia

Patients often rely on diet modifications to control their symptoms of functional dyspepsia associated with acid hypersensitivity (epigastric pain syndrome or ulcer-like dyspepsia) or sensation of slow gastric emptying (postprandial distress syndrome or motor-like dyspepsia) as discussed in ▶ Chaps. 2 and 12.

Gastritis (or bland) diet avoiding foods linked to stomach irritation (PB*) and fat-free diet (PB*) are commonly used.

29.2.3 Dumping Syndrome

In patients with vagotomy and deficient pyloric function (e.g., after pyloroplasty or distal gastric resection), food can be rapidly emptied from the stomach and lead to dumping syndrome manifested by (a) abdominal pain (rapid intestinal distension by emptied gastric contents and fluids osmotically transferred from the systemic circulation in response to the hyperosmolar intestinal content), (b) diarrhea (rapid transit of hyperosmolar unabsorbed intestinal chyme), (c) hypotension (circulating hypovolemia due to the influx of fluid from the circulation to the intestine to dilute the hyperosmolar intestinal lumen content), and (d) hypoglycemia (following a pathological rise in serum insulin induced by the rapid glucose duodenal load). Observed in operated patients, the dumping syndrome is well managed by diet modifications.

Anti-dumping diet (CS*) includes:

- Low-simple sugars food (avoid concentrated sweets such as jam, desserts, goodies, etc.) to decrease the osmolarity of the luminal content and limit the postprandial insulin rise
- High-protein, high-fat nutrients to reduce gastric emptying speed
- Splitting liquid/solid nutrients: wait a minimum of 30 min after meals before consuming fluids (more rapidly emptied from the stomach and carrying with them solid foods)
- Increasing viscosity of food with guar gum or pectin can be useful to slow down their gastric emptying;
- Frequent small meals to decrease the gastrointestinal load
- Lie down after meals to decrease severity of symptoms

In cases of severe symptoms resistant to diet modifications, pharmacological treatment with somatostatin analogues can be used. In more complex cases, surgical revision of the postsurgical anatomy may be necessary.

29.2.4 Post-gastrectomy

The stomach is not a vital organ and can be removed, but diet modifications are required after total or partial gastrectomy. Post-gastrectomy diet (CS*) includes:

- Small meals (to comply with the reduced volume of the neo-stomach; tolerance to distension can increase with time), and eating at frequent intervals (to secure adequate daily caloric intake)
- Anti-dumping diet (described above) is often required
- Blenderized food can help to palliate the missing gastric grinding of food and optimize nutrient absorption.

29.3 Intestinal Disorders

29.3.1 Celiac Disease

Although its indication in celiac disease is based "only" on clinical evidence, gluten-free diet (GFD) is certainly the most effective diet treatment for digestive diseases. GFD for life is necessary in patients with celiac disease. Foods containing wheat, rye, and barley must be

excluded. Initially, oats are also removed from the diet because of their frequent contamination with gluten; oats may be reintroduced in limited quantities (40–60 g per day). Corn and rice are normally tolerated. It may be necessary to temporarily avoid dairy products containing lactose or to prefer lactose-free products at the beginning of the dietary treatment if a secondary intolerance is suspected.

29.3.2 Non-celiac Gluten Sensitivity (NCGS)

Some patients, in whom celiac disease has been excluded, may suffer from nonspecific digestive or extradigestive symptoms which are improved by gluten elimination. The identity and pathogenesis of NCGS are unclear. The gluten sensitivity may be transient, which is why some experts recommend re-introducing gluten after 12–24 months of gluten-free diet.

29.3.3 Lactose Intolerance

Lactose intolerance is a dose-dependent phenomenon. Patients can generally reduce their consumption of lactose-containing products without having to restrict themselves completely, since most can tolerate up to 12 g of lactose per day (the equivalent of a 250 ml glass of milk) or more if consumed in small quantities over the day or with other foods. Milk and ice cream have the highest concentration of lactose. Cheese and yogurt contain less lactose; in addition, their bacterial content favors the hydrolysis of lactose. Compared to skimmed or partly skimmed milk, whole milk is generally better tolerated because of its higher fat content, which delays gastric emptying. It is recommended that lactose-containing products be more strictly limited initially and gradually reintroduced to determine individual tolerance.

Lactase supplements (Lactaid®, Lacteeze®) are commonly used to improve symptoms.

Patients with irritable bowel syndrome (IBS) may be more sensitive to lactose intolerance.

29.3.4 Acute Gastroenteritis

Acute gastroenteritis, most often of viral origin, is usually managed by diet modifications for 1–3 days.

The intake of water and electrolytes is essential and is best achieved by glucose-containing solutions, such as the WHO solution (*PB, *CS), to enhance the intestinal absorption of Na^+ and H_2O (as discussed in ► Chap. 3; ► Sect. 3.1.2(b), and ► Chap. 13; ► Sect. 13.4).

Caloric intake, most often, relies on progressive intake of small meals of bland, easy to digest foods. According to various traditions and cultures, various diets, such as the BRAT (banana, rice, apple sauce, toast) diet or the chicken noodle (or rice) soups, are used.

Milk ingestion must sometimes be suspended if the enteritis has damaged intestinal villi enough to lead to a (temporary) lactase deficiency.

Ingestion of food can sometimes induce intestinal peristalsis and enhance abdominal cramps and bowel movements. It is important to understand that it does not correspond to a disease activation or deterioration and that oral intakes are important to compensate for the increased biological losses.

29.4 Colon Disorders

29.4.1 Irritable Bowel Syndrome (IBS)

IBS is characterized by abdominal pain associated with abnormal stools, diarrhea (IBS-D), or constipation (IBS-C) and frequently complicated by bloating.

Classical recommendations were derived from years of clinical experience:

- Balanced meals taken at regular times three times a day combined with good life habits (good sleep, exercise, stress avoidance, etc.) (PB*) are frequently recommended to improve IBS symptoms.
- Limiting alcohol, spices, fats, and caffeine may be beneficial (PB*), especially in IBS-D patients or those with associated dyspepsia symptoms.
- High-fiber diet (EP*), with a daily intake of 25–35 g, to be increased gradually to avoid gas, bloating, and abdominal pain at the beginning of the diet treatment, can be used to improve constipation.
- Low-fermentable diet (i.e., restricted in fermentable foods such as beans, Brussels sprouts, etc.) (PB*) is often necessary to prevent bloating (often aggravated on high-fiber diet).

In 2010, the first papers on evidence-based FODMAP (Fermentable, Oligo, Di, Monosaccharides, And, Polyols) approach for the treatment of functional GI symptoms were published by Australian researchers from Monash University of Melbourne. Relatively close to high-fiber/low-fermentable diets (but more restrictive), the low-FODMAP diet (EV*) may reduce abdominal pain and bloating by limiting colonic production of hydrogen, methane, and carbon dioxide. Under the supervision of an experienced nutritionist, it is suggested to follow this diet for 6–8 weeks until symptoms are resolved. Food will then be reintroduced gradually according to the patient's tolerance.

29.4.2 Chronic Constipation

High–fiber diet (with insoluble bran) has been well shown, in many studies from the 1970s, to improve constipation (EV*). However, although it increased daily stool number or weight, it failed to improve the symptoms of constipation (some studies even showed that they were increased!). Our own explanation is that the beneficial effect of reducing constipation is hidden or annihilated by the digestive bloating induced by the high-fiber diet.

High-fiber diet with soluble psyllium (EV*) was shown to be more effective than the bran diet to reduce symptoms of constipation.

29.4.3 Diarrhea

Many foods can induce diarrhea. The mechanisms involved include the presence of non-absorbed or poorly absorbed substances, such as mannitol, sorbitol (present as sugar substitutes in diet foods, but also in fruits such as prunes), or fructose (in fruits, fruit juices, soft drinks) that, by an osmotic effect, drag water into the intestine, or some (poorly characterized) substances (present in foods such as caffeine or prunes) that stimulate intestinal secretion and/or motility.

In the investigation of chronic diarrhea, an excessive intake of alcohol, diet foods, soft drinks, and caffeine should always be verified.

In patients with diarrhea, the intake of foods susceptible to induce diarrhea (discussed above) should be limited.

A high-fiber diet can be useful to increase the stool bulk and consistency (by dragging water into the fiber bulk).

29.4.4 Bloating

Bloating is the most common symptom reported by patients suffering of functional GI diseases. Long-time ignored by doctors, it often remains a therapeutic challenge (discussed in ► Chap. 14).

Intestinal diseases (celiac disease, lactose intolerance, etc.) leaving unabsorbed nutrients (prone to fermentation and gas production) in the intestinal lumen may need to be ruled out by the appropriate investigations.

Gas production from nutrient fermentation by colonic bacteria often contributes to bloating. These include dairy products, many fruits, some vegetables (cabbage, potatoes, broccoli, etc.), beans, some whole grains such as wheat, and artificial sweeteners. The low-FODMAP diet (EV*) can help reduce these symptoms.

Aerophagia is another mechanism responsible for gas and belching. It can therefore be recommended to reduce carbonated beverages and to avoid excessive chewing of gum (PB*).

29.4.5 Diverticular Disease

From epidemiological data, published by Burkitt in 1971, showing that colon diverticula were more prevalent in countries fed with a low-residue diet than in those eating a high residue diet, the concept that a low intestinal content was generating a high luminal pressure leading to wall diverticula and that a high residue diet could prevent the formation of diverticula was developed. Since then, it became the standard recommended treatment of diverticular disease. However, this concept is debated nowadays as it remains unclear if a high-fiber diet has a role in preventing the occurrence of diverticulosis or diverticulitis.

The elimination from the diet of nuts, seeds, and popcorn that could be responsible for complications (perforation leading to diverticulitis, erosion to diverticular bleeding) of a diverticulum was based mainly on popular beliefs and is no more recommended.

In acute uncomplicated diverticulitis, a liquid diet may be initially considered if necessary, before resuming a progressive diet depending on the patient's tolerance. A residue-free diet has not been shown to improve the course of diverticulitis.

29.4.6 Inflammatory Bowel Disease (IBD)

The cause of IBD remains unclear, but several environmental factors were related to the disease. Fat, animal proteins (especially red meat and processed meats such as deli meats), refined sugars (white sugar, brown sugar, corn syrup, fructose, sucrose), as well as certain emulsifiers (carrageenan, carboxymethyl cellulose E466, and polysorbate 80) and other additives in the form of microparticles (titanium dioxide E171, aluminum silicates) were blamed for increasing the risk of IBD. Several types of diets have been tried in IBD, but the current literature is limited to support their application. The Mediterranean diet, rich in olive oil and fish, fruits, whole grains, and vegetables, may be promising because of its favorable effect on the microbiome.

In the acute phases, a balanced, low-fat diet, free of processed products and additives, can be favored while avoiding dietary restrictions that could lead to nutritional deficiencies in iron, vitamins, and minerals such as zinc. Since insoluble fibers can worsen diarrhea and abdominal pain, it may be helpful to restrict them temporarily until symptoms and inflammation are resolved.

Enteral nutrition could be useful in more severely ill patients to meet nutritional needs and/or reverse a state of malnutrition.

Exclusive enteral nutrition (EEN) is a well-recognized treatment to induce remission of Crohn's disease in children (it seems to be as effective as corticosteroids). The CD TREAT diet, with similar composition to EEN, which excludes gluten, lactose, and alcohol and is composed of certain macronutrients, vitamins, minerals, and fibers, could be a potential substitute for EEN (often requiring a nasogastric tube for its administration).

29.5 Biliopancreatic Disorders

29.5.1 Acute Pancreatitis

The classic treatment of acute pancreatitis, for years, was based on "pancreatic rest" where feeding was interrupted to prevent pancreatic stimulation of enzymes (responsible for autodigestion of the gland) until disappearance of the inflammatory process and/or pain. However, fasting had a deleterious impact on the patient's general condition and evolution, and, although the concept of "pancreatic rest" is maybe still valid on a physiopathological point of view, food exclusion is no more recommended for the treatment of acute pancreatitis.

In mild to moderate acute pancreatitis, a soft, low-fat diet (PB*) can be initiated early, as soon as the first 24 h. It is not necessary to start with a liquid diet. The progression of the diet is based on the patient's tolerance and is independent of serum lipase levels. In more severe acute pancreatitis, enteral nutrition (ER*) will be initiated during the first 24–72 h after admission (not later than 5 days). It is not mandatory to use a naso-jejunal perfusion route nor an elemental formula; polymeric enteral feeds may be administered directly in the stomach (or in the jejunum if not tolerated).

In case where enteral nutrition is not tolerated, parenteral nutrition will be used, but a minimal enteral feeding must be continued in order to prevent atrophy of the intestinal mucosa responsible for bacterial translocation and infection of abdominal effusions

29.5.2 Chronic Pancreatitis

Malnutrition associated with chronic pancreatitis is multifactorial. It results from exocrine pancreatic insufficiency (which can be associated with endocrine insufficiency). Food intake may be limited by the presence of chronic abdominal pain, excessive alcohol consumption, or delayed gastric emptying. Increased metabolic activity due to the inflammatory response contributes to increased energy requirements.

Deficiencies in fat-soluble vitamins are common (vitamins A, D, E, and K), while those in water-soluble vitamins are rather rare (apart from thiamine deficiency which must be evoked in patients consuming alcohol). Magnesium, zinc, copper, and selenium deficiencies can also be observed.

Cessation of alcohol and smoking helps to limit the progression of the disease. Exocrine enzyme supplementation combined with a balanced diet is the cornerstone of nutritional treatment. It is recommended to restrict dietary fibers which act adversely on the mechanism of action of pancreatic enzymes.

A diet restricted in concentrated sugars will also be proposed in case of diabetes.

Oral supplements may be necessary if the dietary intake is insufficient.

29.5.3 Gallstones

There is no nutrition treatment for gallstone disease. However, in patients waiting for surgery, a low-fat diet (PB*) is often suggested to limit postprandial CCK release inducing gallbladder contraction (and biliary colic?).

29.6 Liver Disorders

29.6.1 Cirrhosis Malnutrition

Many cirrhotic patients are malnourished due to decreased intakes and increased metabolic requirements. An energy intake of 35 kcal/kg/day is recommended while aiming for 1.2–1.5 g of protein/kg/day. This will help limit muscle wasting (sarcopenia), which is a major predictor of morbidity and mortality in cirrhotic patients.

Since hepatic and muscular glycogen stores as well as neoglucogenesis are limited, a long period of fasting is poorly tolerated in cirrhotic patients and promotes a catabolic state. A 700 kcal snack can be added at the end of the evening to avoid prolonged fasting during the night.

29.6.2 Ascites

A salt-free diet is the first-line treatment in all cases.

29.6.3 Encephalopathy

Contrary to previous guidelines, it is no longer recommended to restrict protein in cirrhotic for the purpose of

preventing hepatic encephalopathy. Protein restriction worsens sarcopenia, and we now know that adequate muscle mass helps to remove circulating ammonia.

29.6.4 NASH

Patients suffering from non-alcoholic steatohepatitis (NASH) should aim for a minimum loss of 3–5% of their initial weight to improve steatosis and ideally 7–10% to reverse inflammation and fibrosis. A low-caloric diet (reduction of 500–1000 kcal daily compared to the baseline diet) is recommended (e.g., a Mediterranean diet may be promoted considering its beneficial effects on the metabolic syndrome and cardiovascular disease). A reduction in the consumption of foods and beverages rich in fructose (such as soft drinks) may be beneficial.

29.6.5 Metabolic Function Disorders

Rare metabolic disorders such as glycogen-storage diseases, galactosemia, or fructosemia (see ▶ Chap. 8) need diet treatment. Expert nutrition counseling and follow-up are usually required for these rare and complex diseases.

Common diet regimens used for the management of digestive diseases are shown in ◘ Table 29.1.

◘ **Table 29.1** Common diet regimens used for the management of digestive diseases

Regimen	Indication	Food to avoid	Food to include
Soft diet	Esophageal dysphagia Oropharyngeal dysphagia Gastroparesis	Hard textured and/or big sized foods	Solids easy to masticate, small volume (chopped, minced), soft (mashed, blenderized), according to tolerance Liquids: high caloric content
Gastritis (or bland) diet	Functional dyspepsia Ulcer/gastritis GERD	Alcohol, coffee, carbonated drinks, spicy foods, acidic foods (tomatoes, citrus fruits)	Lean meats (chicken, fish) Vegetables Low-acid fruits (berries, apples, melons, bananas)
Fat-free	Functional dyspepsia Gastroparesis Pancreatitis Gallstone Diarrhea	Fried foods Cream/butter	Grilled, boiled lean meat/fish Raw, grilled, boiled vegetables Fruits
Lactose-free	Lactose intolerance	Milk and dairy products	Lactase supplements
Gluten-free	Celiac disease	Wheat, rye, barley (oat)	Rice, corn
Anti-dumping	Dumping syndrome	Concentrated sugars	Fats, proteins
Low residue	Pre-colon surgery-endoscopy, colon diseases	Fibers, whole grain products, nuts, raw or fermentable vegetables (corn, onions, peas, etc.)	White bread, rice/pasta, pealed vegetables, fruits without seeds and skin, lean meat/fish
High-fiber (residue)	Constipation		Beans (lentils, chickpeas, etc.) Vegetables (carrot, broccoli, etc.) Fruits (raspberries, avocado, etc.) Grains (oat, bran, etc.) Nuts/seeds (chia, etc.)
Low-FODMAP	IBS Bloating	Fructose (apple, pear) Lactose (milk, cheese.) Fructans (artichoke, wheat) Galactans (beans, lentils) Polyols (apricot, sorbitol)	Fruit (banana, grape, berries) Vegetables (carrot, potatoes) Grains (rice, oat) Dairy (lactose free milk/cheese) Other (tofu)
Hypoallergenic	Eosinophilic esophagitis	Six foods (milk, wheat, egg, soy, nuts, seafood)	Elemental diet

Supplementary Information

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