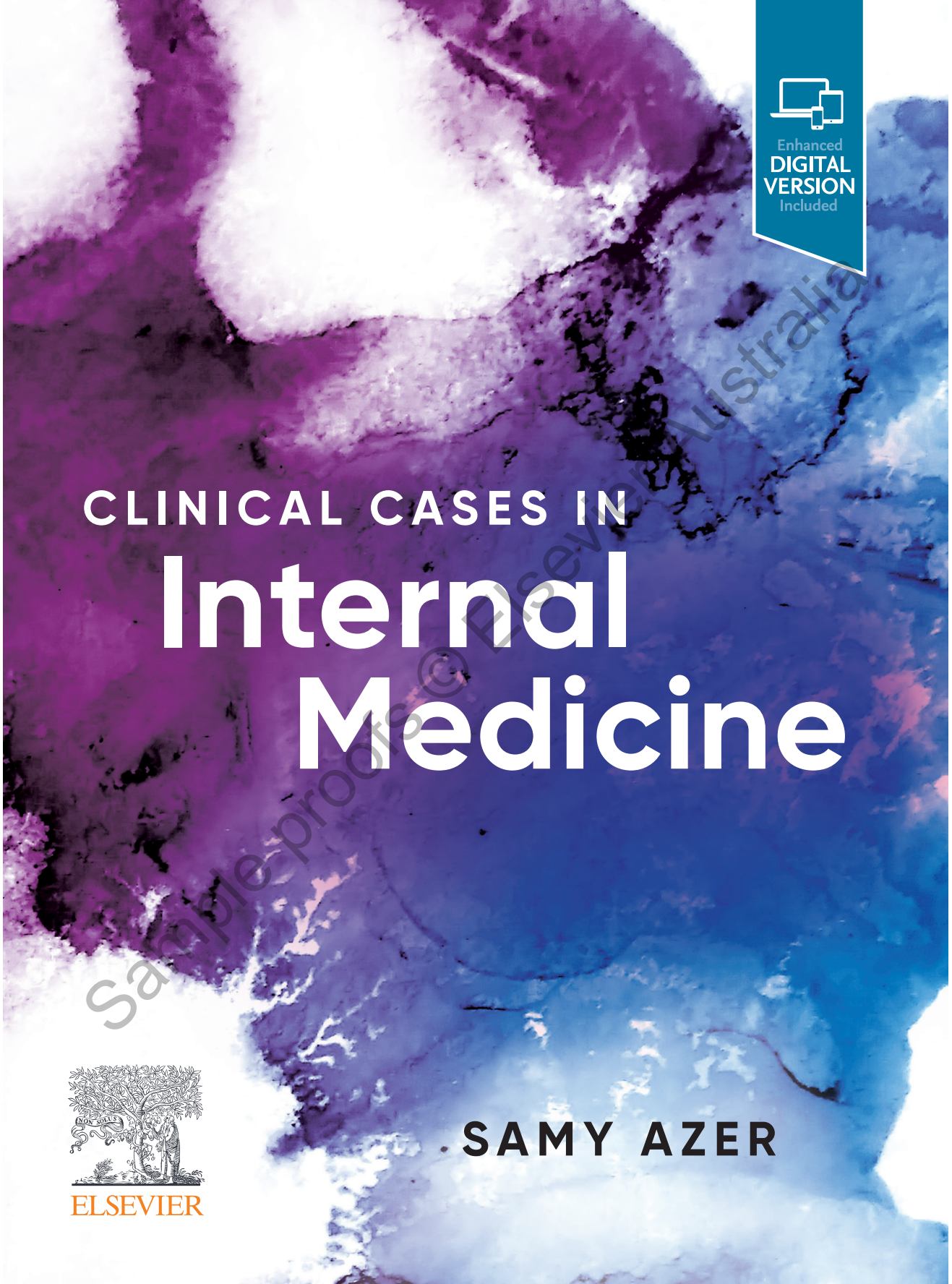

Clinical Cases in
INTERNAL MEDICINE

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To
The memory of my parents

To
My family for their love and support, and

To
My grandchildren – Jemimah, Elizabeth, Christopher, Asher

FOREWORD

To face the challenges of modern health care, future physicians must master not only an extensive knowledge base but also the analytical and integrative thinking skills needed to provide safe, comprehensive patient care in the context of clinical complexity.

While many textbooks present the content of this comprehensive knowledge base, *Clinical Cases in Internal Medicine* additionally guides learners on the *process* to apply knowledge and scientifically understand the various concerns (expressed in lay terms) that patients entrust their physicians to address. In this textbook, the concise and memorable case discussions highlight the differential diagnoses that must be systematically considered and review the mechanisms that explain the patient's signs and symptoms and the basis for why certain treatments work. The tables and figures are truly high-yield and helpful in practice. The questions, throughout the chapter, are framed very thoughtfully around queries that arise in clinical decision-making, in education of patients and families and in preparation for standardised examinations.

This textbook is ideal for students – in both problem-based learning (PBL) and traditional curricula – hoping to deepen their learning through case-based and interactive learning approaches.

Professor Samy Azer is an internationally renowned medical educator, who currently serves as Professor of Medical Education at the College of Medicine, King Saud University in Saudi Arabia. He has formerly served as Professor of Medical Education at the Universiti Teknologi MARA in Malaysia; Visiting Professor of Medical Education at the University of Toyama in Japan; and Senior Lecturer of Medical Education at the Faculty of Medicine, Dentistry and Health Sciences at the University of Melbourne and at the School of Medicine at the University of Sydney in Australia.

Through his commitment to innovations that optimise clinical learning and teaching and through publications and other connections that make these innovations graspable and accessible, Professor Azer has been an inspiration to the global community of medical educators and students alike. I join Professor Azer in his hope that educator colleagues, students and future patients will all benefit from the journey of learning through the cases presented in this text.

Anthony P. S. Guerrero, M.D.
Professor and Chair, Department of Psychiatry
The Char, McDermott, and Andrade Endowed
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FOREWORD

Medical curricula have changed worldwide to reflect the changing roles of health systems and the challenges faced by graduating doctors. The advances in technology and the overwhelming increase in scientific and medical publications add to these challenges and the need to prepare our doctors at the best international standards and reassuring their continuing professional development.

This book addresses these needs as a learning resource to be used by students and other recommended and prescribed resources and enables them to study 50 clinical cases and apply knowledge to clinically relevant topics in their undergraduate curriculum.

Practising clinicians tend to use 'schema' in their reasoning to arrive at a diagnosis based on pattern recognition and previous experience. However, undergraduate students did not have sufficient experience and seeing patients in the wards may not be available for their clinical training. Furthermore, most hospitals are moving to minimally invasive techniques and one-day care and minimising the length of hospital stay with the new developments in diagnosis and patient management. These days there are changes in hospital admission because of the COVID-19 pandemic. These changes have affected bedside teaching worldwide and the need for alternative teaching/learning methods to address the students' learning needs and enhance their clinical skills.

Professor Azer, the chair of the curriculum development and research unit at King Saud University, has written this book with these challenges in mind. The book reflects his international expertise in the field and addresses this area of need. International experts have reviewed the book and provide the core clinical cases taught in internal medicine. Students may use this book together with their clinical sessions and seeing patients in the wards presenting with illnesses described. Students may critically compare between clinical findings they identified in the patient and what was discussed in the clinical cases in the book. They may also answer questions and revise the MCQs at the end of each case.

Together with reading recommended resources and reviewing their lectures, such preparation will help in their clinical learning.

I am proud that Professor Azer is an academic at King Saud University for his achievement and contribution to the medical profession at the global, local and international levels. I want to congratulate the author on this achievement, and it is my pleasure to commend this book as an additional resource to medical students and clinical teachers. This book will be a valuable resource to medical libraries, students and clinicians, medical educators and curriculum designers.

Professor Badran AlOmar
President, King Saud University

PREFACE

Clinical Cases in Internal Medicine is not a textbook covering the whole undergraduate curriculum in internal medicine. Although reading texts and daily engagement with simulated patients and actual patients is vital to enhance your competency in medicine, students also need to complement their learning through case-based learning.

This book is written for students as a learning resource to use with other standard textbooks and resources recommended in this discipline. It comprises 50 cases in internal medicine covering different body systems and focuses on common diseases that all medical students should know.

Learning through cases helps students to master several skills and deepen their understanding by applying theoretical knowledge. It brings factual knowledge to what they face in practice. Case scenarios also stimulate students' thinking to interpret the history findings and clinical findings, generate hypotheses, construct a differential diagnosis, relates basic knowledge from physiology and pathology to the clinical picture, interprets laboratory findings and design a management plan.

Clinical Cases in Internal Medicine can be used on an individual basis or in small-group tutorials with or without a tutor. After reading the case scenarios, students could start answering each question that follows the scenario—one student in the group summarise critical points raised in the group discussion- act as the group scribe, and guiding the group discussion. During this process, students may identify gaps in their knowledge or issues they do not know. Also, questions raised could stimulate further thinking, search for answers/evidence and turning the discussion into a meaningful session. Through active learning, and self-regulated learning and examining other resources, students could deepen their understanding of the case, explore relationships, and turn their learning into engaging and stimulating behaviour.

After completing the case discussion, a section titled 'back to basics' has been included in each case. This section aims at linking knowledge from physiology, pathology, pathogenesis, microbiology and pharmacology with the case clinical discussion. Students may try answering the short-answer questions in this section, then compare their responses with the answers provided. Each case discussion ends with 5-6 multiple-choice questions that students could try on their own, then check at the end their performance against model answers and justification given. At last, the case discussion ends with 'a take-home message'. and 'further readings' from the literature. These resources are recommended for students to dig deeper and read more about current knowledge related to the case.

I wish success to all my current students and graduates at different universities where I was honoured to teach and other universities worldwide enforcing active learning practices.

Samy Azer
Melbourne
2021

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I am particularly indebted to my undergraduate and postgraduate medical students at the University of Sydney and the University of Melbourne in Australia, the University of Toyama in Japan, the Universiti Teknologi MARA in Malaysia and my current students at King Saud University in Saudi Arabia. Their engagement, questions and areas that they found difficult to understand have been an excellent source for me as I prepared the manuscript of this book.

I am indebted to the work of many individuals, particularly the publication team of Elsevier, for providing a professional standard during the book production. I thank Laurence Hunter, the content strategist, Elsevier Oxford, the United Kingdom. He was the first content strategist who handled the book before retiring. I thank Nimisha Goswami, the head of the content strategy, Elsevier India, who also dealt with the book content. I also thank Larissa Norrie, head of content strategy, Australia, who made significant help and support in the book production. Also, I thank Annabel Adair for the proofreading of the book as a freelance proofreader. I deeply appreciate and thank Subodh Kumar, who carried out the content development and project management responsibility. His hard work in preparing the proofs at professional standards is appreciated.

ABBREVIATIONS

5-HT	5-hydroxytryptamine
ACE	Angiotensin-converting enzyme
AChR	Anti-acetylcholine receptor
ACTH	Adrenocorticotrophic hormone
ADH	Antidiuretic hormone
AFB	Acid-fast bacillus
AHR	Airway hyper-reactivity
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
Anti-La (or SS-B) autoantibodies	These occur in 10%–20% of patients with systemic lupus erythematosus and 50% of patients with primary or secondary Sjögren syndrome; maternal anti-La (SS-B) autoantibodies are associated with neonatal lupus syndromes, particularly congenital heart block
Anti-Ro (anti-SS-A) autoantibodies	These are anti–Sjögren-syndrome-related antigen A autoantibodies; also called anti-Ro
Anti-U1-RNP	It is a serological marker for MCTD; It can be also detected in patients with systemic sclerosis or SLE
APACHE-II	Acute Physiology and Chronic Health Evaluation II
APC	Adenomatous polyposis coli
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AV node	Atrioventricular node
B. burgdorferi	*Borrelia burgdorferi*
BCG	*Bacillus Calmette–Guérin* vaccine
BCR-ABL	It is a mutation formed by the combination of two genes, known as BCR and ABL; the mutated chromosome 22 is called the Philadelphia chromosome (referring to the city where researchers first discovered Ph chromosome)
BG	Blood glucose
BMD	Bone mass density
BMI	Body mass index
BNP	Brain natriuretic peptide
BPPV	Benign paroxysmal positional vertigo
C, T, L, S nerve roots	C, cervical; T, thoracic; L, lumbar; S, sacral nerve roots
C. jejuni	*Campylobacter jejuni*

C. trachomatis	*Chlamydia trachomatis*
C3, C4	Complement fragments C3 and C4
C3NeF	C3 nephritic factor
cAMP	Cyclic 3′,5′-adenosine monophosphate
CAP	Community-acquired pneumonia
$CD4^+$	A T-helper white blood cell
$CD8^+$	It is a cytotoxic T-cell; also known as T-killer cell or cytotoxic T-lymphocyte
CEA	Carcinoembryonic antigen
CFU	Colony-forming unit
CK-MB	Creatine kinase myocardial band
CML	Chronic myeloid leukaemia
CMV	Cytomegalovirus
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CRF-1	Corticotrophin-releasing factor-1
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT scan	Computed tomography scan
cTn	Cardiac troponin
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
CTPA	Computed tomography pulmonary angiography
CURB-65 score	C, confusion; U, urea; R, respiratory; B, blood pressure; 65, age $>$ 65
CXCL	Chemokines playing a role in chemoattractant for several immune cells, and angiogenesis/arteriogenesis and cancer progression
CYP2E1	It is a member of the cytochrome P450, which is involved in metabolism of xenobiotics
D receptor	Dopamine receptor
Delta wave	In ECG, the delta wave is a slurred upstroke in the QRS complex, commonly associated with pre-excitation syndrome such as WPW
DHEAS	Dehydroepiandrosterone sulphate
DIP	Distal interphalangeal joints
DKA	Diabetic ketoacidosis
DMARDs	Disease-modifying antirheumatic drugs
DNA	Deoxyribonucleic acid

DR4	It is a serotype of HLA, which is associated with extra-articular rheumatoid arthritis, obstructive hypertrophic cardiomyopathy, IgA nephropathy, certain types of systemic lupus erythematosus and polymyalgia rheumatica
dsDNA	Double-stranded DNA
DVT	Deep venous thrombosis
DXA (or DEXA)	Dual-energy x-ray absorptiometry
E. coli	*Escherichia coli*
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECL	Enterochromaffin-like cells
EHEC	Enterohaemorrhagic *Escherichia coli*
EIEC	Enteroinvasive *Escherichia coli*
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
EMG	Electromyogram
EML4-ALK	EML4 is echinoderm microtubule-associated protein-like 4 gene that has been fused to the anaplastic lymphoma kinase (ALK) gene; this fusion leads to the production of a protein, EML4-ALK; first isolated from small cell lung cancer
eNOS	Endothelial nitric oxide synthase
EPEC	Enteropathogenic *Escherichia coli*
ERCP	Endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
ETEC	Enterotoxigenic Escherichia coli
FAP	Familial adenomatous polyposis
FEV_1	Forced expiratory volume of 1 second
FGF23	Fibroblast growth factor 23
FRAX	Fracture Risk Assessment Tool
FVC	Forced vital capacity
G6PD deficiency	Glucose-6-phosphate dehydrogenase deficiency
GABA	Gamma-aminobutyric acid
GADA	Glutamate decarboxylase alpha
GDP	Guanosine diphosphate or guanosine 5'-diphosphate
GGT	Gamma-glutamyl transferase
GH	Growth hormone
GINA	Global Institute for Asthma
GN	Glomerulonephritis
GnRH	Gonadotrophin-releasing hormone
GP	Globus pallidus
GTP	Guanosine-5′-triphosphate

H. influenzae	*Haemophilus influenzae*
H. pylori	*Helicobacter pylori*
H1-receptor	Histamine antagonist receptor-1
HAP	Hospital-acquired pneumonia
HAV	Hepatitis A virus
Hb	Haemoglobin
HbA_{1c}	Haemoglobin A_{1c}
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HGPRT	Hypoxanthine-guanine phosphoribosyltransferase
Hib	*Haemophilus Influenzae* type b
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
hs-cTnT	High-sensitivity cardiac troponin T
IA2A	Insulinoma-associated protein 2 autoantibody
IAA	Islet cell autoantigen
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IBS-C	Constipation-predominant IBS
IBS-D	Diarrhoea-predominant IBS
IBS-M	Mixed bowel pattern IBS
IBS-U	Unclassified IBS
ICA	Islet cell antibodies
Ig	Immunoglobulin
IGF-1	Insulin-like growth factor type 1
IL	Interleukin
IM	Intramuscular
INR	International normalised ratio
ITP	Immune thrombocytopenic purpura
IU	International unit
IV	Intravenous
JVP	*Jugular venous pressure*
K. *pneumoniae*	*Klebsiella pneumoniae*
Kv1−4 antibodies	These are the antibodies directed to the potassium voltage-gated channel; subfamily members 1–4
LA	Left atrium
LDDST	Low-dose dexamethasone suppression test

LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LMWH	Low-molecular-weight heparin
LRP_4	Lipoprotein receptor-related peptide 4
LTB_4	Leukotriene B_4
LTD_4	Leukotriene D_4
LV	Left ventricle
M. catarrhalis	*Moraxella catarrhalis*
MALT	Mucosa-associated lymphoid tissue
MCHC	Mean corpuscular haemoglobin concentration
MCTD	Mixed connective tissue disease
MCV	Mean corpuscular volume
MEN type 1	Multiple endocrine neoplasia type 1
MERS-CoV	Middle East respiratory syndrome coronavirus
MGDF	Megakaryocyte growth and development factor
MGUS	Monoclonal gammopathy of undetermined significance
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
MuSK	Muscle specific tyrosine kinase
N. meningitides	*Neisseria meningitidis*
$NADP^+$	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced nicotinamide adenine dinucleotide phosphate; it used in anabolic cellular reactions
NAPQI	*N*-acetyl-*p*-benzoquinone imine
NICE	National Institute for Health and Care Excellence
NLRP3	NLRP3 inflammasome complex is implicated as a regulator of the innate inflammatory phenotype of several diseases, including gout and type 2 diabetes
NPA	Neutral protamine aspart
NPH	Neutral protamine Hagedorn
NPL	Neutral protamine lispro
NSAIDs	Nonsteroidal anti-inflammatory drugs
OP receptor	Opioid receptors
OPG	Osteoprotegerin
OS	Opening snap
P wave	In ECG, the P wave represents atrial depolarisation, atrial contraction or atrial systole
P. aeruginosa	*Pseudomonas aeruginosa*
P. falciparum	*Plasmodium falciparum*
P. jirovecii	*Pneumocystis jirovecii*
P. malariae	*Plasmodium malariae*
P. mirabilis	*Proteus mirabilis*

P. ovale	*Plasmodium ovale*
P. vivax	*Plasmodium vivax*
p53	Tumour suppressor gene p53 (a 53-kilodalton [kDa] protein)
PAS stain	Periodic acid–Schiff stain
pCO_2	The partial pressure of carbon dioxide
PCR	Polymerase chain reaction
PCV	Packed cell volume
PDGFR	Platelet-derived growth factor receptor
PE	Pulmonary embolism
PEF	Peak expiratory flow
PET scan	Positron emission tomography scan
PfEMP1	*P. falciparum* erythrocyte membrane protein 1
PG	Prostaglandin
PGE_2	Prostaglandin E_2
pH	Potential of hydrogen or power of hydrogen; it is a scale to specify the acidity or basicity of an aqueous solution
Ph chromosome	Philadelphia chromosome
PIP	Proximal interphalangeal joints
PKCiota (PKCI)	Protein kinase Ciota
PLA2R	Phospholipase A2 receptor
PO	Per oral
POEMS syndrome	It is a syndrome characterised by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes
PTH	Parathyroid hormone
Q wave	In ECG, the Q wave represents left-to-right depolarisation of the interventricular septum
R wave	In ECG, the R wave is the first upward deflection after the P wave; it represents early ventricular depolarisation
RA	Right atrium
RANKL	Receptor activator of nuclear factor κβ ligand
RBCs	Red blood cells
RF	Rheumatoid factor
RNA	Ribonucleic acid
RV	Right ventricle
S. aureus	*Staphylococcus aureus*
S. flexneri	*Shigella flexneri*
S. pneumoniae	*Streptococcus pneumoniae*
S. saprophyticus	*Staphylococcus saprophyticus*
S. typhimurium	*Salmonella typhimurium*
S1 + S2 heart sounds	First and second heart sounds

S3 heart sound	The third heart sound, is an extra heart sound, also known as the ventricular gallop; it occurs just after S2
S4 heart sound	The fourth heart sound, is an extra heart sound, also known as the atrial gallop; it occurs just before S1 when the atria contract to force blood into the left ventricle; it can be heard in acute myocardial infarction, cardiomyopathy, aortic stenosis and left bundle branch block
SA node	Sinoatrial node
SAH	Subarachnoid haemorrhage
SaO_2	Oxygen saturation
SARS-CoV	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SLE	Systemic lupus erythematosus
SPEP	Serum protein electrophoresis
SSTR2	Somatostatin receptor type 2
ST segment	In ECG, the ST segment represents the interval between ventricular depolarisation and repolarisation
T wave	In ECG, the T wave represents the repolarisation of the ventricles
T3	Tri-iodothyronine
T4	Thyroxine
TB	Tuberculosis
TGF-ß	Transforming growth factor-beta
Th-1 or T_{h1} cell	T-helper cell-type 1
TH1	T-helper type 1 cells are a lineage of $CD4^+$
TH2	T-helper type 2 cells are a distinct lineage of $CD4^+$
TIA	Transient ischemic attack
TIBC	Total iron-binding capacity
TNF-α	Tumour necrosis factor-alpha
TNM staging	Staging of cancer: T, tumour size; N, spread to lymph nodes; M, metastasis
TP53 gene	It is located on the short arm of chromosome 17 (17p13.1) and its mutation plays a role in cancer development
TPMT	Thiopurine methyltransferase
TRAb	TSH receptor IgG antibody, also known as thyrotrophin receptor antibody
TRAs	Thrombopoietin receptor agonists
TSH	Thyroid-stimulating hormone
tTG	Tissue transglutaminase

TTP	Thrombotic thrombocytopenic purpura
UGI	Upper gastrointestinal
UPEP	Urine protein electrophoresis
UTI	Urinary tract infection
V/Q scan	Ventilation/perfusion scan
VAP	Ventilation-associated pneumonia
WBC	White blood cell
WPW syndrome	Wolff–Parkinson–White syndrome
Y. enterocolitica	*Yersinia enterocolitica*
ZN stain	Ziehl–Neelsen stain

CONTENTS

SECTION 1

Gastroenterology and Hepatobiliary Systems

CASE 1.1

'I Have Tummy Pain …'

Lilian Murad, a 70-year-old retired teacher, is brought by an ambulance to the emergency department of a local hospital because she is suffering from mild upper abdominal pain for the last 2 days and feeling unsteady during walking. Mrs Murad has severe osteoarthritis and she takes 600 mg of ibuprofen three times a day for the arthritis pains. On examination, her resting pulse rate is 110/min, and her blood pressure is 140/75 mm Hg, lying flat (100/50 mm Hg, sitting). She looks pale but not jaundiced. On abdominal palpation, mild tenderness in the epigastrium is found. The liver and spleen are not palpable. Per rectum examination reveals soft black tarry stool on the gloved examining finger. The cardiovascular and respiratory examination reports are normal.

CASE DISCUSSION

Q1. On the basis of Mrs Murad's presentation, what is your diagnosis?

Q2. What is your differential diagnosis?

Q3. What are the key clinical features of this disease? What are the scientific bases for these features?

Q4. What is the pathophysiology underlying these changes?

Q5. What are your management goals and management options?

ANSWERS

1. The findings of using ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), tachycardia, postural drop of blood pressure, tenderness in the epigastrium, pallor and the presence of soft black tarry stool (melaena stool) are suggestive of bleeding from a gastric ulcer. Upper gastrointestinal (UGI) bleeding is a common clinical problem and has been associated with increasing NSAID use and the high prevalence of *Helicobacter pylori* infection in patients with bleeding peptic ulcer. Rapid assessment and resuscitation should precede the diagnostic evaluation, particularly in patients with haemodynamic changes (such as elevated heart rate and postural changes in blood pressure) due to severe bleeding.

2. The differential diagnosis:
- Peptic ulcer bleeding (60%–65% of cases)
- Gastritis and duodenitis (8% of cases)
- Oesophageal varices (6% of cases)

- Mallory–Weiss tear (4% of cases)
- Gastric malignancy (1%–2% of cases)
- Arteriovenous malformation (angiodysplasias) (10% of cases)
- Oesophagitis or oesophageal ulcer
- Duodenal ulcer
- Pancreatic cancer (rare cause)
- No identified cause

The following are essential for the diagnosis of peptic ulcer bleeding:

- Haematemesis, melaena stool, history of aspirin or NSAID use, abdominal pain, nocturnal symptoms, history of peptic ulcer bleeding or confirmed *H. pylori* infection.
- Early upper endoscopy (within 24 hours) confirms the diagnosis and allows for targeted treatment (e.g. injection of a sclerosant or epinephrine, thermocoagulation, allocation of metallic clips and rubber banding).

3. Symptoms and signs:

- Abdominal pain, coffee ground–like emesis, haematemesis, dyspepsia, soft black tarry stools, bright red blood per rectum (occurs when there is a loss of more than 1000 mL of blood), warfarin, aspirin, NSAIDs, selective serotonin reuptake inhibitors (SSRIs) or corticosteroid use, or history of peptic ulcer disease.
- Previous abdominal surgery, previous episodes of UGI bleeding, alcohol use and smoking.
- Ask about and assess for chronic renal or liver diseases, or chronic obstructive pulmonary disease.
- Heavy alcohol ingestion may be suggestive of Mallory–Weiss tear.
- Signs of chronic liver disease may indicate that the bleeding is due to portal hypertension.

4. Pathophysiological and laboratory features:

- The common causes of peptic ulcer disease are (i) use of NSAIDs: about 5%–20% of patients who use NSAIDs over long periods develop peptic ulcer disease, particularly in elderly patients; (ii) *H. pylori* infection (Gram-negative mobile spiral rod) is found in 48% of patients with peptic ulcer disease; (iii) acid hypersecretory states (e.g. Zollinger–Ellison syndrome); and (iv) stress-induced ulcers, e.g. after acute illness, multiorgan failure, ventilator support, extreme burns (Curling ulcer), head injury (Cushing ulcers). Fig. 1.1.1 shows pathology and pathogenesis of peptic ulcer disease – injurious and defence mechanisms.
- *H. pylori* infection causes peptic ulcer disease through several mechanisms including (i) the presence of an outer inflammatory protein in the bacterium, (ii) the presence of a functional cytotoxin-associated gene island in the bacterial chromosome causing virulence and ulcerative changes, (iii) decreased gastric mucosal production and decreased duodenal mucosal bicarbonate secretion and (iv) increased resting and meal-stimulated gastrin levels. Fig. 1.1.2 shows *H. pylori* adherent to gastric mucosa.
- NSAIDs cause inhibition of the cyclooxygenase (COX) and inhibition of prostaglandins and their protective COX-2–mediated effects. This results in decreased

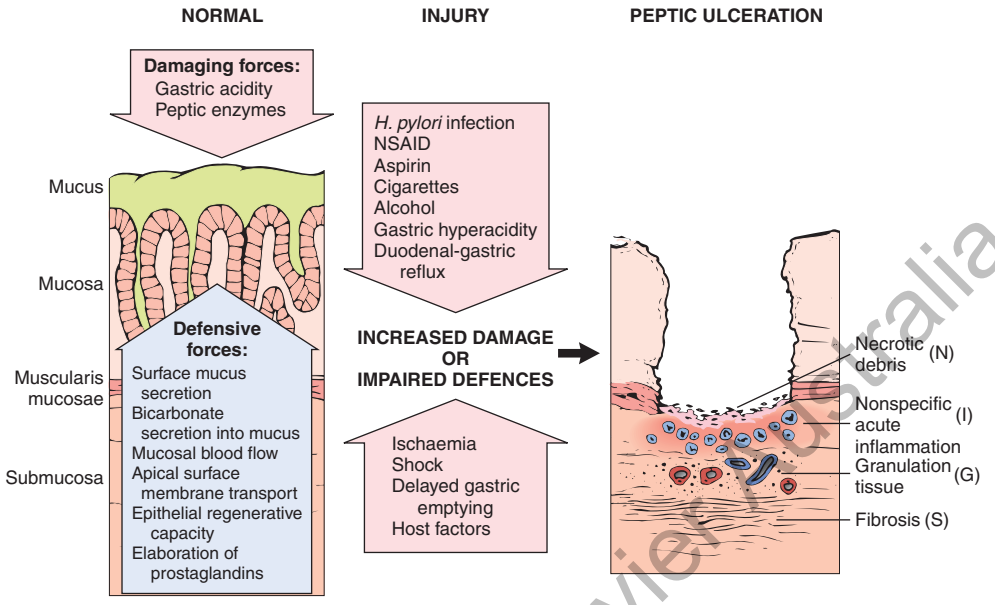

Figure 1.1.1 Peptic ulcer disease pathogenesis. Injurious and defence mechanisms. The peptic ulcer is characterised by necrotic tissues (N), acute inflammatory changes (I), granulation tissues (G) and fibrosis (S). *(Source: Kumar V, Abbas AK, Fausto N, Mitchell R. Robbins Basic Pathology, 8th Edition. London, UK: Elsevier; 2007.)*

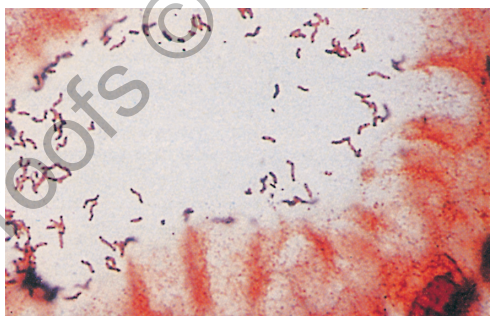

Figure 1.1.2 *H. pylori* silver stain showing spiral-shaped organisms adherent to the gastric mucosa. *(Source: Goering R, Dockrell N, Zuckerman M, Wakelin D, Roitt I, Mims C, Chiodini P. Mims' Medical Microbiology. 4th ed. London, UK: Elsevier; 2007.)*

mucus secretion and bicarbonate secretion, decreased mucosal blood flow and disturbed epithelial cell proliferation, and hence peptic ulcer disease.

- There is evidence that coexisting *H. pylori* infection increases the likelihood of intensity of NSAID-induced damage.
- Laboratory tests needed to assess the condition of Mrs Murad include complete blood count, platelet count, prothrombin time, international normalised ratio (INR), serum creatinine, liver function tests and blood typing and screening. Remember that haematocrit is not a reliable indicator of severity of acute bleeding.

5. Management goals:
- Correct any haemodynamic changes.
- Assess risks.
- Stop bleeding.
- Manage the cause of bleeding.

A. Correct any haemodynamic changes. (i) Patients with haemodynamic compromise should be given 0.9% saline or lactated Ringer injections and crossmatched for 2–4 units of packed red blood cells. (ii) Blood transfusion should be administered to those with a haemoglobin level of 70 g/L or less. The haemoglobin should be maintained at 90 g/L. (iii) Patients with active bleeding and coagulopathy (and INR > 1.8) should be considered for fresh frozen plasma. If there is thrombocytopenia, platelet transfusion should be considered.

B. Assess risk. Clinical assessment should be for whether the bleeding is from upper or lower GI tract. Assess the patient's age, presence of shock, systolic blood pressure, heart rate and comorbid conditions. Assess risk for rebleeding. Review the Rockall risk scoring system (for further reading, check Rockall et al., 1996).

C. Stop bleeding. Nasogastric tube is placed for aspiration. Intravenous proton-pump inhibitor is used in patients admitted for active bleeding. Early upper endoscopy (within the first 24 hours of presentation) should be considered. Gastric lavage to clear the stomach of blood increases the success of localisation of the source of bleeding. Early endoscopy confirms the diagnosis and allows for targeted treatment (e.g. injection of a sclerosant or epinephrine, thermocoagulation, allocation of metallic clips and rubber banding).

BACK TO BASIC SCIENCES

Q1. What are the functions of the main cells in the stomach?
- Mucous neck cells → produce soluble mucus that lubricates the chime.
- Stem cells → proliferate to replace all the specialised cells lining the fundic glands.
- Parietal (oxyntic) cells → produce hydrochloric acid (HCl) and the gastric intrinsic factor (IF), which is essential for the absorption of vitamin B12, mainly in terminal ileum.
- Peptic (chief) cells → secrete pepsinogen.
- Enterochromaffin cells → store serotonin (5-HT).
- Enterochromaffin-like (ECL) cells → synthesise and secrete histamine.
- Pyloric glands contain mucus and endocrine cells including gastrin cells (G-cells), which release gastrin, usually in response to gastric distension and the presence of nutrients (amino acids and amines).
- D-cells (endocrine cells) → release somatostatin in response to HCl. Somatostatin inhibits the release of HCl from the parietal cells.

Q2. What are the noxious factors that may expose the gastric mucosa to damage?

- HCl, pepsinogen, pepsin, bile salts.
- Medications, alcohol, bacteria.

Q3. Briefly discuss the gastric mucosal defence system.

It comprises three level barriers:

- Pre-epithelial: Represented by a physicochemical barrier comprising a mucus–bicarbonate–phospholipid layer. This barrier forms a pH gradient ranging from 1 to 2 at the gastric luminal surface and reaching 6–7 along the epithelial cells.
- Epithelial: Represented by (i) mucus production, epithelial cell ionic transporters and intracellular tight junctions; (ii) epithelial cells, which generate heat shock proteins that prevent protein denaturation; (iii) production of growth factors and prostaglandins. These growth factors include epidermal growth factor (EGF), transforming growth factor (TGF) and fibroblast growth factor (FGF) that promote epithelial protection. Prostaglandins and growth factors play a role in epithelial cell renewal and formation of new vessels (angiogenesis).
- Subepithelial: The production of HCO_3^-, which neutralises the acid generated by the parietal cells. The formation of effective microcirculatory bed, the removal of toxic by-products and the continuing supply of oxygen and micronutrients.

Prostaglandins provide central role in the protection. A key enzyme that regulates the rate-limiting step in prostaglandin synthesis is cyclooxygenase (COX), which is present in two isoforms (COX-1 and COX-2).

Q4. What are the main differences between COX-1 and COX-2?

- Cyclooxygennase-1 (COX-1) is expressed in a host of tissues including stomach, platelets, kidneys and endothelial cells. This enzyme is important for maintaining the integrity of the renal function, platelet aggregation and the GI mucosal integrity.
- Cyclooxygenase-2 (COX-2) is inducible by inflammation stimuli. Therefore, it is expressed in inflammatory cells including macrophages, leukocytes, fibroblasts and synovial cells.

The applications of these differences are as follows:

(i) Aspirin and NSAIDs demonstrate their anti-inflammatory effects by inhibiting COX-1. Therefore, toxicity such as mucosal ulceration and renal dysfunction can occur in relation to COX-1 inhibition.

(ii) Aspirin even in small doses can inhibit platelet aggregation via inhibiting COX-1 isoenzyme.

(iii) The highly selective COX-2 NSAIDs have the potential effects of decreasing inflammation without causing toxicity to the stomach mucosa or the kidney. However, selective COX-2 drugs have adverse effects on the cardiovascular system such as myocardial infarction.

Q5. What are the most common causes of peptic ulcer disease?
H. pylori infection and the use of NSAIDs are the most common causes of peptic ulcer disease.

Q6. What are the other diagnoses that should be considered in the differential diagnosis of peptic ulcer disease?
The other diagnoses are oesophagitis, functional dyspepsia, gastritis, gastro-oesophageal reflux, cholangitis, cholecystitis, cholelithiasis, oesophageal perforation, inflammatory bowel disease, coeliac disease, irritable bowel syndrome, gastric cancer, viral hepatitis and Zollinger–Ellison syndrome.

Q7. What do you know about *Helicobacter pylori*?
H. pylori is a Gram-negative helical rod-shaped bacterium that colonises in the gastric mucosa. It is estimated to be present in one-half of the world population. It is present in >90% of patients with duodenal ulcers and in 30%–60% of patients with gastric ulcers. Infection occurs via the faecal–oral route and during early childhood and persists for decades. Infection with *H. pylori* is one of the common causes of peptic ulcer disease and is a risk factor for mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma.

Q8. What are the two most accurate tests for identifying *H. pylori* infection?
The urea breath test and the stool antigen test.

Q9. What are the advantages and disadvantages of the serologic tests?
The serologic tests aim at detecting immunoglobulin G specific to *H. pylori* in the serum. Therefore, the test cannot distinguish between an active infection and a past infection. The serologic tests can be used in mass population surveys and in patients who cannot stop taking proton-pump inhibitors (e.g. those with GI bleeding).

Q10. What are the main complications of peptic ulcer disease?
The main complications are bleeding, perforation, gastric outlet obstruction and gastric cancer.

REVIEW QUESTIONS

Q1. Which *one* of the following gastric cells is responsible for HCl secretion?
A. Enterochromaffin cells
B. Enterochromaffin-like (ECL) cells
C. D-cells
D. Peptic (chief) cells
E. Parietal cells

Q2. Regarding COX-1, which *one* of the following statements is correct?
A. Inducible by inflammation
B. Expressed in macrophages
C. Expressed in the stomach
D. Its inhibition causes platelet aggregation

Q3. Which *one* of the following is correct about *H. pylori*?
A. Is Gram-positive
B. Causes peptic ulcer disease in >90% of infected patients
C. Produces uric acid
D. Causes gastric cancer
E. Causes Zollinger–Ellison syndrome

Q4. Patients with bleeding gastric ulcers due to low-dose aspirin taken for secondary cardiovascular prevention should: (*select one response*)
A. Stop taking aspirin.
B. Take an antiplatelet drug instead.
C. Take low-dose aspirin twice weekly after bleeding stops.
D. Resume the use of aspirin together with a proton-pump inhibitor.

Q5. There is evidence from randomised trials that administration of a proton-pump inhibitor to patients with UGI bleeding soon after presentation is associated with: (*select one response*)
A. Significant reduction of the risk of further bleeding.
B. Significant reduction of the need of surgery to manage bleeding.
C. No significant reduction in death.
D. No reduction of the need for endoscopic therapy.

Q6. In patients with UGI bleeding, which *one* of the following is *not* associated with increased risk of further bleeding?
A. Tachycardia > 100 beats/min
B. Hypotension – systolic < 100 mm Hg
C. Age > 60 years
D. Major coexisting condition
E. White blood cell count > 13×10^9/L

ANSWERS

A1. **E.** Parietal cells in the stomach are responsible for HCl secretion.

A2. **C.** COX-1 is expressed in the stomach. Other items are correct for COX-2.

A3. **D.** *H. pylori* cause gastric cancer.

A4. **D**. If aspirin was used for primary prevention, aspirin has been shown to result in a small reduction in the absolute risk of cardiovascular events. However, the absolute reduction in cardiovascular events is much greater when aspirin is used for secondary prevention. Therefore, aspirin should be resumed within 1–7 days after bleeding stops. Co-therapy with a proton-pump inhibitor should be considered (for further reading, check Bhatt et al., 2008).

A5. **C**. A meta-analysis of six randomised trials showed that the use of a proton-pump inhibitor soon after presentation was associated with no significant reduction of the risks of further bleeding, surgery or death. However, the administration of a proton-pump inhibitor was associated with a decrease in the frequency of high-risk endoscopic findings (e.g. active bleeding) and the need for endoscopic therapy (for further reading, check Sreedharan et al., 2010).

A6. **E**. Higher risk of further bleeding or death in relation to UGI bleeding is calculated from Glasgow-Blatchford score (range from 0 to 23). The score comprises blood urea, haemoglobin level, systolic blood pressure, heart rate and other variables including melaena, syncope and evidence of hepatic disease and cardiac failure. White blood cell count is not a parameter in such assessments (for further reading, check Gralnek et al., 2015).

TAKE-HOME MESSAGE

- Peptic ulcers due to *H. pylori* infection or the use of NSAIDs are the most common causes of UGI bleeding.
- The differential diagnosis includes peptic ulcer disease (60%–65%), gastritis/duodenitis (8%), oesophageal varices (65%), Mallory–Weiss tear (4%), gastric malignancy (1%–2%) and arteriovenous malformation (10%).
- The clinical picture is characterised by abdominal pain, dizziness, haematemesis and melaena stool (soft black tarry stool).
- Management goals are to correct haemodynamic changes, assess risks, stop bleeding and manage the cause of bleeding.

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CASE 1.2

'I Am Losing Weight …'

Asma Ali, a 7-year-old primary school student, comes in with her mother to see a general practitioner because she is suffering from chronic diarrhoea and abdominal discomfort. She has been feeling tired over the last few months and has lost 3 kg in body weight over the last 8–9 months. On examination, nothing significant is found. Laboratory tests show that she has a haemoglobin level of 90 g/L (normal = 115–160 g/L) with an iron-deficiency picture on the blood film. Serum ferritin is low, confirming iron-deficiency anaemia. Her stool analysis shows undigested food and fat globules.

CASE DISCUSSION

Q1. On the basis of Asma's presentation, what is your diagnosis?

Q2. What is your differential diagnosis?

Q3. What are the key clinical features of this disease? What are the scientific bases for these features?

Q4. What is the pathophysiology underlying these changes?

Q5. What are your management goals and management options?

ANSWERS

1. The findings of chronic diarrhoea, abdominal discomfort, tiredness, loss of body weight and iron-deficiency anaemia are suggestive of malabsorption. The presence of undigested food and fat globules in the stool analysis is also consistent with the diagnosis of malabsorption, such as coeliac disease. However, further assessment is needed to confirm the diagnosis.

2. The differential diagnosis:

- Autoimmune enteropathy
- Bacterial overgrowth
- Crohn disease
- Giardiasis
- Occult gastrointestinal bleeding
- Intestinal lymphoma
- Lactose intolerance
- Soy protein intolerance

- Tropical sprue
- Tuberculosis

The following are essential for the diagnosis of coeliac disease:

- Typical presentations: Weight loss, chronic diarrhoea, tiredness, abdominal distension, abdominal discomfort and flatulence.
- Atypical presentation: Iron-deficiency anaemia, osteoporosis, low serum albumin and dermatitis herpetiformis.
- The diagnosis is confirmed by serologic tests (IgA endomysial antibody and IgA tTG antibody tests), both of which have a >90% sensitivity and >95% specificity for the diagnosis of coeliac disease. Endoscopic mucosal biopsy of the proximal jejunum is the standard method for confirming the diagnosis.
- Clinical improvement on gluten-free diet.

3. Symptoms and signs:

- The classic symptoms of malabsorption such as coeliac disease include chronic diarrhoea, steatorrhoea, weight loss, abdominal distension, weakness, muscle wasting or growth retardation. These symptoms are usually present in young children (younger than 2 years).
- Adults are less likely to present with gastrointestinal symptoms. They may have dyspepsia, chronic diarrhoea or flatulence. Usually adults present with extraintestinal 'atypical' manifestations including fatigue, depression, tiredness, iron-deficiency anaemia, osteoporosis, delayed puberty or reduced fertility.
- Clinical examination may be normal or shows signs of malabsorption such as loss of body weight, loss of muscle mass or subcutaneous fat, pallor due to anaemia, easy bruising (due to vitamin K deficiency), ankle oedema (due to low serum albumin), hyperkeratosis (due to vitamin A deficiency), bone pain (due to osteomalacia), osteoporosis (due to vitamin D deficiency) or peripheral neuropathy. Abdominal examination may reveal abdominal distension and hyperactive bowel sounds.

4. Pathophysiological and laboratory features:

- The common causes of steatorrhoea (malabsorption of fats) are (i) conditions affecting the pancreas such as chronic pancreatitis and pancreatic cancer; (ii) conditions affecting bile salt availability such as primary biliary cirrhosis and intrahepatic cholestasis; and (iii) conditions affecting the small intestine and interfering with absorption such as coeliac disease, tropical sprue, giardiasis and bacterial overgrowth syndrome.
- Regardless of the cause, a 72-hour quantitative stool collection, preferably on a defined diet, must be obtained to determine stool fat content to establish the diagnosis of steatorrhoea.
- Coeliac disease is an autoimmune disease triggered by exposure to dietary gluten in genetically susceptible individuals. Gliadin, the alcohol-soluble protein of gluten, cannot be fully broken down in the intestine and generally this protein remains in the intestinal lumen of all individuals. In genetically sus-

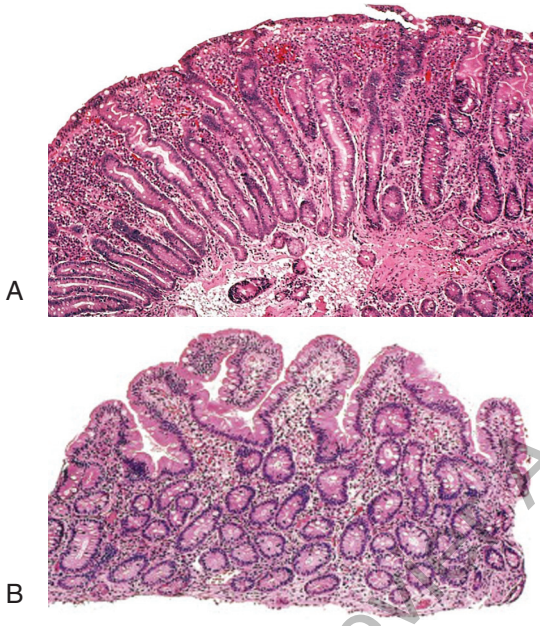

Figure 1.2.1 (A) Intestinal biopsy showing changes consistent with coeliac disease (flattened villi, hyperplasia of crypts and increased intestinal lymphocytes). (B) Regeneration of intestinal villi after starting the patient on a gluten-free diet. *(Source: Goldman L, Schafer AI. Goldman-Cecil Medicine. 25th ed. Elsevier; 2016.)*

ceptible patients, the gliadin particle passes through the epithelial layer of the small intestine and stimulates immune response. The gliadin proteins then bind to the human leukocyte antigen class II DQ2 or DQ8 molecules, which activates CD4 T-cells in the intestinal mucosa. This autoimmune activation produces chronic inflammation of the proximal small bowel mucosa leading to villus atrophy and malabsorption, mainly of fats, iron and fat-soluble vitamins (Fig. 1.2.1A and B).

- The severity of the clinical picture depends on the severity and extent of intestinal damage.
- Persons at an increased risk of coeliac disease are (i) first-degree relatives of a person with coeliac disease, (ii) second-degree relatives of a person with coeliac disease, (iii) those with Down syndrome, (iv) those with Turner syndrome, (v) those with autoimmune thyroid disorders, (vi) those with immune globulin A deficiency and (vii) those with type 1 diabetes mellitus.
- Serologic testing and small bowel biopsy are highly sensitive and specific in diagnosing coeliac disease. Those at an increased risk should be investigated including (i) patients with a family history of coeliac disease; (ii) those with associated autoimmune disorders; (iii) patients presenting with gastrointestinal symptoms such as abdominal pain, chronic diarrhoea, malabsorption, weight loss and bloating; and (iv) patients with premature osteoporosis, iron-deficiency anaemia, low serum albumin and unexplained abnormal liver function tests.

- Other laboratory tests needed to assess the condition of Asma include complete blood count, blood film, iron studies, B12 and blood folate levels, prothrombin time, international normalised ratio (INR), liver function tests, serum albumin, blood calcium and electrolytes, and blood urea and creatinine.

5. Management goals:
- Adherence to a gluten-free diet (serologic monitoring for coeliac disease could help in assessing adherence)
- Patient education
- Monitoring for associated conditions (osteoporosis, autoimmune thyroiditis)
- Monitoring for complications

BACK TO BASIC SCIENCES

Q1. Briefly discuss the epidemiology of coeliac disease.
- Coeliac disease affects 0.6%–1.0% of the population worldwide. It shows a high prevalence in North Africa and the Middle East population. It is rare in black Africans.
- It is more common in females (female to male ratio is 2–3:1).
- The frequency of coeliac disease is rising in developing countries because of changes in wheat production and possibly increased consumption of Western foods and awareness of the disease.
- The disease is increased in persons who have a first-degree relative affected, type 1 diabetes mellitus, Hashimoto thyroiditis or other autoimmune disorders.
- Coeliac disease can present at any age. It is commonly diagnosed in early childhood. However, the diagnosis may be delayed up to 10 years from the time of first presentation.
- Genetic background plays a role in the disease and HLA-DQ2 haplotype is expressed in the majority of patients. HLA-DQ8 is expressed in 5%–10% of patients.

Q2. Briefly discuss the pathogenesis of coeliac disease.
- The disease occurs as a result of an inappropriate immune body response to an external trigger (dietary gluten protein) found in wheat, rye and barley in individuals who are genetically predisposed to the disease.
- The disease in the majority of patients is associated with HLA-DQ2 or HLA-DQ8 haplotype but other genes have been identified and involved in the disease susceptibility.
- The disease is immune mediated and is dependent on the presentation of gluten peptides to T-cells. This process necessitates prior deamidation of glutamine residue by tissue transglutaminase.
- Although the HLA expression is important in the pathogenesis, there is evidence of non-HLA genetic component with over 40 regions harbouring susceptibility genes for coeliac disease.

- The immunological changes result in chronic inflammatory changes of the mucosa of the small intestine, infiltration of the lamina propria, increased intraepithelial lymphocytes, crypt hyperplasia and intestinal mucosal atrophy (loss of villi). These changes impair the absorptive functions of the small intestine, resulting in malabsorption of fat- and lipid-soluble vitamins (A, D, E and K) as well as iron, folate and calcium.

Q3. Briefly discuss the clinical picture of coeliac disease.

- The disease is frequently asymptomatic.
- Although it is commonly diagnosed in early childhood (usually because of profuse diarrhoea and failure to thrive after weaning), the disease may be diagnosed at any age and the diagnosis may be delayed up to 10 years after the first presentation.
- Common presenting signs and symptoms:
  1. Loose bowel motions and steatorrhoea (excessive loss of fats in stools because of failure of fat absorption)
  2. Bloating, recurrent abdominal pain and symptoms similar to those of irritable bowel syndrome (therefore, all patients with irritable bowel syndrome should be serologically investigated for coeliac disease)
  3. Weight loss
  4. Tiredness and chronic fatigue
  5. Iron-deficiency anaemia (in those with duodenal and early jejunum involvement)
  6. Anaemia due to deficiency of vitamin B12 (terminal ileum involvement) and folate (early jejunum involvement)
  7. Vitamin D deficiency, reduced bone mineral density and osteomalacia in adults and rickets in children
  8. Peripheral neuropathy, proximal muscle pains, gluten ataxia and epilepsy
  9. Dermatitis herpetiformis (rare)

Q4. Briefly discuss the complications associated with untreated coeliac disease.

1. Osteoporosis
2. Impaired splenic functions
3. Infertility and recurrent abortions in females
4. Cancer and T-cell lymphoma
5. Adenocarcinoma of the jejunum (rare)
6. Peripheral neuropathy and gluten ataxia
7. Ulcerations and inflammation of the jejunum and ileum
8. Refractory coeliac disease despite strict gluten-free diet over 12 months

Q5. Would you expect to find elevated serum coeliac antibodies and intestinal mucosal atrophy in all patients with coeliac disease?

No. Patients may show positive coeliac autoantibodies in their sera, whereas intestinal mucosa on biopsies may be normal.

Overt intestinal mucosal atrophy may develop later over time. The serum antibodies usually appear earlier.

Mucosal atrophy may not be seen early in the disease development.

Q6. What are the investigations recommended for the diagnosis of coeliac disease?

1. Serological tests: Serum IgA anti-tissue transglutaminase (tTG) antibodies. In patients with concomitant IgA deficiency, IgG anti-tissue transglutaminase antibodies can be measured instead.
2. Biopsy of the small intestine and histological examination may be done.
3. Testing for HLA-DQ2 and DQ8 may be used to investigate people at risk (family members of a person with coeliac disease). The disease is unlikely in persons who are negative for both HLA-DQ2 and HLA-DQ8.
4. Other investigations may be performed for assessing complicated cases such as magnetic resonance imaging.

Q7. What are the intestinal histological changes characteristics of coeliac disease?

1. Increased number of intraepithelial lymphocytes
2. Elongation and changes in crypts
3. Total villous atrophy

REVIEW QUESTIONS

Q1. Which *one* of the following statements about coeliac disease is correct?

A. Negative serologic results exclude the diagnosis
B. A biopsy of small intestine is required in all patients
C. HLA-DQ2 haplotype is expressed in majority of patients
D. The disease is particularly common in black Africans

Q2. Which *one* of the following is *not* involved in the pathogenesis of coeliac disease?

A. The HLA-DQ2 haplotype
B. Non-HLA genes
C. Enzymatically modified gluten protein
D. Coeliac serum autoantibodies
E. IgA deficiency

Q3. Which *one* of the following is *not* among the clinical presentation of coeliac disease?

A. Iron-deficiency anaemia
B. Anaemia due to vitamin B12 and folate deficiency
C. Peripheral neuropathy
D. Osteomalacia
E. Acute renal failure

Q4. Which *one* of the following laboratory test results will help in the diagnosis of coeliac disease in patients with IgA deficiency?

A. Raised serum AST and ALT levels
B. Low serum vitamin D level
C. Raised serum alkaline phosphatase
D. Positive IgG antibodies against tissue transglutaminase
E. Raised fat content in the stools

Q5. Which *one* of the following skin lesions may be found with coeliac disease?

A. Allergic dermatitis
B. Dermatitis herpetiformis
C. Erythema multiforme
D. Hyperpigmentation
E. Livedo reticularis

ANSWERS

A1. **C.** HLA-DQ2 haplotype is expressed in 90% of patients. The HLA-DQ8 haplotype is expressed in 5% of patients. Negative serologic results do not exclude the diagnosis particularly if the clinical picture is consistent with coeliac disease. Intestinal biopsy is needed in these patients.

Patients, particularly children, with positive serological tests (anti-tTG antibody titre more than 10 times the upper limit of normal) and a clinical picture suggestive of coeliac disease do not need intestinal biopsy for confirmation of the diagnosis.

Coeliac disease is commonly seen in North Africans and in the Middle East population. It is rare in black Africans.

A2. **E.** Although IgA deficiency may occur concomitantly with coeliac disease, there is no evidence that IgA deficiency is involved in the pathogenesis of the disease.

A3. **E.** Acute renal failure is not among the clinical picture of coeliac disease.

Patients with coeliac disease commonly present with steatorrhoea, weight loss, chronic fatigue, depression, iron deficiency, vitamin B12 and folate deficiency, peripheral neuropathy, gluten ataxia, osteomalacia, fractures and proximal muscle weakness and pains.

A4. **D**. In patients with IgA deficiency and clinical presentation suggestive of coeliac disease, IgG rather than IgA anti-tissue transglutaminase antibodies are recommended for the diagnosis.

A5. **B**. Dermatitis herpetiformis is closely related to coeliac disease. It occurs in 2%–5% of patients with coeliac disease and consists of itchy vesicular skin rash on elbows, knees, buttocks and scalp.

TAKE-HOME MESSAGE

- The typical presentation of malabsorption includes weight loss, chronic diarrhoea, tiredness, abdominal distension, abdominal discomfort and flatulence.
- Atypical presentation may include iron-deficiency anaemia, osteoporosis, low serum albumin and/or dermatitis herpetiformis.
- The diagnosis is confirmed by serologic tests (IgA endomysial antibody and IgA tTG antibody tests).
- Both tests have a >90% sensitivity and >95% specificity for the diagnosis of coeliac disease. Endoscopic mucosal biopsy of the proximal jejunum is the standard method for confirming the diagnosis.
- Clinical improvement on gluten-free diet also supports the diagnosis.
- In patients with IgA deficiency and clinical presentation suggestive of coeliac disease, IgG rather than IgA anti-tissue transglutaminase antibodies are recommended for the diagnosis.
- Complications associated with untreated coeliac disease may include osteoporosis, impaired splenic functions, infertility and recurrent abortions in females, cancer and T-cell lymphoma, adenocarcinoma of the jejunum (rare), peripheral neuropathy and gluten ataxia.

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CASE 1.4

'As Dark as Coffee Grounds . . . '

Aaron William, a 58-year-old unemployed man, is brought by an ambulance to a local hospital because of vomiting about half a litre of blood. This is the first time for him to vomit blood and he describes its colour as dark as coffee grounds. Mr William has a long history of alcoholism and he gives an 8-month history of progressive increases of his abdominal girth. On examination, he looks cachectic, his resting pulse is 110/min, his blood pressure is 110/70 mm Hg and his sclera is icteric. There are several spider naevi over his face, shoulders and arms and he has palmar erythema of both hands. He has gynaecomastia and prominent abdominal veins. Abdominal examination reveals a significant protuberant abdomen, shifting dullness and enlarged spleen (about 6 cm below the left costal margin). The lower liver margin is difficult to detect, and he has testicular atrophy. He has pitting oedema of the ankles. Laboratory investigations show low haemoglobin, leukopenia and thrombocytopenia. He also has low serum albumen, a serum bilirubin of 100 μmol/L, elevated alkaline phosphatase and γ-glutamyl transferase, and elevated prothrombin time. Ultrasound of the abdomen shows a shrunken liver, splenomegaly and significant free fluid in the peritoneal cavity (ascites).

CASE DISCUSSION

Q1. On the basis of Mr William's presentation, what is your diagnosis?

Q2. What is your differential diagnosis?

Q3. What are the key clinical features of this disease? What are the scientific bases for these features?

Q4. What is the pathophysiology underlying these changes?

Q5. What are your management goals and management options?

ANSWERS

1. The findings of chronic alcoholism, vomiting blood, jaundice, spider naevi, palmar erythema, gynaecomastia, prominent abdominal veins, testicular atrophy, increased abdominal girth (due to ascites), splenomegaly, shrunken liver and peripheral oedema are consistent with the diagnosis of liver cirrhosis, portal hypertension and impairment of the liver functions. The laboratory investigation results of anaemia, leukopenia and thrombocytopenia are consistent with hypersplenism; the increased

serum alkaline phosphatase and serum bilirubin are consistent with cholestatic changes in the liver due to cirrhosis. The raised γ-glutamyl transferase is induced by alcohol and reflects cholestasis. The coagulopathy is due to impaired liver functions.

2. The differential diagnosis:
- Chronic viral hepatitis
- Chronic alcoholism
- Haemochromatosis
- Wilson disease
- α_1-Antitrypsin deficiency
- Primary biliary cirrhosis
- Secondary biliary cirrhosis
- Nonalcoholic fatty liver disease
- Heart failure
- Constrictive pericarditis

3. Clinical features

Symptoms:
- Asymptomatic
- Fatigue
- Anorexia
- Weight loss
- Muscle wasting
- Jaundice
- Abdominal distension (increased abdominal girth)
- Increased pruritus and itching marks
- Bulging in flanks
- Abdominal pain
- Vomiting blood
- History suggestive of the cause (e.g. tattooing, blood transfusion, intravenous drug use, alcohol consumption and travelling to countries where viral hepatitis is endemic)
- Severe symptoms and end-stage liver disease

Signs:
- Hands: Palmar erythema, pallor, white nails and finger clubbing; jaundice all over the skin in severe cases
- Eyes: Jaundice (yellowish discolouration of the sclerae) and pallor of the conjunctivae
- Spider naevi (on arms, shoulders, above the nipple lines, neck and face)
- Gynaecomastia in males
- Loss of axillary and pubic hair in males and females
- Abdominal distension and caput medusae
- Splenomegaly
- Decreased liver span and increased nodularity of the liver
- Shifting dullness and evidence of the presence of ascites

- Oedema of lower limbs
- Testicular atrophy in males
- Hepatorenal syndrome – oliguria/anuria
- Pleural effusions
- Hepatopulmonary syndrome
- Signs of hepatic cell failure
- Signs suggestive of encephalopathy

4. Laboratory investigations:

- Full blood count – low haemoglobin and thrombocytopenia (hypersplenism)
- Liver function tests – low serum albumin and raised international normalised ratio (INR)
- Liver transaminases and serum alkaline phosphatase – usually mildly elevated
- Blood electrolytes – decreased serum sodium
- Blood urea – may be within normal limits (because of liver failure and loss of urea cycle)
- Serum creatinine – elevated (when serum creatinine >130 mmol/L, it indicates poor prognosis)
- Serum iron studies including serum iron, total iron-binding capacity, ferritin and serum transferrin
- Serum folate and B12 level (folate deficiency may be present; B12 is usually within normal limits)
- Viral markers to exclude viral hepatitis as the cause
- Serum immunoglobulins
- Serum autoantibodies
- Serum α_1-antitrypsin
- Serum copper and ceruloplasmin to exclude Wilson disease
- Genetic markers
- α-Fetoprotein, to early detect hepatocellular carcinoma

Radiological investigations:

- Ultrasound examination – size and shape of the liver, fatty infiltration, fibrosis, echogenicity and nodularity
- FibroScan and transient elastography – to assess liver fibrosis
- CT scan of the upper abdomen – hepatosplenomegaly, dilated collaterals and enhanced scans, which can show defects of hepatocellular carcinoma
- Endoscopy – upper gastro-oesophageal endoscopy to detect oesophageal varices, and treatment (colonoscopy may be indicated)
- MRI to differentiate benign from malignant masses
- MRI angiography for vascular anatomy/changes

Liver biopsy:

- This is the 'gold standard' that helps in the diagnosis of severity and the staging of chronic liver hepatitis

- Histological assessment, and chemical assessment of iron (to exclude or confirm haemochromatosis) and copper (Wilson disease)
- Digital analysis of picrosirius red staining for collagen content in the specimens

5. Pathological features:

The causes of cirrhosis:

- Alcohol
- Chronic viral hepatitis (B or C)
- Nonalcoholic fatty liver disease
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Autoimmune liver disease
- Haemochromatosis
- Wilson disease
- α_1-Antitrypsin deficiency

It is important to note here that the most common three causes are (i) chronic viral hepatitis B or C, (ii) nonalcoholic fatty liver disease and (iii) chronic alcohol consumption.

The major complications of cirrhosis:

- Ascites
- Hepatic cell failure
- Hepatic encephalopathy
- Hepatocellular carcinoma
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Hepatic hydrothorax
- Portal vein thrombosis (may be associated with hepatocellular carcinoma)
- Spontaneous bacterial peritonitis (fever, abdominal pain, abdominal tenderness, altered mental status, sepsis)
- Variceal haemorrhage (haematemesis, melaena)
- Portal hypertension
- Portal hypertensive gastropathy (substantial bleeding, diffuse mucosal oozing, no other lesions can be found to explain anaemia)

The mechanisms involved in the pathogenesis of ascites in cirrhosis are as follows:

- Portal hypertension → portosystemic shunt → ↑ nitric oxide → splanchnic vasodilation
- Portosystemic shunt → decrease in systemic arterial pressure → activation of the renin–angiotensin system → elevation of aldosterone → salt and water retention by the kidneys
- Shift of blood to splanchnic circulation → underfilling of systemic circulation → sympathetic activation

- Underfilling of circulation → elevated atrial natriuretic hormone secretion → increased glomerular filtration → ↑ loss of water and sodium → inhibition of renin–angiotensin system
- Cirrhosis → decreased albumin synthesis → decreased oncotic pressure → transduction of fluid → ascites
- Increased blood in splanchnic circulation → vasodilation of splanchnic circulation + increased capillary permeability of the intestinal capillaries → ascites

The pathophysiological changes involved in the development of varices in patients with liver cirrhosis are as follows:

- Portal hypertension
- Increased resistance to portal blood flow and increased portal venous blood flow
- Increased portal-pressure gradient (the differences between portal vein pressure and hepatic vein pressure)
- Distortion of vascular architecture by fibrosis
- Endothelial dysfunction and decreased nitric oxide bioavailability
- Formation of portosystemic collaterals (gastro-oesophageal varices form the important collateral development as a result of the changes)

6. Management goals and options:

- Prevention: Hepatitis A and B vaccination
- Treatment of the cause of cirrhosis
- Management of complications
- Regular measurement of α-fetoprotein and ordering ultrasound of the liver (every 6 months) for early detection of hepatocellular carcinoma
- Salt restriction
- Stopping alcohol
- Avoiding taking aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) because of the risks of bleeding
- Patient education

Fig. 1.4.1 summarises the management of cirrhosis.

BACK TO BASIC SCIENCES

Q1. What are the risk factors for alcoholic liver disease?

- Gender: Women are at a higher susceptibility to alcoholic liver disease.
- Quantity and duration: 40–80 g/day of ethanol produces fatty liver and 160 g/day for 10–20 years produces cirrhosis.
- Hepatitis C: Together with higher intake of ethanol, it increases the severity of liver pathology at a younger age and decreases survival. Alcohol also decreases the efficacy of interferon-based antiviral therapy.
- Genetics: Gene polymorphism of alcohol dehydrogenase may lead to alcoholic liver disease.

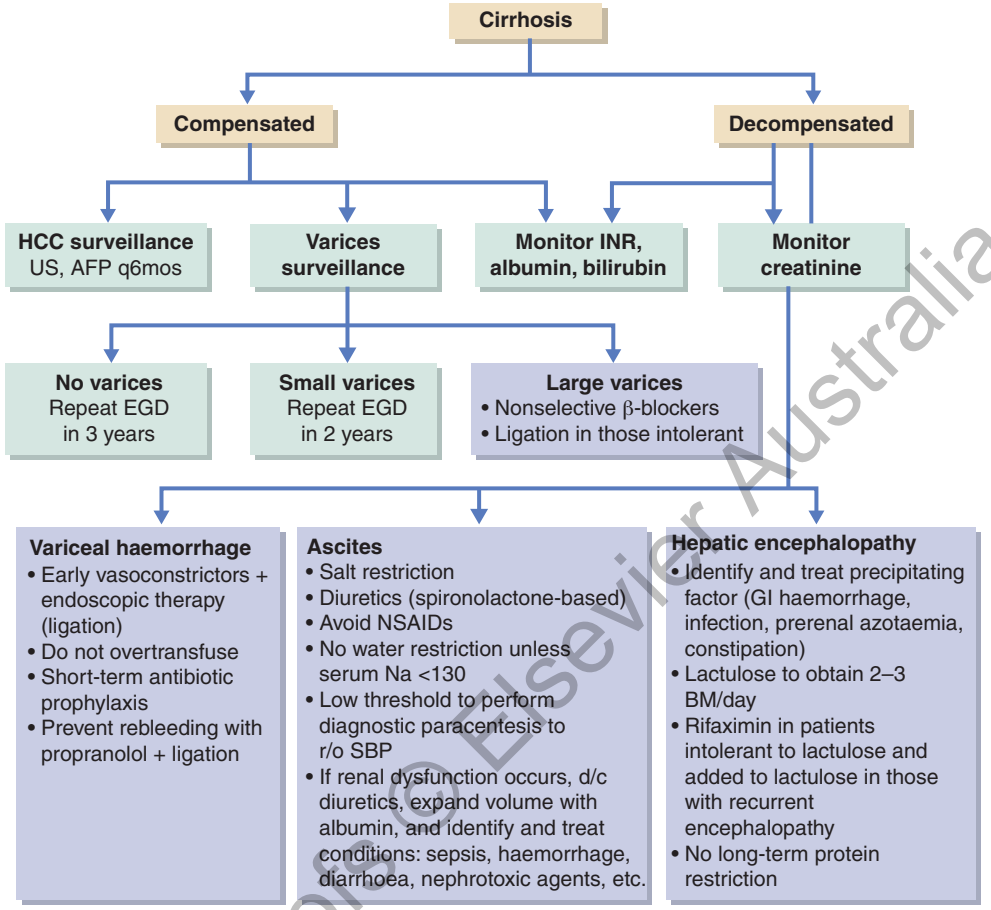

Figure 1.4.1 Management of cirrhosis. AFP, α-fetoprotein; BM, bowel movement; d/c, discontinue; EGD, oesophagogastroduodenoscopy; GI, gastrointestinal; HCC, hepatocellular carcinoma; INR, international normalised ratio; Na, sodium; NSAIDs, nonsteroidal anti-inflammatory drugs; r/o, rule out; SBP, spontaneous bacterial peritonitis; US, ultrasound. *(Source: Goldman L, Schafer AI. Goldman-Cecil Medicine. 25th ed. Elsevier; 2016.)*

- Obesity/fatty liver: It may play a role by affecting fatty acid synthesis and transport.
- Beverage type: It is not clear whether beverage type is a risk factor.

Q2. What is the threshold for developing alcoholic liver disease?

- Men: Intake of >60–80 g/day of alcohol for 10 years (about 5–7 beers/day)
- Women: Intake of 20–40 g/day of alcohol for 10 years (about 1.5–3 beers/day)

Q3. Describe the pathogenesis of alcoholic liver disease.

a. Three pathological processes are involved: (i) autoimmune response (as a result of adduct formation), (ii) fibrotic response as a result of stellate cell activation and collagen production and (iii) inflammatory response (involving Kupffer cells and the release of TNF-α, IL-1, IL-6, TGF-β).

b. Alcohol has a direct hepatotoxic effect and also causes the production of toxic protein–aldehyde adducts.
c. Alcohol increases lipogenesis and inhibits fatty acid oxidation. These changes trigger fatty liver changes and stellate cell activation.
d. Endotoxins, oxidative stress, immunological activity and proinflammatory cytokines contribute to liver injury.
e. The transition between fatty liver and the development of alcoholic hepatitis is characterised by ballooning degeneration, necrosis, polymorphonuclear infiltration and fibrosis in the periventricular and perisinusoidal space of Disse. Mallory bodies may be present but their presence is neither specific nor necessary for the diagnosis.
f. Alcoholic hepatitis is the precursor of the development of liver cirrhosis.

Q4. What are the causes of cirrhosis?

- Alcoholism
- Chronic viral hepatitis (B and C)
- Autoimmune hepatitis
- Nonalcoholic steatohepatitis
- Primary biliary cirrhosis
- Secondary biliary cirrhosis
- Cardiac cirrhosis
- Haemochromatosis
- Wilson disease
- α_1-Antitrypsin deficiency

Q5. What is the definition of cirrhosis?

- Cirrhosis is defined as histopathological changes associated with a variety of clinical manifestations and complications. The histopathological changes comprise fibrosis and architectural distortion, with the formation of regeneration nodules, resulting in a decrease in hepatocellular mass and altered blood supply and liver functions. The pathological changes may start with fatty liver infiltration, transition to hepatitis and activation of hepatic stellate cells to produce collagen and liver fibrosis.
- The histopathological changes in the liver can be staged (stage 3, characterised by nodularity and bridging fibrosis; and stage 4, cirrhosis).
- These changes will interfere with liver functions. Patients with decompensated liver will need liver transplantation.
- Cirrhosis may be (i) micronodular cirrhosis: regenerating nodules <1 cm (this is typical of alcoholic liver disease); and (ii) macronodular cirrhosis: larger regenerating nodules up to several centimetres in diameter (this is typical of cirrhosis caused by viral hepatitis and postnecrotic [posthepatic] cirrhosis).

Q6. What is portal hypertension?

- Portal hypertension is a complication of decompensated liver and comprises (i) development of ascites; (ii) bleeding from oesophageal varices; (iii) splenomegaly; (iv) loss of hepatic function (decompensation) causing jaundice, coagulopathy, hypoalbuminaemia and interference with oestrogen metabolism; and (v) contribution to the development of portosystemic encephalopathy.

Q7. What is Zieve syndrome?

It is a type of haemolytic anaemia with spur cells and acanthocytosis commonly observed in patients with severe alcoholic hepatitis.

Q8. What are the causes of hyperbilirubinaemia?

(i) Prehepatic causes: Haemolytic anaemia (autoimmune, enzyme deficiency, haemoglobinopathy), blood transfusions and haematoma

(ii) Hepatic causes: Hereditary disorders such as Gilbert syndrome and Crigler–Najjar syndrome types I and II, drug-induced liver injury, hepatocellular diseases, viral hepatitis, chronic hepatitis, cirrhosis, alcohol-induced liver injury, alcoholic hepatitis, cholestasis and recurrent jaundice of pregnancy

(iii) Posthepatic causes: Drugs interfering with bilirubin efflux, extrahepatic cholestasis, cholecystitis, cancer of the head of the pancreas, bile duct cancer and biliary stones

Q9. Discuss the mechanisms underlying the development of ascites in patients with cirrhosis.

- The main underlying mechanisms are related to portal hypertension and renal salt and water retention.
- Portal hypertension and increased resistance to blood flow is caused by the following mechanisms: (i) development of hepatic fibrosis and disruption of the normal hepatic architecture causing resistance to normal blood flow in the liver; (ii) activation of hepatic stellate cells resulting in fibrogenesis causing smooth muscle contraction and fibrosis; and (iii) decreased endothelial nitric oxide synthetase (eNOS) production, resulting in decreased nitric oxide production and increased intrahepatic vasoconstriction.
- On the other hand, the circulating levels of nitric oxide are increased (contrary to the low intrahepatic levels), together with increased levels of vascular endothelial growth factor and tumour necrosis factor. These three factors cause splanchnic arterial vasodilation and pooling of blood and decreased renal perfusion.
- The kidneys respond by (i) stimulation of the renin–angiotensin system; (ii) increased antidiuretic hormone release; and (iii) decreased natriuretic hormone release.
- Hypoalbuminaemia: The decreased synthesis of albumin due to liver cell failure results in decreased intravascular oncotic pressure and the leakage of albumin through the lymph into the peritoneal cavity. The increased levels of albumen in the peritoneal cavity favour ascites formation.

- Plasma vasopressin and epinephrine levels are elevated as a result of volume depletion, causing reinforcement of the kidneys and vascular mechanisms.

Q10. Discuss portosystemic encephalopathy in patients with cirrhosis and needed management.

Generally this includes neuropsychiatric changes associated with portosystemic shunting with hepatocellular failure. There are three types of hepatic encephalopathy:

Type A: Hepatic encephalopathy associated with acute liver failure.

Type B: Hepatic encephalopathy associated with portosystemic bypass with no hepatic failure.

Type C: Hepatic encephalopathy associated with cirrhosis and portosystemic shunting.

So type C is the type related to our question.

The pathogenesis of hepatic encephalopathy in cirrhosis and portosystemic shunting is as follows:

- Hyperammonaemia (the failing liver cannot metabolise ammonia)
- Portal hypertension $\longrightarrow$ inflow of toxins produced in the gut (phenols, thiols = mercaptans, short-chain fatty acids, fatty acids) to systemic circulation and end in the brain
- Cytokines and bacterial endotoxins
- Enterally produced γ-aminobutyric acid (GABA) and endogenous benzodiazepines resulting in GABAergic signalling
- Production of false transmitters (octopamine and diazepam)
- Cerebral ischaemia and loss of cerebral autoregulatory blood flow
- Changes in cerebral vascular resistance

Management:

- Eliminate ammoniagenic luminal bacteria – give nonabsorbable antibiotics such as neomycin.
- Restrict protein intake.
- Regulate luminal acidification – give lactulose.
- Treat constipation.
- There is no need for treatment with mannitol or hyperventilation unless there is evidence of cerebral oedema.
- Perform trials of branched-chain amino acids such as isoleucine, leucine and valine to reduce the production of false transmitters.

Q11. What is hepatorenal syndrome?

- This refers to acute renal failure with advanced chronic liver disease (cirrhosis and ascites).
- There is evidence of renal failure and decreased urine output but no proteinuria.
- No histopathological changes in the kidneys occur. The whole change is physiological affecting the renal function. The condition is reversible and renal functions are resumed after liver transplantation.

- Renal function impairment is related to intense systemic arteriolar vasodilation, reduced systemic vascular resistance and renal circulatory vasoconstriction and reduced renal blood flow.
- Other factors involved in the pathogenesis are renin–angiotensin–aldosterone system, sympathetic nervous system and renal prostaglandins.
- The renal failure in these patients is irreversible unless liver transplantation is performed.

REVIEW QUESTIONS

Q1. Which *one* of the following is *not* part of the mechanisms underlying the formation of ascites in cirrhosis?
A. Portal hypertension
B. Hypoalbuminaemia
C. Stimulation of renin–angiotensin
D. Elevated antidiuretic hormone release
E. Elevated intrahepatic nitric oxide

Q2. Which *one* of the following is associated with direct (conjugated) hyperbilirubinaemia?
A. Haemolytic anaemia
B. Drugs interfering with hepatic bilirubin uptake
C. Intrahepatic cholestasis
D. Gilbert syndrome

Q3. Which *one* of the following is *not* a mechanism underlying liver injury caused by chronic ethanol intake?
A. Formation of adducts
B. Decreased TNF-α and IL-1
C. Stimulation of stellate cells
D. Lipid peroxidation
E. Autoimmune response

Q4. Which *one* of the following is *not* a cause of liver cirrhosis?
A. Viral hepatitis C
B. Alcoholism
C. Primary biliary cirrhosis
D. α_1-Antitrypsin deficiency
E. Epstein–Barr virus

Q5. Which *one* of the following is the function of the hepatic stellate cells?
A. Metabolism of vitamin A
B. Production of collagen
C. Synthesis of albumin

D. Immunological response
E. Conjugation of bilirubin

ANSWERS

A1. **E.** The intrahepatic nitric oxide is reduced in liver cirrhosis and this contributes to intrahepatic vascular vasoconstriction. This is because of decreased eNOS production. On the other hand, the extrahepatic nitric oxide is elevated causing splanchnic arterial vasodilation and pooling of blood.

A2. **C.** Intrahepatic cholestasis causes direct (conjugated) hyperbilirubinaemia.

A3. **B.** Chronic ethanol intake causes Kupffer cell stimulation and the release of TNF-α, IL-1, IL-6 and TGF-β.

A4. **E.** Epstein–Barr virus infection may cause hepatitis. However, usually patients recover without long-term complications such as cirrhosis. There are some reports that Epstein–Barr virus infection may cause liver cancer.

A5. **B.** Stimulation of hepatic stellate cells results in collagen production and liver fibrosis. This is part of the mechanisms involved in liver cirrhosis.

TAKE-HOME MESSAGE

- Patients with cirrhosis may be asymptomatic. However, the following symptoms may be present: fatigue, anorexia, weight loss, muscle wasting, jaundice, abdominal distension, increased pruritus, itching marks, bulging in flanks, abdominal pain, vomiting blood, a history suggestive of the cause (e.g. tattooing, blood transfusion, intravenous drug use, alcohol consumption) or severe symptoms and end-stage liver disease.
- The clinical signs in cirrhosis are (i) hands: palmar erythema, pallor, white nails and finger clubbing (in severe cases, jaundice is all over the skin); (ii) eyes: jaundice (yellowish discolouration of the sclerae) and pallor of the conjunctivae; (iii) spider naevi (on the arms, shoulders, above the nipple lines, neck and face); (iv) gynaecomastia in males; (v) loss of axillary and pubic hair in males and females; (vi) abdominal distension and caput medusa; (vii) splenomegaly; (viii) decreased liver span and increased nodularity of the liver; (ix) shifting dullness and evidence of the presence of ascites; (x) oedema of the lower limbs; (xi) testicular atrophy in males; (xii) hepatorenal syndrome – oliguria/anuria; (xiii) pleural effusions; (xiv) hepatopulmonary syndrome; and (xv) signs of hepatic cell failure and signs suggestive of encephalopathy
- The causes of cirrhosis are alcohol, chronic viral hepatitis (B or C), nonalcoholic fatty liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune liver disease, haemochromatosis, Wilson disease, α_1-antitrypsin deficiency and cryptogenic cirrhosis.

- The most common three causes of cirrhosis are (i) chronic viral hepatitis B or C; (ii) nonalcoholic fatty liver disease; and (iii) chronic alcohol consumption.
- Portal hypertension is a complication of decompensated liver and comprises (i) development of ascites; (ii) bleeding from oesophageal varices; (iii) splenomegaly; (iv) loss of hepatic function (decompensation) causing jaundice, coagulopathy, hypoalbuminaemia and interference with oestrogen metabolism; and (v) contribution to the development of portosystemic encephalopathy.
- The pathophysiology underlying the development of portal hypertension in patients with cirrhosis includes (i) increased resistance to portal blood flow and increased portal venous blood flow; (ii) increased portal-pressure gradient (the differences between portal vein pressure and hepatic vein pressure); (iii) distortion of vascular architecture by fibrosis; (iv) endothelial dysfunction and decreased nitric oxide bioavailability; and (v) formation of portosystemic collaterals.
- The goals and options of management are (i) prevention: hepatitis A and B vaccination; (ii) treatment of the cause of cirrhosis; (iii) management of complications; (iv) regular measurement of α-fetoprotein and ultrasound of the liver (every 6 months) for early detection of hepatocellular carcinoma; (v) salt restriction; (vi) stopping alcohol; (vii) avoiding taking aspirin or NSAIDs because of the risks of bleeding; and (viii) patient education.

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CASE 1.5

'There Is Blood in My Stool . . . '

Sue Erving, a 38-year-old manager, presents to her local general practitioner because she is suffering from abdominal pains all over her tummy and urgency to go to the toilet. She has had six to seven loose bowel motions a day for the last 5–7 days and has noticed that her stools contain blood. She feels incomplete emptying her bowels. She also has mild joint pains. She had similar episodes in the past. On examination, her pulse rate is 90/min, her blood pressure is 110/80 mm Hg and her body temperature is 37.8°C. Abdominal examination shows tenderness all over her abdomen but no rigidity. Per rectum examination shows blood on the examining gloved finger. The complete blood count reveals a haemoglobin level of 90 g/L (normal = 115–160 g/L) and an erythrocyte sedimentation rate (ESR) of 45 (normally <20). Further assessment, after hospital admission, including colonoscopy and biopsy, reveals that her colonic mucosa, particularly the rectum and the descending colon, is inflamed.

CASE DISCUSSION

Q1. On the basis of Sue's presentation, what is your diagnosis?

Q2. What is your differential diagnosis?

Q3. What are the key clinical features of this disease? What are the scientific bases for these features?

Q4. What is the pathophysiology underlying these changes?

Q5. What are your management goals and management options?

ANSWERS

1. The findings of bloody diarrhoea, abdominal pain all over, urgency, tenesmus, fever, arthralgia, abdominal tenderness, past history of similar episodes together with anaemia, raised ESR and colonoscopic findings of inflammation limited to the colonic mucosa are suggestive of ulcerative colitis. Further assessment is needed to confirm the diagnosis.
2. The differential diagnosis:
   - Infectious colitis (*Salmonella, Shigella, Campylobacter,* enteroinvasive *Escherichia coli*)
   - Crohn disease
   - Colon cancer
   - Amebiasis

- Antibiotic-associated diarrhoea (*Clostridium difficile* infection)
- Ischaemic colitis
- Radiation colitis
- Cytomegalovirus colitis (in immunocompromised patients)
- Infectious proctitis (gonorrhoea, chlamydia, herpes, syphilis)
- Microscopic colitis
- Viral or parasitic colitis (in immunocompromised patients)

The following are essential for the diagnosis of ulcerative colitis:

- Bloody diarrhoea, lower abdominal pain, tenesmus, urgency, anaemia, negative stool analysis (for *C. difficile* toxins, bacteria, ova and parasites) and negative stool cultures
- Sigmoidoscopy showing inflammation limited to colonic mucosa

3. Symptoms and signs:

- Diarrhoea, rectal bleeding, crampy abdominal pain, faecal urgency (due to colonic inflammation and changes in colonic motility), tenesmus, passage of mucus and evidence of malnutrition.
- When the disease extends beyond the rectum, the blood is usually mixed with stool.
- Diarrhoea is usually nocturnal and postprandial.
- Other symptoms in moderate or severe disease include fever, anorexia, nausea, vomiting and weight loss.
- The clinical course of ulcerative colitis is marked by exacerbations and remissions.
- The main signs are tenderness of the abdomen, tender anal canal and blood on rectal examination. Signs of peritonitis may be found if there are complications such as colonic perforation.
- Extracolonic signs may be present during disease activity (present in 40%–50% of patients) such as arthralgia, oral ulcers, erythema nodosum, pyoderma gangrenosum, episcleritis, uveitis, ankylosing spondylitis and sclerosing cholangitis. Fig. 1.5.1 summarises the complications of inflammatory bowel disease.
- Laboratory findings: During disease activity, acute-phase reactants are elevated: Elevated ESR, elevated platelet count, elevated C-reactive proteins (CRPs) and low haemoglobin are also noted.
- Faecal calprotectin and lactoferrin levels are sensitive and correlate with histological inflammation and predict relapse.
- Serum albumin levels drop rapidly in severe inflammation and severely ill patients.
- Leukocytosis may be present but it is not specific.
- Sigmoidoscopy is used to assess the severity and extent of the disease: (i) mild disease: erythema, decreased vascular pattern and mild friability; (ii) moderate disease: marked erythema, absent vascular patterns and moderate friability; and (iii) severe disease: bleeding and ulcerations. Colonoscopy should not be

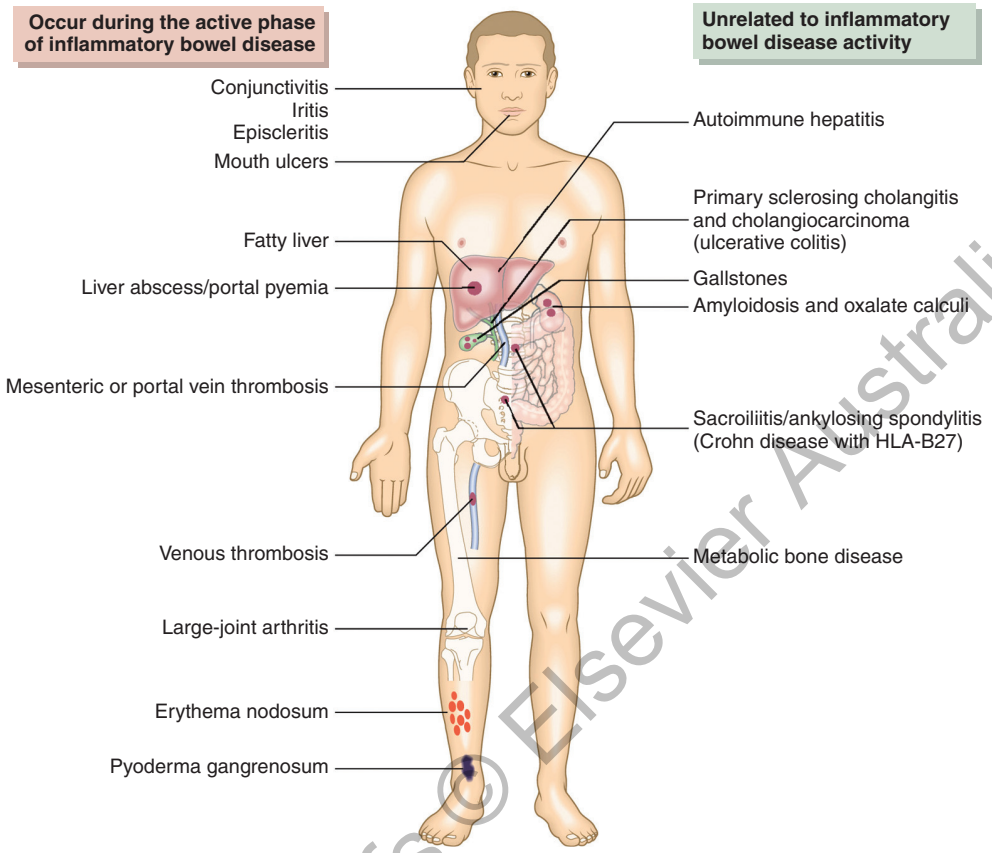

Figure 1.5.1 Complications of inflammatory bowel disease. *(Source: Ralston S, Penman I, Strachan M, Hobson R. Davidson's Principles & Practice of Medicine. 23rd ed. UK: Elsevier; 2018.)*

performed in patients with fulminant disease (risk of perforation) but be indicated after improvement.

- Abdominal radiology: Limited use. Barium enema may precipitate toxic megacolon (colonic dilatation >6 cm on radiographs together with toxic signs and risk of perforation).
- CT scan is not as useful as endoscopy.

4. Pathological features:

- The disease starts in the rectum and extends proximally to involve the colon.
- About 40%–50% of patients have the rectum and rectosigmoid involved, 30%–40% have the inflammation beyond the rectosigmoid and only 20% have the whole colon affected.
- The terminal ileum (2–3 cm) may be inflamed in 10%–20% of patients (backwash ileitis).
- In mild disease, the mucosa is erythematous and has a granular surface.
- In more severe disease, the mucosa is haemorrhagic, ulcerated and oedematous.

- In long-standing cases, the colon becomes featureless, shortened and narrowed.

5. The goals of management are as follows:
- Induction of remission
- Maintenance of remission (maintain symptom-free status)
- Surgical management in patients with complications or patients who failed to respond to medical treatment

A. Induction of remission: Managed according to the level of clinical activity and extent of the disease
- 5-Aminosalicylates (orally, rectally)
- Glucocorticoids (topical, orally)
- Immunosuppressive agents (cyclosporine, azathioprine, 6-mercaptopurine)
- Infliximab (a monoclonal antibody against tumour necrosis factor-alpha [TNF-α])

B. Maintenance of remission
- There is no place for glucocorticoids in the maintenance of remission because of the marked side effects associated with long-term use.
- Maintenance of remission is usually achieved with the use of 5-aminosalicylates orally and/or rectally.
- Azathioprine and 6-mercaptopurine can be used in the maintenance of remission if 5-aminosalicylates are ineffective.

C. Indications for surgery in ulcerative colitis
- Failure of medical therapy
- Toxic megacolon
- Perforation of colon
- Uncontrolled bleeding
- Side effects of medications
- Development of strictures that cannot be resolved via endoscopy
- Development of dysplasia or mass of cancer (colorectal cancer)

Surgical options:
- Traditional proctocolectomy with ileostomy
- Total proctocolectomy with ileal pouch–anal anastomosis
- Proctocolectomy with ileorectal anastomosis
- Proctocolectomy with the formation of a continent ileostomy or Koch's pouch

BACK TO BASIC SCIENCES

Q1. Summarise the main differences between ulcerative colitis and Crohn disease.

There are several differences between ulcerative colitis and Crohn's disease. Table 1.5.1 summarises these differences regarding pathology, clinical picture, endoscopic findings, and management.

Table 1.5.1 Differences between ulcerative colitis and Crohn's disease

Parameter	Ulcerative colitis	Crohn disease
1. Pathology	• Inflammation is restricted to mucosal layer • Continuous inflammation (no 'skip' areas) • Mucosa is infiltrated with lymphocytes and plasma cells • Goblet cells are characteristically absent • Distorted crypts, crypt abscess	• All layers are affected (transmural) • Inflammation is not continuous (skip areas) • Epithelioid granulomas are present
2. Clinical picture	• Rectal bleeding • Bloody diarrhoea • Fatigue • During active disease: Systemic symptoms such as fever, arthritis, erythema nodosum, conjunctivitis, episcleritis, scleritis, mouth ulcers (in 25%–30% of patients)	• Abdominal pain • Fatigue • Nausea, vomiting • Symptoms similar to those of acute appendicitis • Any part of the gastrointestinal tract can be affected (mouth to anus)
3. Endoscopic	• Rectum and descending colon are commonly affected (left > right colon) • Early signs: Loss of vascular patterns with hyperaemia, and mucosal oedema • Mild cases: Mucosa is granular and there is mucopus and contact bleeding • Advanced (severe) cases: Deep ulceration and bleeding	• Ileum is commonly affected (right > left colon) • Rectum is typically spared • Segmental: Skip areas • Aphthoid or confluent deep serpiginous pleomorphic ulcers • Cobblestone pattern • Deep fissures, fistulas, strictures • Increased wall thickness
4. Management	Medical treatment **1.** Induction of remission (5-aminosalicylates, corticosteroids, cyclosporine, infliximab) **2.** Maintenance of remission (5-aminosalicylates, azathioprine, 6-mercaptopurine, methotrexate) Surgical treatment **1.** Indications: Failure of medical therapy, toxic megacolon, perforation, uncontrolled bleeding, cancer **2.** Options: Traditional proctocolectomy with ileostomy, total proctectomy with ileal pouch–anal anastomosis, proctocolectomy with ileorectal anastomosis, proctocolectomy with the formation of a continent ileostomy or Koch's pouch	Aims • Induction and maintenance of remission • Heal the mucosa • Optimise the quality of life for the patient • Patient education Management depends on the site, extent, activity of the disease and presence of complications Drugs commonly used in management: Prednisolone, budesonide, azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab, certolizumab Surgical management and options

Q2. What are the roles of ESR and CRP in the diagnosis of ulcerative colitis?
The diagnosis of ulcerative colitis is based on the clinical picture, stool analysis and stool culture, and sigmoidoscopy findings. Abnormally raised ESR and CRP are relatively insensitive and should not be relied on to exclude the diagnosis.

Q3. What is the role of faecal levels of calprotectin and lactoferrin in detecting inflammatory bowel disease?
Elevated faecal calprotectin and lactoferrin levels are sensitive for detecting inflammatory bowel disease. Faecal calprotectin and lactoferrin levels are sensitive and correlate with histological inflammation and predict relapse. However, these tests do not replace the role of endoscopy.

Q4. Discuss the differential diagnosis of ulcerative colitis. What are the clinical features of each disease/condition you mention? How would you exclude each disease?
The differential diagnosis of ulcerative colitis includes infectious colitis, Crohn disease, ischaemic colitis, microscopic colitis and radiation colitis (Table 1.5.2).

Table 1.5.2 Differential diagnosis and clinical features Crohn disease, with evaluating actions of each disease/condition

Disease/condition	Clinical features	Evaluation/exclusion
1. Bacterial colitis	Loose bowel motions Abdominal pain, tenderness	Stool culture Stool testing for *E. coli* O157:H7
2. Amoebic colitis	Exposure or travel to endemic area Tenesmus, loose motions, mucus and blood in stool, nausea, abdominal tenderness	Stool microscopy Respond to antiamoebic medications
3. *Clostridium difficile* infection	History of antibiotic treatment	Stool examination for *C. difficile* toxins
4. Crohn disease	Shares similar presentation and should be always considered in the differential diagnosis	Endoscopy and histological examination of biopsies
5. Ischaemic colitis	Patients have risk factors for vascular disorders	Endoscopy and histological examination of biopsies
6. Microscopic colitis	Usually no blood in stools	Endoscopy and histological examination of biopsies
7. Viral or parasitic colitis	Patients are immunocompromised	Endoscopy and histological examination of biopsies
8. Radiation colitis	Patients are exposed to radiation therapy of the abdomen or pelvis	Endoscopy and histological examination of biopsies for grading the severity of the disease

Q5. What are the main complications of ulcerative colitis?

- Massive severe bleeding (occurs in less than 1% of patients)
- Toxic megacolon: Diameter >6 cm, affecting the transverse or right colon, may be triggered by electrolyte imbalance and use of narcotics (about 50% of patients recover, and it is managed by urgent colectomy)
- Perforation (as a result of toxic megacolon)
- Strictures
- Colon cancer (the risk increases after 8–10 years of diagnosis)

Q6. How would you rank the severity of active ulcerative colitis?

The severity of active ulcerative colitis could be mild, moderate or severe (Table 1.5.3).

Table 1.5.3 Differential diagnosis of ulcerative colitis

Severity	Number of bowel motions (per day)	Blood in stool	Fever	ESR (mm)	Systemic toxicity
Mild	<4	Small	None	<30	None
Moderate	4–6	Moderate	About 37.5°C		Absent
Severe	7–10	Severe	>37.5°C	>30	Present

ESR, erythrocyte sedimentation rate.

Q7. What is the scientific basis of using infliximab in the treatment of moderate to severe cases?

Infliximab is an anti-TNF-α antibody. The treatment is based on the pathogenesis of ulcerative colitis and the fact that one of the major proinflammatory cytokines involved in the pathogenesis is TNF-α. Experimental and human studies showed that blocking TNF-α moderates the course of the disease.

Q8. Summarise the medical treatment of ulcerative colitis.

The medical treatment of ulcerative colitis, including mechanism of action, dosage and adverse effects, is summarised in Table 1.5.4.

Table 1.5.4 Medical treatment of ulcerative colitis

Medication (route)	Mechanism of action	Dosage in active disease	Maintenance dosage	Adverse effects
5-aminosalicylic acid (oral)	• Unknown • Modulation of inflammatory mediators • Inhibition of tumour necrosis factor (TNF)	2–4.8 g/day in three divided doses	1.2–2.4 g/day	Interstitial nephritis

Table 1.5.4 Medical treatment of ulcerative colitis—cont'd

Medication (route)	Mechanism of action	Dosage in active disease	Maintenance dosage	Adverse effects
5-aminosalicylic acid (enema)		1–4 g/day	2–4 g daily, every third day	Rectal irritation Difficult to retain
Prednisone (oral)	• Anti-inflammatory and immunosuppressive effects • Suppression of cell-mediated immunity • Suppression of humoral immunity causing B-cells to express lower amounts of IL-2 and IL-2 receptors • Inhibit the gene coding for several cytokines and TNF-α	40–60 mg/day until clinical improvement, and then gradual taper by 5–10 mg/week	Not recommended	Adrenal suppression Osteoporosis Cushingoid changes Infection Peptic ulcer Depression Impaired wound healing
Hydrocortisone (enema)		100 mg	Not recommended	Rectal irritation Difficult to retain
Hydrocortisone (10% foam)		90 mg once or twice per day	Not recommended	Rectal irritation
Cyclosporine (IV)	• Immunosuppression • Inhibition of T-lymphocytes (mainly inhibition of T1-helper and T1-suppressor) • Inhibition of lymphokine production	2–4 mg/kg/day	Not recommended	Infection Cardiovascular changes Nephrotoxicity
Azathioprine (oral)	• It has cytotoxic and immunosuppressive activities • Azathioprine is a prodrug, converted in the body to active 6-mercaptopurine • It inhibits purine synthesis ⟶ inhibits cell proliferation, particularly lymphocytes and leukocytes	Not recommended	1.5–2.5 mg/kg/day	Infection Bone marrow suppression Allergic reaction

Continued

Table 1.5.4 Medical treatment of ulcerative colitis—cont'd

Medication (route)	Mechanism of action	Dosage in active disease	Maintenance dosage	Adverse effects
Infliximab (IV)	• Not clearly understood • Blocking TNF-α via apoptosis of TNF-α-expressing inflammatory cells • Apoptosis of inflammatory cells including T-cells and monocytes	5–10 mg/kg on 0, 2 and 6 weeks	5–10 mg/kg every 4–8 weeks	Expensive Infection Lymphoma

REVIEW QUESTIONS

Q1. Which *one* of the following is the first line of treatment of ulcerative colitis?
A. 6-Mercaptopurine
B. Infliximab
C. Cyclosporine
D. 5-Aminosalicylates
E. Glucocorticoids

Q2. Which *one* of the following decreases the incidence of ulcerative colitis?
A. High fat in the diet
B. Appendectomy in early life
C. Smoking cessation
D. Being of North European descent

Q3. Which *one* of the following is *not* involved in the pathogenesis of ulcerative colitis?
A. A breakdown in gut immune system tolerance
B. Alteration in the composition of the gut microbiota
C. Abnormalities in humoral and cellular adaptive immunity
D. Autoimmunity
E. Atypical Th1 response as evident by increased production of interferon-gamma

Q4. Which *one* of the following is *not* a complication of ulcerative colitis?
A. Small intestinal fistulas
B. Autoimmune liver disease
C. Toxic megacolon
D. Colorectal cancer
E. Clotting abnormalities

Q5. Which *one* of the following medications is recommended as maintenance treatment of ulcerative colitis?

A. Prednisone orally
B. Hydrocortisone enema
C. Cyclosporine intravenously
D. Hydrocortisone foam
E. 5-Aminosalicylic acid orally

Q6. Which *one* of the following histological features is *not* found in ulcerative colitis?

A. Infiltration of colonic mucosa with lymphocytes
B. Infiltration of colonic mucosa with plasma cells
C. Epithelioid granulomas
D. Mucosal ulcerations
E. Crypt abscess

ANSWERS

A1. **D.** The first line of treatment of ulcerative colitis is 5-aminosalicylates. The treatment is designed with consideration for the level of clinical activity and extent of disease.

A2. **B.** Appendectomy (surgical removal of an inflamed appendix) in early life is reported to be associated with a decreased incidence of ulcerative colitis. Smoking cigarettes is associated with milder disease, fewer hospitalisations and reduced need for medications. The incidence of ulcerative colitis is lowest in Asia, although there is recent progressive rise in the incidence.

A3. **E.** In Crohn disease, there is atypical Th1 response as evident by increased secretion of interferon-gamma. However, in ulcerative colitis, there is atypical Th2 response as shown by the presence of nonclassical natural killer T-cells in the colon and increased IL-13 production.

A4. **A.** Small intestinal fistulas occur in Crohn disease. They are less likely to be seen in ulcerative colitis.

A5. **E.** Corticosteroids should not be used in maintenance treatment because of their side effects. Usually 5-aminosalicyclic acid is preferred.

A6. **C.** Epithelioid granulomas are characteristically seen in Crohn disease and not in ulcerative colitis.

TAKE-HOME MESSAGE

- Inflammatory bowel disease comprises ulcerative colitis and Crohn disease. The incidence and prevalence of ulcerative colitis are higher compared to those of Crohn disease.

- Smoking is associated with milder ulcerative colitis, fewer hospitalisations and a reduced need for hospitalisation. Also appendectomy in early years reduces the incidence of ulcerative colitis.
- Several mechanisms are involved in the pathogenesis of ulcerative colitis including genetics (genetics are less important, environmental factors are more important in ulcerative colitis), breakdown in gut immune system tolerance, alteration in the composition of gut microbiota, abnormalities in humeral and cellular adaptive immunity, autoimmunity and atypical Th2 response (increased production of IL-13 and nonclassical natural killer T-cells).
- Ulcerative colitis starts in the rectum and extends proximally to involve the colon.
- On the other hand, Crohn disease may involve any part of the gastrointestinal tract from the mouth to the anus (commonly involves the ileocaecal region).
- Clinically patients with ulcerative colitis commonly present with bloody diarrhoea, lower abdominal pain, tenesmus, urgency and anaemia.
- Sigmoidoscopy shows that inflammation limited to colonic mucosa is essential for confirming the diagnosis. Abdominal radiographs and CT scans of the abdomen may be needed but not informative when compared with endoscopy and histological examinations.
- Ulcerative colitis is associated with several complications including toxic megacolon, perforation, uncontrolled rectal bleeding, development of strictures, development of dysplasia and colorectal cancer.
- Ulcerative colitis is associated with systemic, extracolonic complications including arthritis, erythema nodosum, pyoderma gangrenosum, mouth ulcers, autoimmune liver disease, fatty liver, sclerosing cholangitis, eye changes (anterior chamber – conjunctivitis, scleritis, episcleritis, uveitis, iritis), thrombosis, clotting abnormalities and thromboembolic events.
- 5-Aminosalicylic acids (orally and locally) are the first line of treatment. However, in severe cases, other medications are used including corticosteroids (orally and locally), cyclosporine and infliximab.
- Surgical management is limited to cases that failed to respond to medical treatment, or developed complications including colorectal cancer.

FURTHER READINGS

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