Clinical Gastroenterology
Series Editor: George Y. Wu

Marianna G. Mavilia · George Y. Wu *Editors*

Pocket Handbook of GI Pharmacotherapeutics

Third Edition

Humana Press

Pocket Handbook of GI Pharmacotherapeutics

CLINICAL GASTROENTEROLOGY

George Y. Wu, Series Editor

Clinical Gastroenterology is a series of concise monographs on diseases commonly encountered in the clinical practice of Internal Medicine and Gastroenterology. Particular emphasis is placed on areas in which knowledge is advancing rapidly.Each volume is concise, concentrating on "clinical pearls," and new advances in diagnostic and therapeutic technology.

Volumes in the series include practical information of companies or laboratories that perform specialized testing, relative costs of diagnostic and therapeutic options. An emphasis is placed on illustrations, especially diagrams and diagnostic/therapeutic algorithms to permit rapid acquisition of practical information that is not readily available in the major texts.Additional unique features include summaries of key points, recommendations, and indications for requesting GI subspecialty consultation.

The series is of great value to Gastroenterologists and Hepatologists interested in the latest practical developments in the field as well as Internists who have particular interests or large numbers of patients with particular diseases in the field of Gastroenterology-Hepatology.

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Pocket Handbook of GI Pharmacotherapeutics

Edited by

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This book is dedicated to all of my peers and colleagues in the healthcare profession who have fought and continue to fight tirelessly against the global COVID-19 pandemic.
To every doctor, nurse, and first responder who risked their own health and safety, and put on a brave face, underneath their masks, during this time of uncertainty and fear.
And to the medicine, science, and compassion that have carried us through this difficult time.

Preface

Since the publication of the second edition of this handbook, there has been an enormous increase in the number, type, and efficacy of new medications. As a result, the medical armamentarium and therapeutic options have also vastly increased. However, the complexity of pharmacological treatment has also greatly increased. Online databases and references are certainly very helpful in managing and accessing the information. Such databases, references, and guidelines provide detailed information on pharmacology, toxicology, and therapeutics. However, it is often necessary to access several such sites in order to find all desired answers to many common questions. The third edition of the *Pocket Handbook of GI Pharmacotherapeutics* has been specifically designed to address this need by providing frequently needed information such as brand and generic names, therapeutic algorithms, side effects, drug interactions, relative costs, and references for off-label use, all in one location. As in the past, the book is divided into separate parts for gastrointestinal and liver diseases. Each chapter generally begins with diseases and conditions followed by brand and generic names, indications, administration, side effects, drug-drug interactions, alternatives where available, durations, pregnancy/lactation concerns, and relative cost. In addition, there are three new chapters which cover post-transplant medications, acute and chronic pancreatitis pain syndromes, and ascites. Treatment algorithms are provided where available. In addition, an index at the end of the handbook lists all the drugs in alphabetical order for those interested in specific agents.

We believe this book provides a unique and convenient reference which has distilled the essences of GI pharmacological treatment into a single brief volume.

George Y. Wu
Marianna G. Mavilia
Farmington, CT, USA

January 1, 2021

Relative Cost

Cost codes used are "per month" of maintenance therapy or "per course" of short-term therapy (e.g., antibiotic course). Codes are calculated using average wholesale prices for the most common indication and route of each drug at typical adult dosage. For maintenance therapy, costs are calculated based upon a 30-day supply or the quantity that might typically be used in a given month. When multiple forms are available, these codes reflect the least expensive generally available product. Where applicable, codes are given for least expensive available brand name formulation as well as the generic formulation. These codes should be used as a rough guideline only. Check with a local pharmacy for exact costs.

Code	Cost
$	<$25
$$	$25–$49
$$$	$50–$99
$$$$	$100–$199
$$$$$	≥$200
$$$$$ $	≥$500
$$$$$ $$	≥$1000
$$$$$ $$$	≥$2000
$$$$$ $$$$	≥$4000
$$$$$ $$$$$	≥$8000

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1 Gastroesophageal Disorders

Jennifer Onwochei and John Birk

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ABBREVIATIONS (CHAPTER SPECIFIC, FOR COMPLETE LIST SEE APPENDIX B):

CAP	Community-acquired pneumonia
CNS	Central nervous system
OTC	Over the counter
GERD	Gastroesophageal reflux disorder
GU	Genitourinary
PUD	Peptic ulcer disease
PPI	Proton pump inhibitor

MECLIZINE

Class: histamine H1 receptor antagonist
Brand/trade names: Antivert, Less Drowsy (OTC), Medi-Meclizine (OTC), Motion-Time (OTC), Travel Sickness (OTC), Travel-Ease (OTC), Bonine (OTC)
Manufacturer: Pfizer, generic

Dosage:
- Motion sickness: oral: 25–50 mg 1 h before travel, repeat dose q24 h as needed
- Vertigo and nausea: oral: 25–100 mg qd in divided doses

Indication:
- Motion sickness, vertigo, anti-emetic

Contraindications/cautions:
- Hypersensitivity to meclizine or any component of formulation
- CNS depression
- Caution with asthma, glaucoma, prostatic hyperplasia, pyloric/duodenal obstruction, and renal and hepatic impairment (may result in drug accumulation)

Adverse effects:
- Neurologic: drowsiness, fatigue, headache
- Gastrointestinal: vomiting, xerostomia
- Ophthalmic: blurred vision
- Other: anaphylactoid reaction

Drug interaction:
- May enhance the CNS depressant effect of other CNS depressants
- May enhance the anticholinergic effect of other anticholinergic drugs

Pregnancy category: B
Lactation: probably safe in small and occasional doses.
Relative cost: $-$$ (Generic available: $)

DIMENHYDRINATE

Class: histamine H1 receptor antagonist
Brand names: Dramamine (OTC), Criminate (OTC), Motion Sickness (OTC), GoodSense Motion Sickness (OTC)
Manufacturer: generic, LGM pharma

Dosage:
- Oral: 50–100 mg every 4–6 h, not to exceed 400 mg daily
- IM, IV: 50 mg every 4 h, maximum: 100 mg every 4 h
- Rectal: 50–100 mg every 6–8 h as needed

Indication:
- Motion sickness, nausea/vomiting, vertigo

Contraindications/cautions:
- Hypersensitivity to dimenhydrinate or any component of formulation
- CNS depression
- Caution with asthma, seizure d/o, glaucoma, prostatic hyperplasia, pyloric/duodenal obstruction
- Caution with antibiotics that have potential to cause ototoxicity (it may mask symptoms of ototoxicity)
- Caution in the elderly

Adverse effects:
- Cardiovascular: tachycardia
- Neurologic: dizziness, drowsiness, excitation, headache, insomnia, lassitude, nervousness, restlessness
- Dermatologic: rash
- Gastrointestinal: anorexia, epigastric distress, nausea, xerostomia
- Genitourinary: dysuria
- Ocular: blurred vision
- Respiratory: thickened bronchial secretions

Drug interactions:
- May enhance the CNS depressant effect of other CNS depressant
- May enhance the anticholinergic effect of other anticholinergic drugs

Pregnancy category: B
Lactation: small amounts are excreted in the breast milk. Antihistamines may decrease maternal serum prolactin concentrations when administered prior to the establishment of nursing
Relative cost: $ (generic available: $)

ONDANSETRON

Class: selective 5-HT3-receptor antagonist
Brand names: Zofran, Zofran ODT, Zuplenz
Manufacturer: GlaxoSmithKline

Dosage:
- Prevention of postoperative nausea and vomiting:
- Oral: 16 mg administer 1 h prior to induction of anesthesia
- IV or IM: 4 mg as a single dose administered ~30 min before the end of anesthesia or as treatment if vomiting after surgery

Treatment of generalized nausea and vomiting: (off-label use):

- Oral: 4 mg q6–8 h or 8 mg q8–12 h as needed
- IV: 4 mg q6–8 h or 8 mg q8–12 h as needed. Monitor for QT prolongation with higher doses

Indications: cancer chemo-induced nausea and vomiting, postoperative nausea and vomiting, radiotherapy-associated nausea and vomiting

Contraindications/cautions:
- Caution in patients allergic to other 5HT-3 receptor antagonists
- QT prolongation (dose dependent)
- Serotonin syndrome in combination with other serotonergic agents
- Dose limitation in patients with hepatic impairment (Child-Pugh Class C)

Adverse effects:
- Neurologic: headache, fatigue, malaise, drowsiness, agitation, anxiety, sensation to cold
- Dermatologic: pruritus
- Gastrointestinal: diarrhea
- Genitourinary: urinary retention, liver enzyme elevation

- Respiratory: hypoxia
- Other: fever

Drug interactions:
- May enhance the QTc-prolonging effect of QTc-prolonging agents
- May decrease the serum concentrations of CYP3A4 substrates and increase the metabolism of CYP3A4 substrates

Pregnancy: B
Lactation: unknown
Relative cost: $-$$ (generic available: $-$$)

SCOPOLAMINE PATCH

Class: anticholinergic agent
Brand names: Transderm-Scop
Manufacturer: Sandoz, generic

Dosage:
- Motion sickness: apply 1 patch to hairless area of skin behind the ear at least 4 h prior to exposure and q3 d as needed
- Chemotherapy-induced nausea and vomiting: apply 1 patch q72 h

Indications: motion sickness, postoperative nausea and vomiting

Contraindications/cautions:
- Hypersensitivity to scopolamine
- Narrow angle glaucoma
- Caution in patients with hepatic impairment, seizure disorders, hyperthyroidism, GU or GI obstruction, prior psychosis, or ulcerative colitis
- Avoid use in the elderly because of potent anticholinergic adverse effects

Adverse effects:
- Cardiovascular: bradycardia, flushing, orthostatic hypotension, tachycardia
- Neurologic: psychosis, agitation, ataxia, confusion, delusions, dizziness, drowsiness, fatigue, hallucinations, headache, irritability, loss of memory, paranoid behavior, restlessness, sedation
- Dermatologic: dry skin, pruritus, drug eruptions, urticaria
- Endocrine: thirst
- Gastrointestinal: constipation, diarrhea, dry throat, dysphagia, nausea, vomiting, xerostomia

- Genitourinary: dysuria, urinary retention
- Musculoskeletal: tremor, weakness
- Ocular: accommodation impaired, blurred vision, conjunctival infection, cycloplegia, dryness, glaucoma, increased intraocular pain, itching, photophobia, pupil dilation, retinal pigmentation
- Respiratory: dry nose, dyspnea
- Other: angioedema, heat intolerance

Drug interactions:
- May enhance the CNS depressant effect of other CNS depressants
- May enhance the anticholinergic effect of other anticholinergic drugs

Pregnancy category: C
Lactation: secreted into the breast milk. Should be used with caution if administered to a nursing woman
Relative cost: $$ (generic available: $$)

GASTROESOPHAGEAL REFLUX DISORDER (GERD) AND PEPTIC ULCER DISEASE (PUD)

(See Figs. 1.1 and 1.2 for algorithms for the treatment of GERD)

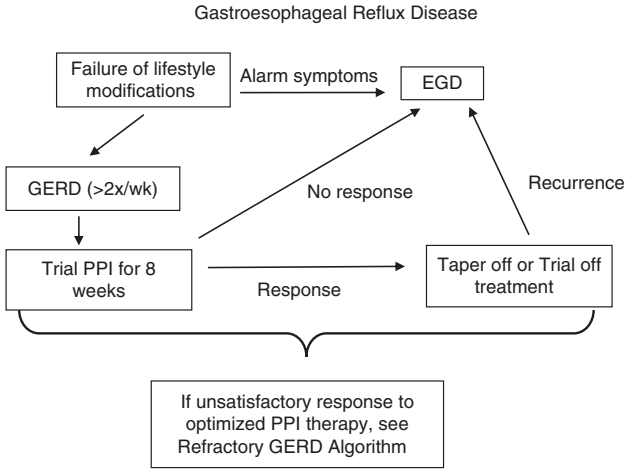

Fig. 1.1 Treatment of simple GERD. (Adapted from: Rezaizadeh and Olson [12])

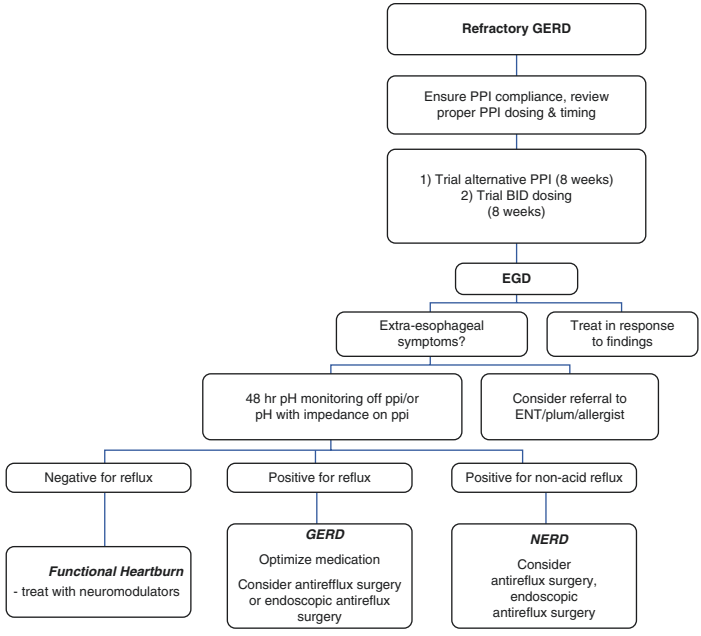

Fig. 1.2 Treatment of refractory GERD. (Sources: Katz et al. [2], Young et al. [11])

Proton Pump Inhibitors (PPI)

PPI CLASS ASSOCIATED EFFECTS:

- PPI use and increased risk of *C. difficile* infection
- PPI use and increased risk of traveler's diarrhea
- Increase risk of community acquired pneumonia (CAP) with PPI use in patients with following risk factors: (1) elderly, (2) shorter duration of treatment (<30 d), (3) low-dose PPI
- Long-term PPI use can cause hypomagnesemia due to decreased intestinal absorption of magnesium, consider monitoring
- Osteoporosis

Omeprazole

Class: proton pump inhibitor
Brand name: Prilosec, prilosec OTC
Manufacturer: AstraZeneca, Proctor and Gamble, Covis pharma

Dosage:
- GERD/erosive esophagitis: 20 mg po qd for 4 weeks
- Gastric ulcer: 40 mg po qd for up to 4–8 weeks
- Duodenal ulcer: 20–40 mg po qd for 4–8 weeks
- *H. pylori* eradication: 20 mg po bid in conjunction with triple therapy
- Stress ulcer prophylaxis: 40 mg po qd initially, then 20–40 mg qd
- ZES: 40 mg bid (may titrate upward early in therapy to a maximum of 180 mg/day); can gradually taper down once acid output has been controlled, maintenance dosage range: 10–180 mg/day

Indications: GERD, peptic ulcer disease (gastric and duodenal ulcer), Zollinger-Ellison syndrome, erosive esophagitis, *Helicobacter pylori* eradication, heartburn (OTC)

Contraindications/cautions:
- Hypersensitivity to omeprazole
- Use with caution in hypocalcemia, hypokalemia, metabolic alkalosis, respiratory alkalosis, Bartter's syndrome (powder for oral suspension contains 1680 mg or 20 meq of sodium bicarbonate)

Adverse effects:
- Gastrointestinal: abdominal pain, diarrhea, pancreatitis, hepatotoxicity
- Neurologic: headache
- Renal: interstitial nephritis
- Musculoskeletal: hip fracture, rhabdomyolysis

Drug interactions:
- Sofosbuvir/ledipasvir: PPI equivalent dose to omeprazole 20 mg may be administered simultaneously with sofosbuvir/ledipasvir under fasting conditions; higher doses should be avoided as they decrease the efficacy of sofosbuvir/ledipasvir
- May interfere with the absorption of drugs where gastric pH is important for bioavailability, e.g., ketoconazole, iron salts, ampicillin esters, and digoxin
- Atazanavir and nelfinavir: may reduce plasma levels of atazanavir and nelfinavir. Concomitant use is not recommended
- Saquinavir: may increase plasma levels of saquinavir. Monitor for toxicity and consider dose reduction of saquinavir
- Co-administration of clopidogrel with 80 mg omeprazole may reduce the pharmacological activity of clopidogrel if given concomitantly or if given 12 h apart
- Cilostazol: increases systemic exposure of cilostazol and one of its active metabolites. Consider dose reduction of cilostazol

- Drugs metabolized by cytochrome P450, e.g., diazepam, warfarin, phenytoin, cyclosporine, disulfiram, benzodiazepines
- Combined inhibitor of CYP 2C19 and 3A4 (e.g., voriconazole) may raise omeprazole levels
- Tacrolimus: may increase serum levels of tacrolimus
- Methotrexate: may increase serum levels of methotrexate

Pregnancy category: C
Lactation: probably safe
Relative cost: $ (generic available: $)

ESOMEPRAZOLE MAGNESIUM (ORAL)

Esomeprazole Sodium (IV)

Class: proton pump inhibitor
Brand name: Nexium
Manufacturer: AstraZeneca, generic

Dosage:
- GERD/erosive esophagitis: 20–40 mg po qd for treatment
- Maintenance therapy in GERD/erosive esophagitis: 20 mg po qd
- Gastric ulcer: 20–40 mg po qd for up to 6 months
- Acute non-variceal upper GI bleed: 80 mg IV bolus followed by continuous infusion at 8 mg/h for 72 h after endoscopic therapy
- *H. pylori* infection: 40 mg po qd in conjunction with triple therapy
- Zollinger-Ellison syndrome: 40 mg po bid, increase up to 240 mg po qd based on symptoms

Indications: Barrett's esophagus, poorly controlled reflux symptoms, erosive esophagitis, dyspepsia (off-label use), *Helicobacter pylori* eradication, peptic ulcer disease, prevention of NSAID-induced gastric ulcers

Contraindications/cautions:
- Hypersensitivity to esomeprazole or benzimidazoles
- Use with caution with liver disease

Adverse effects:
- Gastrointestinal: abdominal pain, constipation, diarrhea, flatulence, nausea, pancreatitis (rare)

- Neurologic: headache
- Dermatologic: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
- Musculoskeletal: hip fracture, rhabdomyolysis

Drug interactions: see omeprazole
Pregnancy category: B
Lactation: probably safe
Relative cost: oral – $-$$, IV – $$$ (generic available: $)

Lansoprazole

Class: proton pump inhibitor
Brand name: Prevacid, generic
Manufacturer: TAP Pharmaceuticals Inc.

Dosage:
- Duodenal ulcer: 15 mg po qd or bid for 4–8 weeks
- *H. pylori* treatment: 30 mg po bid for 10–14 days in combination with triple therapy
- Erosive esophagitis: 30 mg po qd or bid for 4–8 weeks
- Gastric ulcer prophylaxis with NSAID use: 15–30 mg po qd
- Gastric ulcer treatment: 30 mg po qd or bid for 8 weeks
- GERD: 15–30 mg po qd for 8 weeks
- Zollinger-Ellison syndrome: 60 mg po qd to 90 mg bid

Indication: peptic ulcer disease, GERD, hypersecretory conditions, heartburn (OTC)

Contraindications/cautions:
- Hypersensitivity of lansoprazole or any of its components
- Use with caution in phenylketonurics: oral disintegrating tables contain phenylalanine
- Use with caution in liver disease (dose reduction may be required)

Adverse effects:
- Gastrointestinal: abdominal pain, diarrhea, nausea
- Neurologic: headache
- Musculoskeletal: hip fracture, rhabdomyolysis
- Other: fatigue

Drug interactions: see omeprazole
Pregnancy category: B
Lactation: probably safe
Relative cost: $$ (generic available: $-$$)

Pantoprazole Sodium Oral and IV

Class: proton pump inhibitor
Brand name: Protonix
Manufacturer: Pfizer, generic

Dosage:
- Erosive esophagitis (short term): 40 mg po qd for 8 weeks or 40 mg IV for 7–10 days
- Esophagitis maintenance (GERD): 40 mg po qd
- Duodenal ulcer: 40–80 mg po qd for 4–8 weeks
- Acute non-variceal upper GI bleed: 80 mg IV bolus followed by continuous infusion at 8 mg/h for 72 h after endoscopic therapy (Note: recent data suggest equal efficacy of 40 mg IV bid vs. continuous infusion)
- Gastric hypersecretion (long term): 40 mg po bid, can increase to a maximum of 240 mg qd
- Gastric hypersecretion associated with pathologic conditions: 40 mg po bid or 80 mg IV bid; increase up to 240 mg qd

Indications: GERD, erosive esophagitis, gastric hypersecretion

Contraindications/cautions:
- Hypersensitivity to pantoprazole products
- Use with caution in Bartter's syndrome, hypocalcemia, hypokalemia, metabolic alkalosis (powder for oral suspension contains 1680 mg (20 meq) of sodium bicarbonate

Adverse effects:
- Gastrointestinal: diarrhea, pancreatitis, hepatotoxicity
- Renal: interstitial nephritis
- Endocrine: hyperglycemia
- Immunologic: Stevens-Johnson syndrome
- Musculoskeletal: hip fracture, rhabdomyolysis

Drug interactions:
- See omeprazole
- Pantoprazole may increase serum level of methotrexate

Lactation: probably safe
Pregnancy category: B
Relative cost: oral – $-$$, IV – $$$ (generic available: $)

Rabeprazole Sodium

Class: proton pump inhibitor
Brand name: Aciphex
Manufacturer: Eisai

Dosage:
- Duodenal ulcer disease: 20 mg po qd after the morning meal for up to 4 weeks
- Gastric hypersecretion: initial, 60 mg po qd, may increase up to 120 mg; single daily doses up to 100 mg/d may be given; 120 mg dose may require divided doses, 60 mg po bid
- Gastroesophageal reflux disease, erosive or ulcerative, maintenance: 20 mg po qd
- Gastroesophageal reflux disease, erosive or ulcerative, treatment: 20 mg po qd for 4–8 weeks
- Gastroesophageal reflux disease, symptom control: 20 mg po qd for 4 weeks
- *H. pylori* treatment with triple therapy: 20 mg po bid for 7 days

Indication: GERD, duodenal ulcers, *Helicobacter pylori* eradication with triple therapy

Contraindications/cautions:
- Hypersensitivity to rabeprazole/substituted benzimidazoles
- Caution in liver disease

Adverse effects:
- Neurologic: headache
- Immunologic: Stevens-Johnson syndrome
- Musculoskeletal: hip fracture, rhabdomyolysis

Drug interactions: see omeprazole
Pregnancy category: B
Lactation: probably safe
Relative cost: $-$$

Dexlansoprazole

Class: proton pump inhibitor
Brand names: Dexilant, Kapidex [DSC]
Manufacturer: Takeda Pharmaceuticals

Dosage:
- Erosive esophagitis: short term, 60 mg po qd for up to 8 weeks; maintenance therapy, 30 mg po qd for up to 6 months
- Symptomatic GERD: short term, 30 mg po qd for up to 4 weeks

Indications: erosive esophagitis, GERD

Contraindications/cautions:
- Hypersensitivity to dexlansoprazole
- Patients with Child-Pugh class B may require dosage reductions

Adverse effects:
- Gastrointestinal: diarrhea
- Respiratory: upper respiratory tract infection
- Musculoskeletal: increased incidence of osteoporosis related bone fractures

Drug interactions: see omeprazole
Pregnancy category: B
Lactation: excretion in breast milk unknown
Relative cost: $$$$$

HISTAMINE H2 ANTAGONISTS

Famotidine

Class: histamine H2 blocker
Brand names: Pepcid, Pepcid AC
Manufacturer: Merck & Co., Inc

Dosage:
- Duodenal ulcer disease: 40 mg po qhs or 20 mg po bid or 20 mg IV q12 h
- Duodenal ulcer disease (maintenance): 20 mg po qhs
- GERD: 20–40 mg po bid for 12 weeks, 20 mg IV q12 h
- Gastric hypersecretion: 20 mg to 160 mg po q6h, 20 mg IV q12 h
- Gastric ulcer: 40 mg po qhs, 20 mg IV q12 h
- GERD short term system relief: 20 mg po bid for 6 weeks, 20 mg IV q12 h
- Indigestions: 10–20 mg po bid

Indication: GERD, heartburn (OTC only), peptic ulcer disease

Contraindications/cautions:
- Hypersensitivity to famotidine or any of its components
- History of hypersensitivity to other H2 receptor antagonists
- Dose adjustment by 50% or increase interval to 24–36 h for CrCl <50 ml/min

Adverse effects:
- Gastrointestinal: constipation, diarrhea, necrotizing enterocolitis in fetus or newborn, increased liver enzymes

- Neurologic: dizziness

Drug interactions:
- May decrease efficacy of oral iron preparations, antifungals, and atazanavir
- May increase levels of fluvastatin and increase risk of rhabdomyolysis
- H2 blocker equivalent dose to famotidine 40 mg BID may be administered simultaneously with Harvoni under fasting conditions; higher doses should be avoided as they decrease the efficacy of Harvoni. Ideal dosing is 12 h apart

Pregnancy category: B
Lactation: probably safe
Relative cost: $ (generic available: $)

OTHER AGENTS

Sucralfate

Class: agents for peptic ulcer and gastro-esophageal reflux disease/GERD
Brand name: Carafate
Manufacturer: Allergan Pharmaceuticals

Dosage:
- Duodenal ulcer disease, active: 1 g po qid or 2 g po bid for 4–8 weeks

Indication: duodenal ulcer

Contraindications/cautions:
- Hypersensitivity to sucralfate products

Adverse effects:
- Gastrointestinal: constipation, bezoar
- Other: aluminum toxicity, renal impaired patients

Drug interactions:
- To reduce the potential of adversely affecting the absorption of other drugs, administer other drugs 2 h prior to sucralfate

Pregnancy category: B
Lactation: safety unknown (not known if it is excreted in human milk)
Relative cost: $ (generic available: $)

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2 Gastrointestinal Bleeding

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ABBREVIATIONS

IR Interventional radiology
TIPSS Transhepatic portosystemic shunt

(See Fig. 2.1 for an algorithm for the treatment of acute upper GI bleeding)

PANTOPRAZOLE

(See Chap. 1 for drug details)
Class: proton pump inhibitors
Dosage: continuous infusion: 80 mg iv bolus followed by continuous infusion at 8 mg/h for 72 h after endoscopic therapy
Intermittent dosing: 80 mg iv bolus followed by 40 mg iv q12 h
Indication: variceal and non-variceal upper GI bleeding

ESOMEPRAZOLE

(See Chap. 1 for drug details)
Class: proton pump inhibitors
Continuous infusion: 80 mg iv bolus followed by continuous infusion at 8 mg/h for 72 h after endoscopic therapy
Intermittent dosing (off-label dose): 80 mg iv bolus followed by 40 mg iv q12 h
Indication: variceal and non-variceal upper GI bleeding

OCTREOTIDE ACETATE

Class: somatostatin and analogs
Trade name: Sandostatin; Sandostatin LAR Depot; Bynfezia Pen; Mycapssa; Sandostatin; Sandostatin LAR Depot
Manufacturer: MW Encap Ltd., Novartis, Sun Pharmaceutical Industries Ltd.

Dosage:

- Acute variceal hemorrhage: 50 μg iv bolus followed by 50 μg/h iv infusion for 2–5 days. If hemorrhage is not controlled in the first hour, can repeat bolus
- Small intestinal bacterial overgrowth: 50 μg sc qd for 3 weeks

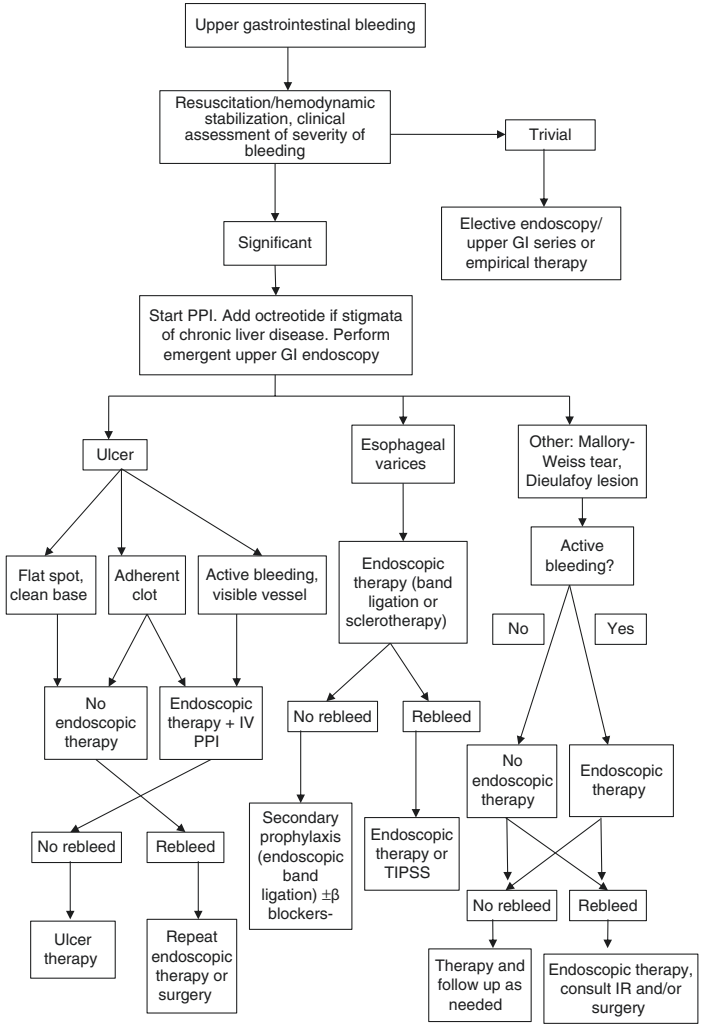

Fig. 2.1 An algorithm for the treatment of acute upper GI bleeding. (Adapted from: Rezaizadeh and Olson [9])

- VIPoma associated diarrhea: 200–300 μg/day sc/iv in 2–4 divided doses and uptitrate based on response. Range: 150–750 μg/day sc/iv
- Carcinoid tumor symptoms: 100–600 μg/day sc/iv in 2–4 divided doses for the first 2 weeks. This can be followed by 50–750,600 μg/day sc/iv (maximum 1500 μg/d, titrate based on response for flushing and diarrhea). After the initial 2 weeks, can switch to depot im 20 mg intragluteally every 4 weeks for 2 months, then modify dose depending on response
- Dose adjustment for carcinoid tumors: increase to 30 mg im q4 wk if symptoms persist and decrease to 10 mg im q4 wk if there is adequate response to the 20 mg dose. Doses greater than 30 mg are not recommended
- Acute carcinoid crisis: 500–1000 μg iv 1–2 h preoperatively or 500 μg sc 1–2 h preoperatively
- Carcinoid crisis prophylaxis: 250–500 μg sc x1; give 1–2 h preoperatively
- Secretory diarrhea: 50–100 μg iv q8 h; increase by 100 μg per dose at 48 h intervals until adequate response is reached, for a maximum dose of 500 μ q8 h
- Dumping syndrome: 50–100 μg sc before meals

Indication: as above

Contraindications/cautions:
- Sensitivity to octreotide or any of its components

Adverse effects:
- Gastrointestinal: abdominal discomfort, constipation, diarrhea, flatulence, nausea, pancreatitis, cholelithiasis, ascending cholangitis, cholecystitis, cholestatic hepatitis
- Neurologic: dizziness, headache, abnormal Schilling test (monitor Vit B12 levels)
- Cardiovascular: cardiac dysrhythmia, congestive heart failure (rare), sinus bradycardia
- Endocrine: hyperglycemia, hypoglycemia, hypothyroidism

Drug interactions:
- Cisapride and pimozide: risk of QT prolongation
- Calcium channel blockers: risk of bradycardia and cardiac conduction abnormalities
- Androgens: risk of hypoglycemia
- Antacids: decrease serum concentration of octreotide

Pregnancy category: B
Lactation safety: unknown
Relative cost: $$$$

VASOPRESSIN

Class: antidiuretic hormones, vasopressin (ADH) and analogs
Tradename: Vasostrict
Manufacturer: Par Sterile Products, LLC

Dosage:
- Variceal bleed: 0.2–0.4 units/min, titrate dose as needed for a maximum dose of 0.8 units/min for a maximum of 24 h at maximum dose; administer with nitroglycerin to control vasoconstrictive complications
- Prophylaxis for postoperative complications: initial, 5 units im (0.25 ml) postoperatively; increase to 10 units (0.5 ml) at subsequent injections repeated at 3 or 4 h intervals if necessary

Indication: as above

Contraindications/cautions:
- Anaphylaxis or hypersensitivity to the drug or its components
- Chronic nephritis with nitrogen retention contraindicates the use of vasopressin until reasonable nitrogen blood levels have been attained
- Caution in patients with heart failure, coronary artery disease, epilepsy, migraines, and asthma

Adverse effects:
- Gastrointestinal: nausea, flatus, abdominal cramps, vomiting
- Neurologic: throbbing headache, tremor, vertigo
- Cardiovascular: myocardial infarction, angina, arrhythmias, hypertension
- Respiratory: bronchospasm
- Endocrine metabolic: water intoxication syndrome, reversible diabetes insipidus after discontinuation
- Immunologic: anaphylaxis
- Dermatologic: gangrenous disorder, sweating, urticaria

Drug interactions:
- Demeclocycline and lithium may decrease antidiuretic effect
- Increased risk of hyponatremia and seizures with polyethylene glycol and sodium phosphate
- Increased antidiuretic effect with carbamazepine and fludrocortisones

Pregnancy category: C
Lactation: probably safe.
Relative cost: $$$$$ (generic available: $)

METOCLOPRAMIDE

Class: agents for gastric acid–related disorders, propulsive
Tradename: Gimoti; Metozolv ODT [DSC]; Reglan
Manufacturer: ANI PHARMS, Evoke Pharma, Salix Pharmaceuticals, Inc.

Dosage:
- IV 10 mg once

Indication: endoscopic adjunct/prokinetic use
Class: dopamine receptor antagonist, 5HT4 receptor agonist, prokinetic

Contraindications/cautions:
- Geriatric population (Beers Criteria) due to high risk of dyskinesia
- Pediatric population due to high risk of dyskinesia, respiratory depression, and death
- Hypersensitivity

Adverse effects:
- Gastrointestinal: dysgeusia, diarrhea
- Neurological: drowsiness, dystonias/tardive dyskinesia, hallucination, parkinsonism, visual disturbances
- Cardiovascular: AV block, bradycardia, heart failure, flushing after high IV doses, hypertension or hypotension, and SVT
- Endocrine: amenorrhea, galactorrhea, gynecomastia, hyperprolactinemia
- Genitourinary: urinary incontinence
- Hematologic: agranulocytosis, methemoglobinemia, sulfhemoglobinemia
- Respiratory: bronchospasm, laryngeal edema

Drug interactions:
- Anticholinergics: diminish effect of the drug
- Dopamine agonists: diminish effect of the drug
- Antipsychotics: metoclopramide may enhance their effect

Pregnancy category: B
Lactation: insufficient data on long-term side effects on infant therefore recommendation is to avoid use while breastfeeding
Relative cost: $

ERYTHROMYCIN

Class: macrolide antibiotic
Tradename: E.E.S. 400 [DSC]; E.E.S. Granules; Ery-Tab; EryPed 200; EryPed 400; Erythrocin Lactobionate; Erythrocin Stearate
Manufacturer: Alpharma US Pharms, Arbor Pharms LLC, Hospira

Dosage:
- IV 3 mg/kg given over 30 min, 30–90 min before EGD or 250 mg single dose given over 5–30 min, 30 min before EGD

Indication: endoscopic adjunct/prokinetic use

Contraindications/cautions:
- Anaphylaxis or hypersensitivity to the drug or its components
- Hypokalemia/hypomagnesemia due to risk of ventricular arrhythmias
- Pre-existing liver disease

Adverse effects:
- Cardiac: ventricular arrhythmias due to prolonged QTc
- Exacerbation of myasthenia gravis
- GI distress such as diarrhea
- Increased risk of hearing loss in the elderly

Drug interactions:
- Class IA and III anti-arrhythmics: due to risk of ventricular arrhythmia
- CYP3A4 inhibitors: atorvastatin, apixaban, cyclosporine, fluconazole, clarithromycin, indinavir, darunavir, and verapamil. Concomitant use with erythromycin can result in increased serum concentrations of these drugs
- Alprazolam: systemic erythromycin may increase serum concentration of alprazolam

Pregnancy category: B
Lactation: safe if usual recommended doses are used. Monitor infant for GI symptoms
Relative cost: $$$

EPINEPHRINE

Class: short-acting beta-2 agonist
Tradename: Adrenalin; Adyphren; Adyphren Amp; Adyphren Amp II; Adyphren II; Auvi-Q; Epinephrine Professional; Epinephrinesnap-EMS; Epinephrinesnap-v; EpiPen 2-Pak; EpiPen Jr 2-Pak; EPIsnap; Symjepi
Manufacturer: King Pharmaceuticals

Dosage:
- Local injection 0.1 mg/ml or 1:10,000 dilution

Indication: endoscopic hemostasis treatment

Contraindications/cautions:
- Hypersensitivity to sympathomimetic amines

Adverse effects:
- Cardiac: arrhythmias

Drug interactions:
- Alpha 1-blockers: may diminish the vasoconstricting effect of epinephrine
- Cannabinoid-containing products: may enhance the tachycardic effect of epinephrine

Pregnancy category: C
Lactation: safe to use
Relative cost: $–$$

HEMOSTATIC NANOPOWDER

Class: cohesive and adhesive hemostatic agent
Tradename: Hemospray
Manufacturer: Cook Medical

Dosage:
- Apply in short 1–2 second bursts until bleeding site is completely covered

Indication: FDA approved for non-variceal upper gastrointestinal bleeding. However, it has been used off-label in esophageal variceal hemorrhage

Contraindications/cautions:
- Can cause eye/skin irritation with inadvertent contact
- Inhalation may worsen existing respiratory disease

Adverse effects:
- One study reported perforation likely due to force of the spray at an inflamed site

Drug interactions:
- Rare

Pregnancy category and lactation:
- Unknown

Relative cost:
- $$$$$ $$$$–$$$$$ $$$$$

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3 Specific Gastrointestinal Motility Disorders

Shaina Lynch

Contents

ABBREVIATIONS (CHAPTER SPECIFIC, FOR COMPLETE LIST SEE APPENDIX B):

CCB	Calcium channel blocker
DES	Diffuse esophageal spasm
PDE-5	Phosphodiesterase-5

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NIFEDIPINE

Class: dihydropyridine calcium channel blockers
Brand names: Adalat CC, Procardia, Procardia XL, Afeditab CR, Nifediac CC, Nifedical XL
Manufacturer: Bayer

Dosages:
- Achalasia: 10–30 mg po before meals may provide minimal benefit
- Diffuse esophageal spasm (DES)/dysphagia predominant symptoms: 10–30 mg po qd

Contraindications/cautions:
- Hypersensitivity to nifedipine or any component of the product
- Caution after acute myocardial infarction (within 4 weeks), congestive heart failure, peripheral edema, hypotension, unstable angina pectoris

Adverse effects:
- Gastrointestinal: constipation, heartburn, nausea, gingival hyperplasia, sore throat
- Neurologic: dizziness, headache, mood changes, nervousness, fatigue
- Cardiovascular: flushing, palpitations, peripheral edema, transient hypotension, cardiac failure
- Respiratory: cough, nasal congestion, wheezing
- Musculoskeletal: muscle cramps, tremor, weakness

Drug interactions:
- Alpha-1-blocker: may enhance the hypotensive effect of blood pressure–lowering agents
- Beta-blockers, amiodarone, octreotide: increased risk of AV block, bradycardia, hypotension
- CYP3A4 inhibitors: may decrease the metabolism of CYP34A substrates
- Macrolide antibiotics: may decrease the metabolism of calcium channel blockers

Pregnancy category: C
Lactation: probably safe
Relative cost: $$$$$ $ (generic available: $-$$)

BOTULINUM TOXIN (ONABOTULINUM TOXIN A)

Class: injectable agents for hyperhidrosis, muscle relaxants, neuromuscular blockers
Brand names: Botox, Botox Cosmetic
Manufacturer: Allergan, Inc.

Dosage:
- Achalasia: 80–100 units im into lower esophageal sphincter

Contraindications/cautions:
- Anaphylaxis
- Antibody formation
- Bleeding disorders or those receiving anticoagulant therapy

Adverse effects:
- Gastrointestinal: dysphagia, indigestion
- Neurologic: headache, ptosis of eyelid, focal facial paralysis, speech disturbance
- Cardiovascular: arrhythmias, hypertension, myocardial infarction, syncope
- Respiratory: upper respiratory infection, dyspnea
- Musculoskeletal: muscle weakness, neck pain
- Dermatologic: injection site pain, erythema multiforme
- Genitourinary: urinary tract infection, bacteriuria, urinary retention
- Ophthalmic: dry eyes, acute angle closure glaucoma, punctate keratitis, visual disturbance
- Immunologic: anaphylaxis
- Other: fever

Drug interactions:
- Anticholinergic agents, aminoglycosides: may potentiate neuromuscular effects of botulinum toxin
- Central acting muscle reactants: may enhance the adverse/toxic effect of botulinum toxin

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$$$ $

ISOSORBIDE DINITRATE

Class: nitrites and nitrates
Brand names: Dilatrate-SR, Isordil, Titradose
Manufacturer: Wyeth

Dosage (sublingual):
- 5–10 mg tid 15–20 min before meals/chest pain predominant symptoms

Contraindications/cautions:
- Hypersensitivity to isosorbide dinitrate or any component of the product
- Anaphylaxis
- Concurrent use of PDE-5 inhibitors
- Angle closure glaucoma

Adverse effects:
- Gastrointestinal: nausea, vomiting, bowel incontinence
- Neurologic: headache
- Cardiovascular: hypotension, rebound hypertension, syncope, unstable angina pectoris
- Musculoskeletal: weakness

Drug interactions:
- PDE-5 inhibitors: may enhance the vasodilatory effect of vasodilators
- CYP34A inducers: may increase the metabolism of CYP34A substrates

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$$ (generic available: $)

GASTROPARESIS

Erythromycin

(See Chap. 2 for more drug details)

Dosage:
- Gastroparesis: 3 mg/kg iv q8 h, 40–250 mg po 3 tid before meals

Metoclopramide

(See Chap. 2)

Azithromycin

Class: macrolide antibiotics
Brand name: Zithromax Tri-Pak, Zithromax Z-Pak; Zmax [DSC]
Manufacturer: Pfizer Labs

Dosage:
- Gastroparesis: 40–250 mg po tid before meals

Prucalopride

- FDA approved, but not for use in gastroparesis. However, there is evidence for off-label use
- See Chap. 4

Domperidone

- Not FDA approved. Use under an FDA Investigational New Drug Application is possible

DUMPING SYNDROME AND ACCELERATED GASTRIC EMPTYING

Octreotide

(See Chap. 2)

Dexlansoprazole

(See Chap. 1)

RAPID TRANSIT DYSMOTILITY OF THE SMALL BOWEL

Loperamide

Class: anti-propulsives
Brand names: Diamode, Imodium, Imodium A-D, Imogen, Imotil, Imperim, Kao-Paverin Caps, Kaodene A-D
Manufacturer: multiple

Dosage:
- Rapid transit: loperamide 4 mg po tid to qid

Contraindications:
- Hypersensitivity to loperamide
- GI hemorrhage/obstruction
- Allergy to other antidiarrheal agents
- Acute ulcerative colitis
- Bacterial enterocolitis caused by an invasive organism (i.e., *Salmonella*, *Shigella*, and *Campylobacter*)
- Pseudomembranous colitis

Adverse effects:
- Gastrointestinal: constipation, abdominal pain, nausea, vomiting, xerostomia, necrotizing enterocolitis in fetus or newborn (rare)
- Neurologic: dizziness, somnolence
- Cardiovascular: QT interval prolongation
- Dermatologic: rash, pruritis, urticaria, angioedema. Stevens-Johnson, toxic epidermal necrolysis, erythema multiforme rare
- Endocrine metabolic: hyperglycemia
- Immunologic: anaphylaxis (rare)
- Other: fatigue

Drug interactions:
- Potassium salts: anticholinergic drugs decrease GI transit, increase local exposure to potassium, thereby causing ulcerative lesions
- CYP3A4 inhibitors (e.g., itraconazole) and CYP2C8 inhibitors (e.g., gemfibrozil): may increase peak plasma concentration and serum exposure time of loperamide
- P-glycoprotein inhibitors (e.g., quinidine, ritonavir): may increase loperamide plasma concentrations

Pregnancy category: B
Lactation: probably safe
Relative cost: $ (generic available: $)

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4 General Gastrointestinal Motility Disorders

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Contents

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DIARRHEA

Dicyclomine Hydrochloride

Class: anticholinergic gastrointestinal antispasmodics
Brand name: Bentyl
Manufacturer: Allergan

Dosage:
- Oral: 10 mg–40 mg qid, maximum dose: 160 mg/day

Intramuscular: 10–20 mg qid (to be used only for 1–2 days), max dose: 80 mg/day

Dosing considerations:
- Hepatic impairment: no specific guidelines available
- Renal impairment: no specific guidelines available

Contraindications/cautions:
- Hot and humid environments
- Age <6 months
- Hypersensitivity
- Active infection
- Breastfeeding
- Gastrointestinal obstruction, ileus
- Glaucoma
- Myasthenia gravis
- Reflux esophagitis, GERD
- Severe ulcerative colitis or toxic megacolon
- Coronary artery disease, cardiac arrythmias, congestive heart failure
- Hypertension
- Unstable cardiovascular status in acute hemorrhage
- Urinary tract obstruction, BPH
- Hepatic disease
- Renal disease
- Hyperthyroidism
- Elderly due to its anticholinergic effects
- Use of contact lenses

Adverse effects:
- Gastrointestinal: constipation, nausea, xerostomia
- Respiratory: angioedema, apnea, asphyxia, dyspnea
- Neurologic: dizziness, confusion, somnolence, amnesia, dyskinesia, insomnia
- Cardiovascular: tachyarrhythmia, hypertension

- Renal: urinary retention
- Dermatologic: diminished sweating, dry skin
- Ophthalmic: blurred vision, cycloplegia, sensitivity to light
- Psychiatric: hallucinations, delirium, mania
- Genitourinary: erectile dysfunction
- Endocrine: lactation suppression
- Musculoskeletal: loss of strength and energy

Drug interactions:
- Potassium salts: anticholinergic drugs decrease GI transit, increase local exposure to potassium, thereby causing ulcerative lesions
- Acetylcholinesterase inhibitors: may diminish the therapeutic effect of acetylcholinesterase inhibitors
- Anticholinergic agents: may enhance the anticholinergic effect of anticholinergic agents
- Eluxadoline: may enhance the constipating effect
- Levosulpiride: may diminish the therapeutic effect
- Mirabegron: may enhance the adverse/toxic effect
- Oxatomide: may enhance the anticholinergic effect of anticholinergic agents. *Risk X: Avoid combination*
- Potassium salts: may enhance the ulcerogenic effect
- Secretin: may diminish the therapeutic effect
- Sincalide: drugs that affect gallbladder function may diminish the therapeutic effect

Pregnancy category: in studies with maternal doses up to 40 mg daily throughout the first trimester, birth defects were not observed; there is no information when used in pregnant women at recommended doses (80–160 mg daily). Antispasmodics are generally used to treat irritable bowel syndrome in pregnant patients only when symptoms are severe
Lactation: dicyclomine is present in breast milk. Due to the potential for serious adverse reactions in the breastfeeding infant, use in breastfeeding women and infants <6 months of age is contraindicated. In addition, anticholinergics may suppress lactation
Relative cost: $ (generic available: $)

Hyoscyamine Sulfate

Class: anticholinergics/antispasmodic
Brand name: Anaspaz; Ed-Spaz; Hyosyne; Levbid; Levsin; Levsin/SL; NuLev; Oscimin; Oscimin SR; Symax Duotab; Symax-SL; Symax-SR
Manufacturer: Anaspaz – Ascher, B. F. & Co., Inc.; Ed-Spaz – Belcher Pharmaceuticals, Inc.; Hyosyne – Alaven (MEDA); Levbid, Levsin/SL,

NuLev – Meda Pharmaceuticals, Levsin – McKesson Corporation; Oscimin – Larken Laboratories; Symax Duotab, Symax-SL, Symax-SR – Capellon Pharmaceuticals, LLC

Dosage:
- Tablet, immediate release/dispersible:
- 0.125–0.25 mg po q4 h or as needed; maximum: 1.5 mg/day

Tablet, extended release:

- 0.375–0.75 mg every 12 h; maximum: 1.5 mg/day

Contraindications/cautions:
- Glaucoma
- Hypersensitivity to hyoscyamine products or other anticholinergic drugs
- Intestinal obstruction, intestinal atony (in elderly, debilitated), severe ulcerative colitis, paralytic ileus, toxic megacolon
- Reflux esophagitis
- Myasthenia gravis
- Obstructive uropathy
- Unstable cardiac disease: congestive heart failure, cardiac arrythmias, coronary artery disease, mitral stenosis
- Pulmonary disease
- Psychosis
- Use of contact lenses
- Elderly due to its anti-cholinergic effects

Adverse effects:
- Gastrointestinal: xerostomia, ileus, dysphagia, constipation, nausea
- Neurologic: dizziness, somnolence, confusion, insomnia, headache
- Cardiovascular: tachyarrhythmia
- Genitourinary: urinary retention, impotence
- Dermatologic: anhidrosis, flushing, urticaria
- Ophthalmic: blurred vision, elevated intraocular pressure, cycloplegia, photophobia, mydriasis
- Psychiatric: psychosis
- Endocrine: lactation suppression

Drug interactions:
- Potassium salts: anticholinergic drugs decrease GI transit, increase local exposure to potassium, thereby causing ulcerative lesions
- Acetylcholinesterase inhibitors: may diminish the therapeutic effect
- Anticholinergic agents: may enhance the anticholinergic effect

- Antacids: may decrease the serum concentration of Hyoscyamine Management: Administer immediate release hyoscyamine before meals and antacids after meals when these agents are given in combination
- Clozapine: may enhance the constipating effect
- Eluxadoline: may enhance the constipating effect
- Ketoconazole: may decrease the serum concentration
- Levosulpiride: may diminish the therapeutic effect
- Opioid agonists: may enhance the adverse/toxic effect
- Secretin: may diminish the therapeutic effect

Pregnancy category: C
Lactation: possibly safe
Relative cost: $ (generic available: $)

Diphenoxylate Hydrochloride/Atropine Sulfate

Class: anti-diarrheal
Brand name: Lomotil
Manufacturer: Pfizer U.S. Pharmaceuticals

Dosage:
- Diarrhea: adjunct: 5 mg (2 tab or 10 ml solution) po qid (maximum dose 20 mg/day of diphenoxylate)

Contraindications/cautions:
- Diarrhea associated with enterotoxin-producing bacteria or pseudomembranous enterocolitis; may prolong and/or worsen diarrhea
- May induce toxic megacolon in ulcerative colitis
- Hypersensitivity to diphenoxylate or atropine products
- Obstructive jaundice, may precipitate hepatic coma in patients with hepatic impairment
- Circumstances where opiates are contraindicated

Adverse effects:
- Gastrointestinal: abdominal discomfort, nausea and vomiting, pancreatitis, toxic megacolon, ileus, pancreatitis, constipation, xerostomia, anorexia
- Respiratory: anaphylactic shock, angioedema
- Neurologic: dizziness, sedation, somnolence, headache
- Skin: pruritus, urticaria
- Psychiatric: euphoria, depression, hallucinations

Drug interactions:
- Potassium salts: anticholinergic drugs decrease GI transit, increase local exposure to potassium, thereby causing ulcerative lesions

- Acetylcholinesterase inhibitors: anticholinergic agents may diminish the therapeutic effect of acetylcholinesterase inhibitors
- CNS depressants: may enhance the adverse/toxic effect of other CNS depressants
- Eluxadoline: anticholinergic agents may enhance the constipating effect
- Nitroglycerin: anticholinergic agents may decrease the absorption
- Aclidinium, amantadine, anticholinergic agents, botulinum toxin-containing products, cimetropium, glycopyrrolate, glycopyrronium, ipratropium, mianserin: may enhance the anticholinergic effect of anticholinergic agents

Pregnancy category: C
Lactation: probably safe
Relative cost: $$ (generic available: $-$$)

Loperamide

Class: anti-diarrheals
Brand name: Imodium, K-Pek II
Manufacturer: Imodium – Johnson & Johnson; K-Pek II – McNEIL-PPC, Inc.

Dosage:
- Diarrhea; 4 mg po after first loose stool initially; then 2 mg after each unformed subsequent stool; not to exceed 16 mg/day

Contraindications/cautions:
- Abdominal pain in the absence of diarrhea
- Bacterial enterocolitis, caused by invasive organisms including *Salmonella*, *Shigella*, and *Campylobacter*; do not use as primary therapy
- Dysentery, acute; do not use as primary therapy
- Ulcerative colitis
- Hypersensitivity to loperamide or to any of the excipients
- Infants below 24 months of age
- Pseudomembranous colitis, associated with the use of broad-spectrum antibiotics
- Hepatic disease
- Circumstances where opiates are contraindicated

Adverse effects:
- Gastrointestinal: abdominal pain, nausea, dyspepsia, flatulence, vomiting, xerostomia, necrotizing enterocolitis in fetus or newborn (rare), ileus, toxic megacolon, constipation
- Neurologic: dizziness, somnolence, fatigue, drowsiness, headache
- Endocrine: hyperglycemia

- Dermatologic: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, bullous rash, pruritus, urticaria
- Respiratory: angioedema, anaphylactic shock, respiratory depression
- Genitourinary: urinary retention
- Cardiovascular: ventricular tachycardia, torsade de pointes, QT prolongation

Drug interactions:
- Potassium salts: anticholinergic drugs decrease GI transit, increase local exposure to potassium, thereby causing ulcerative lesions
- Desmopressin: may increase the serum concentration
- Eluxadoline: may enhance the constipating effect
- QT-prolonging Agents: may enhance the QTc-prolonging effect
- Quinidine: may enhance the CNS depressant effect
- Ramosetron: may enhance the constipating effect
- Sincalide: drugs that affect gallbladder function may diminish the therapeutic effect

Pregnancy category: C
Lactation: probably safe
Relative cost: $ (generic available: $)

Cholestyramine

Class: antilipemic agent, bile acid sequestrant
Brand name: Prevalite
Manufacturer: Upsher Smith labs

Dosage:
- Chronic diarrhea due to bile acid malabsorption (off-label use): 4 g po qd; increase by 4 g at weekly intervals in 1–4 divided doses
- Cholestatic pruritis: 4–6 g po bid 30 min before meals
- Maximum dose: 24 g/day

Contraindications/cautions:
- Biliary cirrhosis, biliary obstruction, cholelithiasis
- Hypertriglyceridemia
- Gastrointestinal obstruction, dysphagia, swallowing disorders
- Coagulopathy
- Phenylketonuria
- Hypothyroidism, as cholestyramine can bind exogenous thyroid hormone
- Renal disease, as cholestyramine resin releases chloride

Adverse effects:
- Gastrointestinal: GI obstruction, peptic ulcer, pancreatitis, GI bleeding, cholelithiasis, colic, constipation, dysphagia, flatulence, nausea, vomiting, diarrhea, steatorrhea, abdominal pain, anorexia, elevated hepatic enzymes
- Ophthalmologic: night blindness, uveitis
- Hematologic: anemia, prolonged bleeding time, hypoprothrombinemia
- Endocrine: osteoporosis
- Metabolic: hyperchloremic acidosis

Drug interactions:
- Amiodarone: may decrease the bioavailability
- Chenodiol: may decrease the serum concentration
- Cholic acid: may decrease the absorption
- Deferasirox: may decrease the serum concentration
- Estrogen derivatives: may decrease the serum concentration of estrogen derivatives
- Ezetimibe: may decrease the absorption
- Leflunomide: may decrease serum concentrations of the active metabolite(s)
- Lomitapide: may decrease the absorption
- Multivitamins/minerals: may decrease the serum concentration
- Niacin: may decrease the absorption
- Phenobarbital: may decrease the serum concentration
- Pravastatin: may decrease the serum concentration
- Progestins: may decrease the serum concentration
- Rosiglitazone: may decrease the serum concentration
- Sincalide: drugs that affect gallbladder function may diminish the therapeutic effect
- Teriflunomide: may decrease the serum concentration
- Thiazide and thiazide-like diuretics: may decrease the absorption
- Thyroid products: may decrease the serum concentration
- Valproic acid: may decrease the serum concentration
- Vancomycin: may diminish the therapeutic effect
- Vitamin D analogs: may decrease the serum concentration
- Vitamin K antagonists: may decrease the serum concentration

Pregnancy category: C
Lactation: given lack of systemic absorption, cholestyramine is probably not present in breast milk
Relative cost: $$$

Imipramine

Class: tricyclic antidepressants
Brand name: Tofranil
Manufacturer: Tofranil: Mallinckrodt Pharmaceuticals

Dosage:
- 10–25 mg po qd at bed time; start low and titrate as necessary

Contraindications/cautions:
- Hypersensitivity to imipramine
- Concomitant use of monoamine oxidase (MAO) inhibitors
- Use in patients during acute recovery after a myocardial infarction
- Cardiac disease (heart failure, history of myocardial infarction, congenital heart disease)
- QT prolongation, AV block
- Electrolyte imbalances
- Psychotic disorders
- Seizure disorders
- Hepatic disease
- Surgery
- Closed angle glaucoma
- Use of contact lenses
- Thyroid disease
- Diabetes mellitus
- Pheochromocytoma
- Intrathecal radiographic contrast administration

Adverse effects:
- Gastrointestinal: bloating, constipation, xerostomia, hepatitis, hepatic failure, ileus
- ENT: glossitis, stomatitis, parotitis
- Neurologic: asthenia, dizziness, headache, somnolence, seizures, serotonin syndrome, stroke, memory impairment, ataxia, peripheral neuropathy
- Psychiatric: suicidal ideation, mania, delirium, psychosis, hallucinations, depression
- Hematologic: agranulocytosis, thrombocytopenia, leukopenia, eosinophilia
- Cardiovascular: cardiac dysrhythmia, heart block, heart failure, hypertension, myocardial infarction (rare), orthostatic hypotension, palpitations, syncope

- Genitourinary: urinary retention, ejaculation dysfunction, impotence, hyponatremia, testicular swelling
- Endocrine: weight gain, SIADH, hypo-/hyperthyroidism, diabetes mellitus
- Ophthalmic: blurred vision, ocular hypertension
- Rheumatologic: vasculitis
- Dermatologic: photosensitivity, hyperpigmentation, flushing, urticaria, alopecia

Drug interactions:
- Antiarrhythmics, class Ia: increased risk of QT prolongation and cardiac arrhythmias
- MAO inhibitors: combination may result in CNS overstimulation, hyperpyrexia, seizures, and death
- Potassium salts: anticholinergic drugs decrease GI transit, increase local exposure to potassium, thereby causing ulcerative lesions.
- Pimozide: increased risk of CNS depression, psychomotor impairment, QT prolongation

Pregnancy category: D
Lactation: probably safe
Relative cost: $ (generic available: $)

Amitriptyline

Class: tricyclic antidepressants
Brand name: only generic
Manufacturer: generic

Dosage:
- 10–25 mg po qd at bedtime. May increase gradually up to 75 mg/day

Contraindications/cautions:
- Hypersensitivity
- Concomitant use of monoamine oxidase (MAO) inhibitors
- Use in patients during acute recovery after a myocardial infarction
- QT prolongation
- Heart failure
- Bradycardia
- Electrolyte abnormalities
- Seizure disorder
- Hepatic disease
- Surgery

- Closed angle glaucoma
- Hypo-/hyperthyroidism
- Diabetes mellitus
- Pheochromocytoma
- Radiographic contrast use
- Sunlight exposure

Adverse effects:
- Gastrointestinal: bloating, constipation/diarrhea, nausea, xerostomia, ileus, hepatic failure, hepatitis
- Neurologic: asthenia, dizziness, headache, somnolence, seizures, stroke, tardive dyskinesia, neuroleptic malignant syndrome-like symptoms, serotonin syndrome, memory impairment, ataxia, peripheral neuropathy
- Hematologic: agranulocytosis, eosinophilia
- Cardiovascular: cardiac dysrhythmia, heart block, hypertension, myocardial infarction (rare), orthostatic hypotension, palpitations, syncope, heart failure
- Pulmonary: angioedema
- Rheumatologic: lupus-like symptoms
- Endocrine/metabolic: weight gain, SIADH, hypo-/hyperglycemia, galactorrhea, gynecomastia, increase/decreased libido
- Genitourinary: oliguria, ejaculation dysfunction, impotence, testicular swelling
- Ophthalmic: blurred vision, ocular hypertension
- Psychiatric: suicidal ideation, hallucinations, delirium, psychosis, mania
- Dermatologic: photosensitivity, pruritus, urticaria, alopecia

Drug interactions:
- Anti-arrhythmic, class Ia: increase risk of QT prolongation and cardiac arrhythmias
- MAO inhibitors: combination may result in CNS overstimulation, hyperpyrexia, seizures, and death
- Potassium salts: anticholinergic drugs decrease GI transit, increase local exposure to potassium thereby causing ulcerative lesions.
- Pimozide: increase risk of CNS depression, psychomotor impairment, QT prolongation

Pregnancy category: D
Lactation: probably unsafe
Relative cost: $ (generic available: $)

CONSTIPATION

Psyllium

Class: fiber supplement, laxative
Brand name:
Evac; Geri-Mucil; Konsyl; Metamucil MultiHealth Fiber; Metamuci; Mucilin SF; Mucilin; Reguloid
Manufacturer: Evac – Bio-Tech Pharmacal; Geri-Mucil – Geri-Care Pharmaceuticals Corp.; Konsyl – Konsyl Pharmaceuticals; Metamucil – Procter & Gamble; Mucilin –Paradigm Pharma Inc.; Reguloid – Rugby Laboratories

Dosage:
- Constipation: 2.5–30 g po qd in divided doses
- Irritable bowel syndrome (off-label use): oral: 10 g/day in 1 or 2 divided doses

Contraindications/cautions:
- Hypersensitivity to psyllium
- Gastrointestinal disease: esophageal strictures, ulcers, stenosis, or intestinal adhesions or difficulty swallowing

Adverse effects:
- Gastrointestinal: abdominal cramps, constipation, diarrhea, esophageal obstruction, intestinal obstruction
- Immunologic: potentially severe (but rare) allergic reactions, anaphylaxis, and asthma
- Ophthalmic: allergic conjunctivitis (rhinoconjunctivitis)
- Respiratory: bronchospasm

Drug interactions
- No major drug interactions known

Pregnancy category: likely safe
Lactation: safety unknown, probably safe
Relative cost: $ (generic available: $)

Methylcellulose

Class: fiber supplement, laxative
Brand name: Citrucel; GoodSense Fiber
Manufacturer: Citrucel – GlaxoSmithKline; GoodSense Fiber – Geiss Destin & Dunn Inc.

Dosage:
- Tablet: two caplets as needed up to 6 times/day; maximum: 12 caplets/day
- Powder: 2 g (1 heaping tablespoon) in 8 oz (240 mL) of cold water; increase as needed by 1 heaping tablespoon up to 3 times/day

Contraindications:
- Hypersensitivity to psyllium
- Intestinal obstruction
- Fecal impaction

Adverse effects:
- Gastrointestinal: abdominal distention and flatulence, nausea

Drug interactions:
- Dichlorphenamide: may enhance the hypokalemic effect of dichlorphenamide

Pregnancy category: B
Lactation: probably safe
Relative cost: $ (generic available: $)

Docusate

Class: emollient stool softeners
Brand name: Colace; Diocto; DocQLace; Docu; Docuprene; DOK; Dulcolax Stool Softener; Surfak
Manufacturer: Colace – Purdue Pharma L.P.; Surfak Chattem, Inc.; Diocto–PharmaTech; DocQLace – Qualitest Products; Docu – Akorn pharmaceuticals; Docuprene – Pharmaceutica North America, Inc.; DOK – Major Pharmaceuticals; Dulcolax Stool Softener – Boehringer Ingelheim Pharmaceuticals Inc.

Dosage:
- Docusate calcium: 240 mg po qd
- Docusate sodium: 50–360 mg po qd or in divided doses
- Rectal: 283 mg per 5 mL: 283 mg (1 enema) qd to tid

Contraindications:
- Hypersensitivity to psyllium
- Intestinal obstruction
- Concomitant use of mineral oil
- Acute abdominal pain, nausea, vomiting
- Rectal GI bleeding

Adverse effects:
- Gastrointestinal: diarrhea
- ENT: throat irritation
- Dermatologic: rash

Drug interactions:
- Mineral oil: increase mineral oil absorption and adverse effects
- Loop diuretics: risk of hypokalemia

Pregnancy category: C
Lactation: safety unknown
Relative cost: $ (generic available: $)

Magnesium Citrate

Class: saline laxatives
Brand name: Citroma; GoodSense Magnesium Citrate
Manufacturer: generic

Dosage:
- Constipation: oral: solution: 195–300 ml given once or in divided doses
- Preparation of bowel for procedure (off label): single-dose, same-day procedure: 10 oz bottle taken 8 h prior to procedure, followed by clear liquids for 2 h (two 10 oz glasses). Four h prior to the procedure, administer 10 oz followed by clear liquids over 1 h. Can be used in conjunction with bisacodyl

Contraindications/cautions:
- Abdominal pain, nausea/vomiting, rectal bleeding
- Heart block
- Low-salt diet
- Severe renal disease
- Myasthenia gravis and neuromuscular disease
- Congestive heart failure
- Electrolyte abnormalities

Adverse effects:
- Gastrointestinal: abdominal pain, diarrhea, flatulence, nausea, vomiting
- Neurologic: asthenia, dizziness
- Respiratory: hypoventilation

Drug interactions:
- Doxercalciferol: increase risk of hypermagnesemia

Pregnancy category: C
Lactation: probably safe
Relative cost: $ (generic available: $)

Mineral Oil

Class: lubricant laxatives
Brand name: Fleet, Kondremul, Muri-lube
Manufacturer: Fleet – C.B. Fleet; Kondremul – Emerson Healthcare; Muri-lube – Fresenius USA

Dosage: constipation:
- Plain liquid: 15–45 mL in 24 h. In single dose or in divided doses
- Suspension (Kondremul): 30–90 mL daily. In single dose or in up to 3 equal divided doses
- Rectal (Fleet Mineral Oil): 118 mL as a single dose

Contraindications/cautions:
- Hypersensitivity to psyllium
- Children less than 2 years of age (rectal administration)
- Children less than 6 years of age (oral administration)
- Colostomy/ileostomy
- Diverticulitis, appendicitis
- Ulcerative colitis, rectal bleeding
- Risk of aspiration (stroke, Parkinson's disease, Alzheimer's disease, esophageal dysmotility) as it can cause lipid pneumonitis

Adverse effects:
- Gastrointestinal: oily rectal leakage, hemorrhoids, abdominal cramps, nausea/vomiting, perianal discomfort, malabsorption
- Dermatologic: anal irritation, pruritus ani
- Other: chronic abuse of laxatives is accompanied by concerns of lipid pneumonitis, lymphoid hyperplasia, and foreign body reactions

Drug interactions:
- Docusate: increase mineral oil absorption and adverse effects
- Mineral oil can impair the absorption of fat-soluble vitamins (ADEK)
- Phytonadione: mineral oil may decrease the absorption of phytonadione

Pregnancy category: not recommended (no FDA risk assigned)
Lactation: possibly unsafe in the long term
Relative cost: $ (generic available: $)

Polyethylene Glycol

Class: osmotic laxatives
Brand name: GaviLAX; Gialax; GlycoLax; MiraLax; PEGyLAX
Manufacturer: GaviLAX – GAVIS Pharmaceuticals, LLC; Gialax – Phlight Pharma, LLC; GlycoLax – Lannett co Inc; MiraLax – Bayer HealthCare LLC; PEGyLAX – M.E. Pharmaceuticals

Dosage:
- Constipation: 17 g (about 1 heaping tablespoon) po qd dissolved in 4–8 oz of water, juice, soda, coffee, or tea
- Preparation of colonoscopy (polyethylene glycol electrolyte solution): 240 mL (8 oz) every 10 min until 4 L are consumed or the rectal effluent is clear. It can be taken in conjunction with bisacodyl tablets

Contraindications/cautions:
- Hypersensitivity to any component, such as polyethylene glycol
- Acute abdomen, ileus or obstruction, toxic colitis or toxic megacolon, or bowel or GI perforation
- Patients at risk of aspiration and/or regurgitation

Adverse effects:
- Gastrointestinal: diarrhea, flatulence, nausea, abdominal cramps, bloating, fecal incontinence
- Immunologic: anaphylaxis
- Dermatologic: pruritus, urticaria

Drug interactions:
- Dichlorphenamide: may enhance the hypokalemic effect of dichlorphenamide
- Digoxin: may decrease the serum concentration of digoxin

Pregnancy category: C
Lactation: probably safe
Relative cost: $ (generic available: $)

Lactulose

Dosage:
- Constipation: 15–30 mL (10–20 g) po qd, maximum dose 60 ml (40 g)/d
- (See Chap. 10 for more drug details)

Senna

Class: stimulant laxatives
Brand name: Ex-Lax Maximum Strength; Ex-Lax; Geri-kot; GoodSense Laxative Pills; GoodSense Senna Laxative; Perdiem Overnight Relief; Senexon; Senna Lax; Senna Laxative; Senna Smooth; Senna-GRX; Senna-Lax; Senna-Tabs; Senna-Time; SennaCon; Senno; Senokot Extra Strength; Senokot XTRA; Senokot
Manufacturer: Ex-Lax – Novartis; Geri-kot – McKesson Brand; GoodSense Laxative Pills – L. Perrigo Company; Perdiem Overnight Relief – Novartis; Senexon – Major Pharmaceuticals; Senna Lax – Guardian Drug Company; Senokot – Purdue Pharma
Dosage: 1–2 tablets (8.6–17.2 mg sennosides) po bid. Max dose: 4 tablets (34.4 mg sennosides) po bid

Contraindications/cautions:
- Nausea/vomiting
- Inflammatory bowel disease
- Rectal bleeding
- Acute surgical abdomen
- Bowel obstruction
- Fecal impaction
- Hypersensitivity to anthraquinone laxatives or to any of the ingredients
- Undiagnosed abdominal pain

Adverse effects:
- Gastrointestinal: abdominal pain, nausea, abdominal bloating, abdominal cramps, flatulence, diarrhea, melanosis coli, cathartic colon
- Renal: urine discoloration, nephritis, hypokalemia
- Respiratory: wheezing
- Other: laxative abuse

Drug interactions
- Dichlorphenamide: may enhance the hypokalemic effect of dichlorphenamide
- Polyethylene glycol-electrolyte solution: may enhance the adverse/toxic effect of polyethylene glycol-electrolyte solution

Pregnancy category: C
Lactation: probably safe
Relative cost: $ (generic available: $)

Bisacodyl

Class: stimulant laxatives
Brand name: Bisac-Evac; Bisacodyl EC; Biscolax; Dulcolax; Ex-Lax Ultra; Fleet Bisacodyl; Fleet Laxative; GoodSense
Manufacturer: Bisac-Evac, Bisacodyl EC, Biscolax – Major Pharmaceuticals; Dulcolax – Boehringer Ingelheim Pharmaceuticals Inc.; Ex-Lax Ultra – Novartis; Fleet Bisacodyl – C.B. Fleet; Fleet Laxative – C.B. Fleet; GoodSense – Geiss Destin & Dunn Inc.
Dosage: 5–15 mg po qd up to 15 mg/day or 10 mg suppository PR once daily. Maximum frequency: 3 times per week

Contraindications/cautions:
- Hypersensitivity to drug
- Nausea, vomiting
- Intestinal obstruction or ileus
- GI perforation
- Toxic megacolon
- Ulcerative colitis

Adverse effects:
- Gastrointestinal: abdominal colic, abdominal discomfort, diarrhea, Proctitis (with suppository use), atony of colon
- Renal: hypokalemia

Drug interactions:
- Antacids: possibly diminish the therapeutic effect of bisacodyl
- Dichlorphenamide: may enhance the hypokalemic effect
- Polyethylene glycol-electrolyte solution: may enhance the adverse/toxic effect

Pregnancy category: C
Lactation: safety unknown
Relative cost: $ (Generic available: $)

Castor Oil

Class: stimulant laxatives
Brand name: GoodSense Castor Oil
Manufacturer: Goodsense
Dosage: constipation: 15–60 ml po as a single dose

Contraindications/cautions:
- Hypersensitivity to drug
- Intestinal obstruction
- Acute abdominal pain, nausea, vomiting
- Symptoms of appendicitis
- Pregnancy

Adverse effects:
- Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea
- Musculoskeletal: cramps
- Metabolic: electrolyte disturbances
- Cardiovascular: hypotension
- Neurologic: dizziness, pelvic congestion syndrome

Drug interactions: no significant interactions
Pregnancy category: X
Lactation: possibly unsafe
Relative cost: $ (generic available: $)

Lubiprostone

Class: chloride-channel activator, laxative
Brand name: Amitiza
Manufacturer: Sucampo Pharmaceuticals, Inc. and Takeda Pharmaceuticals America, Inc.

Dosage:
- Idiopathic constipation, chronic: 24 μg po bid with food
- Irritable bowel syndrome with constipation in females: 8 μg po bid with food

Contraindications/cautions:
- Hypersensitivity
- History of mechanical gastrointestinal obstruction
- Diarrhea
- Hepatic impairment

Adverse effects:
- Gastrointestinal: abdominal distension, abdominal pain, diarrhea, flatulence, nausea, dyspepsia, xerostomia
- Neurologic: headache, dizziness, fatigue
- Cardiovascular: edema, chest discomfort

Drug interactions:
- Levomethadone: may diminish the therapeutic effect of lubiprostone
- Methadone: may diminish the therapeutic effect of lubiprostone

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$$$

Linaclotide

Class: guanylate cyclase-C agonist, causing increased c-GMP concentrations resulting in Cl- and HCO_3 secretion into intestinal lumen
Brand Name: Linzess
Manufacturer: Ironwood Pharmaceuticals

Dosage:
- Chronic idiopathic constipation: 72–145 μg po qd on an empty stomach
- Irritable bowel syndrome with constipation: 290 μg po qd on an empty stomach

Contraindications/cautions:
- Mechanical GI obstruction
- Diarrhea

Adverse effects:
- Gastrointestinal: diarrhea, abdominal pain, flatulence, dyspepsia, GERD, vomiting, dehydration, fecal incontinence, dyspepsia, viral gastroenteritis
- Neurologic: headache
- Respiratory: upper respiratory infection, sinusitis

Drug interactions: no known significant interactions
Pregnancy category: C
Lactation: unknown safety
Relative cost: $$$

Plecanatide

Class: guanylate cyclase-C agonist, causing increased c-GMP concentrations resulting in Cl- and HCO_3 secretion into intestinal lumen
Brand name: Trulance
Manufacturer: Synergy Pharmaceuticals Inc.

Dosage:
- Chronic idiopathic constipation (CIC): oral: 3 mg po qd
- Irritable bowel syndrome with constipation (IBS-C): oral: 3 mg po qd

Contraindications/cautions:
- Mechanical GI obstruction
- Diarrhea

Adverse effects:
- Gastrointestinal: diarrhea, abdominal pain, flatulence, elevated hepatic enzymes
- Genitourinary: urinary tract infection
- Neurologic: headache
- Respiratory: URI, sinusitis, nasopharyngitis

Drug interactions: no known significant interactions
Pregnancy: plecanatide is not expected to result in fetal exposure to the drug. The estimated risk of major birth defects and miscarriage in pregnancies is 2–4% and 15–20%, respectively
Lactation: there is no information regarding the presence of plecanatide in human milk, or its effects on milk production or the breastfed infant
Females and males of reproductive potential: no information available
Relative cost: $$$

Prucalopride

Class: selective serotonin (5HT-4) receptor agonist
Brand name: Motegrity
Manufacturer: Takeda Pharmaceuticals U.S.A., Inc.

Dosage:
- Chronic idiopathic constipation: oral: 2 mg po qd
- Gastroparesis: off-label use

Contraindications/cautions:
- Hypersensitivity to prucalopride
- End-stage renal disease (renal failure) requiring dialysis
- GI perforation or GI obstruction, obstructive ileus, severe IBD, severe diverticulitis, toxic megacolon
- Depression or suicidal thoughts/behavior

Adverse effects:
- Psychiatric: suicidal ideation, depression
- Neurologic: migraine, headache, dizziness
- Respiratory: dyspnea
- Cardiovascular: edema
- Gastrointestinal: abdominal pain, nausea/vomiting, diarrhea, flatulence
- Genitourinary: increased urinary frequency

Drug interactions:
- Anticholinergic agents: may diminish the therapeutic effect
- Fosfomycin: may decrease the serum concentration
- Levosulpiride: may enhance the adverse/toxic effect
- Opioid agonists: may diminish the therapeutic effect
- Sirolimus: may increase the serum concentration

Pregnancy: insufficient data to identify pregnancy related risks and complications. In animal studies, there were no complications during the period of embryogenesis
Lactation: prucalopride is present in breast milk. There is no data on the effects of prucalopride on the breastfed child or the effects on milk production
Females and males of reproductive potential: no information is available
Relative cost: $$$$$ $

IRRITABLE BOWEL SYNDROME-DIARRHEA PREDOMINANT (IBS-D)

Rifaximin

(See Chap. 9 for more drug details)
Dosing: 550 mg tid × 14 d

Alosetron

Class: serotonin (5-HT3) receptor antagonists
Brand name: Lotronex
Manufacturer: Prometheus Laboratories Inc.

Dosage:
- 0.5 mg po bid for 4 weeks, then may increase to 1 mg bid
- Restricted to women with severe IBS diarrhea predominant in which IBS symptoms have lasted 6 months or longer and have not responded to other medications. It should not be used in men or under the age of 18

Contraindications/cautions:
- Hypersensitivity
- Preexisting constipation; do not initiate therapy
- Concurrent use of fluvoxamine; increases alosetron plasma concentrations and half-life
- History of Crohn's disease, or ulcerative colitis, diverticulitis, gastrointestinal perforation and/or adhesions, impaired intestinal circulation or ischemic colitis, intestinal obstruction, intestinal stricture, or toxic megacolon
- Severe hepatic impairment; alosetron is extensively metabolized in the liver
- History of hypercoagulable state, thrombophlebitis
- Patients unable to understand or comply with patient-physician agreement
- Use of anticholinergic medications
- Renal failure, renal impairment

Adverse effects:
- Gastrointestinal: abdominal pain, constipation, nausea, ischemic colitis
- Neurologic: headache (rare)

Drug interactions:
- Fluvoxamine: increases alosetron levels and increases risk of adverse effects
- Apomorphine: may enhance the hypotensive effect
- CYP1A2 inhibitors: may increase the serum concentration
- CYP3A4 inhibitors: may increase the serum concentration
- Eluxadoline: may enhance the constipating effect
- Serotonergic agents: may enhance the serotonergic effect of serotonergic agents, causing serotonin syndrome
- Tobacco: may decrease the serum concentration
- Tramadol: may enhance the serotonergic effect

Pregnancy category: B
Lactation: safety unknown
Relative cost: $$$$$

Eluxadoline

Class: mixed mu opioid receptor agonist, delta opioid receptor antagonist, and kappa opioid receptor agonist
Brand Name: Viberzi
Manufacturer: Allergan
Dosage: 75–100 mg po bid with food
Hepatic impairment: 75 mg po bid

Contraindications/cautions:
- Biliary obstruction, sphincter of Oddi disease or dysfunction, cholecystectomy, pancreatic duct obstruction, alcohol abuse, severe hepatic impair-

ment, mechanical GI obstruction, chronic/severe constipation, pancreatitis abuse potential
- Hypersensitivity

Adverse effects:
- CNS: dizziness, fatigue, drowsiness, impaired cognition
- Dermatologic: skin rash
- GI: constipation, nausea, abdominal pain, sphincter of Oddi spasm, abdominal distention, flatulence, gastroesophageal reflux, GI perforation, elevated hepatic enzymes
- Hepatic: increased ALT and AST
- Respiratory: angioedema, upper respiratory infection, bronchitis, asthma, wheezing, respiratory depression
- Psychiatric: euphoria
- Dermatologic: pruritus, urticaria, maculopapular rash

Drug interactions:
- Alcohol: increase toxic effects of eluxadoline
- Alosetron, analgesics, anticholinergics, opioid agonists: increased constipation
- Antivirals: atazanavir, cyclosporine, eltrombopag, gemfibrozil, lopinavir, rifampin, ritonavir, rosuvastatin, saquinavir, tipranavir, BCRP/ABCG2 inhibitors, OATP1B1/1B3 inhibitors: increase serum concentrations of eluxadoline

Pregnancy: there are no studies in pregnant women that inform any drug-associated risks. In animal studies, no teratogenic effect was observed
Lactation: no data available regarding the presence of eluxadoline in human milk, the effects of eluxadoline on the breastfed infant
Females and males of reproductive potential: no information available
Relative cost: $$$, no generic available

IRRITABLE BOWEL SYNDROME-CONSTIPATION PREDOMINANT (IBS-C)

Lubiprostone: (See drug information in "Constipation" section of this chapter)

Dosing: 8 μg po bid

Linaclotide: (See drug information in "Constipation" section of this chapter)

Dosing: 290 µg po qd

Plecanatide: (See drug information in "Constipation" section of this chapter)

Dosing: 3 mg po qd

Tegaserod

Class: serotonin 5-HT_4 receptor agonist
Brand name: Zelnorm
Manufacturer: Sloan Pharmaceuticals
Dosage: 6 mg po bid
Indication: IBS-C in females <65 years old

Contraindications/cautions:
- Hypersensitivity to tegaserod
- Severe renal impairment or end-stage renal disease
- Hepatic impairment (Child-Pugh class B or C)
- Bowel obstruction
- Symptomatic gallbladder disease, sphincter of Oddi dysfunction
- History of ischemic colitis
- History of myocardial infarction, stroke, transient ischemic attack, angina
- Women >65 years should be assessed for a history of cardiovascular disease or risk factors before initiating therapy

Adverse effects:
- Gastrointestinal: diarrhea, abdominal pain, nausea, flatulence, dyspepsia, increased appetite
- Musculoskeletal: arthropathy, asthenia, tendonitis, increased serum creatine phosphokinase
- Neurologic: headache, migraine, dizziness, vertigo
- Psychiatric: suicidal ideation

Drug interactions:
- Anticholinergic agents: may diminish the therapeutic effect of prokinetic gastrointestinal agents
- Fosfomycin: tegaserod may decrease the serum concentration of fosfomycin

- Opioid agonists: may diminish the therapeutic effect of prokinetic GI agents
- P-glycoprotein/ABCB1 inhibitors: may increase the serum concentration of tegaserod
- Sirolimus: may increase the serum concentration of sirolimus

Pregnancy category: B
Lactation: safety unknown
Relative cost: $$$$$

Tenapanor

Class: sodium/hydrogen exchanger 3 (nh3) inhibitor
Brand name: Ibsrela
Manufacturer: Ardelyx, Inc.

Dosage:
- Irritable bowel syndrome with constipation: oral: 50 mg bid

Contraindications/cautions:
- Mechanical GI obstruction
- Diarrhea
- Renal impairment

Adverse effects:
- Gastrointestinal: diarrhea, flatulence, abdominal distension, rectal bleeding
- Genitourinary: urinary tract infection
- Neurologic: dizziness

Drug interactions: no known significant interactions
Pregnancy: tenapanor is minimally absorbed systemically, fetal exposure to the drug is unlikely. No adverse pregnancy effects described on available data
Lactation: there is no data available on the presence of tenapanor in either human or animal milk, its effects on milk production, or its effects on the breastfed infant
Females and males of reproductive potential: no information available
Relative cost: not available at present

SUGGESTED READING

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5 Inflammatory Bowel Disease

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ABBREVIATIONS (CHAPTER SPECIFIC, FOR COMPLETE LIST SEE APPENDIX B):

6-MP	6-Mercaptopurine
anti-TNFα	Anti-tumor necrosis factor alpha
CBC/diff	Complete blood count with differential
CD	Crohn's disease
ER	Extended release
IBD	Inflammatory bowel disease
IR	Immediate release
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
PML	Progressive multifocal leukoencephalopathy
PPI	Proton pump inhibitor
PUVA	Psoralen and ultraviolet A
TB	Tuberculosis
TPMT	Thiopurine S-methyltransferase
UC	Ulcerative colitis

SULFASALAZINE

Class: anti-inflammatory. This drug is a combination of 5-Aminosalicylate (5-ASA) which has anti-inflammatory properties and sulfapyridine as the carrier that allows the 5-ASA to be delivered to the colon
Brand names: Azulfidine, Azulfidine EN-Tabs
Manufacturer: Sulfasalazine – generic; Azulfidine – Pfizer U.S.

Indications: induction and/or maintenance of remission in mild to moderate ulcerative colitis (UC). May be used to treat the symptoms of mild to moderately active colonic Crohn's disease (CD)

Dosage:
- Consider starting 1 g po q6 to q8h. Maximum dose is 6 g qd if tolerated
- Patients should be supplemented with folic acid 1 gm/d while taking this medicine

Contraindications/cautions:
- Hypersensitivity to sulfasalazine, sulfa drugs, salicylates
- Intestinal or urinary obstruction
- Porphyria
- Cautions if renal or hepatic impairment, G6PD deficiency

Adverse effects:
- Gastrointestinal: dyspepsia, nausea, vomiting, and anorexia. The risk of GI toxicity increases with a dose of >4 g/d
- Neurologic: headache, dizziness
- Reproductive: reversible oligospermia
- Hematologic: hemolysis, neutropenia, agranulocytosis, folate deficiency
- Dermatologic: rash, pruritus, urticaria, Stevens-Johnson syndrome
- Others (rare): pulmonary infiltrate, nephritis, hepatitis, pancreatitis

Drug interactions:
- Cardiac glycosides: may decrease its serum concentration
- Dapsone, local anesthetics (lidocaine/prilocaine), nitric oxide, and/or sodium nitrite use: may enhance the risk of methemoglobinemia
- Eltrombopag, lasmiditan, osimertinib, regorafenib, rolapitant, tafamidis, tedizolid, and teriflunomide, and voxilaprevir: may increase serum concentration of BCRP/ABCG2 substrates
- Warfarin and heparin: risk of bleeding/bruising may be increased
- Methenamine: may produce insoluble precipitate in urine
- Methotrexate and riluzole: may enhance their hepatotoxic effect
- NSAIDs: may enhance nephrotoxic effect of 5-ASA compounds
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: low risk of fetal harm based on human data. 2 mg/d of folic acid supplementation is recommended during pregnancy. (Mesalamine formulations are preferred)
Lactation: poor excretion into breast milk. Metabolites do appear in breast milk and breastfed infants should be monitored for diarrhea, but overall has acceptable lactation safety
Relative cost: $$ (generic available: $$)

MESALAMINE

Class: anti-inflammatory. aminosalicylates
Brand names: Asacol HD (delayed release tablet/PH dependent), Delzicol (delayed release capsule), Pentasa (controlled release capsule), Lialda (delayed release tablet), Apriso (extended release capsule), Rowasa (rectal enema), and Canasa (rectal suppository). These formulations have different drug-delivery systems
Manufacturer: Asacol HD – Abbvie Pharmaceuticals; Delzicol – Abbvie Pharmaceuticals; Pentasa – Takeda Pharmaceuticals; Lialda – Shire Pharmaceuticals; Apriso – Salix Pharmaceuticals; Rowasa (enema) – Alaven, Solvay Pharmaceuticals Inc.; Canasa (suppository) – Abbvie Pharmaceuticals, Axcan Pharma

Indications:
- Induction and maintenance therapy for mild to moderately active ulcerative colitis
- Oral formulation should be used for extensive involvement, while rectal formulations should be considered for proctosigmoiditis (suspension) or proctitis (suppository). Rectal therapies can be added to oral therapies in patients with extensive or left sided ulcerative colitis

Dosage:
- Consider starting the therapy with mesalamine 2–3 g po qd. The dose should be increased in patients who have suboptimal response to the initial dose. The followings are specific maximum daily dose for different formulations:
- Asacol HD: 4.8 g
- Delzicol: 2.4 g
- Pentasa: 4 g
- Lialda: 4.8 g
- Apriso: 1.5 g
- Rowasa enema: 4 g qhs
- Canasa suppository: 1 g qhs

Daily dosage for maintenance of remission of ulcerative colitis:
- Asacol HD: 2.4 g
- Delzicol: 2.4 g
- Pentasa: 2 g
- Lialda: 2.4 g
- Apriso: 1.5 g
- Rowasa enema: 4 g qhs
- Canasa suppository: 1 g qhs
- Note: response to therapy may take 6–8 weeks. Once daily dose is recommended to maximize adherence. Rectal therapy is most efficacious if retained for 8 h

Contraindications/cautions:
- Hypersensitivity to mesalamine or salicylates
- Cautions if renal impairment or risks of myocarditis and pericarditis

Adverse effects:
- Gastrointestinal: abdominal pain, constipation, diarrhea, nausea, vomiting, hepatitis
- Neurologic: asthenia, dizziness, headache
- Musculoskeletal: arthralgia
- Dermatologic: pruritus, urticaria
- Others (rare): paradoxical exacerbation of inflammatory bowel disease, pancreatitis, pericarditis, pneumonitis, nephritis

Drug interactions:
- Azathioprine or 6-mercaptopurine (6-MP): may increase the risk of thiopurine-induced myelosuppression
- Antacids, H2 receptor antagonists, and proton pump inhibitors (PPIs): may diminish the therapeutic effect of extended release mesalamines due to the premature dissolution of the enteric coating in the higher gastric pH
- Cardiac glycosides: mesalamine may decrease their concentration
- Warfarin and heparin: risk of bleeding/bruising may be increased
- NSAIDs: may enhance nephrotoxic effects of 5-ASA compounds
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: overall low risk. It is recommended to switch Asacol HD to alternate mesalamine due to concern of dibutyl-phthalate containing enteric coating which has been shown to be teratogenic in animals
Lactation: acceptable risk. Poor excretion into breast milk, metabolites do appear in breast milk, and infants should be monitored for diarrhea
Relative cost: $$$$

OLSALAZINE

Class: anti-inflammatory. Aminosalicylate prodrug; activated by colonic bacteria
Brand name: Dipentum
Manufacturer: UCB Pharmaceuticals
Indication: induction and maintenance of remission in mild to moderate ulcerative colitis

Dosage:
- Induction: 2–3 g po qd
- Maintenance: 1–2 g po qd

Contraindications/cautions:
- Hypersensitivity to olsalazine or salicylates

Adverse effects:
- Gastrointestinal: abdominal pain, secretory diarrhea, dyspepsia, nausea
- Neurologic: headache, blurred vision
- Renal: interstitial nephritis, renal failure
- Others (rare): hypertension, hypotension, pericarditis, hepatitis, pancreatitis

Drug interactions:
- Azathioprine or 6-MP: may increase the risk of myelosuppression of thiopurines
- NSAIDs: may enhance nephrotoxic effects of 5-ASA compounds
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: overall low risk
Lactation: active metabolite may transfer to breast milk. Monitor infants for diarrhea
Relative cost: $$$$$ $$

BALSALAZIDE

Class: aminosalicylate – a prodrug activated by colonic bacteria to form mesalamine
Brand name: Colazal
Manufacturer: Salix Pharmaceuticals
Route of administration: PO
Indication: induction and maintenance of remission in mild to moderate UC

Dosage:
- Induction of remission: 6.75 g po qd
- Maintenance of remission: as 6.75 g of balsalazide is equivalent to 2.4 g of mesalamine, should consider 6.75 g po qd for maintenance when possible.

Contraindications/cautions:
- Hypersensitivity to balsalazide or salicylates

Adverse effects:
- Gastrointestinal: abdominal pain, diarrhea, nausea, vomiting, pancreatitis
- Neurologic: headache
- Renal: interstitial nephritis, renal failure
- Respiratory: respiratory tract infection

- Musculoskeletal: arthralgia

Drug interactions:
- Azathioprine or 6-MP: may increase the risk of myelosuppression of thiopurines
- NSAIDs: may enhance nephrotoxic effects of 5-ASA compounds
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: overall low risk.
Lactation: acceptable risk; poor excretion into breast milk, metabolites do appear in breast milk, and infants should be monitored for diarrhea
Relative cost: $$$$$ $$

GLUCOCORTICOIDS: PREDNISONE, METHYLPREDNISOLONE AND HYDROCORTISONE

Class: corticosteroid
Brand name: generic
Manufacturer: generic

Indications:
- Induction of remission in active ulcerative colitis or Crohn's disease, not for maintenance therapy
- Corticosteroids may be used as a bolus before infusion of infliximab to reduce the risk of antibody formation

Dosage:
- Moderate to severe active ulcerative colitis or Crohn's disease: prednisone 40–60 mg qd PO with a tapering regimen based on the individual case presentation and history. The higher dose of 60 mg qd is only slightly more effective than 40 mg qd, but it has higher rates of side effects. Long, slow tapering regimen should be avoided when possible. The addition of steroid-sparing agents to the treatment plan will help to taper
- Acute severe ulcerative colitis and selected hospitalized patients with Crohn's disease: Methylprednisolone 40–60 mg iv qd. Patients with acute severe ulcerative colitis should be monitored closely, and a second-line agent should be added to the treatment in the ones who are refractory to 3–5 d iv steroids.

Contraindications/cautions:
- Hypersensitivity to prednisone
- Systemic fungal infections

- Live or attenuated vaccines, especially with higher doses
- Caution if active infection, congestive heart failure, seizure disorder, diabetes, hypertension, osteopenia or osteoporosis, history of tuberculosis

Adverse effects:
- Gastrointestinal: nausea, vomiting, dyspepsia, appetite change
- Cardiovascular: hypertension
- Endocrine metabolic: body fluid retention, decreased body growth, hypernatremia, osteoporosis, hypercortisolism, hyperglycemia, primary adrenocortical insufficiency
- Musculoskeletal: osteonecrosis
- Immunologic: immunosuppression
- Dermatologic: the atrophic condition of the skin, impaired wound healing
- Psychiatric: depression, euphoria, mood swings, anxiety, insomnia
- Ophthalmic: cataract, glaucoma

Drug interactions:
- Vaccines: inadequate immunological response to vaccines and increased risk of disseminated infection with live vaccines
- Concomitant use of other immunosuppressants may increase the risk of infections
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: moderate risk. There is increased risk of gestational diabetes, premature rupture of membranes, preterm birth, oral clefts, decreased birth weight. Hypoadrenalism may occur in newborns. Should use the lowest effective dose and the shortest duration of therapy when possible
Lactation: acceptable risk. Dose-dependent level in breast milk; may consider delaying breastfeeding for 4 h after high-dose maternal use
Relative cost: $$ (generic available: $-$$)

BUDESONIDE

Class: corticosteroids – low systemic bioavailability
Brand name: Entocort (budesonide EC) (oral formulation); Uceris (budesonide multi-matrix (MMX)) (rectal formulation)
Manufacturer: Entocort EC – Perrigo Company plc; Uceris – Salix Pharmaceuticals

Indication:
- Induction of remission in mild to moderately active Crohn's disease affecting the ileum and/or cecum/ascending colon

- Induction of remission in mild to moderately active left-sided ulcerative colitis with suboptimal response to optimized oral and rectal mesalamine therapy
- The low systemic bioavailability of these formulations makes them attractive options for the treatment of milder disease compared to systemic corticosteroids

Dosage:
- Entocort in patients with Crohn's disease: 9 mg po qd for up to 8 weeks. Recurrence can be treated with a repeat course. May be used to maintain remission for up to 4 months with a daily dose of 3–6 mg
- Uceris in patients with ulcerative colitis: 9 mg po qd for up to 8 weeks.
- Rectal foam in ulcerative colitis: 2 mg bid for 2 weeks initially, followed by 2 mg qd for 4 weeks.

Contraindications/cautions:
- Hypersensitivity to budesonide
- Caution in patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer disease, glaucoma, cataracts

Adverse effects (generally well-tolerated with fewer side effects than corticosteroids):
- Gastrointestinal: nausea, abdominal pain, vomiting, dyspepsia
- Dermatologic: easy bruising, acne
- Respiratory infection
- Neurological: dizziness, headache
- Endocrine: adrenal insufficiency and osteoporosis with long-term use

Drug interactions:
- Vaccines: inadequate immunological response to vaccines and increased risk of disseminated infection with live vaccines
- CYP3A4 substrates: avoid combination
- Concomitant use with other immunosuppressants may increase the risk of infections
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: while short courses may be used for the treatment of acute flare, long duration therapy should be avoided due to the increased risk of gestational diabetes, decreased birth weight, oral clefts, and hypoadrenalism in newborns
Lactation: compatible with breastfeeding. A small amount of drug may be present in breast milk
Relative cost: $$$$$ $$$

HYDROCORTISONE RETENTION ENEMA

Class: corticosteroid
Brand name: Cortenema, Colocort, Cortifoam, Proctofoam-HC, Anusol-HC
Manufacturer: Cortenema – ANI Pharmaceuticals; Colocort – Perrigo Pharmaceuticals; Cortifoam – Mylan Pharmaceuticals; Proctofoam-HC – Meda Pharmaceuticals; Anusol-HC (hydrocortisone acetate) – Valeant Pharmaceuticals

Indication:
- Mild to moderately active left-sided ulcerative colitis (proctitis, proctosigmoiditis, and left sided) with inadequate response to rectal mesalamine therapy

Dosage:
- Enema: 100 mg pr qhs for up to 3–4 weeks. It should be tapered gradually if it has been used for a longer duration
- Suppositories: 2–4 divided in bid to tid doses for 2 weeks
- Foam: 1 applicator pr qd or bid for 2–3 weeks. Foam is a better type of treatment in patients who cannot retain the enema

Contraindications/cautions:
- Hypersensitivity to hydrocortisone
- Systemic fungal infections
- Immediate or early postoperative period after ileocolostomy
- Obstruction, abscess, perforation, peritonitis, fresh intestinal anastomosis, extensive fistulas or sinus tracts

Adverse effects:
- Local pain or burning
- Rectal bleeding
- Other possible systemic effects of steroids as mentioned under section on Glucocorticoids (see above)

Drug interactions:
- May have increased risk of infection if used in conjunction with other immunosuppressants
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: topical use of corticosteroids, in general, is not associated with a significant risk of adverse pregnancy outcomes. There may be an increased risk of low birth weight with higher doses and longer treatment duration with potent topical steroids
Lactation: acceptable for use in breastfeeding women
Relative cost: $$$$$ $ (generics available $$$ – $$$$)

6-MERCAPTOPURINE (6-MP)

Class: thiopurine – antimetabolite/purine analog
Brand name: Purinethol and Purixan (generics available)
Manufacturer: Purinethol – GlaxoSmithKline Pharmaceuticals; Purixan – Orphan Pharmaceuticals

Indication:
- Maintenance of remission or as a steroid-sparing agent in both Crohn's disease and ulcerative colitis
- Fistulizing Crohn's disease. Preventing clinical and endoscopic recurrence in postoperative Crohn's disease
- As adjunct therapy to reduce the risk of immunogenicity to biologics in both Crohn's disease and ulcerative colitis
- Should not be used as monotherapy for induction of remission

Dosages:
- It has been previously recommended to start with 50 mg po qd and titrate to a maximum dose of 1.5 mg/kg po qd, or based on the thiopurine methyltransferase (TPMT) activity level
- The following dose adjustments are based on the response, TPMT activity, and 6-MP metabolites level. A lower dose (50 mg/d) may be considered when being used as an adjunct therapy to decrease the risk of immunogenicity to biologics

Contraindications/cautions:
- Hypersensitivity to azathioprine
- Caution with impaired renal function
- Caution with low TPMT activity and should be avoided if the TPMT level is negligible
- Caution with other immunosuppressive agents

Adverse effects:
- Gastrointestinal: nausea, vomiting, GI ulceration, pancreatitis, hepatotoxicity
- Renal: nephrolithiasis, urate nephropathy
- Hematologic: myelosuppression, anemia
- Immune: immunosuppression
- Other: fever, skin and urinary tract cancers, lymphoma, hepatosplenic T-cell lymphoma

Drug interactions:
- Vaccines: inadequate immunological response to vaccines and increased risk of disseminated infection with live vaccines

- Allopurinol: increases the serum levels of 6 thioguanine (6-TGN), the active metabolite of 6MP, which results in severe bone marrow suppression (BMS). When being used concomitantly, it is recommended to reduce the dose of 6MP to a third or quarter and monitor labs closely for early detection of BMS
- Increased risk of myelosuppression with ACE inhibitors, clozapine, mesalamines, sulfasalazine, interferon alfa, balsalazide, mycophenolate mofetil, and a number of anticancer drugs
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: low risk. Continuation of therapy in patients who are maintained in remission with 6-MP monotherapy, decreases the risk of maternal-fetal adverse outcomes. There may be an increased risk of infection when being used as dual therapy with anti-TNFs. Due to the delayed onset of action and risk of pancreatitis, 6-MP should not be started during pregnancy
Lactation: small concentrations detected in breast milk. Compatible with breastfeeding, but delaying breastfeeding 4 h after a dose, may decrease the infant exposure
Relative cost: $$$$ (generic available: $$)

AZATHIOPRINE

Class: thiopurine (antimetabolite/purine analog) – prodrug of 6-MP.
Brand names: Azasan, Imuran (Azathioprine)
Manufacturer: generic

Indications:
- Maintenance of remission or as a steroid-sparing agent in both Crohn's disease and ulcerative colitis
- Fistulizing Crohn's disease. Preventing clinical and endoscopic recurrence in postoperative Crohn's disease
- As adjunct therapy to reduce the risk of immunogenicity to biologics in both Crohn's disease and ulcerative colitis
- Should not be used as monotherapy for induction of remission

Dosage:
- The initial dose should be based on the TPMT level as stated for 6-MP
- The maximum daily dose of 2.5 mg/kg/d has been recommended, but dose adjustment should be based on the response, TPMT activity, and the metabolites level
- Lower dose may be considered when being used as adjunct therapy to decrease the risk of immunogenicity to biologics

Contraindications/cautions:
- Similar to 6-MP (refer to 6-MP contraindications/cautions)

Adverse effects:
- Similar to 6-MP (refer to 6-MP adverse effects)

Drug interactions:
- Similar to 6-MP (refer to 6-MP drug interactions)
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: similar to 6-MP. See above
Lactation: similar to 6-MP. See above
Relative cost: $$$$$ (generics available: $$)

METHOTREXATE (MTX)

Class: antimetabolite (antifolate)
Brand name: Rheumatrex, Trexall, Otrexup, Rasuvo, RediTrex
Manufacturer: Rheumatrex – Dava Pharmaceuticals; Trexall – Teva Pharmaceuticals, generic; Otrexup – Antares Pharmaceuticals; Rasuvo – Medac Pharmaceuticals; RediTrex – Cumberland Pharmaceuticals

Indications:
- Maintenance of remission or as a steroid-sparing agent in Crohn's disease
- Should not be used as monotherapy for induction of remission
- As adjunct therapy to reduce the risk of immunogenicity to biologics in both Crohn's disease and ulcerative colitis

Dosage:
- CD: 25 mg/wk im or sc initially; may dose reduce to 15 mg q1 wk if steroid-free remission is maintained for 4 months. Lower dose of 12.5–15 mg q1 wk po may be prescribed in cases in which methotrexate is given as combination therapy with biologics to reduce antibody formation toward biologics
- Parenteral methotrexate bioavailability is superior to PO especially at doses higher than 15 mg/wk

Contraindications/cautions:
- Hypersensitivity to methotrexate
- Contraindicated in pregnancy
- Chronic liver disease
- Active infection
- Caution when used with other immunosuppressive or myelosuppressive agents

Adverse effects:
- Gastrointestinal: gingivitis, stomatitis, pharyngitis, nausea, abdominal pain, vomiting, enteritis, pancreatitis, diarrhea
- Hepatobiliary: hepatotoxicity, acute hepatitis, hepatic failure, chronic fibrosis, and cirrhosis
- Neurologic: neurotoxicity, headache, drowsiness, blurred vision, malaise, dizziness
- Cardiovascular: pericarditis, pericardial effusion, thromboembolic events
- Pulmonary: pulmonary fibrosis, alveolitis, interstitial pneumonitis,
- Hematologic: pancytopenia, leucopenia, anemia, thrombocytopenia, lymphoproliferative disorders, tumor lysis syndrome
- Dermatologic: rash, pruritus, urticaria, Stevens-Johnson syndrome, erythema, multiforme, toxic epidermal necrolysis, dermatitis
- Renal: nephropathy, renal failure, azotemia, hematuria, proteinuria
- Infectious: opportunistic infections
- Other: lymphomas

Drug interactions:
- Vaccines: inadequate immunological response to vaccines and increased risk of disseminated infection with live vaccines.
- Hepatotoxic agents including azathioprine/6-MP, retinoids, sulfasalazine
- NSAIDs – may increase or prolong serum methotrexate levels
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: contraindicated in pregnancy as it is teratogenic and an abortifacient. Avoid use for 3–6 months prior to conception. Effective contraception must be used in women of childbearing age, during and for 6 months after discontinuing the treatment and during and at least 3 months prior to conception in their male partners.
Lactation: present in breast milk. Nursing is contraindicated during treatment and for 1 week after the final methotrexate dose
Relative cost: $$$$$ (generic available: $$$)

CYCLOSPORINE

Class: calcineurin inhibitor, immunosuppressive agent
Brand name: Gengraf, Neoral, SandIMMUNE
Manufacturer: Gengraf – Abbvie Pharmaceuticals; Neoral and SandIMMUNE – Novartis Pharmaceuticals
Indications: acute severe steroid refractory ulcerative colitis

Dosages:
- 2–4 mg/kg iv qd infused continuously over 24 h
- Patients who respond to iv therapy can be discharged on standard oral dose of 8 mg/kg qd while also being started on thiopurines or vedolizumab, see below
- Oral cyclosporine is usually discontinued within 3 months

Contraindications/cautions:
- Hypersensitivity to cyclosporine or formulation components (IV form contraindicated in those with hypersensitivity to polyoxyethylated castor oil)
- Caution when used in patients with impaired liver or renal function, uncontrolled hypertension, malignancies, concomitant coal tar therapy, radiation, PUVA or UVB treatment, or other immunosuppressive agents

Adverse effects:
- Gastrointestinal: gingival hyperplasia, diarrhea, nausea and vomiting, hepatotoxicity, pancreatitis, GI bleed
- Neurologic: neurotoxicity, intracranial hypertension, headache, tremor, encephalopathy, seizure
- Cardiovascular: hypertension, myocardial infarction
- Renal: reversible or irreversible renal insufficiency, hyperkalemia, hypomagnesemia
- Hematological: leukopenia, thrombocytopenia, hemolytic anemia
- Endocrine: diabetes mellitus, hirsutism, dyslipidemia, hyperuricemia
- Immune: allergic reactions, anaphylaxis
- Other: infections, lymphomas and skin cancers, optic disc edema, pruritus
- Note: given that patients with acute serious ulcerative colitis who are being treated with cyclosporine, are also being treated with high-dose steroid, prophylaxis against pneumocystis pneumonia (PCP) is recommended

Drug interactions:
- Other immunosuppressive agents, allopurinol, CYP3A4 substrates (for complete list, please see drug labeling)

Pregnancy category: limited safety data. Not teratogenic, but may increase the risk of preeclampsia, intrauterine growth restriction, maternal hypertension, gestational diabetes, preterm birth, and low birth weight
Lactation: acceptable risk. Consider alternative drugs if possible. Otherwise monitor infants for possible cyclosporine toxicity as variable levels can be detected in infants
Relative cost: $$$$$ (Generic available: $$$-$$$$)

INFLIXIMAB

Class: anti-tumor necrosis factor alpha (anti-TNFα agent); immunosuppressive agent
Brand name: Remicade, Biosimilars available (Avsola, Inflectra, Renflexis)
Manufacturer: Remicade (infliximab) – J&J Pharmaceuticals; Avsola (infliximab-axxq) – Amgen; Inflectra (infliximab-dyyb) – Celltrion Inc.; Renflexis (infliximab-abda) – Merck

Indication:
- Moderate to severe Crohn's disease or ulcerative colitis including fulminant Crohn's disease and acute severe ulcerative colitis
- Steroid-dependent or refractory, thiopurine refractory Crohn's disease or ulcerative colitis
- Methotrexate refractory Crohn's disease
- Fistulizing Crohn's disease including internal and entro-cutaneous fistulas
- Preventing clinical and endoscopic recurrence in postoperative Crohn's disease.

Dosage:
- Induction of remission: 5 mg/kg iv over 2 h (unless longer duration is needed due to allergic reaction) at weeks 0, 2, and 6
- Maintenance of remission: 5 mg/kg iv q8wk. Some patients may require a higher dose and/or shorter interval between the infusions for a better response and to achieve an adequate blood level. Minimal trough level of ≥7.5 μg/ml should be targeted. Higher level is recommended for patients with fistula
- Combination therapy with thiopurines has demonstrated to increase the infliximab blood level possibly due to decreased risk of immunogenicity. Methotrexate may be used in patients who are not candidates for therapy with thiopurines. In patients with acute severe ulcerative colitis, there is conflicting evidence for accelerated (10 mg/kg initially or additional 5 mg/kg dose within 1 week of initial standard dose) compared to standard dosing and decision on the appropriate dosage should be guided clinically at this time

Contraindications/cautions:
- Hypersensitivity to infliximab
- Active infection
- Congestive heart failure; NYHA Class III, IV
- Caution if latent TB, hepatitis B carrier, chronic infection
- Caution if CNS demyelinating disorder, seizure disorder, vasculitis, or immunosuppression

Adverse effects:
- Gastrointestinal: abdominal pain, nausea, vomiting, hepatotoxicity (rare)
- Cardiovascular: worsening of congestive heart failure, acute coronary syndrome
- Hematologic: leukopenia, neutropenia, thrombocytopenia
- Immunologic: allergic reaction, drug-induced lupus erythematosus, delayed hypersensitivity reaction
- Infectious: opportunistic infection, upper respiratory tract and other infections, disseminated TB, hepatitis B reactivation
- Other: lymphoma, including hepatosplenic T-cell lymphoma (especially when used in conjunction with thiopurines

Drug interactions:
- Vaccines: inadequate immunological response to vaccines and increased risk of disseminated infection with live vaccines
- Other concomitant immunosuppressive agents: may increase risk of serious infections
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: low risk especially when used as monotherapy. Last infusion should be 6–10 weeks prior to estimated delivery date while on q8wk regimen or 4–5 weeks if on q4wk regimens to achieve trough level around delivery time (resume 48 h postpartum)
Lactation: acceptable risk. Detected in low concentrations in breast milk
Relative cost: $$$$$ $$$$

ADALIMUMAB

Class: anti-TNFα; immunosuppressive agent
Brand name: Humira (biosimilars approved by FDA, but not yet available in the USA)
Manufacturer: Abbott Laboratories

Indication:
- Moderate to severe Crohn's disease or ulcerative colitis
- Steroid-dependent or refractory, thiopurine refractory Crohn's disease or ulcerative colitis
- Methotrexate refractory Crohn's disease
- May be effective in treating peri-anal fistulizing Crohn's disease
- Preventing clinical and endoscopic recurrence in postoperative Crohn's disease

Dosage:
- Induction of remission: 160 mg sc at week 0 followed by 80 mg sc at week 2
- Maintenance of remission: 40 mg sc every other week. Some patients may require q1wk injections for a better response and to achieve an adequate blood level. Minimal trough level of ≥5 μg/ml should be targeted

Contraindications/cautions:
- Similar to Infliximab (refer to section on Infliximab)

Adverse effects:
- Similar to Infliximab (refer to section on Infliximab)

Drug interactions:
- Vaccines: inadequate immunological response to vaccines and increased risk of disseminated infection with live vaccines
- Other concomitant immunosuppressive agents: may increase risk of serious infections
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: low risk especially when used as monotherapy. Last injection should be timed 2–3 weeks prior to estimated delivery date while on every 2-week regimen and 1–2 weeks if on a q1wk schedule to achieve trough level at delivery (resume 48 h postpartum)
Lactation: acceptable risk – detected in low concentrations in breast milk
Relative cost: $$$$$ $$$$$ for induction ($$$$$ $$$$ for maintenance therapy)

CERTOLIZUMAB PEGOL

Class: anti-TNFα; long-acting immunosuppressive agent
Brand name: Cimzia
Manufacturer: UCB, Inc.

Indication:
- Moderate to severe Crohn's disease
- Steroid-dependent or refractory, thiopurine or methotrexate refractory Crohn's disease
- May be effective in treating peri-anal fistulizing Crohn's disease and preventing clinical and endoscopic recurrence in postoperative Crohn's disease

Dosage:
- Induction of remission: 400 mg sc at weeks 0, 2, and 4
- Maintenance of remission: 400 mg q4wk
- Intensified dosing may be needed to achieve minimal targeted trough level of ≥20 μg/ml

Contraindications/cautions:
- Similar to Infliximab (refer to section on Infliximab)

Adverse effects:
- Similar to Infliximab (refer to section on Infliximab)

Drug interactions:
- Similar to Infliximab (refer to section on Infliximab)

Pregnancy category: safe. Not actively transported through the placenta due to the pegylated formulation; no change in dosing schedule necessary
Lactation: acceptable risk. Detectable low concentrations in breast milk
Relative cost: $$$$$ $$$$

GOLIMUMAB

Class: anti-TNFα; immunosuppressive agent
Brand name: Simponi
Manufacturer: Janssen Biotech, Inc.

Indication:
- Moderate to severely active ulcerative colitis, steroid refractory or dependent ulcerative colitis

Dosage:
- Induction of remission: 200 mg sc at week 0 followed by 100 mg at week 2
- Maintenance of remission: 100 mg sc every 4 weeks
- Intensified dosing may be needed to achieve minimal targeted trough level of ≥1 μg/ml

Contraindications/cautions:
- Similar to infliximab (refer to section on Infliximab)

Adverse effects:
- Similar to infliximab (refer to section on Infliximab)

Drug interactions:
- Similar to infliximab (refer to section on Infliximab)

Pregnancy category: low risk (especially when used as monotherapy). Last injection should be timed 4–6 weeks prior to estimated delivery date to achieve trough level around delivery time (resume 48 h postpartum)
Lactation safety: acceptable. Small amounts detected in breast milk
Relative cost: $$$$$ $$$$

NATALIZUMAB

Class: selective adhesion molecule inhibitor (alpha4 integrin antagonist – blocks alpha4-beta1 in the brain and alpha4-beta7 in the gastrointestinal tract); monoclonal antibody
Trade name: Tysabri
Manufacturer: Biogen Idec and Elan Pharmaceuticals, Inc.

Indication:
- Moderate to severe Crohn's disease

Dosage:
- 300 mg infused over 1 h q4wk. Note: Available only through a restricted prescribing program (TOUCH) for inducing and maintaining clinical response and remission in adults with moderate to severe Crohn's disease who have had inadequate response to other therapies
- Discontinue if no therapeutic benefit by 12 weeks

Contraindications/cautions:
- Hypersensitivity to natalizumab
- Contraindicated in patients taking other immunosuppressants or TNF inhibitors. For patients who are on corticosteroids when starting natalizumab, the latter should not be started if corticosteroids cannot be tapered off in 6 months
- Current or history of progressive multifocal leukoencephalopathy (PML)
- Active infection
- Caution if anti-JCV (John Cunningham Virus) antibody positive
- Caution if being used for more than 2 years

Adverse effects:
- Neurologic: headache, fatigue, depression, progressive multifocal leukoencephalopathy (PML)
- Dermatologic: rash
- Gastrointestinal: nausea, gastroenteritis, abdominal discomfort, hepatotoxicity
- Genitourinary: urinary tract infections
- Neuromuscular: arthralgias, extremity pain, back pain
- Respiratory: upper respiratory tract infections, lower respiratory tract infections
- Hypersensitivity/infusion-related reactions
- Infections: use may be associated with increased risk of infections, opportunistic infections, and serious herpes infections

Drug interactions:
- Vaccines: inadequate immunological response to vaccines and increased risk of disseminated infection with live vaccines
- Echinacea may diminish the therapeutic effect of immunosuppressants
- Immunosuppressants: concurrent use enhances toxicity and risk of infection
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: low risk. Last infusion should be 4–6 weeks prior to estimated delivery date to achieve trough level at delivery (resume 48 h postpartum)
Lactation: acceptable risk for breastfeeding. Detected in small concentrations in breast milk
Relative cost: $$$$$ $

VEDOLIZUMAB

Class: gut-selective adhesion molecule inhibitor (alpha-4-beta7 integrin inhibitor); monoclonal antibody
Brand name: Entyvio
Manufacturer: Takeda Pharmaceuticals USA, Inc.

Indication:
- Moderate to severe Crohn's disease or ulcerative colitis
- May have a role in fistulizing Crohn's disease

Dosage:
- Induction of remission: 300 mg iv at 0, 2, and 6 weeks
- Maintenance of remission: 300 mg iv q8 wk. Some patients may require more frequent infusions for a better response and to achieve an adequate blood level
- Discontinue therapy in patients who show no evidence of therapeutic benefit by week 14

Contraindications/cautions:
- Hypersensitivity to vedolizumab
- Caution use with other immunosuppressants
- Active infection

Adverse effects:
- Neurologic: headache
- Immunologic: antibody development

- Neuromuscular: arthralgia
- Respiratory: nasopharyngitis
- Hypersensitivity/infusion-related reactions
- Infections: use may be associated with increased risk of infections, opportunistic infections, and serious herpes infections

Drug interactions:
- Vaccines: immunological response to certain vaccines may be diminished and possible increased risk of disseminated infection with live vaccines
- Echinacea may diminish the therapeutic effect of immunosuppressants
- Immunosuppressants: concurrent use may enhance toxicity and risk of infection
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: low risk. Last infusion should be 6–10 weeks prior to estimated delivery date while on q8wk regimen or 4–5 weeks if on q4wk regimen to achieve trough level at delivery (resume 48 h postpartum)
Lactation: acceptable risk for breastfeeding. Detected in small concentrations in breast milk
Relative cost: $$$$$ $$$$$

USTEKINUMAB

Class: interleukin (IL)-12/23 inhibitor, monoclonal antibody
Trade name: Stelara
Manufacturer: Janssen Biotech, Inc.
Indication: Moderate to severely Crohn's disease or ulcerative colitis

Dosage:
- Induction of remission: Single dose weight-based dose of 260 mg (≤55 kg), 390 mg (>55–85 kg), or 520 mg (>85 kg) iv
- Maintenance of remission: 90 mg sc q8wk. Some patients may require injections q4wk for a better response and to achieve an adequate blood level

Contraindications/cautions:
- Hypersensitivity to ustekinumab
- Active infection
- Caution use with other immunosuppressive agents
- Caution if latent TB, hepatitis B carrier, chronic infection
- Caution if concurrent or history of PUVA (psoralen and ultraviolet A)

Adverse effects:
- Gastrointestinal: abdominal pain, diarrhea, nausea, vomiting
- CNS: headache, depression, dizziness
- Immunologic: hypersensitivity, immunogenicity/antibody development
- Neuromuscular: arthralgia
- Respiratory: nasopharyngitis
- Hypersensitivity/infusion-related reactions
- Infections: use may be associated with increased risk of infections, opportunistic infections, and serious herpes infections
- Dermatologic: acne vulgaris, cellulitis, local erythema at injection site
- Other: anaphylaxis, fever, arthralgia, malignant neoplasm, non-melanoma skin cancer

Drug interactions:
- Vaccines: inadequate immunological response to vaccines and increased risk of disseminated infection with live vaccines
- Concomitant use of other immunosuppressive agents: may increase risk of serious infections
- Refer to drug labeling or refer to drug databases for a comprehensive list

Pregnancy category: low risk based on limited human data. Last injection should be timed 6–10 weeks prior to estimated delivery date while on every 8-week regimen and 4–5 weeks if on q4wk schedule to achieve trough level at delivery (resume 48 h postpartum)
Lactation safety: acceptable risk for breastfeeding. Small concentrations detected in breast milk
Relative cost: $$$$$ $$$$$

TOFACITINIB

Class: Janus kinase inhibitor
Brand name: Xeljanz; Xeljanz XR
Manufacturer: Pfizer
Indication: Moderate to severe ulcerative colitis with inadequate response or intolerance to anti-TNFs

Dosage:
- Induction of remission 10 mg po bid (IR) or 22 mg po qd (ER) for at least 8 weeks; may continue for up to 16 weeks if needed

- Maintenance of remission: 5 mg po bid (IR) or 11 mg po qd (ER). The maintenance dose can be increased to that used for inductions if there is a loss of response to the lower doses. The higher doses should be tried for the shortest possible duration after careful assessment of risks and benefits with the goal to maintain the patient on the lowest effective dose

Contraindications/cautions:
- Active infection
- Caution use with other immunosuppressive agents
- Caution if thrombosis risk
- Caution if latent TB, hepatitis B carrier, chronic infection
- Caution in moderate renal or hepatic impairment (reduce dose frequency to qd). Should avoid use in severe renal or hepatic impairment
- Caution in patients at risk of GI perforation (e.g., diverticulitis history)
- Caution use in Asian patients: increased risk of adverse events (e.g., herpes zoster, opportunistic infections, leukopenia, interstitial lung disease, elevated aminotransferases)
- Caution use in elderly patients are at increased risk of infections

Adverse effects:
- Cardiovascular: hypertension, peripheral edema
- Neurologic: headaches, insomnia, paresthesia
- Dermatologic: skin rash, acne vulgaris, pruritus
- Endocrine and metabolic: hypercholesterolemia, dehydration
- Gastrointestinal/hepatic: abdominal pain, diarrhea, nausea, vomiting, gastroenteritis, abnormal liver enzymes, hepatic steatosis, perforation
- Hematologic: anemia, lymphopenia, neutropenia, thromboembolism (venous and arterial)
- Infection: use may be associated with increased risk of infections, opportunistic infections, and serious herpes zoster infections
- Other: fever, elevated creatine phosphokinase, lymphoma, EBV-associated post-transplant lymphoproliferative disorder, skin cancer (non-melanoma), interstitial pulmonary disease

Drug interactions:
- Vaccines: inadequate immunological response to vaccines and increased risk of disseminated infection with live vaccines
- Concomitant use of other immunosuppressive agents should be avoided: may increase risk of serious infections
- Significant interactions with CYP3A4 (major) substrates and CYP2C19 (minor). For complete list, please see drug labeling or refer to drug databases

Pregnancy category: limited pregnancy data. Avoid use in pregnant women if possible, especially during the first trimester until more safety data is available. Women should be advised to stop the medicine at least 1 week before conception
Lactation safety: avoid breastfeeding while on therapy due to limited safety data
Relative cost: $$$$$ $$$

SUGGESTED MONITORING FOR IBD DRUGS

The following recommended tests should be considered in all patients on specific therapies. The need for any other tests should be determined on a case-by-case basis.

Sulfasalazine CBC/diff, BUN/Cr, and liver chemistry at baseline. More frequent monitoring is needed initially but can be done Q3 months if stable. Supplementation with folic acid 1 gm/d is recommended.

5-ASA agents BUN/Cr at baseline and periodically thereafter.

Corticosteroids Periodic blood pressure (BP) and weight check, electrolytes and blood sugar check, chest X-ray and bone density if prolonged exposure (especially in older patients), and ophthalmic exam if prolonged therapy.

Thiopurines TPMT phenotype (enzyme activity preferred) or genotype prior to initiating the treatment to guide the dose. CBC/diff should be followed closely especially after each dose adjustment. Liver chemistry to be checked periodically. Thiopurine metabolites (6-TGN and 6-MMP) should be checked when inadequate or loss of response. Regular dermatologic exams.

MTX Pregnancy test, chest X-ray, CBC/diff, Bun/Cr, and liver chemistries at baseline. Labs should be monitored every 1–2 months if stable.

Cyclosporine During IV therapy: BUN/Cr, liver chemistry, magnesium, potassium, lipid panel and BP at baseline. BUN/Cr and electrolyte to be checked every 1–2 days with close drug level monitoring in

addition to frequent BP check. Daily monitoring of cholesterol level is needed if the initial level is low. During PO therapy: BP checks and labs including CBC, Bun/Cr, electrolyte including magnesium to be done weekly during the first month, bi-weekly for the second month, and then monthly if there is no concern. Cyclosporine trough level should also be monitored.

Anti-TNFα Hepatitis B serology. TB testing (PPD/quantiferon +/− chest X-ray) prior to initiation of treatment in everyone and annually in high-risk populations while on therapy. CBC and liver chemistry should be considered at baseline and periodically while on treatment. Regular dermatologic exams.

Natalizumab Hepatitis B serology including HBsAg, HBcAb, and HBsAb. Consider TB testing at baseline and annually in high-risk populations. Anti-JCV antibody prior and every 6 months while on therapy. This is in addition to monitoring patients for signs of PML through the TOUCH program (new onset or worsening of neurological signs and symptoms – progressive weakness or clumsiness, disturbance of vision, confusion, or changes in personality). CBC and liver chemistry should be considered at baseline and periodically while on treatment.

Vedolizumab Consider hepatitis B serology and TB testing at baseline, although the risk of reactivation of hepatitis B and TB is considered very low.

Ustekinumab Hepatitis B serology. TB testing (PPD/quantiferon +/− chest X-ray) prior to initiation of treatment in everyone and annually in high-risk populations while on therapy. Regular dermatologic exams.

Tofacitinib Hepatitis B serology. TB testing (PPD/quantiferon +/− chest-X ray) prior to initiation of treatment in everyone, and annually in high-risk populations while on therapy. CBC/diff, liver chemistry, and lipid panel at baseline, 4–8 weeks after treatment started and periodically after. Regular dermatologic exams.

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6 General Gastrointestinal Infections

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Contents

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TREATMENT OF ACUTE DIVERTICULITIS

(See Fig. 6.1 for a treatment algorithm for spontaneous bacterial peritonitis; Tables 6.1, 6.2, and 6.3 for treatment for diverticulitis; Table 6.4 for cholecystitis and cholangitis; Table 6.5 for prevention of SBP; Table 6.6 for SBP prophylaxis in the setting of active variceal bleed, cirrhosis; and Table 6.7 for treatment of neutropenic enterocolitis)

CEFOTAXIME

Class: third-generation cephalosporin
Trade name: Claforan
Manufacturer: Sanofi-Aventis

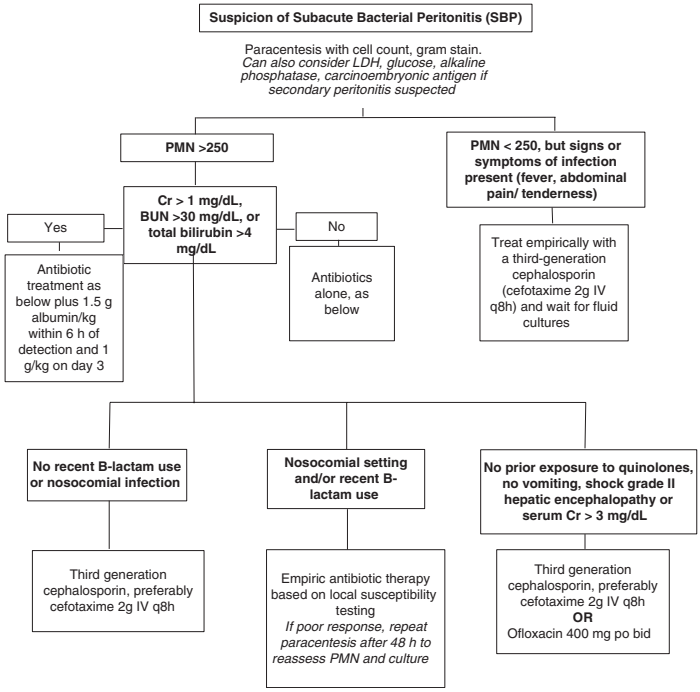

Fig. 6.1 Treatment of spontaneous bacterial peritonitis (SBP) [11]. PMN polymorphonuclear cells

Table 6.1 Treatment of outpatient diverticulitis

Select patients with mild symptoms	*Patients with mild symptoms*
Can consider conservative management with clear liquid diet and appropriate follow-up in selected, otherwise healthy patients with mild diverticulitis such as Hinchey 1 and 1a	Clear liquid diet, appropriate follow-up, and antibiotics: TMP/SMX DS 150/800 mg po q12h **OR** Ciprofloxacin 750 mg po q12h + Metronidazole 500 mg po q6h **OR** Levofloxacin 750 mg po q24h + Metronidazole 500 mg po q6h

[a]Duration of therapy varies with clinical response, usually 7–10 days

Table 6.2 Treatment of inpatient treatment of community-acquired diverticulitis

	Mild-moderate disease or low risk of treatment failure	*Severe disease or high risk of treatment failure*
Single-agent regimen	Ertapenem 1 g iv q24h **OR** Moxifloxacin 400 mg q24h	Meropenem 1 g iv q8h **OR** Imipenem-cilastatin 500 mg IV q6h **OR** Doripenem 500 mg iv q8h **OR** Piperacillin-tazobactam 4.5 g iv q8h
Multiple-agent regimen	Cefotaxime 2 g iv q8h + Metronidazole 500 mg iv q8h **OR** Ceftriaxone 2 g iv q24h + Metronidazole 500 mg iv q8h **OR** Ciprofloxacin 400 mg iv q12h + Metronidazole 500 mg iv q8h **OR** Levofloxacin 750 mg iv q24h + Metronidazole 500 mg iv q8h	Cefepime 2 g iv q8h + Metronidazole 500 mg iv q8h **OR** Ceftazidime 2 g iv q8h + Metronidazole 500 mg iv q8h **OR** Aztreonam 1 g - 2 g iv q8–12h + Metronidazole 500 mg iv q8h + Vancomycin 15–20 mg/kg q8–12h

[a]Duration of therapy should be 4–7 days with adequate source control

Table 6.3 Inpatient treatment of health care–associated diverticulitis

Single-agent regimen	Meropenem 1 g iv q8h **OR** Imipenem-cilastatin 500 mg iv q6h **OR** Doripenem 500 mg iv q8h **OR** Piperacillin-tazobactam 4.5 g iv q6h
Multiple-agent regimen	Cefepime 2 g iv q8h + Metronidazole 500 mg iv q8h **OR** Ceftazidime 2 g iv q8h + Metronidazole 500 mg iv q8h **OR** Ceftazidime-avibactam 2.5 g iv q8h + Metronidazole 500 mg iv q8h (dose decrease needed with CrCl 30–50) **OR** Ceftolozane-tazobactam 1.5 g iv q8h + Metronidazole 500 mg iv q8h *May need to add the antibiotics below if Enterococcus faecalis suspected:* Ampicillin 2 g iv q4h **OR** Vancomycin 15–20 mg/kg iv q8–12h

Should be guided by local microbiologic results. Below are recommended regimens for empiric coverage of likely pathogens

[a]Do not use: cefoxitin/cefotetan due to increased resistance

Dosage:

- Intra-abdominal infections: 2 g iv q8h, total duration 4–7 days following adequate source control
- SBP: 2 g IV q8h
- Dose adjustment necessary for altered kidney function (dependent on Cr clearance)
  - CrCl <20 mL/min/1.73 m^2: dose should be decreased by 50%
  - Dialysis: moderately dialyzable (20–50%); 2 g q24h, on dialysis days, administer after dialysis

Indication: intra-abdominal infections, SBP

Contraindications/cautions:

- Contraindicated if hypersensitivity to component of drug or other cephalosporin
- Use with caution in patients with penicillin allergy, history of colitis, or renal impairment

Table 6.4 Treatment of cholecystitis and cholangitis

	Management	*Antibiotic regimen*	*Duration of treatment*
Community acquired, mild severity	IV fluids, restricted po intake, analgesia, antibiotics, and surgery	Cefazolin 1–2 g iv q8h **OR** Cefuroxime 1.5 g iv q8h **OR** Ceftriaxone 2 g iv q24h	In cholecystitis, antimicrobial therapy can be discontinued within 24 h after cholecystectomy is performed[a]
Community acquired, moderate severity		Piperacillin-tazobactam 4.5 g iv q6h OR Cefepime 2 g q8h **OR** Cefotaxime 2 g q8h **OR** Ertapenem 1 g iv q24h	In cholangitis, 4–7 days of therapy are recommended once source of infection is controlled[a]
Community acquired, severe or high risk of treatment failure		Imipenem-cilastatin 500 mg iv q6h **OR** Meropenem 1 g iv q8h **OR** Doripenem 500 mg iv q8h **OR** Ertapenem 1 g iv q24h **OR** Piperacillin-tazobactam 4.5 g iv q6h **OR** Ceftazidime 2 g iv q8h	4–7 days of therapy are recommended once source of infection is controlled[a]
Bilio-enteric anastomosis of any severity		Addition of metronidazole 500 mg iv q8h to cephalosporins	
Health care–associated biliary infection		Piperacillin-tazobactam 4.5 g iv q6h **OR** Ceftazidime 2 g iv q8h **OR** Imipenem-cilastatin 500 mg iv q6h **OR** Meropenem 1 g iv q8h **OR** Doripenem 500 mg iv q8h **OR** Ertapenem 1 g iv q24h **PLUS** Vancomycin 15–20 mg/kg iv q8–12h	If bacteremia present, should continue treatment for a minimum of 2 weeks[a]

Table 6.4 (continued)

Outcomes in patients treated with a shorter course of antibiotic therapy (<7 days) had similar outcomes to those treated with a longer course of therapy (>7 days) following percutaneous cholecystectomy

[a]Treatment may need to be extended in certain cases including perforation, emphysematous changes, necrosis, the presence of residual stones, or liver abscess

Table 6.5 Prevention of SBP

Patients with cirrhosis, and gastrointestinal hemorrhage	Ceftriaxone 1 g iv q24h × 7 days
Patients who had an episode of SBP or ascitic fluid protein <1.5 g/dL along with impaired renal function (Cr >1.2, BUN >25 or serum Na <130) or liver failure	Long-term TMP-SMX

Table 6.6 SBP prophylaxis in the setting of active variceal bleed, cirrhosis with/without ascites

Patients with cirrhosis with variceal bleed	Primary therapy: Ceftriaxone 1 g iv q24h Alternative therapy: Ciprofloxacin 400 mg iv q12h or 500 mg po BID for 5–7 days

[a]Long-term prophylaxis not indicated unless SBP develops

Table 6.7 Treatment of neutropenic enterocolitis

Single-agent regimen	Piperacillin-tazobactam 3.375 g iv q6h **OR** Imipenem-Cilastin 500 mg iv q6h **OR** 1 g iv q6h
Multiple-agent regimen	Ceftazidime 1 g iv q8–12h **OR** Cefepime 2 g iv q8h **PLUS** Metronidazole 1 g iv q6h

If suspect that patient is at risk for resistant organisms, can add antimicrobial coverage for resistant organisms. If patient does not improve within 72 h, can consider adding antifungal coverage

Adverse effects:
- Cardiovascular: arrhythmia can occur in patients who receive rapid bolus via central venous catheter
- Dermatologic: rash, pruritus
- Gastrointestinal: colitis, diarrhea, nausea, vomiting, *Clostridioides difficile* colitis
- Hematologic and oncologic: eosinophilia

Drug interactions:
- Aminoglycosides: cephalosporins may enhance the nephrotoxic effect of aminoglycosides
- BCG (intravesical): antibiotics may diminish the therapeutic effect of BCG
- *Lactobacillus* and estriol: antibiotics may diminish the therapeutic effect of *Lactobacillus* and estriol
- Probenecid: may increase the serum concentration of cefotaxime. Avoid cefotaxime doses greater than 6 g/day with concurrent probenecid
- Vitamin K antagonists (e.g., warfarin): cephalosporins may enhance the anticoagulant effect of vitamin K antagonists

Pregnancy category: B
Lactation: generally safe, but may cause GI disturbances in infants
Relative cost: $$$$

CEFTRIAXONE

Class: third-generation cephalosporin
Trade name: Rocephin
Manufacturer: Roche Laboratories

Dosages:
- Acute cholecystitis: 1–2 g iv q24h, continue for 1 day after gallbladder removal
- Other intra-abdominal infections: 1–2 g iv q24h, total duration 4–7 days following adequate source control
- SBP prevention in patients with cirrhosis and active GI bleed: 1 g q24h, total duration 7 days
- SBP treatment: 2 g q24 h, total duration 5 days as long as fever and pain have resolved
- No need for renal dose adjustment

Indication: intra-abdominal infections, SBP treatment, and prophylaxis

Contraindications/cautions:
- Contraindicated if hypersensitivity to drug/class or component of drug
- Do not reconstitute, admix, or co-administer with parenteral calcium containing product use
- Caution if hypersensitivity to penicillin, or impaired liver and renal function or vitamin K deficiency

Adverse effects:
- Dermatologic: skin tightness, rash
- Gastrointestinal: pseudo cholecystitis, jaundice, *Clostridioides difficile* diarrhea, increased LFTs
- Respiratory: bronchospasm, allergic pneumonitis
- Hematologic: eosinophilia, thrombocytosis, neutropenia, leukopenia, hemolytic anemia, thrombocytopenia, hypoprothrombinemia, agranulocytosis
- Immunologic: serum sickness, anaphylaxis
- Renal: increased BUN
- Neurologic: headaches, dizziness

Drug interactions:
- Aminoglycosides: cephalosporins may enhance the nephrotoxic effect of aminoglycosides. Cephalosporins may decrease the serum concentration of aminoglycosides
- BCG (intravesical): antibiotics may diminish the therapeutic effect of BCG
- Calcium salts (intravenous): may enhance the adverse/toxic effect of ceftriaxone. Ceftriaxone binds to calcium forming an insoluble precipitate
- *Lactobacillus* and estriol: antibiotics may diminish the therapeutic effect of *Lactobacillus* and estriol
- Probenecid: may increase the serum concentration of cephalosporins
- Ringer's injection (lactated): may enhance the adverse/toxic effect of ceftriaxone
- Vitamin K antagonists (e.g., warfarin): cephalosporins may enhance the anticoagulant effect of vitamin K antagonists

Pregnancy category: B
Lactation: generally safe, but may cause GI disturbances in infants
Relative cost: $-$$$$ $

CEFEPIME

Class: fourth-generation cephalosporin
Trade name: Maxipime
Manufacturer: Bristol-Myers Squibb Company

Dosages:
- Acute cholecystitis: 2 g iv q8–12h, continue for 1 day after gallbladder removal
- Other intra-abdominal infections: 2 g iv q8–12h, total duration 4–7 days following adequate source control
- Dose adjustment necessary for altered kidney function (dependent on Cr clearance):

CrCl (mL/min)	*Dose*	
>60 (usual dose)	2 g q8h	2 g q12h
30–60	2 g q12h	1 g q12h
11–29	1 g q12h	1 g q24h
<11	1 g q24h	500 mg q24h
HD	2 g on dialysis days, administer after HD	

Indication: intra-abdominal infections

Contraindications/cautions:
- Hypersensitivity to drug/class or component of drug
- Caution if impaired liver and renal function or vitamin K deficiency
- Caution in patients with seizure disorder
- Caution in elderly

Adverse effects:
- Dermatologic: rash, pruritus
- Gastrointestinal: diarrhea, nausea, vomiting, increased liver tests
- Endocrine and metabolic: hypophosphatemia, hyperphosphatemia, hypocalcemia
- Hematologic: positive direct Coombs test, eosinophilia, anemia, agranulocytosis, leukopenia, thrombocytopenia
- Neurologic: headache, coma, encephalopathy, confusion, hallucination, neurotoxicity, seizure

Drug interactions:
- Aminoglycosides: cephalosporins may enhance the nephrotoxic effect of aminoglycosides. Cephalosporins may decrease the serum concentration of aminoglycosides
- BCG (intravesical) : antibiotics may diminish the therapeutic effect of BCG
- *Lactobacillus* and estriol: Antibiotics may diminish the therapeutic effect of *Lactobacillus* and estriol
- Probenecid: may increase the serum concentration of cephalosporins
- Vitamin K antagonists (e.g., warfarin): cephalosporins may enhance the anticoagulant effect of vitamin K antagonists

Pregnancy category: B
Lactation: generally safe, but may cause GI disturbances in infants
Relative cost: $-$$$$$

METRONIDAZOLE

Class: imidazole derivative antibiotics
Trade name: Flagyl
Manufacturer: Pfizer Inc.

Dosages:
- *Clostridioides difficile* (non-severe): 500 mg po tid, total duration 10–14 days
- *Clostridioides difficile* (fulminant): 500 mg iv q8h
- Other intra-abdominal infections (anaerobic bacteria): 500 mg po, iv q8h, total duration 4–7 days following adequate source control
- Dose adjustment necessary for hepatic impairment (Child-Pugh class C):
  - Reduce dose by 50%. May also prolong frequency if using iv

Indication: intra-abdominal infections (anaerobic bacteria), *Clostridioides difficile*

Contraindications/cautions:
- Hypersensitivity to drug/class or component of drug
- Contraindicated in the first trimester of pregnancy
- Caution in patients who have taken disulfiram within the last 2 weeks
- Caution with alcohol use
- Caution in patients with blood dyscrasias, Cockayne syndrome, hepatic and severe renal impairment, seizure disorder

Adverse effects:
- Neurologic: convulsive seizures, disulfiram-like reaction with alcohol, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, headache, syncope, dizziness, vertigo, ataxia, depression, weakness, insomnia
- Gastrointestinal: unpleasant metallic taste, diarrhea, nausea, vomiting, abdominal cramping, *Clostridioides difficile* diarrhea
- Dermatologic: rash, pruritus
- Hematologic and oncologic: leukopenia, thrombocytopenia, possibly carcinogenic based on animal studies
- Immunologic: anaphylaxis
- Renal: dysuria, cystitis, polyuria, incontinence

Drug interactions:
- Alcohol (ethyl): metronidazole may enhance the adverse/toxic effect of alcohol, a disulfiram-like reaction may occur
- BCG (intravesical): antibiotics may diminish the therapeutic effect of BCG
- Busulfan: metronidazole may increase the serum concentration of busulfan
- Carbocisteine: metronidazole may enhance the adverse/toxic effect of carbocisteine
- Disulfiram: may enhance the adverse/toxic effect of metronidazole
- Fluorouracil products: metronidazole may increase the serum concentration of fluorouracil products
- Fosphenytoin/phenytoin: may decrease the serum concentration of metronidazole – may increase the serum concentration of fosphenytoin
- *Lactobacillus* and estriol: antibiotics may diminish the therapeutic effect of *Lactobacillus* and estriol
- Lithium: metronidazole may enhance the adverse/toxic effect of lithium
- Lopinavir: metronidazole may enhance the adverse/toxic effect of lopinavir
- Mebendazole: may enhance the adverse/toxic effect of metronidazole
- Mycophenolate: metronidazole may decrease the serum concentration of mycophenolate
- Phenobarbital: may decrease the serum concentration of metronidazole
- Ritonavir: may enhance the adverse/toxic effect of metronidazole
- Tipranavir: metronidazole may enhance the adverse/toxic effect of tipranavir
- Vitamin K antagonists (e.g., warfarin): metronidazole may increase the serum concentration of vitamin K antagonists

Pregnancy category: B
Lactation: conditional safety – potential for adverse reaction. Decision should be made whether to discontinue nursing or discontinue drug
Relative cost: $-$$

LEVOFLOXACIN

Class: fluoroquinolone antibiotics
Trade name: Levaquin
Manufacturer: Ortho-McNeil-Janssen Pharmaceutical

Dosages:
- Intra-abdominal infections (diverticulitis): 750 mg q24h po, iv, total duration 4–7 days following adequate source control
- Dose adjustment necessary for altered kidney function (dependent on Cr clearance):

CrCl (mL/min)	*Dose*
>50 (usual dose)	750 mg q24h
20–50	750 mg q48h
<20	750 mg initial dose then 500 mg q48h
HD or PD	750 mg initial dose, then 500 mg q48h, administer after dialysis

- Do not administer dairy products, antacids, didanosine, sucralfate, multivitamins, or other products that contain calcium, magnesium, aluminum, iron, or zinc within 2 h before or 6 h after administering this drug due to effects of dairy on absorption

Indication: intra-abdominal infections

Contraindications/cautions:
- Contraindicated if hypersensitivity to drug/class or component of drug
- Avoid use in patients with myasthenia gravis due to possible exacerbation of symptoms
- Avoid use in elderly with known history of aortic aneurysm or those at increased risk
- Caution if prolonged QT interval/hypokalemia
- Caution if seizure, CNS disorder, depression, or peripheral neuropathy
- Caution if renal function impaired
- Caution in elderly, patients on steroids or with rheumatoid arthritis or solid organ transplant recipients due to risk of tendon rupture
- Caution in diabetic patients due to risk of fluctuations in glucose levels

Adverse effects:
- Neuropsychiatric: seizures, dizziness, peripheral neuropathy, psychosis, hallucinations, exacerbation of myasthenia gravis
- Cardiovascular: prolonged QT, torsades de pointes, aortic aneurysm or dissection, chest pain
- Gastrointestinal: pseudomembranous colitis, hepatotoxicity, abdominal pain, diarrhea, nausea, vomiting
- Renal: nephrotoxicity
- Hematologic and oncologic: can cause hemolytic reactions in patients with G6PD deficiency
- Immunologic: anaphylaxis, hypersensitivity
- Musculoskeletal: tendon rupture, tendinitis
- Dermatologic: photosensitivity

Drug interactions:
- Agents with blood glucose lowering effects: quinolones may enhance the hypoglycemic effect of agents with blood glucose lowering effects.

Quinolones may diminish the therapeutic effect of agents with blood glucose lowering effects
- Amiodarone, domperidone, haloperidol, hydroxychloroquine, methadone, ondansetron, pentamidine, QT-prolonging antidepressants, QT-prolonging antipsychotics, QT-prolonging IA, IC, III antiarrhythmics, kinase inhibitors, tacrolimus: levofloxacin-containing products may enhance the QTc-prolonging effects
- Antacids: may decrease the absorption of quinolones
- BCG (intravesical): antibiotics may diminish the therapeutic effect of BCG
- Calcium salts: may decrease the absorption of quinolones
- Corticosteroids (systemic): may enhance the adverse/toxic effect of quinolones
- Iron preparations: may decrease the serum concentration of quinolones
- *Lactobacillus* and estriol: antibiotics may diminish the therapeutic effect of *Lactobacillus* and estriol
- Magnesium salts: may decrease the serum concentration of quinolones
- Multivitamins/minerals (with ADEK, folate, iron): may decrease the serum concentration of quinolones. Administer oral quinolones at least 2 h before, or 6 h after, the dose of a multivitamin that contains polyvalent cations
- Mycophenolate: quinolones may decrease the serum concentration of mycophenolate
- Nonsteroidal anti-inflammatory agents: may enhance the neuroexcitatory and/or seizure-potentiating effect of quinolones
- Probenecid: may decrease the excretion of quinolones
- Sevelamer: may decrease the absorption of quinolones
- Sucralfate: may decrease the serum concentration of quinolones
- Varenicline: quinolones may increase the serum concentration of varenicline
- Vitamin K antagonists (e.g., warfarin): quinolones may enhance the anticoagulant effect of vitamin K antagonists
- Zinc salts: may decrease the serum concentration of quinolones

Pregnancy category: C
Lactation: potential for adverse reaction. Decision should be made whether to discontinue nursing or discontinue drug
Relative cost: $-$$$$$

CIPROFLOXACIN

Class: fluoroquinolone antibiotics
Trade Names: Cipro, Cipro XR

Manufacturer: multiple

Dosages:
- Infections: 500 mg po q12 h or 400 mg iv q12h, total duration 4–7 days following adequate source control
- SBP prophylaxis in patients with cirrhosis and active GI bleed: 500 mg po q12h, 400 mg iv q12h, total duration 7 days
- Long-term SBP prophylaxis: 500 mg po q24h
- Dose adjustment necessary for altered kidney function (dependent on Cr clearance):

CrCl (mL/min)	*Oral dose*	*IV dose*
>50 (usual dose)	500 mg q12h	400 mg q12h
30–50	250 mg q12h	400 mg q12h
<30	500 mg q24h	200–400 mg q12–24 h
HD and PD	250 mg q24h after dialysis	200–400 mg q24h after dialysis

- Do not administer dairy products, antacids, didanosine, sucralfate, multivitamins, or other products that contain calcium, magnesium, aluminum, iron, or zinc within 2 h before or 6 h after administering this drug due to effects of dairy on absorption

Indication: intra-abdominal infections, SBP prophylaxis

Contraindications/cautions:
- Contraindicated if hypersensitivity to drug/class or component of drug
- Contraindicated with concurrent use of tizanidine
- Avoid use in elderly with known history of aortic aneurysm or those at increased risk
- Avoid use in patients with myasthenia gravis due to possible exacerbation of symptoms
- Caution in patients with prolonged QT interval/hypokalemia
- Caution if seizure, CNS disorder, peripheral neuropathy or in patients at risk of mental illness
- Caution if renal function impaired
- Caution in diabetic patients due to risk of fluctuations in glucose levels
- Caution in elderly, patients on steroids or with rheumatoid arthritis or solid organ transplant recipients due to risk of tendon rupture
- Ensure adequate hydration to prevent crystalluria

Adverse reactions:
- Neuropsychiatric: seizures, exacerbation of myasthenia gravis, peripheral neuropathy

- Cardiovascular: QT prolongation, aortic aneurysm, aortic dissection
- Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain, pseudomembranous colitis, hepatotoxicity, *Clostridioides difficile* diarrhea
- Renal: nephrotoxicity, crystalluria
- Hematologic: myelosuppression, blood dyscrasias, reduction in absolute platelet count
- Musculoskeletal: tendon rupture, tendinitis
- Immunologic: anaphylaxis, anaphylactic shock, vasculitis, serum sickness
- Dermatologic: photosensitivity, skin reactions, phototoxicity, psychosis, peripheral neuropathy

Drug interactions:
- Agents with blood glucose lowering effects: quinolones may enhance the hypoglycemic effect of agents with blood glucose lowering effects. Quinolones may diminish the therapeutic effect of agents with blood glucose lowering effects
- Antacids: may decrease the absorption of quinolones
- BCG (intravesical): antibiotics may diminish the therapeutic effect of BCG
- Calcium salts: may decrease the absorption of quinolones. Consider administering an oral quinolone at least 2 h before or 6 h after the dose of an oral calcium supplement to minimize this interaction
- Chloroquine: may enhance the hyperglycemic/ hypoglycemic effect of ciprofloxacin
- Chloroquine, clozapine, fosphenytoin/ phenytoin, haloperidol, hydroxychloroquine: may enhance the QTc-prolonging effect of ciprofloxacin (systemic)
- Corticosteroids (systemic): may enhance the adverse/toxic effect of quinolones
- Dofetilide: CYP3A4 Inhibitors may increase the serum concentration of dofetilide
- Duloxetine: CYP1A2 Inhibitors may increase the serum concentration of duloxetine
- Erlotinib: ciprofloxacin may increase the serum concentration of erlotinib
- Iron preparations: may decrease the serum concentration of quinolones
- *Lactobacillus* and estriol: antibiotics may diminish the therapeutic effect of *Lactobacillus* and estriol
- Magnesium salts: may decrease the serum concentration of quinolones
- Methotrexate: ciprofloxacin may increase the serum concentration of methotrexate
- Methylphenidate: may enhance the cardiotoxic effect of quinolones
- Multivitamins/minerals (with ADEK, folate, iron): may decrease the serum concentration of quinolones
- Mycophenolate: quinolones may decrease the serum concentration of mycophenolate

- Nonsteroidal anti-inflammatory agents: may enhance the neuroexcitatory and/or seizure-potentiating effect of quinolones
- Olanzapine: may increase the serum concentration of olanzapine
- Probenecid: may decrease the excretion of quinolones
- Propranolol: may increase the serum concentration of propranolol
- Quinapril: may decrease the serum concentration of quinolones
- Roflumilast: ciprofloxacin may increase the serum concentration of roflumilast
- Ropinrole: may increase the serum concentration of ropinrole
- Sevelamer: may decrease the absorption of quinolones
- Sildenafil: ciprofloxacin may increase the serum concentration of sildenafil
- Sodium picosulfate: antibiotics may diminish the therapeutic effect of sodium
- Spironolactone: may enhance the arrhythmogenic effect of ciprofloxacin
- Sucralfate: may decrease the serum concentration of quinolones
- Thyroid products: ciprofloxacin may decrease the serum concentration of thyroid products
- Tizanidine: ciprofloxacin may increase the serum concentration of tizanidine
- Varenicline: quinolones may increase the serum concentration of varenicline
- Vitamin K antagonists (e.g., warfarin): quinolones may enhance the anticoagulant effect of vitamin K antagonists
- Zinc salts: may decrease the serum concentration of quinolones
- Zolpidem: ciprofloxacin (systemic) may increase the serum concentration of zolpidem

Pregnancy category: C
Lactation: a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother
Relative cost: $-$$$

SULFAMETHOXAZOLE AND TRIMETHOPRIM

Class: sulfonamide and trimethoprim antibiotic combinations
Trade name: Bactrim
Manufacturer: AR Scientific, Inc.

Dosage:
- SBP prophylaxis: 160/800 mg (DS tab) po daily
- Dose adjustment necessary for altered kidney function (dependent on Cr clearance):

CrCl (mL/min)	*Dose*
>30	No dose adjustment necessary
15–30	Reduce dose to 50% of dose
<15 or dialysis	Reduce dose to 25–50% of dose If on dialysis, administer dose after dialysis

Indication: SBP prophylaxis

Contraindications/cautions:
- Contraindicated if hypersensitivity to drug/class or component of drug
- Caution in patients with impaired hepatic or renal function, possible folate deficiency, severe allergies or bronchial asthma, or glucose-6-phosphate dehydrogenase deficiency

Adverse reactions:
- Gastrointestinal: nausea/vomiting, anorexia, hepatitis, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea
- Dermatological: rash, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis
- Hematological: agranulocytosis, aplastic anemias, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, eosinophilia
- Genitourinary: renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria
- Metabolic and nutritional: hyperkalemia
- Neurologic: aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache
- Psychiatric: hallucinations, depressions, apathy, nervousness
- Endocrine: diuresis and hypoglycemia
- Musculoskeletal: arthralgia and myalgia
- Respiratory: cough, shortness of breath, and pulmonary infiltrates

Drug Interactions:
- Diuretics, especially thiazides: increased incidence of thrombocytopenia with purpura
- Warfarin: Bactrim may increase prothrombin time in patients taking warfarin
- Phenytoin: hepatic metabolism may be inhibited by Bactrim
- Cyclosporine: co-administration can cause nephrotoxicity
- Digoxin: levels can increase with Bactrim use
- Indomethacin: can cause an increase of sulfamethoxazole levels

- Tricyclic antidepressants: levels can be decreased with Bactrim use
- Oral hypoglycemics: can be potentiated by Bactrim use
- Angiotensin-converting enzyme inhibitors: can cause hyperkalemia when used with Bactrim

Pregnancy: contraindicated
Lactation: contraindicated
Relative cost: $ (generic available: $-$$)

PIPERACILLIN-TAZOBACTAM

Class: penicillin and beta-lactamase inhibitor combination antibiotics
Trade name: Zosyn
Manufacturer: Pfizer Medical

Dosage:
- Intra-abdominal infections: 3.375 g or 4.5 g iv q6h, total duration of therapy 4–7 days following adequate source control
- Dose adjustment necessary for altered kidney function (dependent on CrCl):

CrCl (mL/min)	*Dose*	
	Mild to moderate infections	*Severe infections or for coverage of Pseudomonas aeruginosa*
>40 (usual dose)	3.375 g q6h	4.5 g q6h
20–40	2.25 g q6h	4.5 g q8h or 3.375 g q6h
<20	2.25 g q8h	4.5 g q12h or 2.25 g q6h
HD	2.25 g q12h, administer after dialysis	2.25 g q8h, administer after dialysis

Indication: intra-abdominal infections

Contraindications/cautions:
- Contraindicated if hypersensitivity to drug/class or component of drug
- Caution in patients with seizure disorders
- Caution in patients with renal impairment

Adverse effects:
- Cardiovascular: shock
- Dermatologic: rash, Stevens-Johnson syndrome, toxic epidermal necrolysis

- Gastrointestinal: diarrhea, *Clostridioides difficile* diarrhea, nausea, vomiting, hepatic insufficiency
- Hematologic: purpuric disease, agranulocytosis, pancytopenia
- Immunologic: drug reaction, serum-sickness-like reaction
- Renal: acute renal failure
- Endocrine: hypoglycemia
- Neurologic: headache, insomnia, rigors, neuromuscular excitability and seizures

Drug interactions:
- Aminoglycosides: penicillins may decrease the serum concentration of aminoglycosides
- BCG (intravesical): antibiotics may diminish the therapeutic effect of BCG
- *Lactobacillus* and estriol: antibiotics may diminish the therapeutic effect of *Lactobacillus* and estriol
- Methotrexate: penicillins may increase the serum concentration of methotrexate
- Mycophenolate: penicillins may decrease serum concentrations of the active metabolite(s) of mycophenolate
- Probenecid: may increase the serum concentration of beta-lactamase inhibitors
- Tetracyclines: may diminish the therapeutic effect of penicillins
- Vancomycin: piperacillin may enhance the nephrotoxic effect of vancomycin.
- Vecuronium: piperacillin may enhance the neuromuscular-blocking effect of vecuronium.
- Vitamin K antagonists (e.g., warfarin): penicillins may enhance the anticoagulant effect of vitamin K antagonists.

Pregnancy category: B
Lactation safety: not expected to cause adverse effects
Relative cost: $$$$$ (generic available for $$$)

ERTAPENEM

Class: carbapenems
Trade name: INVanz
Manufacturer: Merck and Co

Dosage:
- Acute cholecystitis: 1 g iv q24h, total duration for 1 day after gallbladder removal

- Other intra-abdominal infection: 1 g iv q24h, total duration 4–7 days following adequate source control
- Dose adjustment necessary for altered kidney function:
  - CrCl <30 mL/min/1.73 m^2: 500 mg q24h
  - HD: 500 mg q24h. When dose falls on hemodialysis day, administer at least 6 h prior to hemodialysis or wait until after hemodialysis. If dose given within 6 h prior to hemodialysis, give an extra 150 mg after hemodialysis
  - PD: 500 mg q24h

Indication: intra-abdominal infections

Contraindications/cautions:
- Known hypersensitivity to any component of product or other drugs in the same class or in patients who have had anaphylactic reactions to beta-lactams
- Use caution in patients with CNS disorders
- Use with caution in patients with renal impairment

Adverse effects:
- Cardiovascular: edema, chest pain, hypotension
- Dermatologic: rash
- Endocrine: decreased or increased serum potassium, increased serum glucose
- Gastrointestinal: diarrhea, nausea, vomiting, increased LFTs, *Clostridioides difficile* diarrhea
- Genitourinary: vaginitis
- Hematologic/oncologic: thrombocytopenia, neutropenia
- Neurologic: headache, altered mental status, insomnia, dizziness, seizures
- Respiratory: cough, dyspnea

Drug interactions:
- Valproic acid and derivatives: carbapenems, including ertapenem, may decrease the serum concentration of divalproex sodium/valproic acid increasing the risk of breakthrough seizures
- BCG (intravesical): antibiotics may diminish the therapeutic effect of BCG
- *Lactobacillus* and estriol: antibiotics may diminish the therapeutic effect of *Lactobacillus* and estriol
- Probenecid: may increase the serum concentration of ertapenem
- Tacrolimus (systemic): ertapenem may increase the serum concentration of tacrolimus

Pregnancy category: B
Lactation safety: use with caution
Relative cost: $$$$ $$ (generic available for $$$$ $)

INFECTIVE ENDOCARDITIS PROPHYLAXIS FOR GI PROCEDURES

The administration of prophylactic antibiotics solely to prevent endocarditis is not recommended for patients who undergo GI tract procedures, including diagnostic esophagogastroduodenoscopy or colonoscopy as stated in American Heart Association 2007 guidelines.

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7 Specific Gastrointestinal Microbial Infections

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Contents

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CLOSTRIDIOIDES (**FORMERLY** *CLOSTRIDIUM*) *DIFFICILE PSEUDOMEMBRANOUS COLITIS*

(See Fig. 7.1 for an algorithm for the treatment of *Clostridioides difficile* pseudomembranous colitis)

VANCOMYCIN

Class: glycopeptide antibiotics
Brand name: Vancocin
Manufacturer: Pfizer

Dosage:
- First-line agent in *C. difficile* pseudomembranous colitis
- Non-severe or severe *C. difficile* infection: vancomycin 125 mg qid for 10 days

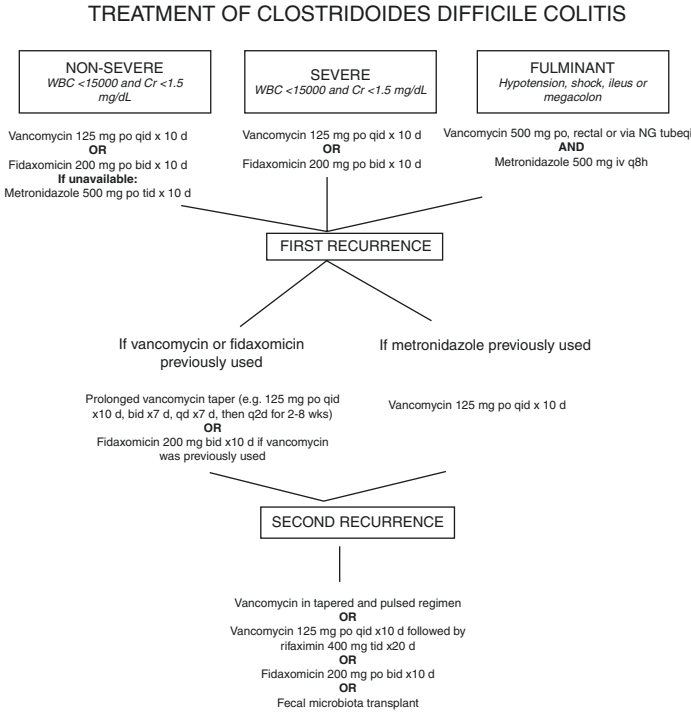

Fig. 7.1 Treatment of *Clostridioides difficile* pseudomembranous colitis. (Algorithm adapted by Drs. Clifford McDonald et al. [65]. With permission)

- Severe: vancomycin 125 mg po qid ×10 d or fidaxomicin 200 mg po bid ×10 d
- Fulminant: vancomycin 125 mg qid with iv metronidazole 500 mg iv q8h

Contraindications/cautions:
- Hypersensitivity to vancomycin products
- Caution if impaired renal function
- Use with caution if hearing loss occurs

Adverse effects:
- Gastrointestinal: nausea and vomiting
- Cardiovascular: hypotension accompanied by flushing
- Renal: nephrotoxicity (rare)
- Hematologic: neutropenia (rare)

- Immunologic: anaphylaxis (rare)
- Dermatologic: erythematous rash on face and upper body (red neck or red man syndrome – infusion rate related)
- Otic: ototoxicity (rare)

Drug interactions:
- Increased nephrotoxicity with tenofovir, cidofovir, acyclovir, cyclosporine, ganciclovir

Pregnancy category: B
Lactation: probably safe
Relative cost: $$$$ (generic available: $–$$$)

FIDAXOMICIN

Class: macrolide antibiotics
Brand name: Dificid
Manufacturer: Merck
Dosing: recommended as alternative treatment option for pseudomembranous colitis
- Initial episode: 200 mg po bid for 10 days
- First recurrence: 200 mg po bid for 10 days
- Second or subsequent recurrence: 200 mg po bid for 10 days

Contraindications/cautions:
- Hypersensitivity reaction including angioedema, dyspnea
- Caution if macrolide allergy

Adverse effects:
- Gastrointestinal: nausea, abdominal distension, abdominal pain
- Hepatic: increased liver enzymes (rare)
- Hematologic: anemia (rare)
- Dermatologic: pruritus, skin rash

Drug interactions:
- Avoid combination with mizolastine, sodium picosulfate, cholera, and typhoid vaccines

Pregnancy category: B
Lactation: safety unknown
Relative cost: $$$

METRONIDAZOLE

(See Chap. 6 on General GI Infections)

HELICOBACTER PYLORI

CLARITHROMYCIN-BASED THERAPY

PPI + amoxicillin (1 g po bid), clarithromycin (500 mg po bid)

BISMUTH QUADRUPLE THERAPY

PPI + metronidazole (500 mg po tid), tetracycline (500 mg po qid), bismuth subsalicylate or subcitrate (po qid)

CONCOMITANT TRIPLE THERAPY

PPI + amoxicillin (1 g po bid), clarithromycin (500 mg po bid), metronidazole (500 mg po tid)

AMOXICILLIN

Class: penicillin antibiotics
Brand names: Amoxicot, Amoxil, Amoxil Pediatric Drops, Biomox, Dispermox, Trimox, Wymox
Manufacturer: Generic; Amoxil – GlaxoSmithKline; Dispermox – Ranbaxy; Trimox – Apothecon Inc.
Dosage: for *H. pylori* eradication: 1 g po bid in combination with PPI and other antibiotics. See table

Contraindications/cautions:
- Hypersensitivity to amoxicillin
- Infectious mononucleosis: risk of developing skin rash
- Caution in phenylketonurics
- Hypersensitivity to cephalosporins: risk of cross reactivity

Adverse effects:
- Gastrointestinal: diarrhea, nausea, vomiting

- Immunologic: immune hypersensitivity reaction
- Dermatologic: rash

Drug interactions:
- Typhoid vaccine, live oral: antibiotic may inactivate vaccine

Pregnancy category: B
Lactation: safe
Relative cost: $ (generic available: $)

BISMUTH SUBSALICYLATE

Class: anti-diarrheals
Brand name: Bismatrol, Pepto-Bismol
Manufacturer: Generic
Pharmacology: cytoprotectant
Dosage: *H. pylori* eradication: 262–524 mg po qid for 10–14 days in combination with PPI and other antibiotics

Contraindications/cautions:
- G6PD deficiency
- Coagulation disorder
- Severe renal impairment

Adverse effects:
- Fecal discoloration
- Tongue discoloration
- Constipation
- Tinnitus

Pregnancy category: inadequate data to assess risk, possible risk of fetal harm
Lactation: safety unknown, considerate alternative

CLARITHROMYCIN

Class: macrolide antibiotics
Brand names: Biaxin, Biaxin Filmtab, Biazin XL
Manufacturer: generic; Biaxin – Abbott Laboratories

Dosage:
- *H. pylori* eradication: 500 mg po bid in combination with PPI and other antibiotics. (See Table 7.1 for treatment of *H. pylori*)

Table 7.1 Treatment of *H. pylori*

H. pylori treatment	*Drug (oral)*	*Duration*	*Eradication rates*	*Indication for use*
Standard	Proton pump inhibitor (PPI) bid, clarithromycin 500 mg bid, amoxicillin 1000 mg bid	10–14 days	70–85%	Non-penicillin (PCN) allergy No prior macrolide exposure Low prevalence of clarithromycin resistant strains of *H. pylori*
PCN allergy	PPI bid, clarithromycin 500 mg bid, metronidazole 500 mg bid	10–14 days	70–85%	PCN allergy Low prevalence of clarithromycin resistant strains of *H. pylori*
Bismuth quadruple therapy	Bismuth 525 mg qid, metronidazole 250 mg qid, tetracycline 500 mg qid, PPI bid	10–14 days	75–90%	Prior macrolide exposure PCN allergy Can substitute doxycycline if tetracycline difficult to obtain
Concomitant or non-bismuth based quadruple therapy	PPI + amoxicillin 1 g bid + clarithromycin 500 mg bid + metronidazole/ tinidazole 500 mg bid	10–14 days	>90%	Low prevalence of clarithromycin resistant strains of *H. pylori*
FQ-based therapy	PPI SD, amoxicillin 1 g bid, levofloxacin 500 mg qd	10 days	87%	Prior macrolide exposure

Adapted from: Chey et al. [2]

Contraindications/cautions
- Concomitant cisapride, pimozide, astemizole, terfenadine, ergotamine, or dihydroergotamine
- Hypersensitivity to clarithromycin, erythromycin, or any macrolide antibiotics
- Dose adjustment required in renal failure patients

Adverse effects:
- Gastrointestinal: abdominal discomfort, abdominal pain, diarrhea, disorder of taste, indigestion, nausea, liver failure
- Neurologic: headache
- Immunologic: immune hypersensitivity reaction (severe), anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Drug interactions:
- phenothiazines, cisapride, dofetilide, pimozide, ranolazine: increase risk of QT prolongation and cardiac arrhythmias.
- Ergot alkaloids: increase risk of ergot toxicity, severe vasospasm, and ischemia.
- Eplerenone: risk of hyperkalemia

Pregnancy category: C
Lactation: possibly safe
Relative cost: $$ (generic available: $)

LEVOFLOXACIN

Class: fluoroquinolone antibiotics, inhibits DNA gyrase promoting breakage of DNA strands
Brand name: Levaquin
Manufacturer: Ortho-McNeil-Janssen Pharmaceuticals
Dosage: *H. pylori* eradication: 500 mg po qd in combination with PPI and other antibiotics. See table

Contraindications/cautions:
- Hypersensitivity to FQs
- Prior cardiac history or underlying QTc prolongation
- In the elderly, concern for toxic psychosis and tendon rupture
- Caution in people with G6PD deficiency and risk of hemolytic reactions
- In patients with myasthenia gravis may increase muscle weakness

Adverse effects:
- GI: nausea, diarrhea, constipation, abdominal pain, dyspepsia, vomiting
- GU: vaginitis
- CV: chest pain, edema
- CNS: headache, insomnia, dizziness
- Derm: skin rash, pruritus

Drug interactions:
- Concomitant administration with other QtC-prolonging agents
- Antacids may decrease absorption

Pregnancy category: C
Lactation: small amounts excreted in breast milk, consider cessation of drug or breastfeeding during administration
Relative cost: $$$ (generic available: $–$$)

TINIDAZOLE

Class: imidazole derivative antibiotics
Brand name: Tindamax
Manufacturer: Mission Pharmacol Company
Pharmacology: causes cytotoxicity by damaging DNA and preventing further synthesis
Dosage: *H. pylori* eradication: 500 mg bid in combination with PPI and other antibiotics

Contraindications/cautions:
- Hypersensitivity to nitroimidazole derivatives (including metronidazole)

Adverse effects:
- CNS: fatigue, malaise, dizziness
- GI: metallic taste, nausea, anorexia, flatulence, dyspepsia, vomiting, constipation
- GU: pelvic pain, urine abnormality
- MS: weakness
- Respiratory: URI

Drug interactions:
- Alcohol and disulfiram: result in toxic effects of disulfiram

Pregnancy category: C
Lactation: contraindicated in nursing mothers and 3 days after cessation of treatment
Relative cost: $$$ (generic available: $$–$$$)

E. COLI (EP AND EI) GASTROENTERITIS

- Ciprofloxacin 500 mg po bid for 3–5 days
- Bactrim 1 double strength tab po bid for 3–5 days

SHIGELLA COLITIS

- Ciprofloxacin: drug of choice: 500 mg po bid for 3 days. If *S. dysenteriae*, extend therapy 5–7 days
- Bactrim: 1 double strength tab (160 mg trimethoprim (TMP)/800 mg sulfamethoxazole (SMX)) po bid for 5 days
- Azithromycin: 500 mg po qd for 1 days, then 250 mg po qd for 3 days

SALMONELLA GASTROENTERITIS

1. Usually symptomatic management with fluids and electrolyte replacement
2. In severely ill, immunocompromised adults and children or elderly patients:
   - Ciprofloxacin 500 mg po bid for 3–7 days or
   - Levofloxacin 500 mg po qd or
   - Trimethoprim-sulfamethoxazole 160 mg/800 mg po bid or
   - Amoxicillin 500 mg po tid or
   - If intravenous therapy were required: a third-generation cephalosporin (ceftriaxone 1 to 2 g iv qd or cefotaxime 2 g iv q8h)

CAMPYLOBACTER GASTROENTERITIS

1. Usually symptomatic management with fluids and electrolyte replacement
2. In severely ill, elderly, pregnant, or immunocompromised patients, and those with bloody stools, high fever, extraintestinal infection, worsening or relapsing symptoms, or symptoms lasting longer than 1 week
   - Azithromycin 500 mg po qd for 3 days or
   - Ciprofloxacin 750 mg po bid for 3 days

VIBRIO CHOLERAE

1. Usually management with fluids and electrolyte replacement either orally or intravenously
2. As adjunct to appropriate rehydration
   - Tetracycline500 mg po qid for 3 days or
   - Doxycycline 300 mg once or
   - Erythromycin 500 mg po qid for 3 days or
   - Azithromycin 1000 mg po once or
   - Ciprofloxacin 1000 mg po once

YERSINIA GASTROENTERITIS

1. Usually symptomatic management with fluids and electrolyte replacement
2. In severely ill, elderly, pregnant, or immunocompromised patients, or those having an underlying comorbid illness
   - Ciprofloxacin 500 mg bid for 5 days or
   - Trimethoprim-sulfamethoxazole in children (TMP 8 mg/kg/d and SMX 40 mg/kg/d bid
   - If septicemia: ceftriaxone 2 g/d combined with gentamicin 5 mg/kg/d in qd to tid for 3 weeks

LISTERIA MONOCYTOGENES

Isolated gastrointestinal illness does not require antibiotic treatment

TRIMETHOPRIM-SULFAMETHOXAZOLE

(See Chap. 6)

CIPROFLOXACIN

(See Chap. 6)

WHIPPLE DISEASE

(See Table 7.2 for treatment of Whipple disease)

AZITHROMYCIN

Class: macrolide antibiotics
Brand name: Zithromax
Manufacturer: Pfizer, Inc.

Table 7.2 Treatment of Whipple disease

Agent	*Dosage*	*Indication*
Ceftriaxone OR Penicillin G	2 gm iv qd General infection: 2 weeks Cardiac involvement: 4 weeks CNS involvement: 2–4 weeks If relapse: ceftriaxone 2 gm iv bid for 4 weeks 2 million units iv q4h General infection: 2 weeks Cardiac involvement: 4 weeks CNS involvement: 4 million units IV q4h for 2–4 weeks If relapse: penicillin G 4 million units q4h for 4 weeks	Initial phase or relapse Alternative agent for initial phase or relapse
Meropenem	1 g iv q8h for 2–4 weeks	If allergy to PCN and ceftriaxone
Trimethoprim-sulfamethoxazole	160 mg/800 mg po bid	Long-term therapy for 1 year; first-line drug; good CNS penetration but CNS relapses may occur
Doxycycline + hydroxychloroquine	100 mg po bid + 200 mg po tid	If sulfa allergy: long-term therapy for 1-year clinical relapses including CNS are well described

Source: Lagier et al. [62]; Boulos et al. [63]; Feurle et al. [64]; Feldman et al. [66]

Dosage:
- Shigella and enterohemorrhagic *E. coli*: 500 mg po qd for 3 days

Contraindications/cautions:
- Hypersensitivity to drug or components
- Use with caution in impaired renal function, impaired hepatic function
- Use with caution in QT prolongation

Adverse effects:
- Gastrointestinal: cholestatic jaundice, pseudomembranous colitis, diarrhea, nausea, abdominal pain, dyspepsia
- Cardiovascular: QT prolongation
- Dermatologic: angioedema, Stevens-Johnson syndrome, pruritus

Drug interactions:
- Increased risk of QT prolongation with cisapride, phenothiazines, pimozide, ranolazine, antiarrhythmics class IA and class III, chloroquine, droperidol, haloperidol, erythromycin, flecainide, methadone, pentamidine, ziprasidone

Pregnancy category: B
Lactation: enters breast milk/use caution
Relative cost: $$$ (generic available: $–$$)

ERYTHROMYCIN

Class: macrolide antibiotics
Brand name: E-mycin
Manufacturer: Abbott

Dosage:
- 250–500 mg po q6 to q12h

Contraindications/cautions:
- Hypersensitivity to drug or components

Adverse effects:
- Gastrointestinal: abdominal pain, anorexia, pancreatitis, pseudomembranous colitis, diarrhea
- Cardiovascular: QT prolongation, torsade de pointes, ventricular arrhythmia
- Otic: hearing loss

Drug interactions:
- Substrate of CYP2B6 and CYP3A4, P-glycoprotein, Inhibits CYP1A2, CYP3A4, P-glycoprotein

Pregnancy category: B
Lactation: enters breast milk/use caution
Relative cost: $ (generic available: $)

DOXYCYCLINE

Class: natural and semi-synthetic tetracycline antibiotics
Brand names: Adoxa, Doryx, Doxy Lemmon, Doxy-Caps, Doxy-D, Monodox, Oracea, Periostat, Vibra-Tabs, Vibramycin, Vibramycin Calcium, Vibramycin Hyclate, Vibramycin Monohydrate
Manufacturer: generic

Dosage:
- *Vibrio cholerae* – 300 mg po one dose

Contraindications/cautions:
- Hypersensitivity to drug or components
- Children less than 8 years old
- Caution in impaired liver function, impaired renal function
- Avoid sun/UV light exposure
- Caution if history of, or predisposition to, candidiasis
- Pregnancy

Adverse effects:
- Dermatologic: photosensitivity, skin discoloration, rash, erythema multiforme, Stevens-Johnson syndrome
- Gastrointestinal: hepatotoxicity, esophagitis, pseudomembranous colitis, pancreatitis, diarrhea, nausea, dyspepsia
- Hematologic: neutropenia, thrombocytopenia, hemolytic anemia
- Other: tooth discoloration in children less than 8 years old, headache, joint pain, pericarditis

Drug interactions:
- Contraindicated with acitretin due to increased risk of pseudotumor cerebri and papilledema
- Increased levels and risk of digoxin, lithium toxicity if given together
- Increased phototoxicity with hydroquinone/retinoic acid combinations

Pregnancy category: D
Lactation: unsafe
Relative cost: $ (generic available: $)

TETRACYCLINE

Class: natural and semi-synthetic tetracycline antibiotics
Brand name: Sumycin
Manufacturer: generic
Dosage: 1 to 2 g/d po bid-qid. Give at least 1 h before or 2 h after meals

Contraindications/cautions:
- Hypersensitivity to drug or components
- Use with caution in impaired renal function, impaired hepatic function
- Use with caution in systemic lupus erythematosus
- Pregnancy

Adverse effects:
- Gastrointestinal: hepatotoxicity, pseudomembranous colitis, pancreatitis, diarrhea, nausea, dyspepsia, abdominal discomfort
- Hematologic: neutropenia, thrombocytopenia, hemolytic anemia
- Dermatologic: photosensitivity, skin discoloration, rash, erythema multiforme, Stevens-Johnson syndrome
- Other: tooth discoloration in less than 8 years old, headache, dizziness

Drug interactions:
- Contraindicated with acitretin due to increased risk of pseudotumor cerebri and papilledema
- Increased levels and risk of digoxin, lithium toxicity if given together
- Increased phototoxicity with hydroquinone/retinoic acid combinations

Pregnancy category: D
Lactation: possibly unsafe
Relative cost: $ (generic available: $)

FUNGAL INFECTIONS

OROPHARYNGEAL CANDIDIASIS

1. HIV negative patients:
   Topical therapy, with either clotrimazole troches (10 mg troche five times daily) or nystatin suspension (400,000 to 600,000 units qid)
2. HIV positive patients:
   For initial episode of oropharyngeal candidiasis in HIV-infected patients with mild disease – topical therapy

3. For patients with recurrent infection, moderate to severe disease, or in those with advanced immunosuppression (CD4 < 100) – fluconazole 200 mg loading dose, followed by 100 to 200 mg qd for 7 to 28 days

ESOPHAGEAL CANDIDIASIS

- Fluconazole 400 mg loading dose followed by 200–400 mg po qd for 14 to 28 days
- Voriconazole 200 mg po bid for 14 to 28 days
- If iv therapy needed – caspofungin 50 mg intravenously for 7–21 days
- Clotrimazole 10 mg troche five times daily for 7–14 days

FLUCONAZOLE

Class: azole antifungals
Brand name: Diflucan
Manufacturer: Pfizer, Inc.

Dosage:
- Esophageal candidiasis: Loading dose of 400 mg po/iv on day 1, then 200 to 400 mg po qd for 14–21 days

Contraindications/cautions:
- Hypersensitivity to drug or components
- Caution in impaired liver function, renal function
- Caution in QT prolongation, pro-arrhythmic conditions, electrolyte abnormalities, heart disease, elderly

Adverse effects:
- Gastrointestinal: hepatotoxicity, nausea, vomiting, abdominal pain, diarrhea, dyspepsia, taste changes
- Neurologic: seizures, headache, dizziness
- Cardiac: QT prolongation, torsades de pointes
- Hematologic: leucopenia, agranulocytosis, thrombocytopenia
- Dermatologic: Stevens-Johnson syndrome, angioedema, rash

Drug interactions:
- Decreased levels of antifungal drug with concomitant use of barbiturates, carbamazepine, rifampin, rifabutin
- Increased risk of QT prolongation with cisapride, droperidol, phenothiazines, pimozide, quinidine, ranolazine, amiodarone

Pregnancy category: C
Lactation: probably safe
Relative cost: $$$ (generic available: $–$$$)

VORICONAZOLE

Class: azole antifungals
Brand name: Vfend
Manufacturer: Pfizer, Inc.

Dosage:
- Esophageal candidiasis: 200 mg po q12h. Treat for 14 days minimum and for 7 days after symptom resolution. Give 1 h before or after meal

Contraindications/cautions:
- Hypersensitivity to drug or components
- Caution in impaired liver function, renal function
- Caution in proarrhythmic conditions, electrolyte abnormalities, galactose intolerance, lactase deficiency, hematologic malignancy

Adverse effects:
- Gastrointestinal: hepatitis, fulminant hepatic failure, nausea, vomiting, diarrhea, abdominal pain, increase in liver transaminases, increase in alkaline phosphatase
- Cardiac: QT prolongation, torsades de pointes, tachycardia
- Dermatologic: Stevens-Johnson syndrome, angioedema, rash
- Other: color vision changes, photophobia, hallucinations, renal failure, peripheral edema

Drug interactions:
- Decreased levels of antifungal drug with concomitant use of barbiturates, carbamazepine, rifampin, rifabutin
- Increased risk of QT prolongation with cisapride, droperidol, phenothiazines, pimozide, quinidine, ranolazine, amiodarone

Pregnancy category: D
Lactation: safety unknown
Relative cost: $$$$ (generic available: $$–$$$)

CASPOFUNGIN

Class: echinocandins antifungals
Brand name: Cancidas
Manufacturer: Merck & Co., Inc.

Dosage:
- Esophageal candidiasis: 50 mg iv q24h for 7–21 days

Contraindications/cautions:
- Hypersensitivity to drug or components
- Caution in impaired liver function

Adverse effects:
- Gastrointestinal: hepatotoxicity, nausea, vomiting, diarrhea, abdominal pain, increase in liver enzymes, increase in alkaline phosphatase
- Pulmonary: adult respiratory distress syndrome, pulmonary edema
- Other: fever, chills, infusion-related reaction, hypercalcemia, hypokalemia, flushing, eosinophilia

Drug interactions:
- Cyclosporine may increase caspofungin levels and risk of hepatotoxicity
- Carbamazepine, dexamethasone, efavirenz, nevirapine, phenytoin, rifabutin, rifampin may decrease caspofungin levels
- Caspofungin may decrease sirolimus, tacrolimus levels

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$$$

CLOTRIMAZOLE

Class: antifungals
Brand name: Mycelex Troche
Manufacturer: Janssen Pharmaceuticals

Dosage:
- Esophageal candidiasis: 10 mg troche five times daily for 7–14 days

Contraindications/cautions:
- Hypersensitivity to drug or components

Adverse effects:
- Gastrointestinal: abnormal liver function

Drug interactions:
- Avoid concomitant use with tolvaptan

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$ (generic available: $–$$)

CRYPTOSPORIDIUM HOMINIS

- Nitzoxanide 500 mg po bid for 7 days
- See below for product details

CYCLOSPORA CAYETANENSIS

- Bactrim 160/800 mg po bid for 7 days

(See Chap. 6 for more drug details)

NITAZOXANIDE

Class: agents for amoebiasis
Brand name: Alinia
Manufacturer: Romark Laboratories, LC

Dosage:
- Infectious diarrhea: 500 mg po q12h for 3 days. Give with food
- *Cryptosporidium hominis*: 500 mg po bid for 7 days

Contraindications/cautions:
- Hypersensitivity to drug or components

- Caution in impaired liver function, renal function
- Caution in biliary disease, diabetes, HIV, immunodeficiency

Adverse effects:
- Gastrointestinal: abdominal pain, diarrhea, nausea
- Other: headache

Drug interactions:
- May increase levels of warfarin and phenytoin

Pregnancy category: B
Lactation: safety unknown
Relative cost: $$$

VIRAL INFECTIONS

CYTOMEGALOVIRUS (CMV)

- *Gastrointestinal disease*
  - Ganciclovir (5 mg/kg po bid) or foscarnet (90 mg/kg po bid) for induction therapy for 3–6 weeks
  - Switch to oral valganciclovir (900 mg bid) to complete induction therapy when presenting clinical manifestations have resolved.
- *Hepatitis*
  - Usually self-limited course. In severe CMV hepatitis, ganciclovir or valganciclovir has been recommended. Consider liver transplant evaluation in fulminant disease

HERPES SIMPLEX (HSV)

- *Gastrointestinal disease*
  - Acyclovir 400 mg po tid for 14 to 21 days. In immunocompromised individuals: 400 mg po five times a day for 14 to 21 days
  - If unable to swallow – acyclovir 5 mg/kg iv q8h for 7 to 14 days or iv foscarnet 40 mg/kg/dose every 8–12 h for 14–21 days
- *Hepatitis*
  - Acyclovir 10 mg/kg iv q8h for up to 21 days for any HSV hepatitis or in cases of severe disseminated disease

EPSTEIN BARR VIRUS (EBV) HEPATITIS

- Usually self-limited course. In severe cases, consider antiviral therapy with either acyclovir or ganciclovir (optimal dosing and duration undefined). Consider corticosteroid therapy and evaluation for liver transplantation in cases of severe fulminant hepatitis

GANCICLOVIR

Class: nucleoside and nucleotide DNA polymerase inhibitor antivirals
Brand name: Cytovene
Manufacturer: Roche Laboratories

Dosage:
- CMV prophylaxis in solid organ transplant: 5 mg/kg iv q12h for 7–14 days, then 5 mg/kg iv q24h × 1 week or 6 mg/kg q24h 5 times/week. Alternative: 1000 mg po tid. Give with food
- CMV gastrointestinal disease: 5 mg/kg iv bid × 3–6 weeks for induction therapy

Contraindications/cautions:
- Hypersensitivity to drug or components
- Hypersensitivity to acyclovir
- Absolute neutrophil count less than 500
- Platelets less than 25,000
- Caution in impaired renal function
- Caution in myelosuppression, elderly

Adverse effects:
- Gastrointestinal: pancreatitis, perforation, diarrhea, vomiting, increased liver transaminases
- Neurologic: seizures, neuropathy
- Hematologic: pancytopenia, anemia
- Other: depression, retinal detachment, hypertension, nephrotoxicity, impaired fertility, fever

Drug interactions:
- Increased risk of nephrotoxicity with cidofovir, aminoglycosides, carboplatin, cisplatin, clofarabine, efavirenz/emtricitabine/tenofovir, tacrolimus
- Increased risk of myelosuppression with clozapine, azathioprine, cisplatin, methotrexate

- Increased risk of seizures with imipenem

Pregnancy category: C
Lactation: unsafe
Relative cost: $$$

VALGANCICLOVIR

Class: nucleoside and nucleotide DNA polymerase inhibitor antivirals
Brand name: Valcyte
Manufacturer: Roche Laboratories

Dosage:
- CMV colitis: 900 mg po bid for 21–42 days

Contraindications/cautions:
- Hypersensitivity to drug or components
- Hypersensitivity to ganciclovir
- Absolute neutrophil count less than 500
- Hemoglobin less than 8 mg/dl
- Platelets less than 25,000
- Caution in impaired renal function
- Caution in myelosuppression, elderly, chemotherapy, pregnancy

Adverse effects:
- Gastrointestinal: diarrhea, vomiting, abdominal pain
- Neurologic: seizures, neuropathy, agitation, psychosis
- Hematologic: aplastic anemia, leucopenia, thrombocytopenia, neutropenia, myelosuppression
- Other: infertility, nephrotoxicity

Drug interactions:
- Increased risk of nephrotoxicity with cidofovir, aminoglycosides, carboplatin, cisplatin, clofarabine, efavirenz/emtricitabine/tenofovir, tacrolimus
- Increased risk of myelosuppression with clozapine, azathioprine, cisplatin, methotrexate
- Increased risk of seizures with imipenem

Pregnancy category: C
Lactation: unsafe
Relative cost: $$$$$

FOSCARNET

Class: non-nucleoside DNA polymerase inhibitor antivirals
Brand name: Foscavir
Manufacturer: Clinigen Group plc

Dosage:
- CMV colitis: 60 mg/kg po q8h or 90 mg/kg q12h for 3–6 weeks

Contraindications/cautions:
- Hypersensitivity to drug or components
- Caution in impaired renal function.
- Caution in myelosuppression, seizure, cardiac disease, electrolyte abnormalities, combination with nephrotoxic agents

Adverse effects:
- Gastrointestinal: pancreatitis, nausea, vomiting, diarrhea
- Neurologic: paresthesias
- Hematologic: anemia, granulocytopenia, leukopenia, thrombocytopenia
- Other: hypomagnesemia, hypokalemia, hypocalcemia, nephrotoxicity, fever

Drug interactions:
- Increased nephrotoxicity with cidofovir, aminoglycosides, carboplatin, cisplatin, clofarabine, efavirenz/emtricitabine/tenofovir, gallium, tenofovir
- May cause QT prolongation with droperidol, erythromycin, amiodarone

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$$$

PROTOZOAN INFECTIONS

ANTIHELMINTHIC THERAPIES

(See Table 7.3 for antihelminthic therapies)

AMEBIASIS

1. To eliminate intraluminal infection
   - 500 to 750 mg po tid for 7 to 10 days

Table 7.3 Antihelminthic therapies

Agent	*Treatment*	*Alternatives*
Angiostrongyliasis	Supportive and corticosteroids	
Ascariasis	Mebendazole 100 mg bid for 3 d	Pyrantel pamoate 11 mg/kg or albendazole 400 mg po once
Cutaneous larva migrans	Ivermectin 200 µg/kg po qd for 1–2 days	Albendazole 400 mg po qd for 3 days
Cysticercosis	Albendazole 15 mg/kg/day po in 2 doses for 10–14 days Concurrent steroids for CNS disease	Praziquantel 50 mg/kg/day po tid for 10–14 days
Dracunculiasis	Metronidazole 250 mg po tid for 10 days plus worm removal	
Echinococcosis/ hydatid cyst	Perioperative albendazole	Albendazole 400 mg po bid for 1–6 months
Enterobiasis/ pinworm	Pyrantel pamoate 11 mg/kg po once or albendazole 400 mg po once or mebendazole 100 mg po once Repeat after 2 weeks	
Hook worm/ ancylostomiasis	Albendazole 400 mg po once or mebendazole 100 mg po bid for 3 days or pyrantel pamoate 11 mg/kg po for 3 days	
Onchocerciasis	Ivermectin 150 µg/kg po once, repeat every 6–12 months	
Flukes		

(continued)

Table 7.3 (continued)

Agent	*Treatment*	*Alternatives*
Liver flukes Intestinal flukes	Praziquantel 25 mg/ kg/day po tid for 1 day	
Lung fluke	Praziquantel 25 mg/ kg/day po for 2 days	
Sheep liver fluke	Triclabendazole 10 mg/kg po once	
Schistosomes		
S. mansoni *S. haematobium*	Praziquantel 40 mg/kg/day po in 2 doses for 1 day	
S. japonicum, *S. mekongi*	Praziquantel 60 mg/kg/day po in 3 doses for 1 day	
Strongyloidiasis	Ivermectin 200 μg/kg/day po for 2 days If immunocompromised: repeat at 2 weeks	Albendazole 400 mg po qd for 3–7 days
Tapeworm intestinal infections	Praziquantel 5–10 mg/kg po once	
Trichinellosis	Steroids for severe symptoms plus mebendazole 200–400 mg po tid for 3 days, then 400–500 mg po tid for 10 days	Albendazole 400 mg po bid for 10–14 days
Trichuriasis (whipworm)	Mebendazole 100 mg po bid for or albendazole 400 mg po qd for 3 days	Ivermectin 200 Mg/kg/d po for 3 days

Adapted from Rezaizadeh and Olson [61]

- Tinidazole 2 g po qd for 3 days

2. To eliminate intraluminal encysted organisms
   - Paromomycin: 25–30 mg/kg/day po tid for 7 days

GIARDIASIS

- Treatment of choice: tinidazole po 2 g single dose
- Alternative agents: Nitazoxanide 500 mg po bid for 3d. Metronidazole 250 mg po tid for 5d

PARASITIC INFESTATIONS

ANGIOSTRONGYLIASIS

- Supportive and corticosteroids

ASCARIASIS (*A. LUMBRICOIDES*)

- Treatment of choice: mebendazole 100 mg po bid for 3 days
- Alternative treatments: pyrantel pamoate 11 mg/kg or albendazole 400 mg once

CUTANEOUS LARVA MIGRANS

- Treatment of choice: ivermectin 200 µg/kg po qd for 1–2 days
- Alternative treatments: albendazole 400 mg po qd for 3 days

CYSTICERCOSIS (*TAENIA SOLIUM*)

- Treatment of choice: albendazole 15 mg/kg/day po bid for 10–14 days
- Alternative treatments: praziquantel 50 mg/kg/day po tid for 10–14 days
- Concurrent steroids for CNS disease

DRACUNCULIASIS (GUINEA WORM DISEASE)

- Metronidazole 250 mg po tid for 10 days plus worm removal

ECHINOCOCCOSIS (HYDATID CYST)

- Treatment of choice: perioperative albendazole followed by surgery
- Alternative treatments: albendazole 400 mg po bid for 1–6 months

ENTEROBIASIS (PINWORM)

- Pyrantel pamoate 11 mg/kg po once
- Albendazole 400 mg po once
- Mebendazole 100 mg po once
- Repeat after 2 weeks

HOOK WORM (ANCYLOSTOMIASIS)

- Albendazole 400 mg po once or
- Mebendazole 100 mg po bid for 3 days or
- Pyrantel pamoate 11 mg/kg po for 3 days

LYMPHATIC FILARIASIS (*W. BANCROFTI, B. MALAYI, B. TIMORI*)

- Diethylcarbamazine 6 mg/kg po once

LOAISIS (*M. STREPTOCERCA, O. VOLVULUS, D. MEDINENSIS*)

- Diethylcarbamazine 8 to 10 mg/kg/day po tid for 21 days

TROPICAL PULMONARY EOSINOPHILIA

- Diethylcarbamazine 6 mg/kg/day po tid for 14–21 days

TRYPANOSOMA CRUZI (CHAGAS DISEASE)

- Benznidazole for acute infection only: 5 to 7 mg/kg/day po bid for 60 days

ONCHOCERCIASIS (RIVER BLINDNESS)

- Ivermectin 150 µg/kg po once; repeat every 6–12 months

FLUKE INFECTIONS

- Liver flukes (*Clonorchis sinensis*), intestinal flukes (*Fasciolopsis buski*): praziquantel 25 mg/kg/d po tid for 1 day
- Lung fluke (*Paragonimus westermani*): praziquantel 25 mg/ kg/day po tid for 2 days
- Sheep liver fluke: triclabendazole 10 mg/kg po once

SCHISTOSOMIASIS

- *S. mansoni, S. haematobium*: praziquantel 40 mg/kg/d po in bid × 1 day
- *S. japonicum, S. mekongi*: praziquantel 60 mg/kg/d po in tid × 1 day

STRONGYLOIDIASIS

- Treatment of choice: ivermectin 200 µg/kg/d po for 2 d. If immunocompromised 200 µg/kg/d po for 2 days and repeat at 2 weeks
- Alternative treatments: albendazole 400 mg po qd for 3–7 days.

TAPEWORM INTESTINAL INFECTIONS (*TAENIA SAGINATA*)

- Praziquantel 5–10 mg/kg po for 1 day

TRICHINELLOSIS (ROUNDWORM)

- Treatment of choice: steroids for severe symptoms plus mebendazole 200–400 mg po tid for 3 days, then 400–500 mg po tid for 10 days
- Alternative treatments: albendazole 400 mg po bid for 10–14 days

TRICHURIASIS (WHIPWORM)

- Treatment of choice: mebendazole 100 mg po bid for 3 days or albendazole 400 mg po qd for 3 days
- Alternative treatments: ivermectin 200 Mg/kg/day po for 3 days

ALBENDAZOLE

Class: antinematodal agents, benzimidazole
Brand name: Albenza
Manufacturer: GlaxoSmithKline, generic

Dosages:
- Ancylostomiasis and necatoriasis: 400 mg po as a single dose
- Ascariasis: 400 mg po as a single dose
- Clonorchiasis: 10 mg/kg po qd for 7 days
- Cutaneous larva migrans: 400 mg po qd for 3 days
- *Echinococcus granulosus* infection, hydatid disease: 60 kg or greater, 400 mg po bid for three 28-day cycles
- Enterobiasis: 400 mg po as a single dose; repeat in 2 weeks
- Enterocolitis, eosinophilic – infection by *Ancyclostoma caninum*: 400 mg po as a single dose
- Infection by Gnathostoma: 400 mg po bid for 21 days
- Infection by Microsporidia: intestinal due to *E. intestinalis*, 400 mg po bid for 21 days

Contraindications:
- Hypersensitivity to albendazole or benzimidazole products
- Pregnancy
- Use with caution in impaired liver function

Adverse effects:
- Gastrointestinal: abdominal pain, nausea, vomiting, hepatotoxicity
- Neurologic: headache
- Renal: acute renal failure (rare)
- Hematologic: agranulocytosis, granulocytopenia, leukopenia, pancytopenia, thrombocytopenia (rare)

Drug interactions:
- Increased risk of albendazole toxicity with praziquantel and dexamethasone

Pregnancy category: C
Lactation: safe
Relative cost: $$$

MEBENDAZOLE

Class: antinematodal agents, benzimidazole
Brand name: Emverm
Manufacturer: Impax Laboratories, Inc.

Dosages:
- Ancylostomiasis and necatoriasis: 100 mg po bid for 3 days
- Ascariasis: 100 mg po bid for 3 days
- Enterobiasis: 100 mg po once
- Trichuriasis: 100 mg po bid for 3 days
- *treatment may be repeated in 3 weeks in all above conditions

Contraindications/cautions:
- Hypersensitivity to mebendazole products
- Caution if prolonged use

Adverse effects:
- Gastrointestinal: abdominal pain, diarrhea, hepatitis
- Neurologic: headache, seizure
- Dermatologic: rash, angioedema
- Hematologic: neutropenia, agranulocytosis

Drug interactions: No significant drug interactions
Pregnancy category: C

Lactation: safe
Relative cost: $$$

IVERMECTIN

Class: antinematodal agents
Brand name: Stromectol
Manufacturer: Merck & Co., Inc.

Dosages:
- Infection by *Onchocerca volvulus*: 150 μg/kg, single oral dose; retreatment interval between 3 and 12 months. Give on empty stomach
- Intestinal strongyloidiasis: 200 μg/kg, single oral dose

Contraindications/cautions:
- Hypersensitivity to ivermectin or components
- Pregnancy
- Asthma

Adverse effects:
- Gastrointestinal: disease of gastrointestinal tract, nausea, vomiting, diarrhea
- Neurologic: dizziness, headache
- Dermatologic: pruritus

Drug interactions: no significant drug interactions
Pregnancy category: C
Lactation: safety unknown
Relative cost: $$ (generic available: $$)

PRAZIQUANTEL

Class: antitrematodal agents
Brand name: Biltricide
Manufacturer: Bayer

Indications:
- Schistosomiasis: 20 mg/kg po tid for 1 day
- Clonorchiasis: 25 mg/kg po tid for 1 day
- Tapeworms: 5–25 mg/kg po once
- Intestinal flukes: 25 mg/kg po tid for 1 day

Contraindications/cautions:
- Hypersensitivity to praziquantel
- Ocular cysticercosis
- History of seizures

Adverse effects:
- Gastrointestinal: abdominal pain
- Cardiovascular: cardiac dysrhythmia, heart block
- Neurologic: dizziness, headache, seizure
- Other: malaise

Drug interactions:
- Chloroquine may decrease praziquantel levels
- Combination may increase albendazole levels

Pregnancy category: B
Lactation: Avoid breastfeeding for 3 days after last dose
Relative cost: $$$

THIABENDAZOLE: NO LONGER AVAILABLE IN THE USA

Class: antinematodal agents, benzimidazole
Brand name: Mintezol
Manufacturer: Merck & Co., Inc.

Dosages:
- Ascariasis: (not first-line therapy): 50 mg/kg/d q12 h po for 2 days
- Cutaneous larva migrans – for 2 days
- Visceral larva migrans – for 7 days
- Trichinosis – for 2–3 days
- Dracunculosis – for 3 days

Contraindications/cautions:
- Hypersensitivity to thiabendazole products
- Prophylactic treatment of pinworm infestation

Adverse effects:
- Gastrointestinal: nausea, vomiting, anorexia, diarrhea, hepatotoxicity
- Neurologic: central nervous system finding, dizziness, drowsiness
- Dermatologic: erythema multiforme, Stevens-Johnson syndrome

Drug interactions:
- Combination may increase theophylline levels and risk of toxicity

Pregnancy category: C
Lactation: safety unknown
Relative cost: $

PYRANTEL PAMOATE

Class: antinematodal agents
Brand name: Ascarel, Pamix, Pin-X
Manufacturer: generic

Dosages:
- Enterobiasis: 11 mg/kg (up to maximum 1 gm) po once
- Ascariasis: 11 mg/kg (up to maximum 1 gm) po once

Contraindications/cautions:
- Hypersensitivity to drug
- Pregnancy
- Liver disease

Adverse effects:
- Gastrointestinal: abdominal discomfort, nausea, vomiting
- Neurologic: dizziness, headache, somnolence

Drug interactions: no major drug interactions
Pregnancy category: generally regarded as unsafe
Lactation: safety unknown
Relative cost: $ (generic available: $)

TINIDAZOLE

Class: imidazole derivative antibiotics
Brand name: Tindamax
Manufacturer: Mission Pharmacal Company

Dosages:
- Intestinal amebiasis: 2000 mg po qd for 3 days
- Amebic liver abscess: 2000 mg po qd for 3–5 days
- Giardiasis: 2000 mg po once. Give with food

Contraindications/cautions:
- Hypersensitivity to drug or components
- Caution in impaired liver function
- Caution in disulfiram use, alcohol use, CNS disorder, blood dyscrasia

Adverse effects:
- Gastrointestinal: candidiasis, nausea, vomiting
- Neurologic: seizures, peripheral neuropathy
- Pulmonary/: bronchospasm
- Hematologic: thrombocytopenia
- Dermatologic: Stevens-Johnson syndrome, erythema multiforme
- Other: menorrhagia

Drug interactions:
- Disulfiram like reaction with alcohol, lopinavir/ritonavir, tipronavir, diazoxide, ethanol
- May increase levels of lithium, phenytoin, cyclosporine, tacrolimus

Pregnancy category: C
Lactation: avoid/ breastfeeding during treatment and for 72 h after discontinuation. No human data available to assess risk of infant harm
Relative cost: $$$ (Generic available: $$)

PAROMOMYCIN

Class: aminoglycoside antibiotics
Brand name: Humatin
Manufacturer: King Pharmaceuticals, Inc.

Dosages:
- Intestinal amebiasis: 25–35 mg/kg/day po divided in tid for 5–10 days
- Hepatic encephalopathy: 1000 mg po qid for 5–6 days
- Cryptosporidial diarrhea in HIV: 1500–3000 mg po divided 3–6 times per day. Alternative: 1000 mg po bid × 12 weeks in combination with azithromycin 600 mg po qd for 4 weeks. Give with food

Contraindications/cautions:
- Hypersensitivity to drug or components
- Use with caution in impaired renal function
- Use with caution in intestinal obstruction, inflammatory bowel disease, neurotoxic agents, ototoxic agents, dehydration, neuromuscular disease, auditory or vestibular dysfunction

Adverse effects:
- Gastrointestinal: malabsorption syndrome (prolonged use), enterocolitis, nausea, abdominal cramps, diarrhea
- Other: nephrotoxicity, ototoxicity, neurotoxicity

Drug interactions:
- Increased risk of nephrotoxicity with acyclovir, aminoglycoside, cyclosporine, flucytosine, foscarnet, ganciclovir, mitomycin, penicillamine, sirolimus, vancomycin

Pregnancy category: C
Lactation: probably safe
Relative cost: $$$ (generic available: $$$)

IODOQUINOL

Class: antifungals
Brand name: Yodoxin
Manufacturer: Glenwood, LLC

Dosage:
- Intestinal amebiasis: 650 mg po tid for 20 days. Give after meals, repeat treatments should be performed in 2–3-week intervals

Contraindications/cautions:
- Hypersensitivity to drug or components
- Hypersensitivity to iodine
- Use with caution in hepatic dysfunction
- Use with caution in thyroid disease

Adverse effects:
- Gastrointestinal: nausea, vomiting, abdominal pain
- Dermatologic: pruritus, skin discoloration
- Other: optic neuritis, peripheral neuropathy, headache

Drug interactions:
- Inadequate immunologic response to concomitant live oral typhoid vaccine
- May decrease levels of mycophenolate mofetil

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$$$

DIETHYLCARBAMAZINE

Class: antihelminthics
Brand name: Hetrazan
Manufacturer: Wyeth

Dosage:
- Loiasis: 8 to 10 mg/kg/day po tid for 21 days
- Lymphatic filariasis: 6 mg/kg/day po qd or tid for 12 days

Contraindications/cautions:
- Hypersensitivity to drug or components

Adverse effects:
- Neurologic: encephalopathy
- Gastrointestinal: nausea

Drug interactions:
- Inadequate studies

Pregnancy category: X
Lactation: breast milk excretion unknown
Relative cost: $$$

BENZNIDAZOLE

Class: agents for leishmaniasis and trypanosomiasis
Brand name: Rochagan
Manufacturer: Brazilian Government (not commercially available in the USA)

Dosage:
- Chagas disease: 5 to 7 mg/kg/day po bid for 60 days

Contraindications/cautions:
- Hypersensitivity to drug or components

Adverse effects:
- Neurologic: convulsions, seizures, peripheral neuropathy

Drug interactions:
- Enhance toxic effect of disulfiram

Pregnancy: avoid using during pregnancy; possible risk of fetal harm

Lactation: breastfeeding during therapy not recommended
Relative cost: $

TRICLABENDAZOLE

Class: benzimidazole antihelminthics
Brand name: Egaten
Manufacturer: Novartis

Dosage:
- Fascioliasis: 10 mg/kg po q12h for 2 doses

Contraindications/cautions:
- Hypersensitivity to drug or components

Adverse effects:
- Gastrointestinal: self-limited biliary obstruction, abdominal cramping

Drug interactions:
- No known interactions

Pregnancy category: B
Lactation: safety unknown
Relative cost: $$$

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8 Hepatitis

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Contents

CHRONIC HEPATITIS B

(See Figs. 8.1 and 8.2 for algorithms for the treatment of HBV, and Table 8.1 for treatment of HBV in special populations)

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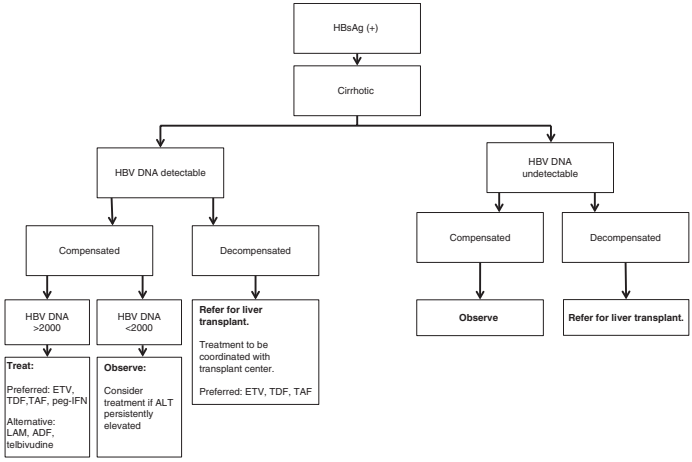

Fig. 8.1 Evaluation and treatment decisions for HBV infections. (Source: Terrault et al. [1])

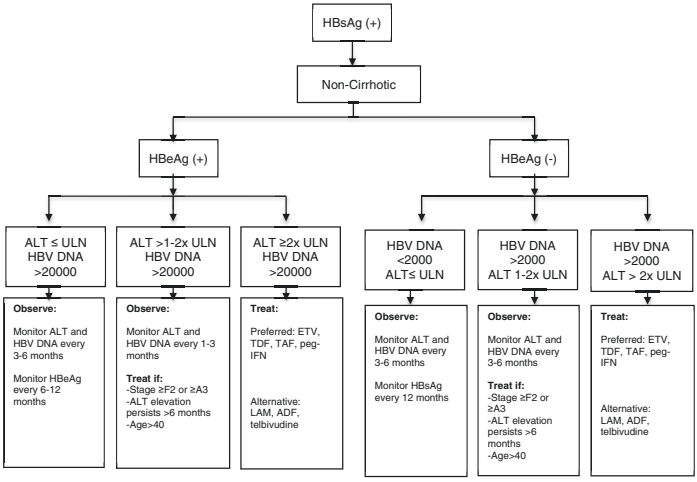

Fig. 8.2 Treatment of HBV infections. (Source: Terrault et al. [1])

Entecavir

Class: nucleoside and nucleotide analog antivirals
Brand name: Baraclude
Manufacturer: Bristol-Myers Squibb

Table 8.1 Treatment of HBV in special populations

Special population	*Preferred treatment agent (s)*
HBV-HCV coinfection	ETV, TDF, TAF
HBV-HDV coinfection/ superinfection	Peg-IFN
HBV-HIV coinfection	HAART regimen should include two of the following agents active against HBV: TAF or TDF, lamivudine, emtricitabine

Source: Terrault et al. [1]

Dosage:
- Nucleoside-naive: 0.5 mg po qd
- Lamivudine-refractory: 1 mg po qd
- Decompensated liver disease: 1 mg po qd
- Note: should be taken on an empty stomach, 2 h before or after meals

Contraindications/cautions:
- Hypersensitivity to drug
- HBV exacerbation if discontinued

Adverse effects:
- Lactic acidosis/ severe hepatomegaly
- Severe acute hepatitis upon discontinuation
- HIV resistance in untreated HIV positive patients
- Nephrotoxicity
- Cardiovascular: edema
- Hepatic: ascites, increased liver enzymes, encephalopathy
- Gastrointestinal: nausea, increased lipase, increased amylase, hyperbilirubinemia, diarrhea
- Neurologic: dizziness, headache, fatigue
- Dermatologic: skin rash
- Other: fever, insomnia

Drug interactions:
- Quinidine, quinine
- Dofetilide

Pregnancy category: C
Lactation: unknown
Relative cost: $$$$$ $$ (generic available $$)
Dosage adjustments:

Renal impairment:

Nucleoside-naïve:
- CrCl >50: no adjustment
- CrCl 30–49: 50% normal dose daily or normal dose every 48 h
- CrCl 10–29: 30% normal dose daily or normal dose every 72 h
- CrCl <10: 10% normal dose daily or normal dose every 7 days
- Hemodialysis: 10% normal dose, give after hemodialysis

Hepatic impairment: no adjustment

Tenofovir Dipovoxil Fumarate (TDF)

Class: nucleoside analog antivirals
Brand name: Viread
Manufacturer: Gilead Pharmaceuticals, Inc.
Dosage: 300 mg po qd

Contraindications/cautions:
- Hypersensitivity to drug
- HIV resistance
- Alcoholism
- Obesity

Adverse effects:
- Lactic acidosis/ severe hepatomegaly
- Severe acute hepatitis upon discontinuation
- Neurologic: headaches, peripheral neuropathy
- Gastrointestinal: abdominal pain, diarrhea, nausea, pancreatitis, diarrhea
- Renal: nephropathy, Fanconi syndrome, hyperphosphatemia, hematuria
- Hematological: neutropenia
- Metabolic: hypercholesterolemia, hypertriglyceridemia, osteomalacia, osteopenia/osteoporosis, bone fractures
- Skeletal: decreased bone density, back pain, arthralgias
- Dermatological: rash
- Psychiatric: depression
- Other: fever, insomnia, fatigue, anorexia, myalgia

Drug interactions:
- Truvada and Atripla contain tenofovir, didanosine
- Atanazovir and lopinavir/ritavir increase tenofovir concentrations
- Caution in when co-administering with other nephrotoxic agents such as salicylates, cisplatin, chlofarabine, cyclosporine
- Adefovir

- Dofetilide
- Orlistat
- Voxilaprevir
- Tacrolimus
- Tolvaptan

Pregnancy category: B
Lactation: acceptable
Relative cost: $$$$$ $$ (generic: $)
Dosage adjustments:

Renal impairment:
- CrCl 30–49: 300 mg po q48h
- CrCl 10–29: 300 mg po q72-96 h
- CrCl <10: not defined
- Hemodialysis: 300 mg po q1wk after hemodialysis

Hepatic impairment: no adjustment

Tenofovir Alafenamide (TAF)

Class: nucleoside analog antivirals
Brand name: Vemlidy
Manufacturer: Gilead
Dose: 25 mg po qd

Contraindications/cautions:
- Alcoholism
- Obesity
- Black and Hispanic patients – weight gain

Adverse effects:
- Renal: hypophosphatemia, lactic acidosis
- Metabolic: hypercholesterolemia, hypertriglyceridemia, osteomalacia, osteoporosis, glucosuria
- Gastrointestinal: pancreatitis, dyspepsia, abdominal pain, nausea, diarrhea
- General: arthralgia, myalgia, weakness, headache, fatigue, cough, rash

Drug interactions:
- Adefovir
- Inhibitors of P-gp substrates
- Anticonvulsant
- Rifampin, rifabutin, rifapentine
- Orlistat

- St John's wort
- Tacrolimus

Pregnancy: available data have demonstrated no significant difference in risk of birth defects with TAF use compared to risk in general population. No adverse developmental effects were observed in animal studies (See Appendix A)
Lactation: it is not known whether TAF and its metabolites are present in breast milk (See Appendix A)
Reproduction: no data have been reported on impact to male or female reproduction (See Appendix A)
Relative cost: $$$$$ $$

Pegylated Interferon α-2a

Class: interferons
Brand name: Pegasys
Manufacturer: Roche

Dosage:
- 180 μg sc weekly for 48 weeks

Contraindications/cautions:
- Hypersensitivity to drug
- Autoimmune hepatitis, decompensated liver disease (Child-Pugh class B, C)
- Significant pre-existing psychiatric disease
- Autoimmune thyroid disease
- Cardiac disease
- Pregnancy (with ribavirin use)
- Neonates, infants
- Alcoholism, seizures, and psychiatric disorders
- Anemia, neutropenia, thrombocytopenia, bone marrow suppression
- Hyper-/hypoglycemia in diabetics
- Should not be administered with live vaccines

Adverse effects:
- Neurologic: headache, insomnia, memory impairment, decreased concentration, peripheral neuropathy, stroke
- Hematologic: neutropenia, thrombocytopenia, anemia, thrombotic thrombocytopenic purpura
- Gastrointestinal: pancreatitis, hyperbilirubinemia, nausea, vomiting, diarrhea
- Musculoskeletal: fatigue, weakness, myalgia, arthralgia
- Dermatologic: alopecia, pruritis, injection site inflammation, injection site reaction, dermatitis, xeroderma

- Psychiatric: anxiety, irritability, depression, psychotic disorder, suicide, hallucinations
- Endocrine: weight loss, hypothyroidism, hyperthyroidism, growth stunting, hypertriglyceridemia
- Hepatic: increased liver enzymes, hepatic decompensation
- Misc.: arrhythmias, MI, autoimmune disorders, cough, dyspnea, blurred vision, fatigue, fever

Drug interactions:
- Use with anti-retroviral nucleoside reverse transcriptase inhibitors (NRTIs) increases risk of hepatotoxicity
- Ethanol
- Filgrastim, G-CSF
- Methadone

Pregnancy category: C
Lactation: unknown
Relative cost: $$$$$ $$$$

Dosage Adjustments for PEG-Interferon α-2a (Pegasys)

Depression:
- For mild depression: no dosage change necessary
- For moderate depression: decrease dose to 135 µg sc q1wk; if necessary, decrease to 90 µg. If symptoms improve or stable for ≥4 weeks, continue reduced dosing or return to normal dose
- For severe depression: discontinue treatment immediately and permanently; obtain immediate psychiatric consultation

Hematological:
- For neutrophil count <750/mm^3: decrease dose to 135 µg sc q1wk
- For neutrophil count <500/mm^3: suspend treatment until neutrophil count >1000/mm^3; reinstitute at 90 mcg sc q1wk and monitor ANC
- For platelet count <50,000/mm^3: decrease dose to 90 µg sc q1wk
- For platelet count <25,000/mm^3: discontinue treatment

Hepatic impairment:
- Decompensated hepatic disease (e.g., Child-Pugh class B or C) should not be treated with peg-interferon α-2a
- Progressive ALT increases above baseline: decrease the dose to 135 µg sc q1wk, resume after resolution of ALT flare
- ALT increases up to 5 times upper normal limit: decrease dose to 135 µg sc q1wk or temporary discontinuation of treatment

- ALT increases up to 10 times upper normal limit: discontinuation of therapy should be considered

Renal impairment:
- CrCl ≥ 30 ml/min: no dosage adjustment needed. (180 μg)
- CrCl < 30 ml/min: 135 μg sc q1wk. Close monitoring for adverse reactions which may require dosage reduction to 90 μg until adverse reactions subside is recommended
- Intermittent hemodialysis: 135 μg sc q1wk. Monitor patients closely

Pegylated Interferon α-2b

Class: interferon
Brand name: Intron A, Sylatron
Manufacturer: Merck

Dosage:
- Chronic hepatitis B: 1.0–1.5 μg/kg sc q1wk for 48 weeks

Contraindications/cautions:
- Hypersensitivity to drug
- Decompensated liver disease (Child-Pugh B, C)
- Severe depression
- Significant pre-existing psychiatric disease
- Autoimmune disorders
- Cerebrovascular disease
- Coronary artery disease
- Alcoholism
- Serious infection
- Bone marrow suppression, anemia, thrombocytopenia
- Should not be administered with live vaccines

Adverse effects:
- Neurological: confusion, insomnia, decreased concentration, headache
- Hematologic: neutropenia, anemia, autoimmune thrombocytopenia, myelosuppression
- Gastrointestinal: colitis, pancreatitis, anorexia, nausea, diarrhea
- Hepatic: increased liver enzymes
- Dermatologic: injection site reaction, alopecia, pruritus, exfoliative dermatitis
- Cardiovascular: chest pain, edema, hypertension
- Psychiatric: depression, irritability

- Renal: proteinuria, nephrotic syndrome
- Endocrine: weight loss, amenorrhea, hypo-/hyperglycemia in diabetics
- Other: influenza-like illness, pulmonary toxicity, retinal hemorrhage, fatigue, fever

Drug interactions
- Lidocaine
- Clozapine
- Anti-retroviral non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Anti-retroviral nucleoside reverse transcriptase inhibitors (NRTIs)
- Pegfilgrastim
- Agents metabolized via CYP1A2 or CYP2D6

Pregnancy category: C
Lactation: unknown
Relative cost: $$$$$ $$$

Dosage adjustments for PEG-interferon α-2b:

General:
- Severe adverse reactions: modified dosage (50% reduction) or therapy should be temporarily discontinued until the adverse reactions resolve. If reaction persists, therapy should be discontinued

Depression:
- Clinical depression: monitor closely during treatment and for 6 months after treatment
- Severe depression: discontinue immediately and seek psychiatric consult

Hematological:
- ANC < 500/ mm^3 or platelets <50,000/ mm^3: discontinue treatment

Hepatic:
- Liver function abnormality or hepatic decompensation (Child-Pugh B, C): discontinue

Renal:
- CrCl > 50 ml/min: no dosage adjustment
- CrCl 30–50 ml/min: 25% dose reduction
- CrCl 10–29 ml/min: 50% dose reduction
- Intermittent hemodialysis: 50% dose reduction

Other:
- Pulmonary toxicity, pancreatitis, triglycerides>1000 mg/dl: discontinue

Lamivudine

Class: nucleoside analog antivirals
Brand name: Epivir, Epivir-HBV
Manufacturer: GlaxoSmithKline

Dosage:
- Chronic hepatitis B: 100 mg po qd for at least 6 months after HBeAg seroconversion or HBsAg clearance
- Chronic hepatitis B/HIV coinfection: 300 mg po qd

Contraindications:
- Hypersensitivity
- Alcoholism
- Obesity
- HIV resistance

Adverse effects:
- Gastrointestinal: decreased appetite, nausea, vomiting, diarrhea, pancreatitis, hepatomegaly, splenomegaly, relapsing type B viral hepatitis, hyperbilirubinemia
- Neurologic: headache, fatigue, insomnia, dizziness, neuropathy
- Renal: renal impairment
- Hematologic: neutropenia
- Endocrine metabolic: lactic acidosis, lipodystrophy, hyperglycemia
- Other: rash, increased CPK, arthralgias, rhabdomyolysis, lymphadenopathy
- Psychiatric: depression

Drug interactions:
- Sorbitol-containing medications
- Anti-retroviral nucleoside reverse transcriptase inhibitors (NRTIs)

Pregnancy category: C
Lactation: acceptable
Relative cost: $$$$$ (generic available $$$)
Dosage adjustments for lamivudine

Renal impairment:
- CrCl >50: no adjustment
- CrCl 30–49: 100 mg po once then 50 mg po qd
- CrCl 15–29: 100 mg once then 25 mg po qd
- CrCl 5–14: 35 mg once then 15 mg po qd

- CrCl <5: 35 mg once then 10 mg po qd
- Hemodialysis/peritoneal dialysis: no adjustment required

Hepatic impairment: no adjustment

Adefovir Dipivoxil

Class: nucleotide analog antivirals
Brand name: Hepsera
Manufacturer: Gilead Sciences
Dosage: chronic hepatitis B: 10 mg po qd

Contraindications:
- Hypersensitivity to drug

Adverse effects:
- Severe acute hepatitis upon discontinuation
- Renal: nephrotoxicity, hypophosphatemia
- HIV resistance in untreated HIV positive patients
- Lactic acidosis/ severe hepatomegaly
- Gastrointestinal: abdominal pain, diarrhea, indigestion, nausea
- Neurologic: headache, fatigue
- Dermatologic: pruritus, rash
- Other: hypophosphatemia, back pain

Drug interactions:
- Anti-retroviral nucleoside reverse transcriptase inhibitors (NRTIs)
- Protease inhibitors
- Nephrotoxic medications
- Mannitol

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$$$ $$ (generic available $$$$$)
Dosage adjustments:

Renal impairment:
- CrCl >50 mL/min: no adjustment
- CrCl 30–49 mL/min: 10 mg po q48h
- CrCl 10–29 mL/min: 10 mg po q72h
- CrCl <10 mL/min: not defined
- Hemodialysis: 10 mg po q7d, no supplement after dialysis

Hepatic impairment: no adjustment required

CHRONIC HEPATITIS C

(See Table 8.2. Treatment of options for HCV by genotype according to FDA approval, Table 8.3 for combination drugs for HCV, Table 8.4 for treatment options by genotype, and Table 8.5 for simplified HCV treatment regimens)

Sofosbuvir

Class: NS5B RNA polymerase inhibitor
Brand name: Sovaldi (sofosbuvir only); also used in the following combinations: Epclusa (sofosbuvir/velpatasvir), Harvoni (sofosbuvir/ledipasvir), Vosevi (sofosbuvir/velpatasvir/voxilaprevir)
Manufacturer: Gilead

Table 8.2 Treatment of options for HCV by genotype according to FDA approval

FDA-approved DAAs according to genotype (Duration 12 weeks except as indicated)					
1	*2*	*3*	*4*	*5*	*6*
	Mavyret[d]	Mavyret[d]	Mavyret[d]	Mavyret[d]	Mavyret[d]
Vosevi	Vosevi	Vosevi	Vosevi	Vosevi	Vosevi
Epclusa	Epclusa	Epclusa[a]	Epclusa[a]	Epclusa	Epclusa
Harvoni[a]	Sovaldi/ RBV	Sovaldi/ Daklinza	Harvoni	Harvoni	Harvoni
Zepatier[e]	PEG-IFN/ RBV[b]	Sovaldi/ RBV[b]	Zepatier		
Sovaldi/ Daklinza		PEG-IFN/ RBV[c]			
PEG-IFN/ Sovaldi/RBV			PEG-IFN/ Sovaldi/RBV		

Source: AASLD-IDSA Hepatitis C Guidance Panel. American Association for the Study of Liver Disease- Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology 2020; 71: 686–721
[a]24 weeks – treatment experienced
[b]24 weeks
[c]48 weeks
[d]8 weeks – non-cirrhotics
[e]16 weeks – GT1a with NS5A RAS

Table 8.3 Combination drugs for HCV

Brand name	*Generic name*
Epclusa	Sofosbuvir/velpatasvir
Harvoni	Sofosbuvir/ledipasvir
Vosevi	Sofosbuvir/velapatasvir/voxilaprevir
Mavyret	Glecprevir/pibrentasvir
Zepatier	Elbasvir/grazoprevir

Table 8.4 Treatment options by genotype according to the AASLD-IDSA guidelines

Genotype 1		
Therapy	*Non-cirrhotic*	*Cirrhotic*
Elbasvir/ grazoprevir *GT1b or GT1a without NS5A RAS* *GT1a with NS5A RAS*	Rx naïve/ PEG RBV experienced: 12 weeks Rx naïve: 16 weeks + RBV	Rx naïve/ PEG RBV experienced: 12 weeks Rx naïve: 16 weeks + RBV (compensated only)
Glecaprevir/ pibrentasvir	Rx naïve: 8 weeks	Rx naïve: 12 weeks (compensated only)
Ledipasvir/ sofosbuvir	Rx naïve/PEG RBV experienced: 12 weeks Non-black, HIV negative, HCV RNA <6 million IU/ mL: 8 weeks	Rx naïve: 12 weeks Rx experienced: 24 weeks ± RBV 12 weeks + RBV
Sofosbuvir/ velpatasvir	Rx naïve: 12 weeks	Rx naïve: 12 weeks Rx experienced: 24 weeks + RBV
Daclatasvir/ sofosbuvir	Rx experienced: 12 weeks ± RBV	12 weeks ± RBV
Sofosbuvir/ velpatasvir/ voxilaprevir	Rx experienced: 12 weeks	Rx experienced: 12 weeks (compensated only)
Genotype 2		
Therapy	*Non-cirrhotic*	*Cirrhotic*
Glecaprevir/ pibrentasvir	Rx naïve: 8 weeks Rx experienced: 12 weeks	Rx naïve: 12 weeks (compensated only)

(continued)

Table 8.4 (continued)

Sofosbuvir/ velpatasvir	Rx naïve: 12 weeks	Rx naïve: 12 weeks PEG/RBV experienced: 12 weeks+ RBV DAA experienced: 24 weeks + RBV
Sofosbuvir/ velpatasvir/ voxilaprevir	Rx experienced: 12 weeks	Rx experienced: 12 weeks (compensated only)
Daclatasvir/ sofosbuvir	–	12 weeks + RBV
Genotype 3		
Therapy	*Non-cirrhotic*	*Cirrhotic*
Glecaprevir/ pibrentasvir	Rx naïve: 8 weeks	Rx naïve: 12 weeks (compensated only)
Sofosbuvir/ velpatasvir	Rx naïve: 12 weeks	Rx naïve: 12 weeks PEG/RBV experienced: 12 weeks + RBV DAA experienced: 24 weeks + RBV
Daclatasvir/ sofosbuvir	12 weeks	12 weeks + RBV (compensated only)
Sofosbuvir + elbasvir/ grazoprevir	–	PEG/RBV experienced: 12 weeks
Sofosbuvir/ velpatasvir/ voxilaprevir	–	Rx experienced: 12 weeks + RBV (compensated only)
Genotype 4		
Therapy	*Non-cirrhotic*	*Cirrhotic*
Glecaprevir/ pibrentasvir	Rx naïve: 8 weeks	Rx naïve: 12 weeks (compensated only)
Sofosbuvir/ velpatasvir	Rx naïve/PEG-RBV experienced: 12 weeks	Rx naïve: 12 weeks Decompensated: 12 weeks + RBV Decompensated, DAA experienced: 24 weeks+ RBV
Elbasvir/ grazoprevir	Rx naïve/ PEG-RBV experienced: 12 weeks	Rx naïve: 12 weeks (compensated only)
Ledipasvir/ sofosbuvir	Rx naïve: 12 weeks	Rx naïve: 12 weeks Decompensated: 12 weeks +RBV

Table 8.4 (continued)

Daclatasvir/ sofosbuvir	–	Decompensated: 12 weeks +RBV
Sofosbuvir/ velpatasvir/ voxilaprevir	–	Rx experienced: 12 weeks (compensated only)
Therapy	*Genotype 4*	*Genotype 5 and 6*
Glecaprevir/ pibrentasvir	Rx naïve: 8 weeks	Rx naïve: 12 weeks (compensated only)
Sofosbuvir/ velpatasvir	Rx naïve: 12 weeks	Rx naïve: 12 weeks Decompensated: 12 weeks Decompensated, DAA failure: 24 weeks +RBV
Ledipasivir/ sofosbuvir	Rx naïve: 12 weeks	Rx naïve: 12 weeks Decompensated: 12 weeks Decompensated, DAA failure: 24 weeks +RBV
Sofosbuvir/ velpatasvir/ voxilaprevir	–	Rx experienced: 12 weeks + RBV (compensated only)

Source: AASLD-IDSA HCV Guidance Panel Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clinical Infectious Diseases, 2018; 67:1477–92

Table 8.5 Simplified treatment regimens

Eligible population	*Treatment regimen (s)*	*Duration*
Chronic HCV, noncirrhotic, treatment naive, *any genotype*	Glecaprevir (300 mg)/ pibrentasvir (120 mg)	8 weeks
	Sofosbuvir (400 mg)/ velpatasvir (100 mg)	12 weeks
Chronic HCV, compensated cirrhosis, treatment naive	*Any genotype:* Glecaprevir (300 mg)/ pibrentasvir (120 mg)	8 weeks
	Genotype 1, 2, 4, 5, 6: Sofosbuvir (400 mg)/ velpatasvir (100 mg)	12 weeks

Dosage: 400 mg po qd; used in combination with either ledipasvir, velapatasvir, voxilaprevir, daclatisvir, simeprevir, ribavirin, and/or pegylated interferon for treatment of chronic hepatitis C

Contraindications/cautions:
- Black boxed warning: HBV exacerbation

Adverse effects:
- Serious, symptomatic bradycardia when co-administered with amiodarone and another HCV direct acting antiviral
- Fatigue
- Headache
- Elevations of bilirubin, lipase, and creatine kinase
- Anemia, neutropenia

Drug interactions:
- Drugs that are P-gp inducers in the intestine (e.g., rifampin, St. John's wort) can decrease sofosbuvir plasma concentrations
- Amiodarone: risk of severe symptomatic bradycardia

Pregnancy category: B
Lactation: safety unknown
Relative cost: $$$$$ $$$$$

Ledipasvir/Sofosbuvir

Class: NS5A polymerase inhibitor/NS5B polymerase inhibitor
Brand name: Harvoni
Manufacturer: Gilead
Dosage: 90 mg–400 mg po qd; duration of therapy typically 12 weeks, but 24 weeks in treatment-experienced patients with genotype 1.
Indications: genotype 1, 4, 5, or 6

Contraindications:
- Black boxed warning: hepatitis B exacerbation

Adverse effects:
- Serious, symptomatic bradycardia when co-administered with amiodarone
- Fatigue
- Headache
- Elevations of bilirubin, lipase, and creatine kinase
- Hypo-/hyperglycemia in diabetic patients

Drug interactions:
- Acid-reducing agents: can potentially decrease ledipasvir concentration

- Amiodarone: risk of symptomatic bradycardia
- Digoxin: increased digoxin level with co-administration
- Anticonvulsants (carbamazepine, phenytoin, phenobarbital, oxcarbazepine): decrease concentrations of both ledipasvir and sofosbuvir; co-administration not recommended
- Anti-mycobacterials (rifabutin, rifampin, rifapentine): decreased ledipasvir and sofosbuvir concentrations
- HIV antiretrovirals: regimens containing tenofovir (increased tenofovir concentrations); tipranavir/ritonavir: decreased ledipasvir and sofosbuvir concentrations
- Drugs that are P-gp inducers in the intestine (e.g., rifampin, St. John's wort): can decrease ledipasvir and sofosbuvir concentrations
- Rosuvastatin: co-administration may increase rosuvastatin concentration
- Anticoagulants: specifically warfarin: fluctuations in INR

Pregnancy category: B
Lactation: safety unknown

- Relative cost: $$$$$ $$$$$ (generic $$$$$ $$$$)

Glecaprevir/Pibrentasvir

Class: NS3/4A protease inhibitor/ NS5A protein inhibitor
Brand name: Mavyret
Manufacturer: Abbvie
Dosage: 300–120 mg po qd
Indications: genotypes 1–6

Contraindications/cautions:
- Black boxed warning: HBV exacerbation
- Contraindicated in decompensated cirrhosis

Adverse effects:
- Hyperbilirubinemia/jaundice
- Headache
- Fatigue
- Nausea
- Pruritis
- Diarrhea

Drug interactions:
- Statins: risk of myopathy/rhabdomyolysis
- Drugs that are P-gp inducers in the intestine (e.g., rifampin, St. John's wort): can decrease glecaprevir/pibrentasvir concentrations

Pregnancy: no adequate human data are available to establish whether or not glecaprevir/pibrentasvir increases risk during pregnancy. In animal reproduction studies, no adverse developmental effects were observed (See Appendix A)
Lactation: it is not known whether glecaprevir and/or pibrentasvir are present in breast milk. (See Appendix A)
Reproduction: no data have been reported on impact to male or female reproduction (See Appendix A)
Relative cost: $$$$$ $$$$$

Elbasvir/Grazoprevir

Class: NS3/4A protease inhibitor/NS5A protein inhibitor
Brand name: Zepatier
Manufacturer: Merck & Co., Inc.
Dosage: 50–100 mg po qd
Indications: genotypes 1, 4

Contraindications/cautions:
- Black boxed warning: hepatitis B exacerbation
- Contraindicated in decompensated cirrhosis

Adverse effects:
- Anemia
- Abnormal liver chemistry, hyperbilirubinemia
- Nausea
- Fatigue
- Headache
- Diarrhea
- Rash
- Pruritis

Drug interactions:
- Anticoagulants: specifically warfarin: fluctuations in INR
- CYP3A inducers: decrease plasma concentration of elbasvir/grazoprevir

Pregnancy: there are no data available to establish whether or not elbasvir/grazoprevir increased risk during pregnancy. No adverse developmental outcomes were observed in animal studies (See Appendix A)
Lactation: it is not known whether elbasvir and/or grazoprevir are present in breast milk (See Appendix A)
Reproduction: no data have been reported on impact to male or female reproduction (See Appendix A).
Relative cost: $$$$$ $$$$

Sofosbuvir/Velpatasvir/Voxilaprevir

Class: NS3/4A protease inhibitor/ NS5A protein inhibitor/NS5B RNA polymerase inhibitor
Brand name: Vosevi
Manufacturer: Gilead
Dosage: 400–100–100 mg mg po qd (sofosbuvir, velpatasvir, voxilaprevir)
Indication: genotypes 1–6

Contraindications/cautions:
- Black boxed warning: HBV exacerbation
- Not recommended for patients with moderate to severe hepatic impairment (Child Pugh B and C)
- Anticoagulants: specifically warfarin: fluctuations in INR

Adverse effects:
- Hypo-/hyperglycemia in diabetics
- Headache
- Fatigue
- Diarrhea
- Nausea
- Rash

Drug interactions:
- Alpelisib
- Amiodarone – risk of severe bradycardia
- Drugs that inhibit CYP3A4 inhibitors
- Proton pump inhibitors

Pregnancy category: there are inadequate data to establish whether or not sofosbuvir/velpatasvir/voxilaprevir increases risk during pregnancy. In animal reproduction studies, no adverse developmental outcomes were observed (See Appendix A)
Lactation: it is not known whether sofosbuvir and/or velpatasvir and/or voxilaprevir are present in breast milk (See Appendix A)
Reproduction: no data have been reported on impact to male or female reproduction (See Appendix A)
Relative cost: $$$$$ $$$$$

Daclatasvir

Class: NS5A inhibitor
Brand name: Daklinza

Manufacturer: Bristol-Myers Squibb
Dosage: 60 mg po qd used in combination with sofosbuvir; FDA indication for treatment of HCV genotype 3 infection. Duration of treatment 12 weeks
Dose modification: reduce dosage to 30 mg/day with strong CYP3A inhibitors and increase dosage to 90 mg/day with moderate CYP3A inducers

Contraindications/cautions:
- Black boxed warning: HBV exacerbation

Adverse effects:
- Serious, symptomatic bradycardia when co-administered with sofosbuvir and amiodarone
- Fatigue
- Headache
- Nausea/ diarrhea
- Elevation of lipase
- Anemia
- Hyperbilirubinemia
- Dizziness
- Insomnia

Drug interactions:
- CYP 3A inhibitors and inducers
- Dabigatran (co-administration increases dabigatran concentration)
- Anti-arrhythmics: amiodarone, digoxin
- HMG CO-A reductase inhibitors: increases concentration of statin
- Anticoagulants: specifically warfarin: fluctuations in INR

Pregnancy: there are inadequate human data available to determine whether or not daclatasvir increases risk during pregnancy. In animal reproduction studies, no evidence of fetal harm was observed (See Appendix A)
Lactation: it is not known whether daclatasvir is present in breast milk (See Appendix A)
Reproduction: no data have been reported on impact to male or female reproduction (See Appendix A)
Relative cost: $$$$$ $$$$$

Ribavirin

Class: nucleoside RNA synthesis inhibitor
Brand name: Copegus; Rebetol; Ribasphere; Virazole; Moderiba
Manufacturer: Genetech, Inc.; Merck & Co., Inc.; Kadmon Pharmaceuticals, LLC; Valeant Pharmaceuticals; Abbvie; generic

Dosage: chronic hepatitis C (in combination with peginterferon α 2a)
- <75 kg: 1000 mg po qd, in 2 divided doses
- ≥75 kg: 1200 mg po qd, in 2 divided doses

Contraindications/cautions:
- Hypersensitivity to drug
- Cardiac disease, significant or unstable; potential worsening due to drug-induced anemia
- Pregnancy or pregnant partner of male patient; may cause birth defects and/or death of the exposed fetus
- Hemoglobinopathy (such as thalassemia major and sickle-cell anemia)
- Decompensated liver disease
- Autoimmune hepatitis
- Renal function impairment (CrCl <50 ml/min)
- May lead to male infertility

Adverse effects:
- Gastrointestinal: abdominal pain, nausea, vomiting, pancreatitis, constipation
- Hematologic: hemolytic anemia, cardiac and pulmonary events have occurred, thrombotic thrombocytopenic purpura (less than 1%), bone marrow suppression
- Dermatologic: pruritus, rash
- Psychiatric: depression, suicidal ideation, hallucinations, anxiety
- Metabolic: hyperthyroid
- Other: fever, fatigue, headache, anorexia

Drug interactions:
- Anti-retroviral protease inhibitors
- Anti-retroviral non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Azathioprine

Pregnancy category: X
Lactation: unknown
Relative cost: $$$$$ $$ (generic available $$$)

Ribavirin Dosage Adjustments

- No cardiac history and hemoglobin <10 g/dl: decrease dose to 600 mg po qd (200 mg po qam and 400 mg po qpm)
- No cardiac history and hemoglobin <8.5 g/dl: permanently discontinue ribavirin therapy

- History of cardiovascular disease with hemoglobin decreases by ≥2 g/dl during any 4-week period: decrease ribavirin dose to 600 mg po qd. If the hemoglobin remains <12 g/dl after 4 week on the reduced dose, discontinue ribavirin therapy. Can re-start ribavirin at 600 or 800 mg po qd

Hepatic impairment: no specific guidelines are available

Patients with renal impairment:
- CrCl ≥ 50 ml/min: closely monitor older patients (>50 years old) for development of anemia, especially if renal function impairment coexists
- CrCl < 50 ml/min: oral ribavirin therapy should *not* be given

Pegylated Interferon α-2a

Class: interferons
Brand Name: Pegasys
Manufacturer: Roche

Dosage:
- Chronic hepatitis C – 180 μg weekly sc for 12 weeks in conjunction with a direct-acting antiviral agent and weight-based ribavirin

(See the section on hepatitis B above for contraindications/ adverse effects/ pregnancy category and relative cost)

AUTOIMMUNE HEPATITIS

Treatment options for AIH:

1. Combination therapy: prednisone with azathioprine (preferred) OR
2. Prednisone monotherapy.
3. Alternative therapy: budesonide +/– azathioprine
4. Alternative adjunct therapy in place of azathioprine includes MMF

Azathioprine

(See Chap. 5 for more drug information)

Prednisone

(See Chap. 5 for more drug information)

Dosage:

1. Combination therapy [with azathioprine]: Start with 30 mg po qd and taper down to 10 mg po qd within 4 weeks in combination with azathioprine 50 mg po qd
2. Prednisone monotherapy: 40–60 mg po qd for 2 weeks, and then decrease to 20 mg within 4 weeks.

Prednisone tapering recommendations:
- Taper 2.5–5 mg every 2–4 weeks
- Target dose of 5–10 mg daily, or lowest dose that maintains laboratory remission

Budesonide

(See Chap. 5 for more drug information)
Dose for AIH: 9 mg po qd

Mycophenylate Mofetil (MMF)

Class: pyrimidine synthesis inhibitor
Brand: Cellcept, Myfortic
Manufacturer: Genentech, Novartis
Dosage: 500–1500 mg po BID; maximum dose: 3 g/day
Indication: second-line therapy for patients with intolerance or incomplete response to AZA

Contraindications/cautions:
- Black boxed warning: fungal infection, herpes infection, immunosuppression, progressive multifocal leukoencephalopathy, lymphoma, new primary malignancy, post-transplant lymphoproliferative disorder
- Use with caution in patients with gastrointestinal ulcers
- Phenylketonuria
- Avoid live vaccines

Adverse effects:
- Photosensitivity
- Hematologic: anemia, leukopenia, thrombocytopenia, bone marrow suppression
- Renal: renal impairment, uremia, hypokalemia, hypomagnesemia
- Cardiorespiratory: chest pain, arrhythmia, pericardial and pleural effusion, hypertension, peripheral edema
- Endocrine: hyperglycemia in diabetics, hyperuricemia

- Gastrointestinal: diarrhea, abdominal pain, nausea, cholestasis, hepatic encephalopathy, ileus
- Neurologic: seizures, visual impairment, hearing loss, headache
- Other: hypoalbuminemia, fever

Drug interactions:
- Antacids
- Azathioprine
- Agents that cause myelosuppression such as chemotherapeutics
- Cholestyramine, colesevelam
- Rifampin
- Natalizumab
- Iron salts

Pregnancy category: D
Lactation: safety unknown
Relative cost: $$$$$ $$ (generic $)
Dosing adjustments:

Renal dosing:
- CrCl > 25 ml/min: no adjustment
- CrCl < 25 ml/min: maximum dose 1 g po BID
- Hepatic impairment: no adjustment necessary

ALCOHOLIC HEPATITIS

(See Fig. 8.3 for an algorithm for the treatment of alcoholic hepatitis)

Prednisolone

Class: corticosteroid
Brand names: Millipred, Omnipred, Orapred, Orapred ODT, Prelone, Veripred 20, Pediapred, PredForte, Pred Mild, Prelone
Manufacturer: generic
Dosage: 40 mg po qd for 28 days followed by 2–4-week taper
Indication: patients with alcoholic hepatitis who have a Maddrey score of 32 or greater or MELD 20 or higher

Contraindications/cautions:
- Known hypersensitivity reaction to prednisolone or its components
- Gastrointestinal bleeding
- Pancreatitis

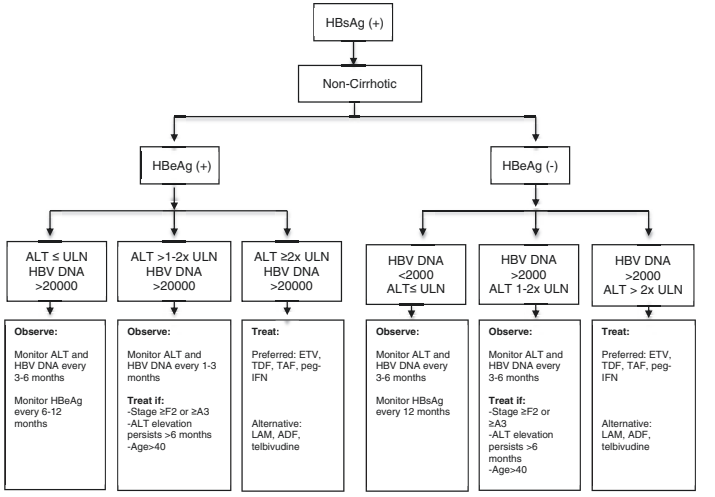

Fig. 8.3 Management of alcoholic hepatitis

- Active infection
- Opportunistic infections: (e.g., latent or active tuberculosis, varicella, acute herpes simplex keratitis or ocular herpes simplex virus, systemic fungal infection)
- Concomitant administration of live or attenuated viral vaccine
- Caution in: renal failure, diabetes mellitus, osteoporosis, psychiatric disorder, recent surgery, hypertension, hypothyroidism, myasthenia gravis, coagulation or thromboembolic disorders, recent myocardial infarction, heart failure

Dose adjustments:
- Renal dosing: caution in renal impairment
- Hepatic dosing: Not defined
- Geriatric dosing: use at lowest effective dose
- Hyperthyroidism: may require higher dosing due to increased clearance

Adverse events:
- General: delayed wound healing, immunosuppression, opportunistic infections, growth suppression, anaphylaxis, insomnia, edema
- Gastrointestinal: mucosal ulceration or perforation, pancreatitis
- Neurological: psychosis, pseudotumor cerebri, seizures, headache, mood swings, vertigo
- Hematologic: petechiae, ecchymoses

- Skin: pigmentation abnormalities, thinning skin, facial erythema, urticaria
- Cardiovascular: hypertension, congestive heart failure
- Endocrine: adrenal insufficiency, Cushing's syndrome, hyperglycemia/diabetes mellitus, hypokalemic alkalosis, hirsutism
- Musculoskeletal: myopathy, osteoporosis/osteopenia, tendon rupture
- Ocular: cataract formation, exophthalmos, optic neuritis, glaucoma

Drug interactions:
- No major drug interactions

Pregnancy category: C
Relative cost: $ (generic available $)
*Note: prednisolone is not FDA approved for use in alcoholic hepatitis

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9 Portal Hypertension

Marianna G. Mavilia and George Y. Wu

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NADOLOL

Class: non-selective beta-blocker
Brand name: Corgard
Manufacturer: Pfizer

Dosage:
- 20–40 mg po bid
- Dose should be adjusted every 2–3 days to achieve a resting HR 55–60 bpm

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- Maximum dose: 160 mg/day in patients without ascites, 80 mg/ day in patients with ascites

Contraindications/cautions:
- Consider dose adjustment in patients with renal impairment
- Avoid abrupt discontinuation
- Hyperthyroidism
- AV nodal block, bradycardia, cardiogenic shock, heart failure, hypotension, sick sinus syndrome
- Pheochromocytoma
- Asthma, COPD
- Peripheral artery disease, Raynaud's phenomenon
- Myasthenia gravis
- Elderly

Adverse effects:
- Cardiovascular: heart failure, bradycardia, AV block, hypotension, peripheral vasoconstriction
- Gastrointestinal: constipation
- Hematologic: agranulocytosis, TTP
- Respiratory: bronchospasm
- Other: sexual side effects, angioedema, depression, hallucinations, headache, dizziness

Drug interactions:
- Chlorthalidone, clonidine, cocaine, crizotinib, antiarrhythmics

Pregnancy category: C
Lactation: contraindicated
Relative cost: $$$$ (generic available: $)

PROPRANOLOL

Class: non-selective beta-blocker
Brand name: Inderal, InnoPran XL
Manufacturer: AstraZeneca

Dosage:
- 20–40 mg po bid
- Dose should be adjusted every 2–3 days to achieve a resting HR 55–60 bpm
- Maximum dose: 320 mg/d in patients without ascites, 160 mg/d in patients with ascites

Contraindications/cautions:
- Black box warning: abrupt discontinuation can cause myocardial ischemia/infarction, arrhythmias, or severe hypertension
- Hyperthyroidism
- Acute heart failure, AV block, bradycardia, cardiogenic shock, hypotension, sick sinus syndrome, Wolff-Parkinson-White syndrome
- Pheochromocytoma
- Cerebrovascular disease
- Diabetes mellitus, hypoglycemia
- Asthma, COPD
- Myasthenia gravis
- Depression
- Elderly

Adverse effects:
- AV block, bradycardia, heart failure
- Bronchospasm
- Visual impairment
- Seizures
- Hypotension
- Hypoglycemia
- Drug interactions: antiarrhythmics, antacids, chlorthalidone, clonidine, cocaine, crizotinib

Pregnancy category: C
Lactation: contraindicated
Relative cost: $$$$$ $$ (generic available: $)

CARVEDILOL

Class: non-selective beta-blocker
Brand name: Coreg, Coreg CR
Manufacturer: generic

Dosage:
- 6.25–6.5 mg po bid
- Maximum dose: 12.5 mg/d

Contraindications/cautions:
- Contraindicated in severe hepatic impairment
- Consider dose adjustment for renal impairment

- Avoid abrupt discontinuation
- Hyperthyroid
- Pheochromocytoma
- Acute heart failure, AV block, bradycardia, cardiogenic shock, hypotension, sick sinus syndrome
- Cerebrovascular disease
- Asthma, COPD
- Peripheral vascular disease
- Myasthenia gravis
- Depression
- Elderly

Adverse effects:
- AV block, bradycardia, heart failure
- Bronchospasm
- Visual impairment
- Seizures
- Hypotension
- Hypoglycemia

- Drug interactions: chlorthalidone, clonidine, cocaine, crizotinib, antiarrhythmics

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$$$ (generic available: $)

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10 Cholestasis

Marianna G. Mavilia and George Y. Wu

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ABBREVIATIONS (CHAPTER SPECIFIC, FOR COMPLETE LIST SEE APPENDIX B)

OCA	Obeticholic acid
PBC	Primary biliary cholangitis
PSC	Primary sclerosing cholangitis
UDCA	Ursodeoxycholic acid

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PRIMARY BILIARY CHOLANGITIS (PBC)

Ursodiol, Ursodeoxycholic Acid (UDCA)

Class: bile acid agents
Brand name: URSO Forte, Actigall
Manufacturer: Generic; URSO Forte – Axcan Pharma; Actigall – Watson Pharmaceuticals

Dosage:
- Primary biliary cirrhosis:13–15 mg /kg po qd
- Primary sclerosing cholangitis: 20–30 mg/kg po qd
- Autoimmune hepatitis: 10 mg/kg po qd (initial therapy to induce remission as well as during continuation phase)

Contraindications/cautions:
- Hypersensitivity to drug or bile acids
- Gallstones: calcified cholesterol, radiopaque stones, radiolucent bile pigment stones
- Unremitting acute cholecystitis
- Acute cholangitis
- Biliary obstruction

Adverse effects:
- Gastrointestinal: diarrhea, nausea, vomiting
- Musculoskeletal: backache

Drug interactions:
- Concomitant fibric acid derivatives, oral contraceptives, bile acid binding resins and antacids may decrease ursodiol efficacy

Pregnancy category: B
Lactation: safety unknown
Relative cost: $$

Obeticholic Acid (OCA)

Class: farnesoid X receptor agonist
Brand name: Ocaliva
Manufacturer: Intercept Pharmaceuticals
Dosage: 5–10 mg po qd
Indication: adjunct therapy in patients with inadequate response to at least 1 year of treatment with UDCA or monotherapy in patients with UDCA intolerance

Contraindications/cautions:
- For patients with intolerable pruritis, an antihistamine or bile acid binding resin should be administered within 4 h of OCA
- Black box warning: contraindicated in patients with complete biliary obstruction
- Dose adjustment should be considered in patients with Child-Pugh Class B or C disease

Adverse effects:
- Gastrointestinal: hepatic encephalopathy, biliary obstruction, constipation, hepatitis, cholangitis, jaundice, abdominal pain
- Dermatologic: eczema, pruritis, rash
- Endocrine: decreased HDL level, hypothyroidism
- Other: peripheral edema, dizziness, fever

Drug interactions: CYP1A2 substrates
Pregnancy category: safety unknown
Lactation: safety unknown
Relative cost: $$$$$ $$$$ (no generic available)

PRIMARY SCLEROSING CHOLANGITIS (PSC)

UDCA

(See above)

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11 Hepatic Encephalopathy

Marianna G. Mavilia and George Y. Wu

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ABBREVIATION (CHAPTER SPECIFIC, FOR COMPLETE LIST SEE APPENDIX B)

HE Hepatic encephalopathy

LACTULOSE

Class: *non-absorbed disaccharide, osmotically active laxative*

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Brand name: Cephulac, Cholac, Constulose, Acilac, Constilac, Enulose, Generlac, Kristalose
Manufacturer: generic
Indications: treatment of an acute episode of HE, secondary prophylaxis after an episode of overt HE, constipation

Dosages:
- Treatment and prophylaxis of hepatic encephalopathy: start with 30–45 ml (20 gm/30 ml) po tid to qid, then adjusted to achieve 2–3 soft formed stools/day or 300 ml (200 gm) mixed with 700 ml of water or saline rectally as a retention enema (retain for 30–60 min) every 4–6 h as needed
- Constipation: 15–30 ml po once or twice daily

Contraindications/cautions:
- Hypersensitivity to galactose or other lactulose products
- Galactosemia
- Elderly

Adverse effects:
- Gastrointestinal: bloating symptom, diarrhea, epigastric pain, eructation, flatulence, nausea, vomiting, cramps
- Endocrine metabolic: hypernatremia, hypokalemia

Drug interactions:
- Increases anticoagulation effects of warfarin

Pregnancy category: B
Lactation: safety unknown
Relative cost: $ (generic available: $)

NEOMYCIN

Class: *non-absorbed antibiotics, aminoglycoside antibiotics*
Brand name: Neo-Fradin
Manufacturer: generic

Dosage:
- Hepatic encephalopathy: 1–3 po qid for 5–6 days, maximum 12 g/d; do not use longer than 2 weeks

Contraindications/cautions:
- Black box warning: dehydration, ototoxicity, neurotoxicity, nephrotoxicity, neuromuscular disease, parkinsonism, respiratory depression/insufficiency

- Hypersensitivity to neomycin/aminoglycosides
- Inflammatory/ulcerative gastrointestinal disease
- Intestinal obstruction

Adverse effects:
- Gastrointestinal: diarrhea, nausea, vomiting
- Neurologic: neuromuscular blockade
- Respiratory: respiratory tract paralysis, concomitant anesthesia, muscle relaxants
- Renal: nephrotoxicity, dehydration
- Otic: ototoxicity

Drug interactions: surfactant anti-infectives
Pregnancy category: D
Lactation: contraindicated
Relative cost: $ (generic available: $)

RIFAXIMIN

Class: *non-absorbed antibiotics*
Brand name: Xifaxan
Manufacturer: Salix Pharmaceuticals

Dosage:
- Hepatic encephalopathy: 550 mg po bid
- Maximum dose: 1100 mg/d

Contraindications/cautions:
- Hypersensitivity to rifaximin
- Gastrointestinal inflammation, colitis
- Gastrointestinal bleeding

Adverse effects:
- Gastrointestinal: constipation, nausea, vomiting, abdominal pain, pseudomembranous colitis, hepatitis
- Neurologic: headache, dizziness
- Immunologic: immune hypersensitivity reaction, angioedema
- Renal: proteinuria
- Other: exfoliative dermatitis, peripheral edema, anemia

Drug interactions:
- Rifaximin is a CYP3A inducer and can affect metabolism of other drugs metabolized by CYP3A enzymes.

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$$$$ $$ (generic available: $$)

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12 Ascites

Marianna G. Mavilia and George Y. Wu

Contents

ABBREVIATIONS (CHAPTER SPECIFIC, FOR COMPLETE LIST SEE APPENDIX B)

BUN	Blood urea nitrogen
CJD	Creutzfeldt-Jakob disease
DRESS	Drug reaction with eosinophilia and systemic symptoms
	SBP
	Spontaneous bacterial peritonitis
TIPS	Transhepatic portosystemic shunt

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ASCITES MANAGEMENT

(See Fig. 12.1 for an algorithm for treatment of ascites)

Furosemide

Class: loop diuretic
Brand name: Lasix
Manufacturer: generic
Dosage
Starting dose: 40 mg po qd
Maximum dose: 160 mg po qd

Contraindications/cautions:
- Sulfonamide hypersensitivity

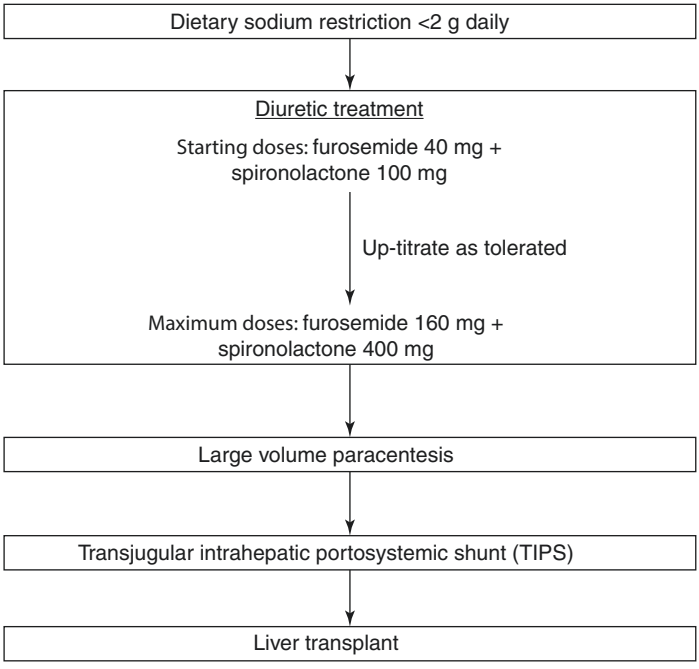

Fig. 12.1 Step-wise approach to ascites management. (Source: Runyon [1])

Adverse effects:
- Renal: hypocalcemia, acid-base imbalance, hypochloremia, hypokalemia, hypomagnesemia, hyponatremia, renal impairment, interstitial nephritis
- Metabolic: hyperglycemia in diabetics, hyperuricemia, gout
- Gastrointestinal: diarrhea, constipation, pancreatitis
- Cardiovascular: hypovolemia, hypotension
- Endocrine: drug-induced systemic lupus erythematosus
- Other: otoxicity

Drug interactions:
- Desmopressin – severe hyponatremia
- Dofetilide – risk of hypokalemia, hypomagnesemia
- Mannitol – renal toxicity
- Anti-hypertensive agents – increase risk of hypotension
- Non-ionic contrast media – renal toxicity

Pregnancy category: C
Lactation: safety unknown
Relative cost: $$ (generic: $)

Spironolactone

Class: aldosterone antagonist, potassium-sparing diuretic
Brand name: Aldactone
Manufacturer: Pfizer, generic
Dosage:
Starting dose: 100 mg po qd
Maximum dose: 400 mg po qd

Contraindications/cautions:
- Hyperkalemia
- Addison's disease

Adverse effects:
- Renal: acid base disorder, hyperkalemia
- Cardiovascular: arrhythmias
- Endocrine: antiandrogenic effects, hyperuricemia, gout
- Dermatologic: Steven-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug interactions:
- Angiotensin II receptor blockers, ACE inhibitors – hyperkalemia
- Antihypertensives – hypotension

- SGLT2 inhibitors – hypovolemia
- Digoxin
- Eplerenone
- Mannitol
- Oral potassium supplements
- Tacrolimus
- Trimethoprim

Pregnancy category: C
Lactation: acceptable
Relative cost: $$$$$ (generic: $)

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

Cefotaxime

Class: third-generation cephalosporin antibiotics
Brand name: Claforan
Dosage: 2 g iv q8h
Indication: firs- line treatment of SBP
For details on contraindications/cautions, adverse events, drug interaction, pregnancy/lactation safety, and relative cost, see Chap. 6

Ofloxacin

Class: fluoroquinolone antibiotics
Brand name: Ofloxacin
Dosage: 400 mg po bid
Indication: second-line agent for treatment of SBP in patients without prior exposure to quinolones, vomiting, shock, grade II, or greater hepatic encephalopathy or creatinine >3 g/dL
For details on contraindications/cautions, adverse events, drug interaction, pregnancy/lactation safety, and relative cost see Chap. 6

Ceftriaxone

Class: third-generation cephalosporin antibiotics
Brand name: Ceftrisol Plus, Rocephin
Indication: SBP prophylaxis in patients with cirrhosis and GI bleeding

For details on contraindications/cautions, adverse events, drug interaction, pregnancy/lactation safety, and relative cost, see Chap. 6

Norfloxacin

Class: fluoroquinolone antibiotics
Brand name: Noroxin
Indication: SBP prophylaxis in patients with cirrhosis and GI bleeding, or long-term prophylaxis in patients who have survived an episode of SBP
For details on contraindications/cautions, adverse events, drug interaction, pregnancy/lactation safety, and relative cost, see Chap. 6

Trimethoprim-Sulfamethoxazole

(See Chap. 6 for more details)
For details on contraindications/cautions, adverse events, drug interaction, pregnancy/lactation safety, and relative cost, see section on "General Bacterial Infections"

Albumin

Class: preserved human serum, parenteral colloid
Brand name: Albuked, Albumarc, Albuminar, Albuminex, AlbuRx, Albutein, Buminate, Flexbumin, Kedbumin, Macrotec, Plasbumin
Manufacturer: CSL Behring and many others

Dosage:
- SBP treatment: 25% solution 1.5 mg/kg body weight iv within 6 h of diagnosis, followed by 1 mg/kg iv on day 3
- Post-paracentesis treatment: 25% solution 6–8 g iv for every 1 L of ascites fluid removed

Indication:
- Treatment of SBP in patients with creatinine >1 mg/dL, BUN >30 mg/dL, or total bilirubin >4 mg/dL
- Treatment post paracentesis if >5 L of ascites is removed

Contraindications/cautions:
- Albumin hypersensitivity
- Caution in patients with heart failure, pulmonary edema, renal failure, and hypertension
- Remote possibility of Creutzfeldt-Jakob disease (CJD) or other viral infections

Adverse effects:
- Nausea
- Abdominal pain
- Hypervolemia

Drug interactions: none
Pregnancy category: C
Lactation: unknown
Relative cost: $$ per 12.5 mg dose

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13 Overload Disorders

Jennifer Onwochei and Roopjeet K. Bath

Contents

ABBREVIATIONS (CHAPTER SPECIFIC, FOR COMPLETE LIST SEE APPENDIX B):

EM	Extensive metabolizer
IM	Intermediate metabolizer
PM	Poor metabolizer

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HEREDITARY HEMOCHROMATOSIS

(See Fig. 13.1 for an algorithm for the treatment of hemochromatosis)

Deferoxamine

Class: iron chelator
Brand name: Desferal
Manufacturer: Novartis, Generic, Pfizer

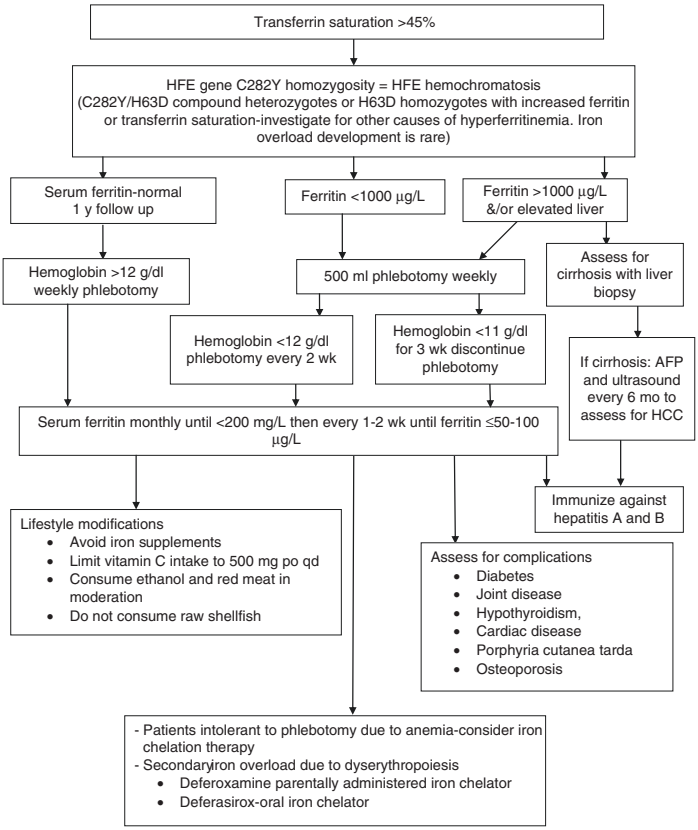

Fig. 13.1 Management of hemochromatosis. (Source: Bacon et al. [2])

Dosages:
- Acute iron toxicity:
- 1000 mg im initially followed by 500 mg im q4h for up to 2 doses. Subsequent doses of 500 mg can be given q4-12h. Maximum dose: 6 g/days
- 15 mg/kg/h iv for first 1000 mg, then 500 mg q4h iv up to 2 doses
- Chronic iron overload:
  - 20–40 mg/kg/d sc infusion for 1000–2000 mg q8-24h
  - 40–50 mg/kg/d iv infusion q8-12h
  - Maximum 1 g qd in absence of transfusions, 6 g qd if patient received transfusions

Dose adjustments:
- Severe renal impairment/ anuria: contraindicated
- CrCl 10–50 mL/min, CRRT: administer 25–50% of normal dose

Indications: as above

Contraindications/cautions:
- Hypersensitivity to deferoxamine or any component of the formulation, patients with severe renal disease or anuria

Adverse effects:
- Cardiovascular: flushing, hypotension, tachycardia, shock, edema
- Neurologic: headache, fever, dizziness, neuropathy, seizure, exacerbation of aluminum-related encephalopathy (dialysis)
- Dermatologic: angioedema, rash, urticaria
- Endocrine/metabolic: growth retardation in children, hypocalcemia
- Gastrointestinal: abdominal discomfort or pain, diarrhea, nausea and vomiting
- Genitourinary: dysuria
- Hematologic: thrombocytopenia, leucopenia
- Local: injection site burning, erythema, eschar, induration, irritation, pain, swelling, wheal, or vesicle formation
- Neuromuscular and skeletal: arthralgia, leg cramps, myalgia, paresthesias
- Ocular: decreased acuity, blurred vision, dichromatopsia, maculopathy, night vision or peripheral vision impairment, visual loss, visual field defects, optic neuritis, cataracts, retinal pigmentary abnormalities
- Renal: renal impairment, urine discoloration
- Respiratory: acute/adult respiratory distress syndrome, asthma
- Miscellaneous: anaphylaxis, hypersensitivity reaction, infections

Drug interactions: ascorbic acid, may enhance the adverse/toxic effect of deferoxamine
Pregnancy category: C
Lactation: limited data. Maybe safe
Relative cost: $$$

Deferasirox

Class: iron chelator
Brand names: Exjade, Jadenu
Manufacturer: Novartis

Dosages:
- Exjade:
  - Initial 20 mg/kg po qd
  - Maintenance dose 20–30 mg/kg po qd adjusted q3–6 months based on serum ferritin levels. Doses up to 40 mg/kg po qd for serum ferritin levels persistently >2500 μg/L
- Jadenu:
  - Initial 14 mg/kg po qd, increase by 3.5–7 mg/kg po qd q3 months based on ferritin; maximum 28 mg/kg po qd

Dose adjustments

Renal impairment:
- Creatinine clearance >40 to <60 ml/min: reduce initial dose by 50%
- Creatinine clearance <40 ml/min or serum creatinine >2 times age-appropriate ULN it is contraindicated

Hepatic impairment:
- Consider dose adjustment or discontinuation for severe or persistent elevations in liver function tests

Indications: chronic iron overload

Contraindications/cautions:
- Hypersensitivity to deferasirox or any component of the formulation
- Platelet count <50,000/mm^3
- Poor performance status and high-risk myelodysplastic syndromes or advanced malignancies
- Renal impairment as above

Adverse effects:
- Neurologic: fever, headache, fatigue
- Dermatologic: rash (dose related), urticaria
- Gastrointestinal: abdominal pain, diarrhea, nausea, vomiting, (all dose related), aminotransferase elevations
- Renal: increased serum creatinine (dose related), proteinuria
- Respiratory: cough, nasopharyngitis, pharyngolaryngeal pain, bronchitis, tonsillitis, rhinitis
- Musculoskeletal: arthralgia, back pain
- Miscellaneous: ear infection

Drug interactions: aluminum hydroxide, cholestyramine, CYP2C8 substrates, CYP3A4 substrates, phenobarbital, phenytoin, rifampin, ritonavir
Pregnancy category: C
Lactation: unknown
Relative cost: $$$$$$

WILSON'S DISEASE

Penicillamine

Class: chelating agent
Brand name: Cuprimine
Manufacturer: Valeant Pharmaceuticals
Dosage: 750–1500 mg po in divided doses po tid or qid

Contraindications:
- Hypersensitivity to drug/class/component
- Pregnancy
- Breastfeeding
- History of penicillamine-related aplastic anemia or agranulocytosis
- Renal impairment
- Hypersensitivity to penicillin

Indication: Wilson's disease & cystinuria

Adverse effects:
- Gastrointestinal: nausea, vomiting, epigastric pain, hepatic failure, pancreatitis, intrahepatic cholestasis (rare), hepatitis (rare)
- Neurological: myasthenia gravis
- Renal: nephrotic syndrome, renal failure
- Hematological: aplastic anemia, leukopenia, agranulocytosis, thrombocytopenia
- Immunological: hypersensitivity reaction, SLE
- Dermatological: exfoliative dermatitis, pemphigus, toxic epidermal necrolysis (rare)

Pregnancy category: D
Lactation: limited data. May be safe.
Relative cost: $$$$$$

Trientine

Class: copper chelator
Brand name: Syprine
Manufacturer: Merck & co., Inc.
Dosage: 250–500 mg po qid, maximum: 2 g po qd
Indications: Wilson's disease and copper overload

Contraindications:
- Hypersensitivity to drug/class/component
- Rheumatoid arthritis
- Biliary cirrhosis
- Cystinuria

Adverse effects:
- Hematological: iron deficiency anemia
- Immunological: lupus, contact dermatitis

Pregnancy category: C
Lactation: limited data. May be safe
Relative cost: $$$$$$$

Tetrathiomolybdate

Class: chelator/blocks copper absorption
Brand names: Decuprate, Coprexa
Manufacturer: Pipex Pharmaceuticals, Inc.

Dosage:
- Varies
- May start with 120–140 mg po qd and increased to 200–260 mg po qd in divided doses

Indication: copper toxicosis, Wilson's disease (especially neurologic symptoms)

Adverse Effects:
- Bone marrow suppression
- Mildly elevated transaminases

Pregnancy category: Unknown
Lactation: unknown
Relative cost: $$$$$

Zinc Sulfate

Class: dietary supplement/metallothionein inducer (blocks copper absorption)
Brand names: Orazinc, Zincate
Manufacturer: Mericon Industries Inc.
Dosage: 50 mg elemental zinc po tid (oral zinc sulfate is approximately 23% elemental zinc)
Indication: zinc deficiency, Wilson's disease

Adverse reactions:

- Gastrointestinal: nausea, stomach upset, heartburn, biochemical pancreatitis
- Immunological: may have immunosuppressant effects
- Other: zinc accumulation

Pregnancy category: C
Lactation: unknown
Relative cost: $

GAUCHER'S DISEASE

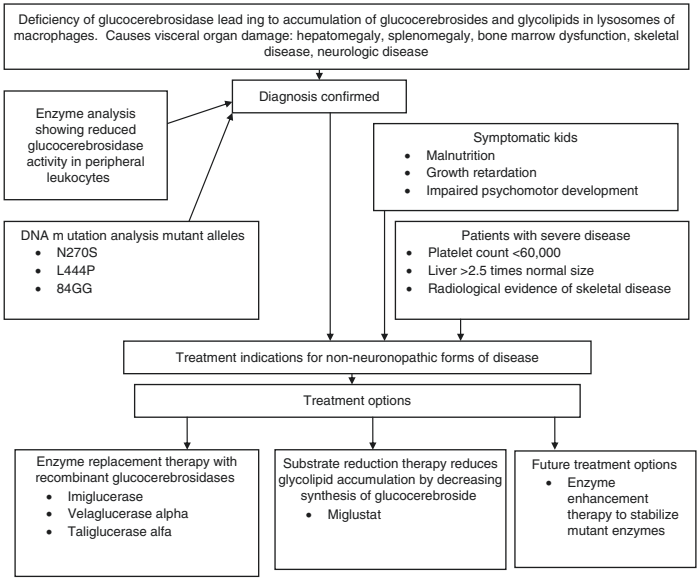

Fig. 13.2 Treatment of Gaucher's disease. (Adapted from Bath [13])

(See Fig. 13.2 for an algorithm for the treatment of Gaucher's Disease)

Imiglucerase (Glucocerebrosidase)

Class: replacement enzyme
Brand name: Cerezyme
Manufacturer: Genzyme

Dosages:
- 30–60 units/kg iv q2wk, dosing individualized based on disease severity. Range: 2.5 units/kg iv 3 times/wk-60 units/kg as frequently as q1wk. Average dose 60 units/kg administered q2wk

Contraindications/cautions:
- Hypersensitivity to imiglucerase or any component of the formulation

Adverse effects:
- Miscellaneous: hypersensitivity reaction including pruritus, flushing, urticaria, angioedema, bronchospasm
- Cardiovascular: tachycardia
- Central nervous system: headache, dizziness, fatigue, fever
- Dermatologic: rash, pruritus
- Gastrointestinal: nausea, abdominal discomfort, vomiting, diarrhea
- Local injection site burning, swelling, or sterile abscess
- Neuromuscular and skeletal: backache
- Miscellaneous: anaphylactoid reactions
- Antibody formation: development of IgG antibodies has been reported in 15% of patients and may increase the risk of hypersensitivity reactions

Drug interactions:
- No known significant interactions

Pregnancy category: C
Lactation: excretion in breast milk unknown, use caution
Relative cost: $$$$$$$

Velaglucerase Alfa (Glucocerebrosidase)

Class: replacement enzyme
Brand name: VPRIV
Manufacturer: Shire

Dosages:

- 60 units/kg iv administered every other week based on disease severity/activity
- Range of 15–60 units/kg have been evaluated in clinical trials

Indication: Gaucher's disease

Contraindications/cautions:
- None listed by manufacturer

Adverse effects:
- Neurologic: headache, fatigue, fever, dizziness
- Gastrointestinal: abdominal pain, nausea
- Hematologic: aPTT prolonged
- Respiratory: upper respiratory tract infections
- Miscellaneous: infusion-related reactions, hypersensitivity reactions
- Cardiovascular: flushing, hyper or hypotension, tachycardia
- Dermatologic: rash, urticaria

Drug interactions:
- No known significant interactions

Pregnancy category: B
Lactation: excretion in breast milk unknown, use with caution
Relative cost: $$$$$$$

Taliglucerase Alfa

Class: replacement enzyme
Brand name: Elelyso
Manufacturer: Pfizer

Dosages:
- IV: 60 units/kg q2wk
- Dosing is individualized based on disease severity

Indication: Gaucher's disease

Contraindications/cautions:
- None listed by manufacturer

Adverse effects:
- Neurologic: headache, fatigue, dizziness
- Hypersensitivity: hypersensitivity reaction, increased risk in antibody-positive patients; patients switching from imiglucerase
- Neuromuscular and skeletal: arthralgia, limb pain
- Immunologic: antibody formation

Drug interactions:
- No known significant interactions

Pregnancy category: not assigned
Lactation: excretion in breast milk unknown, use with caution
Relative cost: $$$$$$$$

Miglustat

Class: glucosylcermide synthase inhibitor
Brand name: Zavesca
Manufacturer: Actelion

Dosages:
- 100 mg po tid
- Dose may be reduced to 100 mg po qd to bid in patients with adverse effects

Indication: type 1 Gaucher's disease

Contraindications/cautions:
- Hypersensitivity to miglustat or any component of the formulation, pregnancy

Adverse effects:
- Neurologic: headache, dizziness, memory impairment, migraine
- Gastrointestinal: diarrhea, weight loss, abdominal pain, flatulence, nausea, vomiting, constipation, xerostomia, bloating, anorexia, dyspepsia, epigastric pain
- Neuromuscular and skeletal: tremor, weakness, leg cramps, paresthesia
- Ocular: visual disturbances
- Endocrine/metabolic: menstrual disorder
- Hematologic: thrombocytopenia

Drug interactions:
- Imiglucerase: miglustat increases the clearance of imiglucerase; combination therapy is not indicated

Pregnancy category: X

- Decreased fetus weight, fetal loss, and difficult or delayed births observed in animal studies
- Women of reproductive age should use contraception
- Adverse effects on spermatogenesis and reduced fertility were observed in male animal studies
- Manufacturer recommends male patients use reliable contraception during therapy and for 3 months following treatment

Lactation: excretion in breast milk unknown, but it is not recommended

Relative cost: $$$$$$$$$

Eliglustat

Class: glucosylcermide synthase inhibitor
Brand name: Cerdelga
Manufacturer: Genzyme

Dosages:
- Dosage is based on patient CYP2D6 metabolizer status (extensive metabolizers [EMs], intermediate metabolizers [IMs], or poor metabolizers [PMs])
  - EMs and IMs: 84 mg po bid
  - PMs: 84 mg qd
- *Missed dose:* if a dose is missed, take the prescribed dose at the next scheduled time; do not double the next dose

Indication: type 1 Gaucher's disease

Contraindications/cautions:
- Hypersensitivity to eliglustat or any component of the formulation
- Hereditary problems of galactose intolerance

Adverse effects:
- Neurologic: headache, dizziness, fatigue
- Gastrointestinal: diarrhea, nausea, vomiting
- Neuromuscular and skeletal: limb pain and arthralgia
- Cardiovascular: palpitations, cardiac arrhythmias

Drug interactions:
- CYP2D6 inhibitors and CYP3A4 inducers/inhibitors
- Immunomodulators

Pregnancy category: C
Lactation: excretion in breast milk unknown, but it is not recommended
Relative cost: $$$$$$$$$$

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14 Pruritus

Marianna G. Mavilia and George Y. Wu

Contents

(See Table 14.1 for treatment of pruritus)

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Table 14.1 Medications for the treatment of pruritus [1–5]

Drug	*Regimen (po)*	*Efficacy*	*Adverse effects*
Diphenhydramine hydroxyzine	25–50 mg qid 25 mg qid	Rarely provide significant relief apart from sedation	Drowsiness
Cholestyramine	4–6 gm 30 min before meals (or doses may be taken before and after breakfast without an evening dose)	Beneficial in most patients	Fat malabsorption, decreased absorption of other medications, constipation
Rifampin	300 mg bid	Beneficial in some but not all controlled trials to date	Inducer of hepatic drug metabolizing enzymes, potential hepatotoxicity, red-orange discoloration of urine and secretions
Naltrexone	50 mg qd	Beneficial in small controlled trials	Opiate withdrawal symptoms, rare hepatotoxicity
Sertraline	50–100 mg qd	May be beneficial in cholestatic pruritus	Serotonin syndrome, mood changes, sexual side effects

DIPHENHYDRAMINE

Class: first-generation antihistamine
Brand names: Benadryl, Nytol, Sominex, Unisom, Banophen, Dicopanol, Diphenhist, Dytuss, Genahist, Geri-Dryl, Pharbedryl, QlearQuil, Quenalin, Relief, Siladryl, Triaminic, ZzzQuil, Delsym, Diphedryl, Vanamine
Manufacturer: generic; Benadryl – Johnson &Johnson Consumer Inc.; Nytol – Omega Pharma; Sominex – Actavis; Unisom – Sanofi Pharmaceuticals; Banophen – Major Pharmaceuticals; Dicopanol – Fusion Pharmaceuticals; Diphenhist – BIO-PHARM; Dytuss-Lunsco, Inc.; Genahist – Teva Pharmaceuticals; Geri-Dryl – Geri-Care Pharmaceutical Corp.;

Pharbedryl – Pharbest Pharmaceuticals; QlearQuil – Procter & Gamble Manufacturing Company; Quenalin – Qualitest Pharm; Siladryl – Silarx Pharmaceuticals, Inc.; Triaminic – Novartis Consumer Health, Inc.; ZzzQuil – Procter & Gamble Manufacturing Company; Delsym – Reckitt Benckiser; Diphedryl – RiteAid; Vanamine – GM pharmaceuticals, Inc.

Dosage:
- 25–50 mg po qid
- Maximum dose: 300 mg/d

Contraindications/cautions:
- Caution in patients with breathing problems, tachycardia/arrhythmias, glaucoma, and difficultly with urination
- Dose adjustment may be required for patients with hepatic impairment due to hepatic metabolism

Adverse effects:
- Drowsiness
- Excitability
- Restlessness
- Xerostomia
- Headache
- Asthenia
- Dizziness

Drug interactions:
- Alcohol, sedatives, tranquilizers, alpha blockers, sympathomimetics

Pregnancy category: B
Lactation: contraindicated
Relative cost: $ (generic available: $)

HYDROXYZINE

Class: anxiolytic, non-benzodiazepine, first-generation (sedating) antihistamine, anti-emetic
Generic preparations: hydroxyzine hydrochloride, hydroxyzine pamoate
Brand names: Vistaril, Atarax
Manufacturer: generic; Vistaril – Pfizer Pharmaceuticals; Atarax – Alliance Pharmaceuticals

Dosage:
- 25 mg po qid
- Maximum dose: 400 mg/d

Dose adjustment:
- Dose adjustment may be required for patients with hepatic impairment due to hepatic metabolism
- CrCl ≤50 ml/min: decrease dosage by 50%

Contraindications/cautions:
- Hypersensitivity to the drug or its components
- Elderly
- Asthma, COPD
- QT prolongation
- Glaucoma

Adverse effects:
- Neurological: drowsiness, headache, seizures, tardive dyskinesia
- Cardiac: QT prolongation, torsades de pointes
- Gastrointestinal: constipation
- Psychiatric: hallucinations
- Dermatologic: pruritus, rash, urticarial
- Other: dry mouth, urinary retention, blurred vision

Drug interactions:
- CNS depressants (including narcotics, non-narcotic analgesics, barbiturates, alcohol)

Pregnancy category: C
Lactation: contraindicated
Relative cost: $ (generic available: $)

CHOLESTYRAMINE

Class: bile acid sequestrant and ion-exchange resin
Brand names: Prevalite, Locholest, Locholest Light
Manufacturer: generic; Prevalite – Upsher-Smith Laboratories, Inc.; Locholest, Locholest Light – Alliance Pharmaceuticals

Dosage:
- 4–6 g po bid 30 min before meals (or doses may be taken before and after breakfast without an evening dose)
- Maximum dose: 16 g/day

Contraindications/cautions:
- Complete biliary obstruction
- Hypertriglyceridemia

- Constipation, ileus, gastrointestinal obstruction
- Coagulopathy
- Hypersensitivity to drug or its components

Adverse effects:
- Gastrointestinal: constipation, abdominal pain, flatulence, nausea, vomiting, diarrhea, dyspepsia, eructation, anorexia, steatorrhea, cholelithiasis
- Other: bleeding tendencies, osteoporosis, night blindness

Drug interactions:
- May inhibit absorption of fat-soluble vitamins
- Enhanced lipid-lowering effect with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins)
- Other interactions include spironolactone, oral phosphate supplements, phenylbutazone, warfarin, thiazide diuretics, propranolol, tetracycline, penicillin G, phenobarbital, thyroid and thyroxine preparations, estrogens and progestins, and digitalis

Pregnancy category: C
Lactation: caution
Relative cost: $$ (generic available: $)

RIFAMPIN

Class: antibiotics for tuberculosis, rifamycin antibiotics
Brand names: Rifadin, Rimactane
Manufacturer: generic; Rifadin – Aventis Pharmaceuticals; Rimactane – Sandoz Pharmaceuticals

Dosage:
- 300 mg po bid

Contraindications/cautions:
- Hypersensitivity to drug or its components
- Impaired liver function: monitor liver function tests every 2–4 weeks during therapy
- Diabetes mellitus
- Elderly
- Dose adjustment may be required for patients with hepatic impairment due to hepatic metabolism

Adverse effects:
- Neurological: dizziness, visual disturbances, drowsiness

- Gastrointestinal: reflux, nausea, vomiting, hepatotoxicity, pseudomembranous colitis
- Systemic: fever, edema, red-orange discoloration of urine and secretions
- Musculoskeletal: muscle weakness
- Endocrine: menstrual disturbances
- Dermatologic: flushing, urticarial, rash

Drug interactions:
- Anticonvulsants, digoxin, antiarrhythmics, oral anticoagulants, antifungals, barbiturates, β-blockers, calcium channel blockers, chloramphenicol, clarithromycin, corticosteroids, cyclosporine, cardiac glycoside preparations, clofibrate, oral or other systemic hormonal contraceptives, dapsone, diazepam, doxycycline, fluoroquinolones, haloperidol, oral hypoglycemic agents, levothyroxine, methadone, narcotic analgesics, progestins, quinine, tacrolimus, theophylline, tricyclic antidepressants (TCAs), and zidovudine, atovaquone, isoniazid, ketoconazole, probenecid, contrimoxazole, sulfasalazine, and antacids

Pregnancy category: C
Lactation: contraindicated
Relative cost: $$$$$ (generic available: $$)

URSODEOXYCHOLIC ACID

(See Chap. 10)

NALTREXONE

Class: agents for opioid dependence, agents used in alcohol dependence
Brand names: ReVia, Vivitrol, Depade
Manufacturer: generic; ReVia – Teva Pharmaceuticals; Vivitrol – Alkermes, Inc.; Depade – Mallinckrodt Pharmaceuticals

Dosage:
- 50 mg po qd

Contraindications/cautions:
- Concomitant opioid analgesic use, current physiological opioid dependence, acute opioid withdrawal, or failure of naloxone challenge test
- Hypersensitivity to drug or its components

- Dose adjustment may be required for patients with hepatic impairment or renal impairment

Adverse effects:
- Gastrointestinal: nausea, vomiting, anorexia, appetite disorder, hepatic enzyme abnormalities, hepatoxicity, peptic ulcer, constipation
- Psychiatric: depression, insomnia
- Neurological: opioid withdrawal symptoms, dizziness, syncope, headache, somnolence, blurred vision
- Other: nasopharyngitis, toothache, injection-site reactions, dysuria, edema

Drug interactions:
- Opioids
- Alcohol

Pregnancy category: C
Lactation: contraindicated
Relative cost: $$$$$ $$ (generic available: $)

SERTRALINE

Class: antidepressant, selective serotonin reuptake inhibitor
Brand name: Zoloft
Manufacturer: generic; Zoloft – Pfizer Pharmaceuticals

Dosage:
- 50–100 mg po qd

Contraindications/cautions:
- Use of monoamine oxidase inhibitor medications (MAOIs) concomitantly or within 14 days
- Hypersensitivity to drug or its components
- Bipolar disorder
- Seizure disorder
- Hyponatremia
- Dose adjustment may be required for patients with hepatic impairment due to hepatic metabolism

Adverse effects:
- Neurologic: serotonin syndrome, mood changes, somnolence, tremor, dizziness, headache, agitation, insomnia, visual impairment, seizures
- Gastrointestinal: diarrhea, dyspepsia, nausea, constipation, anorexia

- Reproductive: sexual side effects
- Other: dry mouth, fatigue, SIADH

Drug interactions:

- Serotonergic drugs (including triptans, TCAs, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's wort) and with drugs that impair metabolism of serotonin (MAOIs), pimozide, disulfram, warfarin, digoxin, sumatriptan, lithium, phenytoin, and valproate, aspirin, nonsteroidal anti-inflammatories (NSAIDs), alcohol, cimetidine, diazepam and tolbutamide

Pregnancy category: C
Lactation: caution
Relative cost: $$$$$ (generic available: $)

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15 Post-Liver Transplant

Jennifer Onwochei and Michael Einstein

Contents

ABBREVIATIONS (CHAPTER SPECIFIC, FOR COMPLETE LIST SEE APPENDIX B)

CMV	Cytomegalovirus
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid products
mTOR	Mammalian target of rapamycin
NSAID	Nonsteroidal anti-inflammatory drug
PCP	Pneumocystis pneumonia
PRES	Posterior reversible encephalopathy syndrome
TPMT	Thiopurine S-methyltransferase

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IMMUNOSUPPRESSANT DRUGS

Glucocorticoids

Class: steroids

Dosages:
- Variable – depending on the transplant center, underlying liver disease, and history of rejections

Indication:
- Induction of immunosuppression, treatment of acute cellular rejection, maintenance of immunosuppression

See Chap. 5 for additional drug details.

Tacrolimus

Class: calcineurin inhibitor
Generic name: Tacrolimus FK506
Brand name: Prograf, Advagraf, Envarsus
Manufacturer: Astellas Pharma

Dosages:
- Starting 0.1–0.15 mg/kg po qd q12h and adjust to the desired trough level

Dose adjustments:
- Renal impairment – none, but tacrolimus can cause renal toxicity, which may require dose adjustment
- Hepatic impairment – mild-moderate – none required. Severe – dose reduction should be considered

Indications:
- Maintenance of immunosuppression

Contraindications/cautions:
- Hypersensitivity/anaphylaxis
- Caution with patients with myocardial hypertrophy

Adverse effects:
- Cardiovascular: cardiac arrhythmia, angina pectoris, bradycardia, cardiomyopathy, edema, hemorrhagic stroke, syncope
- Neurologic: headache, insomnia, psychological d/o, myasthenia, seizure, pseudotumor cerebri, vertigo, posterior reversible encephalopathy syndrome (PRES)

- Dermatologic: skin atrophy, acne vulgaris, dermatitis, skin photosensitivity, skin rashes
- Endocrine and metabolic: Cushing's syndrome, DM, electrolyte abnormalities – hyperkalemia, hyperuricemia, hyperphosphatemia, hyponatremia, hyperglycemia, acidosis
- Gastrointestinal: abdominal distention, abdominal pain, anorexia, aphthous ulcer, cholestasis, GERD, vomiting, diarrhea, constipation, oral candidiasis
- Genitourinary: hemorrhagic cystitis
- Hematologic: leukocytosis (transient)
- Infection: overall increased susceptibility to infections – viral, bacterial, and fungal
- Renal: acute renal failure, increased blood urea nitrogen, increased serum creatinine, renal insufficiency, renal tubular necrosis

Drug interactions:
- CYP3A4 inhibitors (e.g., indinavir, amiodarone, imatinib, nilotinib atazanavir, ceritinib, dronedarone, clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, fluconazole, ritonavir, verapamil, nelfinavir, goldenseal, and grapefruit): may increase tacrolimus concentrations; monitor concentrations, and adjust tacrolimus dose as needed
- CYP3A4 inducers (e.g., carbamazepine, fosphenytoin, primidone, efavirenz, rifabutin, modafinil, nafcillin, bosentan, phenobarbital, phenytoin, rifampicin, St. John's Wort, and glucocorticoids): may decrease tacrolimus concentrations, monitor concentrations. and adjust tacrolimus dose as needed. Other examples include the following:
- Mycophenolic acid products (MPA): can increase MPA exposure after crossover from cyclosporine to tacrolimus; monitor for MPA-related adverse reactions and adjust mycophenolate mofetil or MPA dose as needed
- Avoid live vaccinations while on tacrolimus
- NSAIDs (may worsen nephrotoxic effect)

Pregnancy category: not assigned. Use is not recommended
Lactation: probably safe, limited data show low concentrations in breastmilk
Relative cost: $$$

Cyclosporine

Class: calcineurin inhibitor
Brand names: Gengraf, Neoral, Sandimmune
Manufacturer: Novartis Pharmaceutical
Dosages: varies based on institution.

- Oral dose on average – 8 ± 4 mg/kg/d in 2 divided doses
- IV dose – initial dose: 5–6 mg/kg/d or one-third of the oral dose as a single dose; infused over 2–6 h

Dose adjustments:
- Renal impairment – none specified but watch closely and adjust based on serum levels
- Hepatic impairment – none specified but watch closely and adjust based on serum levels

Indications:
- Maintain immunosuppression and prevent organ rejection
- Treat chronic rejection

Contraindications/cautions:
- Hypersensitivity

Adverse effects (similar to tacrolimus):
- Cardiovascular: edema, hypertension
- Neurologic: headache, paresthesia, tremor, PRES
- Dermatologic: hypertrichosis
- Endocrine and metabolic: hirsutism, increased serum triglycerides
- Gastrointestinal: nausea, diarrhea, gingival hyperplasia, abdominal distress, dyspepsia
- Infectious: overall increased susceptibility to infections
- Renal: renal insufficiency

Drug interactions:
- Drugs that increase cyclosporine concentrations: calcium channel blockers, antifungals, glucocorticoids, fluconazole, azithromycin, allopurinol, clarithromycin, amiodarone, erythromycin, bromocriptine, colchicine, dalfopristin, danazol, imatinib metoclopramide, nefazodone, oral contraceptives
- Drugs/dietary supplements that decrease cyclosporine concentrations: nafcillin, carbamazepine, bosentan, St. John's wort, rifampin, oxcarbazepine, octreotide, phenobarbital, orlistat, phenytoin, sulfinpyrazone, terbinafine, ticlopidine
- HIV protease inhibitors could potentially increase the concentrations of cyclosporine so use with caution
- Use of live vaccines should be avoided while on cyclosporine

Pregnancy category: C
Lactation: levels in milk vary. Due to potential serious adverse effects, should consider discontinuing breastfeeding
Relative cost: $$

Azathioprine

(See Chap. 5 for additional drug details)

Mycophenolate Mofetil

Class: anti-metabolite
Brand name: Cellcept
Manufacturer: Genentech
Use: maintenance of immunosuppression and treatment of rejection

Dosages:
- Oral: 1 g po bid when used in combination with other immunosuppressants, 1.5 g bid when used in combination with cyclosporine
- IV: equivalent to oral dose

Dose adjustments:
- Renal impairment – none
- Hepatic impairment – none

Indications:
- To maintain immunosuppression and prevent rejection

Contraindications/cautions:
- Hypersensitivity to MMF and polysorbate 80

Adverse effects:
- Cardiovascular: tachycardia, edema, hypertension, hypotension
- Neurologic: headache, insomnia, depression, confusion, myasthenia, paresthesias
- Dermatologic: cellulitis, skin rashes
- Endocrine and metabolic: adrenal suppression, cushingoid state, Cushing syndrome, diabetes mellitus, electrolyte abnormalities (hypomagnesemia, hypokalemia, hyperuricemia, acidosis, hyperglycemia)
- Gastrointestinal: abdominal distention, nausea, diarrhea, vomiting, constipation, peptic ulcer disease, increased liver enzymes, hepatitis
- Hematologic: leukopenia, anemia, leukocytosis, thrombocytopenia.
- Infectious: overall increased susceptibility to infections – viral, fungal, and bacterial
- Renal: increased serum creatinine, increased BUN

Drug interactions: multiple drugs including but not limited to the following:
- Acyclovir and ganciclovir: coadministration with mycophenolate mofetil can potentially increase levels of both drugs

- Decrease mycophenolate mofetil levels: cholestyramine and bile acid sequestrants, rifampin, ciprofloxacin, amoxicillin plus clavulanic acid, norfloxacin and metronidazole combination, sevelamer, antacids, cyclosporine, proton pump inhibitors
- Increase mycophenolate mofetil levels: pimecrolimus, probenecid
- Mycophenolate mofetil may enhance the adverse/toxic effect of live vaccines
- Mycophenolate mofetil may diminish the therapeutic effect of inactivated vaccines
- Variable effect with oral contraceptive (use with caution)

Pregnancy category: D
Lactation: limited data – unclear
Relative cost: $$

Sirolimus

Class: mammalian target of rapamycin (mTOR) inhibitor
Brand name: Rapamune
Manufacturer: Pfizer
Dosage: not FDA approved for liver transplant, but it is used off label

Dosage adjustment:
- Renal impairment – for maintenance, reduce by approximately one third in patients with mild or moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment. It is not necessary to modify the loading dose
- Hepatic impairment – none

Indication:
- Organ rejection prophylaxis (used in combination with other immunosuppressant)

Contraindications/cautions:
- Hypersensitivity to sirolimus

Adverse effects:
- Hepatic artery thrombosis (particularly immediately after transplant so not to be used earlier than 30 days after liver transplantation), delayed wound healing, hyperlipidemia, bone marrow suppression, mouth ulcers, skin rashes, albuminuria, and infections, hypersensitivity, angioedema

Drug interactions – avoid use with the following:
- Cyclosporine may increase sirolimus concentrations when co-administered with sirolimus

- Strong CYP3A4/P-gp inducers as it may result in decreased concentrations of sirolimus
- Strong CYP3A4/P-gp inhibitors as it may result in increased concentrations of sirolimus

Pregnancy category: use only if the potential benefit outweighs the potential risk to the embryo/fetus
Lactation safety: unknown, weight risks and benefits of breastfeeding with patient
Relative cost: $$$$

Everolimus

Class: mTOR inhibitor
Brand name: Afinitor, Zortress
Manufacturer: Novartis

Dosage:
- Oral: Initial: 1 mg bid (in combination with tacrolimus [reduced dose required] and a corticosteroid; adjust maintenance dose if needed at a 4- to 5-day interval based on serum concentrations, tolerability, and response
- *If trough is < 3 ng/ml:* double total daily dose
- *If trough > 8 ng/ml on 2 consecutive measures:* decrease dose by 0.25 mg bid

Dosage adjustment:
- Renal impairment – for maintenance, reduce by approximately one third in patients with mild or moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment. It is not necessary to modify the loading dose
- Hepatic impairment – none

Indication:
- Organ rejection prophylaxis (used in combination with other immunosuppressant)

Contraindications/cautions:
- Hypersensitivity to everolimus or to other rapamycin derivatives
- Not to be used earlier than 30 days after liver transplantation
- Caution in geriatric patients

Adverse effects:
- Hepatic artery thrombosis (particularly immediately after transplant, so should not be used earlier than 30 days after liver transplantation), delayed wound healing, hyperlipidemia, bone marrow suppression, mouth ulcers, skin rashes, albuminuria, and infections, hypersensitivity, angioedema

Drug interactions:
- Cyclosporine may increase everolimus concentrations when co-administered with everolimus
- Cautious use with inducers of CYP3A4
- Cautious use with inhibitors of CYP3A4

Pregnancy category: use only if the potential benefit outweighs the potential risk to the embryo/fetus
Lactation safety: Present in breast milk. Breast feeding is not recommended
Relative cost: $$$$$$$$$

INFECTION PROPHYLAXIS AGENTS

Antifungal Prophylaxis

Fluconazole
(See Chap. 7)

PCP Prophylaxis

Trimethoprim/Sulfamethoxazole (TMP/SMX) Single Strength (SS)
(See Chap. 6 for more drug details)
Class: antibiotic
Dosage: po qd × 3 mo (post op)
Indication: PCP prophylaxis, first line
*Alternatives in patients who are allergic to TMP-SMX: atovaquone, dapsone

Antiviral Prophylaxis

Valganciclovir
(See Chap. 7 for more drug details)
Class: antiviral
Brand name: Valcyte
Manufacturer: Genentech

Dosage:
- 450 mg po qd for 90 days post op
- If oral administration is not tolerated, iv ganciclovir 5 mg/kg every 24 h can be used

Renal impairment: needs dose adjustment

- CrCL 25–39 ml/min – 450 mg po every other day
- CrCl 10–24 ml/min – 450 mg q2wk
- CrCl <10 ml/min or on hemodialysis – 450 mg po q1wk

See Chap. 7 for additional drug details.

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16 Acute and Chronic Pancreatitis Pain Syndromes

Leon D. Averbukh and George Y. Wu

Contents

(See Fig. 16.1 for a treatment algorithm for chronic pancreatitis, Table 16.1 for opioid equivalences)

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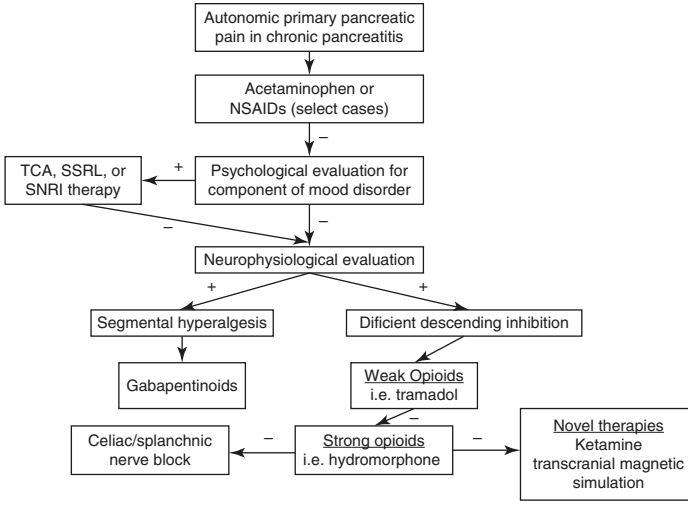

Fig. 16.1 Pain management of chronic pancreatitis. (Adapted from Drewes et al. [11])

Table 16.1 Relative opioid equivalence

Medication	*Route*	*Units*	*Equivalent*
Morphine	IV	mg	10
Morphine	PO	mg	30
Fentanyl	IV	mg	0.1
Fentanyl	IV	mcg	0.1
Fentanyl	Epidermal patch	mg	0.1
Fentanyl	Epidermal patch	mg	100
Fentanyl	Epidural	mg	0.1
Fentanyl	PO	mg	0.229
Fentanyl	PO	mcg	229
Alfentanil	IV	mg	0.67
Meperidine	IV	mg	75
Meperidine	PO	mg	333
Demerol	IV	mg	75
Oxycodone	PO	mg	20
Percocet	PO	mg	20
Percocet 5/325	PO	tabs	6
Darvocet	PO	tabs	1
Propoxyphene	PO	tabs	1

(continued)

Table 16.1 (continued)

Medication	*Route*	*Units*	*Equivalent*
Oxycortin	PO	mg	20
Hydrocodone	PO	mg	30
Vicodin 5/500	PO	tabs	6
Vicodin 7.5/500	PO	tabs	4
Tramadol	PO	mg	150
Hydromorphone	IV	mg	1.5
Hydromorphone	PO	mg	7
Dilaudid	IV	mg	1.5
Dilaudid	PO	mg	7
Remifentanil	IV	mg	0.1
Sufertanil	IV	mg	0.01
Methadone	PO	mg	20
Codeine	PO	mg	200

Adapted from Ayad et al. [12]

TRAMADOL

Class: analgesic, opioid
Brand names: Ultram, Ultram ER, Rybix, Ryzolt
Manufacturers: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; Victory Pharma; Purdue Pharma L.P.

Dosage:
- Immediate release formulation: 50–100 mg po q4-6h (maximum 400 mg qd)
- Extended release formulations:
- Ultram ER
  - Patients not currently on immediate-release: 100 mg po qd; titrate up every 5 days (maximum dose 300 mg po qd)
  - Patients currently on immediate-release: calculate the 24-h immediate release total dose and start the total extended release daily dose (round dose to the next lowest 100 mg increment); titrate up (maximum dose 300 mg po qd)
- Ryzolt
  - Patients not currently on immediate-release: 100 mg po qd; titrate up Q2-3d by 100 mg/day (maximum dose 300 mg po qd)
  - Patients currently on immediate-release: calculate 24-h immediate release total dose and start total extended release daily dose (round dose to the next lowest 100 mg increment); titrate up (maximum: 300 mg po qd)

- Dosage patients >65 years old: use caution and start at a lower dose
- Immediate release formulation: >75 years old: do not exceed 300 mg/d
- Extended release formulation: >75 years old: use with great caution

Dose adjustments:

Renal Insufficiency

Immediate release: CrCl <30 mL /min: give 50–100 mg po q12 h (maximum: 200 mg/day)
Extended release: should not be used in patients with CrCl <30 mL/min

Hepatic Impairment

- Immediate release: cirrhosis: recommended dose: 50 mg po q12h
- Extended release: should not be used in patients with severe (Child-Pugh class C) hepatic dysfunction (Ryzolt should not be used in any degree of hepatic insufficiency)

Contraindications: hypersensitivity to tramadol or opioids; opioid-dependent patients; acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs; while using or within 14 days of using MAOI therapy
Ryzolt is also contraindicated in severe or acute bronchial asthma, hypercapnia, or severe respiratory depression without a closely monitored setting

Common adverse effects:
- General: malaise, sweating, fever, decreased appetite, fatigue
- Cardiovascular: flushing, postural hypotension, chest pain
- Respiratory: upper respiratory tract symptoms
- Central nervous system: dizziness, headache, somnolence, insomnia, restlessness, confusion, weakness, tremor, paresthesia, visual disturbances
- Dermatologic: pruritus
- Gastrointestinal: constipation, nausea, vomiting, dyspepsia, dry mouth, flatulence
- Psychiatric: anxiety, depression
- Musculoskeletal: joint pain, back pain

Drug interactions:
- Increased risk of CNS depression: ethanol, methotrimeprazine, valerian, St John's wort, kava kava, gotu kola
- Increased risk of serotonin syndrome: tricyclic antidepressants (TCAs), monoamine oxidase (MAO) inhibitors, triptans, venlafaxine, trazodone,

lithium, sibutramine, meperidine, dextromethorphan, St John's wort, serotonin–norepinephrine reuptake inhibitors (SNRIs), and serotonin reuptake inhibitors (SSRIs)
- Increased risk of seizures: TCAs, SSRIs, MAO inhibitors
- Increased circulating levels of tramadol: conivaptan, dasatinib, CYP3A4 inhibitors
- Decreased circulating levels/therapeutic effects of tramadol: CYP2D6 inhibitors, CYP3A4 inducers, deferasirox

Pregnancy category: C
Lactation: enters breast milk; not recommended
Relative cost: $$$ (generic available: $$)

HYDROMORPHONE

Class: analgesic, opioid
Brand names: Dilaudid-HP; Dilaudid; Exalgo
Manufacturers: Purdue Pharma LP, Mallinckrodt Pharmaceuticals

Dosage:
- Acute pain (moderate-to-severe):

Oral
Opiate-naive: 2–4 mg q4-6h as needed; elderly/debilitated patients may require lower doses; patients with prior opiate exposure may require higher doses. Usual dosage range: 2–8 mg q3-4h as needed

IV

- Opiate-naive: 0.2–0.6 mg q2-3h as needed; patients with prior opiate exposure may tolerate higher initial doses. Critically ill patients (unlabeled dose): 0.7–2 mg (based on 70 kg wt) q1-2h as needed. More frequent dosing may be required
- Note: when administered intravenously, one-fifth of the oral dose will provide similar analgesia
- Continuous infusion: Usual dosage range: 0.5–1 mg/h (based on 70 kg patient) or 7–15 µg/kg/h. Patient-controlled analgesia (PCA): Opiate-naive: Consider lower end of dosing range: Usual concentration: 0.2 mg/mL; demand dose: Usual: 0.1–0.2 mg; range: 0.05–0.4 mg; lockout interval: 5–10 min. Epidural: Bolus dose: 1–1.5 mg; Infusion concentration: 0.05–0.075 mg/mL; infusion rate: 0.04–0.4 mg/h; demand dose: 0.15 mg; lockout interval: 30 min
- IM, SC use may result in variable absorption and a lag time to peak effect.

Opiate-naive: 0.8–1 mg q4-6h as needed; patients with prior opiate exposure may require higher initial doses. Usual dosage range: 1–2 mg q4-6h as needed

- Rectal: 3 mg q4-8h as needed
- Chronic pain:

Extended release formulation (Exalgo)
Dosing range: 8–64 mg po q24h. Only for use in opioid tolerant patients; all other extended release opioids should be stopped when beginning therapy. Start Exalgo at 50% of the calculated total daily dose q24h, not increased more often than q3-4d; titrate the dose with increases of 25–50% of the current daily dose. If more than two extra doses are needed within 24 h for 2 consecutive days, consider increasing dose, but more often than q24h. When discontinuing Exalgo, gradually decrease the dose by 25–50% q2-3d. If converting from transdermal fentanyl to Exalgo, start Exalgo 18 h after removal of the patch. Every 12 mg qd of Exalgo is equal to a fentanyl dose of 25 μg/h transdermally

Dose adjustments:
- Dosing in elderly patients

Oral: 1–2 mg q4-6h. Tolerance may develop requiring higher doses

- Renal insufficiency: Exalgo. Moderate impairment: Start at a lower dose and monitor closely. Severe impairment: Consider using another analgesic
- Hepatic impairment: Exalgo. In patients with moderate and severe hepatic impairment, start at a lower dose and monitor closely. Consider using another analgesic

Contraindications: hypersensitivity to hydromorphone or any component of the formulation; acute or severe asthma, severe respiratory depression (in absence of resuscitative equipment or ventilatory support); severe CNS depression

Adverse effects:
- Cardiovascular: dysrhythmia (bradycardia/ tachycardia), extrasystoles, facial flushing, abnormal blood pressure, palpitations, peripheral edema, peripheral vasodilation, syncope
- Central nervous system: sleep disturbance (abnormal dreams, insomnia), dizziness/lightheadedness, vertigo, drowsiness, encephalopathy, CNS depression, memory impairment, confusion, cognitive disorder, increased intracranial pressure, headache, seizure, attention disturbance, abnormal coordination, agitation/panic attacks/aggression/depression, suicidal ideation, dysphoria, hallucinations, fatigue, hyper-reflexia, paresthesias, hypothermia, malaise, chills
- Dermatologic: excess sweating, pruritus, rash/urticaria
- Endocrine and metabolic: decreased amylase, dehydration, hypokalemia, erectile dysfunction/hypogonadism/decreased libido/decreased testosterone, fluid retention, elevated serum uric acid

- Gastrointestinal: constipation/diarrhea, abdominal distention, anal fissure, anorexia, bezoar (Exalgo), biliary tract spasm, diverticulosis/−itis, duodenitis, abnormal taste perception, dysphagia, burping, flatulence, abnormal gastric emptying/motility/ileus (Exalgo), gastroenteritis, hematochezia, intestinal obstruction (Exalgo), colonic perforation (Exalgo), nausea, pain with defecation, stomach cramps, vomiting, weight loss, dry mouth
- Genitourinary: urinary complaints, ureteral spasm
- Hepatic: abnormal liver function tests
- Local: pain at injection site (I.M.), wheal/flare over vein (I.V.)
- Neuromuscular and skeletal: joint pain, dyskinesia, muscle complaints, myoclonus, paresthesia, tremor, weakness
- Ocular: blurred vision, diplopia, dry eyes, miosis, nystagmus
- Otic: tinnitus
- Respiratory: apnea, bronchospasm, dyspnea, hyperventilation, hypoxia, laryngospasm, rhinorrhea
- Miscellaneous: antidiuretic effects, balance disorder, diaphoresis, difficulty ambulating, histamine release, physical and psychological dependence

Drug interactions:
- Increased risk of CNS depression: alcohol, valerian, St John's wort, kava kava, gotu kola
- Increased risk in adverse effects: alvimopan, desmopressin, MAO inhibitors
- Increased risk of hypotension/orthostasis: antipsychotics (phenothiazines), thiazide diuretics
- Decreased analgesic effect of hydromorphone: mixed agonist / antagonist opioids, ammonium chloride
- Increased analgesic effect of hydromorphone: amphetamines
- Increased risk of serotonin syndrome: serotonin reuptake inhibitors (SSRIs)
- Increased risk of bradycardia: succinylcholine
- Therapeutic effect decreased by hydromorphone: pegvisomant

Pregnancy category: C
Lactation: enters breast milk thus use is not recommended
Relative cost: $$ (generic available: $-$$)

GABAPENTIN

Class: anticonvulsant, structurally related to GABA, but it does not bind to GABA-A or GABA-B receptors, and it does not appear to affect the synthesis or uptake of GABA
Brand name: Neurontin
Manufacturers: Pfizer Inc.

Dosage:
- Chronic pain: oral: 300–1800 mg po qd given in 3 divided doses
- Postoperative pain: 300–1200 mg po 1–2 h prior to surgery

Dose adjustments for renal insufficiency:
- Hemodialysis patients: dialyzable, no adjustment
- CrCl <15 mL/min: decrease the daily dose in proportion to creatinine clearance
- CrCl is 15–29 mL/min: 200–700 mg po qd
- CrCl is 30–59 mL/min: 200–700 mg po bid
- CrCl ≥60 mL/min: 300–1200 mg po tid
- Dose reduction in elderly patients may be needed

Contraindications: hypersensitivity to gabapentin

Common adverse effects:
- General: fever, fatigue, change in appetite, weight gain
- Central nervous system: somnolence, dizziness, ataxia, weakness, headache, memory impairment, abnormal speech, abnormal coordination, hyperesthesia, tremor, abnormal gait, syncope
- Cardiovascular: palpitations
- Psychiatric: depression, anxiety
- Gastrointestinal: diarrhea/constipation, nausea/vomiting, abdominal pain, dry mouth/throat, dyspepsia, flatulence
- Renal: renal impairment, hematuria
- Hematologic: leukopenia, anemia, thrombocytopenia
- Musculoskeletal: back pain, muscle pain
- Miscellaneous: viral infections

Drug interactions:
- Increased risk of CNS depression: alcohol, methotrimeprazine, valerian, St John's wort, kava kava, gotu kola
- Decreased anticonvulsant effect: ketorolac, mefloquine
- Decreased seizure threshold: evening primrose

Pregnancy category: C
Lactation: enters breast milk thus use with caution
Relative cost: $$$ (generic available: $$)

AMITRIPTYLINE

Class: tricyclic antidepressant, (tertiary amine), increases the synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane

Brand name: Elavil
Manufacturers: AstraZeneca Pharmaceuticals, LP

Dosage:
- Depression: 50–150 mg po qd in a single dose at bedtime or in divided doses (maximum dose 300 mg po qd)
- Chronic pain (unlabeled use): Initial: 25 mg po qhs (maximum dose 100 mg/d)

Dose adjustments:
- Dosage in elderly patients: initial: 10–25 mg po at bedtime; dose should be increased in 10–25 mg increments q1wk if tolerated; dose range: 25–150 mg po qd
- Renal insufficiency: non-dialyzable
- Hepatic impairment: use with caution monitoring plasma levels and patient response

Contraindications/cautions:
- Hypersensitivity to amitriptyline or any component of the formulation
- Use of MAO inhibitors within the past 14 days
- Acute recovery phase following myocardial infarction

Adverse effects:
- Cardiovascular: orthostatic hypotension, hypertension, arrhythmia (nonspecific ECG changes), tachycardia, palpitations, AV conduction abnormalities/heart block, cardiomyopathy, myocardial infarction, stroke, syncope
- Central nervous system: anxiety, insomnia, coma, fatigue, impaired cognitive function, seizure, extrapyramidal symptoms, hallucinations, dizziness, impaired coordination, ataxia, headache, nightmares, hyperpyrexia, suicidal ideation
- Dermatologic: rash, urticaria, photosensitivity, alopecia
- Endocrine and metabolic: syndrome of inappropriate anti-diuretic hormone secretion, abnormal blood glucose
- Gastrointestinal: nausea, vomiting, anorexia, weight gain, dry mouth, stomatitis, constipation/diarrhea, ileus, abnormal taste perception, black tongue
- Genitourinary: urinary retention
- Hematologic: bone marrow depression, eosinophilia, purpura
- Neuromuscular and skeletal: paresthesias, peripheral neuropathy, numbness, tremor, weakness
- Ocular: blurred vision, mydriasis, increased ocular pressure
- Otic: tinnitus
- Miscellaneous: withdrawal reaction, diaphoresis

Drug interactions:
- Increased risk of CNS depression: alcohol, propoxyphene, valerian, St John's wort, kava kava, gotu kola
- Increased risk of neurotoxic effect: lithium
- Increased risk of serotonin syndrome: monoamine oxidase (MAO) inhibitors, serotonin reuptake inhibitors (SSRIs), sibutramine
- Increased QTc-prolonging effect: alfuzosin, artemether, chloroquine, ciprofloxacin, dronedarone, nilotinib, pimozide, quinidine, ziprasidone, thioridazine, tetrabenazine, gadobutrol, lumefantrine, quinine
- Increased vasopressor effect of: alpha−/beta-agonists (direct-acting)
- Increased risk of orthostatic hypotension: altretamine, MAO inhibitors
- Increased stimulatory and cardiovascular effect: amphetamines
- Increased anti-platelet effect: aspirin, NSAIDs (COX-2 Inhibitor)
- Increased anticoagulant effect: vitamin K antagonists (e.g., warfarin)
- Increased serum concentration: bupropion, cimetidine, cinacalcet, conivaptan, divalproex, quinidine, terbinafine, valproic acid, grapefruit juice, duloxetine, protease inhibitors, SSRIs
- Increased risk of adverse effects: beta 2-agonists, desmopressin, dexmethylphenidate, methylphenidate, metoclopramide
- Increased risk of seizures: tramadol
- Serum concentration of amitriptyline decreased by: barbiturates, carbamazepine, St John's wort, peginterferon alfa-2b
- Increases anticholinergic effects of: pramlintide
- Increases hypoglycemic effects of: sulfonylureas
- Decreased therapeutic effects/serum concentration of: iobenguane I-123, acetylcholinesterase inhibitors
- Increased therapeutic effect/serum concentration of: yohimbine
- Decreased antihypertensive effects of: alpha 2-agonists

Pregnancy category: C
Lactation: enters breast milk thus use is not recommended during lactation
Relative cost: $ (generic available: $)

DULOXETINE

Class: antidepressant, serotonin/norepinephrine reuptake inhibitor
Brand name: Cymbalta
Manufacturers: Eli Lilly and Co.
Dosage:
Chronic pain syndromes (unlabeled use): Oral: 60 mg po qd
Dose adjustments:

Renal insufficiency:
- Not recommended for use in CrCl <30 mL/min or ESRD
- In mild-moderate impairment, lower starting doses can be considered with titration up based on response and tolerability

Hepatic impairment: not recommended for use in hepatic impairment

Contraindications:
- Current use or within 2 weeks of MAO inhibitor use; uncontrolled narrow-angle glaucoma

Common adverse effects:
- General: fever, weight gain/loss
- Central nervous system: somnolence, fatigue, headache, dizziness, insomnia, weakness, blurred vision
- Cardiovascular: palpitations
- Respiratory: cough, nasopharyngitis, upper respiratory infection
- Gastrointestinal: nausea, dry mouth, constipation/diarrhea, decreased appetite, flatulence, abnormal liver enzymes
- Renal: SIADH
- Psychiatric: agitation/anxiety, abnormal sleep/dreams, hallucinations, irritability
- Dermatologic: rash, Stevens-Johnson syndrome
- Misc.: decreased libido

Drug interactions:
- Increased risk of CNS depression: alcohol, methotrimeprazine, valerian, St John's wort, SAMe, kava kava, and gotu kola
- Increased risk of serotonin syndrome: sibutramine, serotonin reuptake inhibitors (SSRIs), monoamine oxidase (MAO) inhibitors
- Increased vasopressor and tachycardic effect of: alpha−/beta-agonists
- Decreased antihypertensive effect of: alpha 2-agonists
- Increased antiplatelet effect of: aspirin, NSAIDs (nonselective)
- Increased serum concentration of drug or active metabolite of: fesoterodine, nebivolol
- Decreased metabolism of duloxetine when combined with: fluvoxamine, paroxetine
- Decreased therapeutic effect of: iobenguane I-123, codeine
- Increased risk of hepatotoxicity: alcohol
- Increased risk of orthostatic hypotension: MAO inhibitors
- Decreased metabolism of: tricyclic antidepressants, CYP2D6 substrates, tamoxifen, thioridazine
- Decreased serum concentration of CYP2D6 substrates: peginterferon alfa-2b
- Increased serum concentration of CYP2D6 substrates: darunavir
- Increased metabolism of CYP1A2 substrates: CYP1A2 inducers
- Decreased metabolism of CYP1A2 substrates: CYP1A2 inhibitors

Pregnancy category: C
Lactation: enters breast milk thus use is not recommended
Relative cost: $$$$ (generic available: $$$)

OCTREOTIDE

Class: antidiarrheal; antidote; somatostatin analog
Brand names: Sandostatin LAR; Sandostatin
Manufacturers: Novartis Pharmaceuticals Corp.
Dosage:
Chronic pancreatitis: 200 μg sc tid
Octreotide LAR (depo-octreotide) at a dose of 60 mg im q1mo for daily constant pain
Diarrhea: initial: 50–100 iv μg q8h; increase by 100 μg/dose at 48 h intervals; maximum dose: 500 μg q8h
Diarrhea associated with chemotherapy:
Low grade or uncomplicated, 100–150 μg sc q8h
Severe, 100–150 μg sc q8h; may increase to 500–1500 μg iv or sc q8h.
Complicated, 100–150 μg iv or sc tid or iv infusion: 25–50 μg/h; may increase to 500 μg 3 tid until controlled
Diarrhea associated with graft versus host disease: 500 μg iv q8h; discontinue within 24 h of resolution; maximum duration of therapy: 7 days
Esophageal variceal bleeding: 25–50 μg iv bolus followed by continuous iv infusion of 25–50 μg/h
Malignant bowel obstruction: 150–300 μg sc bid
Dose adjustments:
Dosing in elderly patients should begin at the lower end of dosing range
Renal insufficiency: non-dialysis-dependent renal impairment: no dosage adjustment required. Dialysis-dependent renal impairment: depot injection: initial dose: 10 mg im q4wk; adjust dose based on response (clearance is reduced by approximately 50%)
Hepatic impairment: liver cirrhosis: depot injection: Initial dose: 10 mg im q4wk; adjust dose based on response

Contraindications:
- Hypersensitivity to octreotide or any component of the formulation

Common adverse effects:
- Cardiovascular: bradycardia, chest pain, hypertension, arrhythmia, peripheral edema
- Central nervous system: headache, malaise, fatigue, fever, dizziness, confusion, paresthesia, memory loss, abnormal gait

- Respiratory: cough, upper respiratory symptoms
- Dermatologic: pruritus
- Endocrine and metabolic: hyperglycemia
- Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea/constipation, flatulence, cholelithiasis/biliary sludge, biliary duct dilatation, cramping, tenesmus, dyspepsia, fat malabsorption/steatorrhea, feces discoloration, decreased appetite
- Local: injection site pain
- Neuromuscular and skeletal: back pain, arthropathy, myalgia
- Respiratory: upper respiratory infection, dyspnea
- Miscellaneous: antibodies to octreotide, flu-like symptoms
- Psychiatric: anxiety, depression, hallucinations

Drug interactions:
- Increased QTc prolongation: alfuzosin, artemether, chloroquine, ciprofloxacin, dronedarone, gadobutrol, lumefantrine, nilotinib, pimozide, quinine, tetrabenazine, thioridazine, ziprasidone
- Decreased metabolism of codeine
- Decreased serum concentration of cyclosporine
- Increased hypoglycemic effect of hypoglycemic agents (i.e., sulfonylureas), alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, and stinging nettle
- Increased adverse effects of: pegvisomant

Pregnancy category: B
Lactation: excretion in breast milk unknown thus, use with caution
Relative cost: $$$$$

CELIAC/SPLANCHNIC NERVE BLOCK

Indication:
Patients with abdominal pain secondary to a history of chronic pancreatitis who are non-responders or incomplete responders to alternative medical pain therapies. Splanchnic nerve block is generally reserved for those patients who fail to experience symptom alleviation with celiac nerve block.
Procedure:
Techniques including radiofrequency ablation or neurolytic blocks with either catheter introduced alcohol or phenol are used for analgesia by anterior CT approach or fluoroscopic transdiscal approach.

Contraindications:
- Local infection
- Coagulopathy
- Sepsis
- Tumors resulting in anatomical distortion
- Abdominal and/or thoracic aneurysms

Potential complications:
- Hypotension
- Diarrhea
- Pneumothorax (higher risk in splanchnic nerve block)
- Chylothorax
- Nerve injuries including paraplegia

Relative cost: $$$

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17 Pancreatic Insufficiency

Bashar Sharma and John Birk

Contents

(See Table 17.1 for pancreatic enzyme preparations and contents)

PANCRELIPASE

Class: pancreatic enzymes
Brand names: Creon, Pancreaze, Pertzye, Viokace, Zenpep
Manufacturers: Abbott Inc., AbbVie, Chiesi USA Inc., Nestlé, Vivus Inc.
Pharmacologic category: porcine-derived digestive enzymes with varying amounts of lipase, amylase and protease

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Table 17.1 Pancreatic enzyme preparations and contents in USP units

Enteric coated preparations (Brand names)	*Lipase*	*Protease*	*Amylase*
Pertzye	4000	14,375	15,215
Pertzye	8000	28,750	30,250
Pertzye	16,000	57,500	60,500
Pertzye	24,000	86,250	90,750
Zenpep	3000	10,000	14,000
Zenpep	5000	17,000	24,000
Zenpep	10,000	32,000	42,000
Zenpep	15,000	47,000	63,000
Zenpep	20,000	63,000	84,000
Zenpep	25,000	79,000	105,000
Zenpep	40,000	126,000	168,000
Zenpep	40,000	136,000	218,000
Creon	3000	9500	15,000
Creon	6000	19,000	30,000
Creon	12,000	38,000	60,000
Creon	24,000	76,000	120,000
Creon	36,000	114,000	180,000
Pancreaze	2600	6200	10,850
Pancreaze	4200	14,200	24,600
Pancreaze	10,500	35,500	61,500
Pancreaze	16,800	56,800	98,400
Pancreaze	21,000	54,700	83,900
Non-enteric coated preparations			
Viokace	10,440	39,150	39,150
Viokace	20,880	78,300	78,300

Adapted from: pdr.net/drug-summary

Dosage:

- Initial oral dose: lipase 500 units/kg po per meal
- Dosage range: lipase 500–2500 units/kg po per meal
- Maximum dose: lipase 10,000 units/kg po qd or lipase 4000 units/g of fat per day
- Adjust the dose based on body weight, clinical symptoms, and stool fat content
  - Allow several days before adjusting the dose
  - The total daily dose reflects approximately 3 meals per day and 2–3 snacks per day
  - Half the mealtime dose should be given with a snack

- Doses of lipase greater than 2500 units/kg/meal or greater than 10,000 lipase units/kg/day or greater than 4000 lipase units/g fat ingested/day) should be used cautiously and only with documentation of 72 h fecal fat measurement
- Doses of lipase greater than 6000 units/kg/meal are associated with colonic stricture
- The enzyme supplement should be taken with meals or snacks and swallowed whole immediately without crushing or chewing with a generous amount of liquid, otherwise mucosal irritation can occur. If needed, capsules can be opened and added to a small amount (about 10 ml) of an acidic food (pH ≤4) such as applesauce, which should be at room temperature and swallowed right after mixing followed by water or juice to ensure complete swallowing

Indications:
- Exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, or pancreatectomy

Contraindications/precautions:
- Hypersensitivity to pork protein or to the products
- Acute pancreatitis
- History of meconium ileus, distal intestinal obstruction, prior intestinal surgery, or inflammatory bowel syndrome: increases risk of fibrosing colonopathy and strictures

Adverse effects:
- Neurologic: dizziness
- Gastrointestinal: abdominal pain, dyspepsia, diarrhea, flatulence, choledocholithiasis, early satiety, vomiting, constipation, nausea, intestinal obstruction, fibrosing colonopathy, duodenitis, gastritis, abnormal liver function tests
- Other: lymphadenopathy, infection (streptococcal and viral), otalgia, nasal congestion, peripheral edema, cough, epistaxis, blurred vision
- Musculoskeletal: neck pain, muscle pain/spasm
- Dermatologic: skin rashes
- Hematologic/oncologic: anemia, carcinoma recurrence (rare), neutropenia
- Renal: renal cysts
- Endocrine/metabolic: hyper-/hypoglycemia, hyperuricemia
- Immunologic: allergic reaction/anaphylaxis (rare)

Drug interactions:
- There are no known significant interactions
- H_2 blockers, proton pump inhibitors, and antacids may lower the effectiveness of the enzymes

- May reduce the pharmacologic effect of alpha-glucosidase inhibitors and should not be administered concurrently
- May decrease oral iron absorption

Pregnancy: use during pregnancy only when clearly needed. Animal reproduction studies have not been conducted and adequate studies in humans are not available
Lactation: excretion in breast milk is unknown; use with caution
Relative cost: $$$$$$

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18 Gut Malabsorption and Enzyme Deficiencies

Leon D. Averbukh and George Y. Wu

Contents

ABBREVIATIONS (CHAPTER SPECIFIC, FOR COMPLETE LIST SEE APPENDIX B)

SBS	Short bowel syndrome
SI	Small intestine
SIBO	Small intestine bacterial overgrowth

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LACTASE DEFICIENCY

Lactase

Class: enzyme supplement
Brand names: Lactaid Original (3000 FCC units lactase), Lactaid Fast Act (9000 FCC units lactase), Lactase (5000 FCC units lactase)
Manufacturers: McNeil Nutritionals, LLC; Watson Pharmaceuticals; Schwarz Pharma

Dosage:
- Tablets: 1–3 tablets po with meals
- Liquid: 5–15 drops po per quart of milk
- Capsules: 1–2 capsules po with quart of milk or meal; adjust dose based on response

Adverse effects:
No significant adverse effects or drug interactions
Lactation: unknown excretion into breast milk; use caution
Pregnancy category: unknown
Relative cost: $ (generic available: $)

VITAMIN B_{12} DEFICIENCY/PERNICIOUS ANEMIA

Vitamin B12 (Cyanocobalamin)

Class: water-soluble vitamin
Brand names: CaloMist, Ener-B, Nascobal, Twelve Resin-K, Cobex, Crystamine, Vibisone, Eligen B12
Manufacturers: Fleming and Company; Strativa Pharmaceuticals, Eligen, Sandoz, Cytex
Dosage and indications:

Vitamin B12 Deficiency

Intranasal
- Nascobal: 500 μg in one nostril q1wk. This spray should be administered at least an hour before or after ingestion of hot foods or liquids
- CaloMist: initial dose of 25 μg per nostril, for a total daily dose of 50 μg. This dose may be increased up to 100 μg (25 μg in each nostril, bid for those with inadequate response to initial dosing

Oral
- 1000–2000 µg qd for 1–2 weeks followed by maintenance dosing of 1000 µg
- Note: in cases of mild B_{12} deficiency, supplementation with reduced doses of 500–1000 µg daily may be considered

Parenteral
- 100 µg qd for 6–7 days followed by administration of the dose on alternating days for 7 days. Subsequent administration stretched to 100 µg every 3–4 days for 2–3 weeks. Once normalization of B_{12} is achieved, patients are maintained on monthly 100 µg injections.

Pernicious Anemia

- *Oral*: 1000–2000 µg qd for life
- *Parenteral:* 100 µg qd for 6–7 days followed by administration of the dose on alternating days for 7 days. Subsequent administration stretched to 100 µg every 3–4 days for 2–3 weeks. Once normalization of B_{12} is achieved, patients are maintained on monthly 100 µg injections
- For patients in remission without involvement of the nervous system, dosing regimens include: intranasal (Nascobal): 500 µg in one nostril q1wk
- *Transdermal*: available over the counter, but not currently clinically validated.

Contraindications:
- Hypersensitivity to drug, class, or cobalt; hereditary optic atrophy; caution if uremia, myelosuppression, or folic acid deficiency

Adverse effects:
- Cardiovascular: congestive heart failure, peripheral vascular thrombosis
- Neurologic: headache, pain, anxiety, dizziness, hypoesthesia, incoordination
- Dermatologic: urticaria, itching, exanthema
- Gastrointestinal: nausea, vomiting, diarrhea, dyspepsia, glossitis
- Hematologic: polycythemia vera
- Neuromuscular and MSK: weakness, abnormal ambulation, arthritis, back pain, myalgia, paresthesia
- Respiratory: dyspnea, pulmonary edema, rhinitis
- Miscellaneous: anaphylaxis (IV), infection

Drug interactions:

- Decreased cyanocobalamin therapeutic effect due to decreased absorption in the GI tract with concomitant use of aminosalicylic acid, colchicine, chloramphenicol, metformin, proton pump inhibitors, and vitamin C

Pregnancy category: C
Lactation: enters breast milk; safe
Relative cost: im/oral $, intranasal $$$$$ $

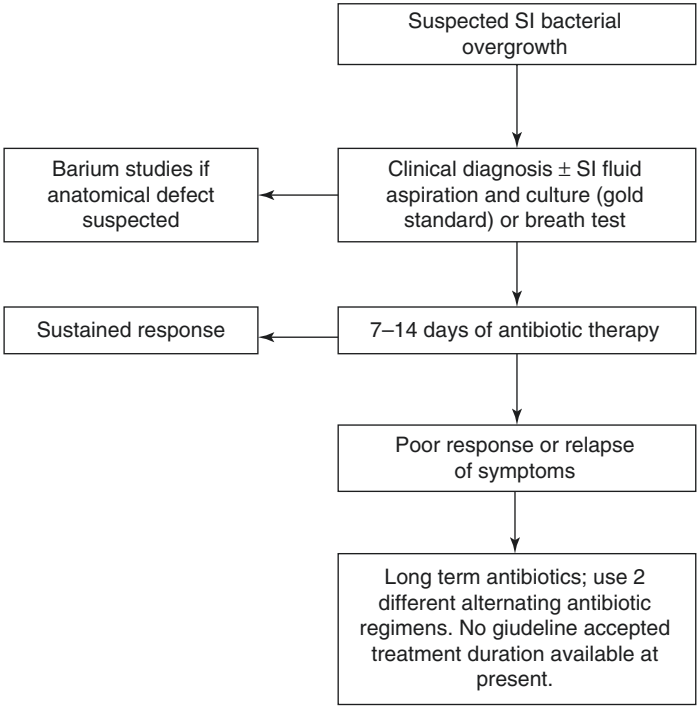

Fig. 18.1 Treatment of small bowel bacterial overgrowth. (Adapted from the ACG Clinical Guideline on small intestinal bacterial overgrowth (Pimentel et al. [4]))

SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

Non-absorbable Antibiotics

(See Fig. 18.1 for an algorithm for the treatment of small bowel bacterial overgrowth)
Rifaximin
(See Chap. 11)

Systemic Antibiotics

Amoxicillin Clavulanate
Class: penicillin antibiotic
Brand name: Augmentin
Manufacturer: GlaxoSmithKline

Dosage:
- 500–875 mg po bid or 250–500 mg po tid, usually for 1–2 weeks rotating with another antibiotic for 2 weeks

Contraindications/cautions:
- Hypersensitivity to drug or class
- Hepatic dysfunction or cholestatic jaundice with amoxicillin-clavulanic acid
- Caution if impaired liver function

Adverse reactions:
- Gastrointestinal: cholestatic jaundice, hepatotoxicity, diarrhea, pseudomembranous colitis
- Central nervous: seizures
- Renal: interstitial nephritis
- Hematological: anemia, leucopenia, thrombocytopenia
- Immunological: hypersensitivity reaction, angioedema
- Dermatological: rash, urticaria, contact dermatitis, erythema multiforme

Drug interactions:
- Avoid concomitant live oral typhoid vaccine due to inadequate vaccine response
- May increase methotrexate levels

Pregnancy category: B
Lactation: probably safe
Relative cost: $$-$$$ (generic available: $-$$)

Neomycin

(See Chap. 11)
Tetracycline/Doxycycline
(See Chap. 7)
Trimethoprim/Sulfamethoxazole
(See Chap. 6)
Ciprofloxacin/ Norfloxacin
(See Chap. 6)
Metronidazole:

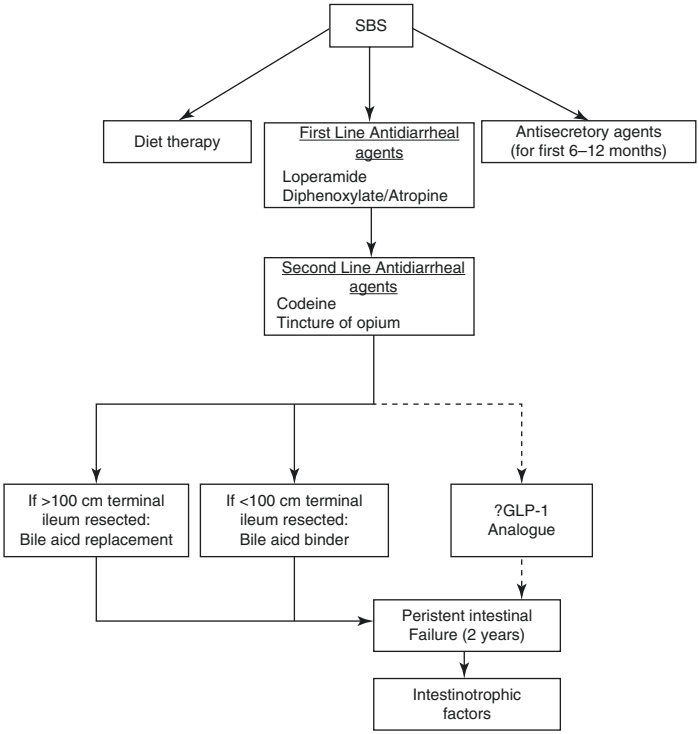

Fig. 18.2 Treatment of short bowel syndrome. (Adapted from Parrish and DiBaise [5])

(See Chap. 6)
Probiotics/Prebiotics/Synbiotics
No significant data exist at this time as to the efficacy of probiotics, prebiotics, or synbiotics in the treatment of SIBO

SHORT BOWEL SYNDROME (SBS)

(See Fig. 18.2 for an algorithm for the treatment of short bowel syndrome)

Antisecretory Agents

Proton Pump Inhibitors
(See Chap. 1)
Octreotide
(See Chap. 2)
Histamine-2 Receptor Antagonists
(See Chap. 1)
Clonidine
Class: alpha-2-agonist
Brand name: Catapres, Kapvay
Manufacturer: Boehringer Ingelheim, Concordia Pharmaceuticals
Dosage:
Starting dose 0.05–0.1 mg bid
Typical range 0.1 to 0.4 mg/d
Indications:

Contraindications:
- Hypersensitivity to alpha-2-agonists
- Bradycardia
- Hypotension
- Severe coronary artery disease
- Previous myocardial infarction
- Use with caution in patient with a history of depression and syncope

Adverse effects:
- Cardiovascular: hypotension (rebound hypertension with rapid drug withdrawal), sexual dysfunction, atrioventricular block, bradycardia, dizziness, congestive heart failure
- Neurologic: headache, fatigue
- Gastrointestinal: constipation, abdominal pain, diarrhea, nausea
- Hematologic: thrombocytopenia, hypersensitivity, angioedema
- Psychiatric: emotional instability, depression

Drug interactions:
- Increased drowsiness when combined with barbiturates, phenothiazines, benzodiazepines, and opioids
- Increased blood pressure when combined with tricyclic antidepressant medications
- Bradycardia when combined with digoxin, beta blockers, calcium channel blockers (diltiazem and verapamil)
- Hypotension when combined with angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, and diuretics
- Dizziness when combined with antipsychotics such as clozapine, aripiprazole, and quetiapine

Pregnancy category: C
Lactation: enters breastmilk, advised against use
Relative cost: brand name $$, generic $

Antimotility Agents

Loperamide
(See Chap. 4)
Diphenoxylate/ Atropine
(See Chap. 4)

Codeine

Class: opioid
Brand name: none, brand names only for combination medications
Manufacturer: Qualitest pharmaceuticals, Teva pharmaceuticals, Lannett Company
Dosage: 15–60 mg qid (tablet or liquid) for SBS
Contraindications:
Hypersensitivity to codeine, respiratory depression, paralytic ileus, intestinal obstruction, asthma, children less than 12 years old, monoamine oxidase use

Adverse effects:
- Cardiovascular: bradycardia, hypotension
- Neurologic: sedation, tremor, weakness
- Dermatologic: pruritis
- Gastrointestinal: constipation, nausea, vomiting, pancreatitis, abdominal cramps

- Hematologic: hypersensitivity
- Psychiatric: chemical dependence
- Pulmonary: bronchospasm
- Renal: urinary retention

Drug interactions:
- Increased risk of CNS and respiratory depression as well as hypotension when codeine is combined with other opioids, antihistamines, antipsychotics, antianxiety medications, or other CNS depressants including antiemetics, sedatives, hypnotics, and general anesthetics
- Increased risk of urinary retention and/or severe constipation when combined with anticholinergic medications
- Increased effect of either antidepressant or codeine when combined with MAO inhibitors or tricyclic antidepressants. Avoid codeine in patients who have taken MAO inhibitors within the past 14 days
- Additive effects with alcohol, advise alcohol avoidance

Pregnancy category: C
Lactation: enters breast milk, advise against use
Relative cost: generic $$-$$$

Tincture of Opium

Class: opiate
Brand name: Opium deodorized (laudanum)
Manufacturer: Edenbridge Pharmaceuticals
Dosage: 0.3–2.0 mL up to qid

Contraindications:
- Acute diarrhea caused by poisoning unless toxic material is first removed from the GI tract
- Acute diarrhea caused by organisms that penetrate intestinal mucosa
- Caution when using in patients with asthma, prostatic hyperplasia, opiate dependence, and hepatic disease

Adverse effects:
- Cardiovascular: bradycardia, hypotension
- Neurologic: sedation, tremor, weakness
- Dermatologic: pruritis
- Gastrointestinal: constipation, nausea, vomiting, abdominal cramps
- Hematologic: hypersensitivity
- Psychiatric: chemical dependence
- Pulmonary: bronchospasm
- Renal: urinary retention

Drug interactions:
- Increased risk of CNS and respiratory depression as well as hypotension when codeine is combined with other opioids, antihistamines, antipsychotics, antianxiety medications, or other CNS depressants including antiemetics, sedatives, hypnotics, and general anesthetics
- Increased risk of urinary retention and/or severe constipation when combined with anticholinergic medications
- Additive effects with alcohol use, advise alcohol avoidance

Pregnancy category: B (D for high doses or long term)
Lactation: enters breast milk, advised against use
Relative cost: $$$$$ $

Bile Acid Binders

Cholestyramine
(See Chap. 13)

Intestinotrophic Factors

Somatropin
Class: recombinant human growth hormone
Brand name: Zorbtive, Genotropin, Omnitrope, Humatrope, Norditropin, Saizen, Serostim
Manufacturer: Pfizer, Sandoz, Eli Lilly, Novo Nordisk, Merck, Serono,
Dosage: 0.1 mg/kg/day sc qd for 4 weeks; maximum dose: 8 mg/day

Contraindications:
- Multiple accidental traumas
- Active malignancy
- Diabetic retinopathy
- Hypersensitivity to somatropin

Adverse effects:
- Endocrine: hypoglycemia/hyperglycemia and impaired glucose tolerance, acromegaly (with long term overdose), hypoadrenalism, pancreatitis, hypothyroidism
- MSK: carpal tunnel, arthralgia, fluid retention, lipoatrophy at injection site
- Neurologic: intracranial Hypertension
- Oncologic: possible malignant nevi transformation

Drug interactions:

- Oral estrogens and diabetic medications including insulin may reduce somatotropin efficacy
- Somatotropin upregulates cytochrome P450 which may increase clearance of compounds affected by cytochrome P450. Data are limited at this time

Pregnancy: B
Lactation: not studied
Relative cost: $$$$$ $$$$$
Teduglutide
Class: GLP-2 analog
Brand name: Gattex
Manufacturer: Takeda Pharmaceuticals
Dosage: 0.05 mg/kg sc qd
Dose adjustments:

Renal insufficiency:
- CrCl <50 ml/min: reduce dose by 50%

Contraindications: none
Monitor patient on oral drugs requiring titration or with a narrow therapeutic window

Adverse reactions:
- Gastrointestinal: abdominal pain, nausea, abdominal distension, pancreatitis, intestinal obstruction, small bowel neoplasia, cholecystitis, cholangitis, cholelithiasis
- Infectious: increased risk of upper respiratory infections
- MSK: injection site reactions
- Neurologic: headaches

Drug interactions:
Monitor patient on oral drugs requiring titration or with a narrow therapeutic window
Pregnancy category: B
Lactation: breast feeding not recommended
Relative cost: $$$$$ $$$$$
Exenatide
Class: GLP-1 analog
Brand name: Byetta
Manufacturer: Amylin Pharmaceuticals
This medication is currently under investigation for use in SBS and is not currently FDA approved for this indication
Antibiotic therapy
(See section on “SIBO” above)

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Appendix A: Pregnancy and Lactation Labeling Rule

On June 30, 2015, the FDA placed into effect drug labeling changes for information pertaining to pregnancy, lactation, and reproductive safety. This change is referred to as the Pregnancy and Lactation Labeling Rule (PLLR). Medications approved after June 30, 2015, have pregnancy, lactation, and reproductive safety reported according to the PLLR and will be reported as such for the purposes of this book.

Pregnancy information is listed in section 8 of the FDA product information sheets. Following the PLLR, section 8.1 describes safety considerations pertaining to pregnancy, including labor and delivery. Section 8.2 describes safety considerations pertaining to lactation and breastfeeding. Section 8.3 describes safety considerations pertaining to reproductive risk for both males and females, such as infertility risk and contraception recommendations.

Prior to enactment of PLLR, pregnancy safety was denoted by lettered categories- A, B, C, D, and X. In this book, drugs approved prior to June 30, 2015, will have pregnancy information denoted by the letter category system.

The letter categories are defined as follows:

A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.

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C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Appendix B: Abbreviations

ADV	Adefovir
ALT	Alanine aminotransferase
Alt	Alternative
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AV	Atrioventricular
AZA	Azathioprine
bid	Twice a day
Bpm	Beats per minute
CJD	Creutzfeldt-Jakob disease
cont	Continue
COPD	Chronic obstruction pulmonary disorder
CrCl	Creatinine clearance
dL	Deciliter
DRESS	Drug reaction with eosinophilia and systemic symptoms
ETV	Entecavir
g	Gram
h	Hour
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HDL	High-density lipoproteins
HE	Hepatic encephalopathy
HIV	Human immunodeficiency virus
HR	Heart rate
im	Intramuscular
INR	International normalized ratio
iv	Intravenous
LAM	Lamivudine

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MAOI	Monoamine oxidase inhibitor
min	Minute
mo	Month
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NSAID	Nonsteroidal anti-inflammatory drug
OCA	Obeticholic acid
P-gp	p-glycoprotein
po	Oral
pr	Per rectum
qam	Every morning
qd	Daily
qpm	Every evening
q1wk	Every week
Rx	Treat
SBP	Spontaneous bacterial peritonitis
sc	Subcutaneously
SIADH	Syndrome of inappropriate antidiuretic hormone release
SSRI	Selective serotonin reuptake inhibitor
TAF	Tenofovir alafenamide
TCA	Tricyclic antidepressant
TDF	Tenofovir disoproxil fumarate
tid	Three times a day
TTP	Thrombotic thrombocytopenic purpura
qid	Four times a day
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
wk	Week
y	Year

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