Selected Infections of the GI Tract and Liver

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LEARNING OBJECTIVES

1. Design a treatment plan for a patient with fungal or viral esophageal infection.
2. Construct an optimal treatment plan for managing *Clostridium difficile*–associated diarrhea, taking into account disease severity and recurrence.
3. Design a plan for treating proctocolitis or proctitis secondary to sexually transmitted organisms.
4. Recommend an empiric antibiotic regimen for the most common infections of the biliary system according to severity.
5. Select a strategy for preventing GI infections secondary to surgery or procedures.
6. Design and monitor pharmacologic therapy for treating various intestinal and liver parasites.

ABBREVIATIONS IN THIS CHAPTER

AE	Alveolar echinococcosis
CDI	*Clostridium difficile* infection
CE	Cystic echinococcosis
CMV	Cytomegalovirus
ERCP	Endoscopic retrograde cholangiopancreatography
FMT	Fecal microbiota transplantation
HSV	Herpes simplex virus
IDSA	Infectious Diseases Society of America
SSI	Surgical site infection
TACE	Transarterial chemoembolization

Table of other common abbreviations.

INTRODUCTION

The digestive system or GI tract is a diverse set of organs including the oropharynx, esophagus, stomach, small and large intestines, rectum, pancreas, and hepatobiliary system. These tissues are exposed to the environment, including microbes constituting the host microbiome and pathogens. The microbiome and the immune system of the GI tract protect against pathogenic organisms, but the GI tract is nevertheless vulnerable to infection by viruses, bacteria, fungi, and parasites ranging from single-celled amoebas to multicellular helminths.

This chapter focuses on selected infections of the GI tract and liver. A complete discussion of infections common in the developing world is outside the scope of this chapter; however, some of these infections will be mentioned for the benefit of those practicing abroad or among immigrant populations.

OROPHARYNGEAL AND ESOPHAGEAL INFECTIONS

In the patient with immunocompromise, infectious esophagitis is most commonly associated with *Candida* spp., herpes simplex virus (HSV), and cytomegalovirus (CMV); it is less commonly associated with *Cryptosporidium*, *Mycobacterium avium* complex, histoplasmosis, leishmaniasis, and syphilis.

Fungal Infections

Considered potential normal flora of the GI tract, *Candida* spp. are opportunistic pathogens in susceptible hosts such as those with immunocompromise. *Candida albicans* is most commonly isolated, followed by *C. glabrata* and *C. krusei*. Risk factors for oropharyngeal and esophageal candidiasis include dentures in older adults, recent antibiotics, radiation and/or chemotherapy of head and neck, immune deficiency, and inhaled steroids. Although the availability of effective antiretroviral therapy has led to a decreased incidence of candidiasis, oropharyngeal and esophageal candidiasis in patients with HIV infection remain most common when $CD4^+$ T-lymphocyte counts are less than 200 cells/mm^3.

Treatment options for mucosal candidiasis are shown in Table 1-1. For mild oropharyngeal candidiasis (asymptomatic or mild symptoms), treatment with topical agents is considered as effective as oral systemic therapy. Topical agents also reduce drug-drug interactions, systemic adverse reactions, and the potential for antifungal resistance. However, their unpleasant taste and need for frequent dosing, as with clotrimazole and nystatin, and lack of efficacy in esophageal disease are significant disadvantages. When appropriate oral mucosal contact cannot be ensured with topical agents, or when systemic therapy is warranted, oral fluconazole is the drug of choice for oropharyngeal disease because of its equal or improved effectiveness, convenience, and better tolerability. Pregnant women should always be given topical therapy, if possible.

Esophageal disease always requires systemic therapy, and all major U.S. and European guidelines recommend fluconazole as the preferred agent (Lortholary 2012). Oropharyngeal candidiasis with dysphagia or odynophagia usually predicts esophageal candidiasis, and a therapeutic and diagnostic trial with systemic fluconazole is recommended as a cost-effective alternative to endoscopy. If signs and symptoms of disease persist beyond 7–14 days of appropriate antifungal therapy, however, confirmatory culture and endoscopy are necessary to rule out causes of refractory disease other than azole resistance.

Alternatives to fluconazole, although less well tolerated, include itraconazole, posaconazole, voriconazole, echinocandins, and amphotericin B. Itraconazole oral solution is recommended for oropharyngeal and esophageal fluconazole-refractory disease. Because of variable absorption, itraconazole oral capsules are considered less effective than oral solution. Posaconazole oral suspension is also efficacious for oropharyngeal and esophageal disease unresponsive to fluconazole. Posaconazole is also better tolerated and has fewer drug interactions than itraconazole and voriconazole. Posaconazole delayed-release tablets have more reliable absorption, less stringent food requirements, and once-daily dosing compared to oral suspension. Although there is poor evidence for the use of delayed-release tablets for the treatment of esophageal candidiasis, expert opinion and U.S. guidelines suggest this extended-release formulation, given these advantages, could be considered for esophageal disease.

Caspofungin, micafungin, and anidulafungin are associated with higher esophageal disease relapse rates than is fluconazole. Furthermore, there is potential for acquired resistance to echinocandins during therapy with these drugs (Perlin 2015). Intravenous amphotericin B deoxycholate or lipid formulations are effective for esophageal candidiasis, but nephrotoxicity limits use for this indication.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic knowledge of GI tract anatomy
- Basic microbiology of common viruses, bacteria, fungi, and parasites
- Pharmacology of antimicrobials used for GI tract infections, including dosing, mechanism of action, drug interactions, and adverse effects
- Published guidelines on infections of the GI tract

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources are available for readers desiring additional background information on this topic.

- Infectious Diseases Society of America (IDSA), CDC, and NIH. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. 2015.
- IDSA. Clinical Practice Guideline for the Management of Candidiasis. 2016.
- IDSA and Society for Healthcare Epidemiology of America (SHEA). Clinical Practice Guideline for *Clostridium difficile* Infection in Adults. 2010.
- American College of Gastroenterology. Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections. 2013.
- IDSA and Surgical Infection Society (SIS). Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children. 2010.
- IDSA, American Society of Health-System Pharmacists (ASHP), SIS, and SHEA. Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery. 2013.
- CDC. Sexually Transmitted Diseases Treatment Guidelines. 2015.

Most U.S. and European guidelines do not recommend routine primary prophylaxis against *Candida* mucosal disease. A randomized trial showed that suppressive therapy with fluconazole three times per week resulted in fewer episodes of oropharyngeal and esophageal candidiasis and other fungal invasive infections than with episodic treatment. These strategies resulted in similar rates of fluconazole-resistant isolates (Goldman 2005). Because of high cost, low mortality of the disease, high efficacy of episodic treatment, and potential for drug interactions and development of antifungal resistance, chronic suppressive therapy with fluconazole is only recommended for recurrent disease or severe recurrences of oropharyngeal or esophageal disease.

Viral Esophagitis

In contrast to the endoscopic appearance of fungal esophagitis (friable plaques that can involve the entire esophagus), viral esophagitis appears as erythematous ulcers of the esophageal mucosa. Viruses associated with esophageal disease include CMV, HSV, varicella-zoster virus, and primary HIV infection.

Cytomegalovirus disease is usually associated with significant host immunosuppression, and for patients with HIV infection, initiating antiretroviral therapy for immune restoration is paramount to its management. After colitis, esophagitis is the second most common CMV-related disease in the GI tract. Updated guidelines on CMV treatment from the Infectious Diseases Society of America (IDSA), NIH, and CDC were published in 2015. Recommended initial CMV esophagitis treatment is intravenous ganciclovir 5 mg/kg every 12 hours, transitioning to valganciclovir 900 mg by mouth every 12 hours when the patient can tolerate oral treatment and there are no concerns for impaired absorption. Total recommended treatment duration is 21–42 days or until resolution of signs and symptoms. For mild disease in patients with HIV infection who can promptly be initiated on antiretrovirals, either withholding CMV therapy or initiating oral valganciclovir is warranted if the patient can

Table 1-1. Therapy for Oropharyngeal and Esophageal Candidiasis

	First-line Treatment	Alternative	Chronic, Suppressive Therapy	Comments
Oropharyngeal candidiasis	Fluconazole 100–200 mg PO daily	Clotrimazole 10 mg troches five times daily Nystatin 100,000 U/mL suspension 4–6 mL four times daily Nystatin 200,000 U pastilles 1–2 pastilles four times daily Miconazole 50 mg buccal tablet daily Itraconazole 200 mg oral solution PO daily Posaconazole 400 mg oral suspension PO BID for 3 days, then 400 mg daily	Only if recurrent or severe recurrence: • Fluconazole 100–200 mg PO three times a week or • Fluconazole 100 mg PO daily	Topical agents recommended only for mild disease Treatment length usually 7–14 days
Esophageal candidiasis	Fluconazole 200–400 mg PO or IV daily Any echinocandin	Itraconazole 200 mg oral solution PO daily Posaconazole 400 mg oral suspension PO BID or 100 mg delayed-release tablets 300 mg po daily Voriconazole 200 mg PO or IV BID Amphotericin B deoxycholate 0.6 mg/kg IV daily Amphotericin B lipid formulation 3–4 mg/kg IV daily	Only if recurrent or severe recurrence: • Fluconazole 100–200 mg PO daily	Treatment length usually 14–21 days Higher rates of esophageal candidiasis relapse associated with echinocandins than with fluconazole

BID = twice daily; IV = intravenously; PO = orally.

Information from: Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1-50.

take oral drugs. Colony-stimulating growth factors can be considered for neutropenic patients to augment immune restoration. In patients who cannot tolerate ganciclovir or with ganciclovir resistance, intravenous foscarnet 60 mg/kg every 8 hours or 90 mg/kg every 12 hours is an alternative. Because ganciclovir and valganciclovir can cause anemia, neutropenia, thrombocytopenia, nausea, diarrhea, and kidney toxicity, close monitoring is required. Monitoring should include CBCs, serum electrolytes, and renal function twice per week. Chronic maintenance therapy for GI disease is typically recommended only in the presence of concomitant retinitis; however, it can be considered in recurrent disease.

CLOSTRIDIUM DIFFICILE

C. difficile is the most common cause of infectious diarrhea in hospitalized patients in the United States and Europe. *C. difficile* sporulation allows survival in the environment for long periods. Disease pathogenesis involves ingestion of spores into a disrupted gut microbiota, germination in the small intestine, and growth of vegetative cells in the colon. *C. difficile* is not an invasive organism, but its toxins contribute to mucosal epithelial damage, pseudomembranous colitis, and subsequent systemic disease that may result in sepsis and death.

Microbiota disruption by systemic antimicrobial exposure is the leading risk factor for *C. difficile* infection (CDI). The risk is greater with increasing number of agents and duration of exposure. Risk is greater with clindamycin, fluoroquinolones, and second- or higher-generation cephalosporins than with penicillins, macrolides, β-lactamase inhibitors, carbapenems, vancomycin, and metronidazole; the lowest risk is seen with aminoglycosides, tetracyclines, trimethoprim, sulfonamides, and rifampin. Other risk factors for CDI include patient age; prior hospitalization; duration of hospitalization; residence in a long-term care facility; severity of concurrent, underlying illness; use of gastric acid–reducing agents, particularly proton pump inhibitors and histamine-2 blockers; and abdominal surgery or manipulation of the GI tract, including tube feeding. Antibiotic exposure after an initial episode of *C. difficile* disease significantly increases recurrence risk, particularly in older adults and those who are severely ill.

Treatment recommendations by IDSA and the Society for Healthcare Epidemiology of America (SHEA) and by the American College of Gastroenterology (ACG) classify CDI according to severity of disease and whether it is a first or recurrent episode. Figure 1-1 summarizes IDSA/SHEA and ACG recommendations for the treatment of CDI, as well as possible alternative treatments.

Metronidazole and vancomycin have been the mainstays of *C. difficile* treatment for more than 3 decades because of early studies showing similar efficacy, tolerability, and relapse rates. However, recent data analyses have shown that metronidazole is inferior to oral vancomycin for the treatment of CDI. A 2014 prospective randomized, placebo-controlled study comparing a toxin-binding polymer, tolevamer, with metronidazole and vancomycin showed statistically significant decreased clinical cure rates for metronidazole (72.7%) than vancomycin (81.1%) (Johnson 2014). In addition, increased metronidazole treatment failures and resistant isolates have been reported in the literature. Metronidazole is associated with adverse effects such as GI complaints, disulfiram-like reaction with concomitant alcohol, and peripheral neuropathy with extended use. Because of increased reported resistance and cumulative neurotoxicity, metronidazole is not recommended beyond the first *C. difficile* recurrence. According to the 2014 study cited previously, it should likely only be used as an alternative to either oral vancomycin or fidaxomicin for patients with mild disease (Johnson 2014).

Oral metronidazole is also inferior to vancomycin for severe CDI. When oral metronidazole 250 mg four times daily was compared with oral vancomycin 125 mg four times daily, cure rates were similar for mild disease (98% vancomycin vs. 90% metronidazole) and were superior for vancomycin over metronidazole in severe disease (97% vs. 76%) (Zar 2007). The oral vancomycin dose should be 125 mg four times daily for mild, moderate, or severe disease. In a 1989 study that evaluated response rates in patients with probable or proven *C. difficile* colitis, vancomycin 125 mg four times daily was as effective as a dose of 500 mg four times daily (Fekety 1989). A more recent retrospective study showed that oral vancomycin dosages of 500 mg/day did not differ from dosages higher than 500 mg/day with respect to clinical cures when adjusted for baseline characteristics (Lam 2013). Although IDSA/SHEA guidelines recommend oral vancomycin doses of 500 mg four times daily for severe, complicated CDI, data supporting doses higher than 125 mg four times daily for patients without severe-complicated CDI are lacking.

Fidaxomicin was approved for treatment of *C. difficile*–associated diarrhea in 2011 on the strength of two phase III trials (Cornely 2012; Louie 2011). These trials compared oral fidaxomicin 200 mg twice daily with oral vancomycin 125 mg four times daily and found noninferiority of cure rates (87.7%–88.2% for fidaxomicin vs. 85.8%–86.8% for vancomycin) and recurrence rates. Fidaxomicin protects gut microbiota compared with vancomycin and metronidazole, and no significant resistance has been reported. Because of high cost, fidaxomicin is not recommended first line for mild disease, and its use in severe, complicated disease lacks support in the literature. However, a retrospective study evaluated readmission rates and length of stay from recurrences with CDI in patients who received initial treatment with either oral fidaxomicin or oral vancomycin (Gallagher 2015). Fewer patients who received fidaxomicin were readmitted with CDI within 90 days compared with those who received oral vancomycin (20.4% vs. 41.3%; p=0.027). The cost of readmissions from recurrent CDI was $484,800 for the vancomycin group and $196,200 for the fidaxomicin group, with lower estimated per-patient losses for the institution in the fidaxomicin group than in the

vancomycin group ($3286 vs. $6333). Smaller studies suggest the utility of fidaxomicin "chasers" or tapering doses after initial treatment with vancomycin in recurrent disease (Soriano 2014; Johnson 2009; Johnson 2007).

Rifaximin had symptom resolution rates similar to oral vancomycin in a randomized trial of 20 patients with CDI (Boero 1990). When rifaximin was studied as eradication therapy for 14 days after standard treatment with metronidazole, 16 of 22 patients who completed treatment were stool negative for *C. difficile* in an open-label study (Basu 2010). Compared with placebo, rifaximin also had lower rates of recurrent diarrhea as a 20-day "chaser" after standard therapy with vancomycin or metronidazole in a small randomized study (Garey 2011). Similar to other rifamycins, development of resistance is common with rifaximin and limits its use.

Fecal microbiota transplantation (FMT) is the fastest, most effective strategy for treating patients with several recurrences of CDI (Cammarota 2015; Kelly 2014; Youngster 2014; van Nood 2013). An open-label, randomized trial of patients with recurrent infection compared 20 subjects who received a

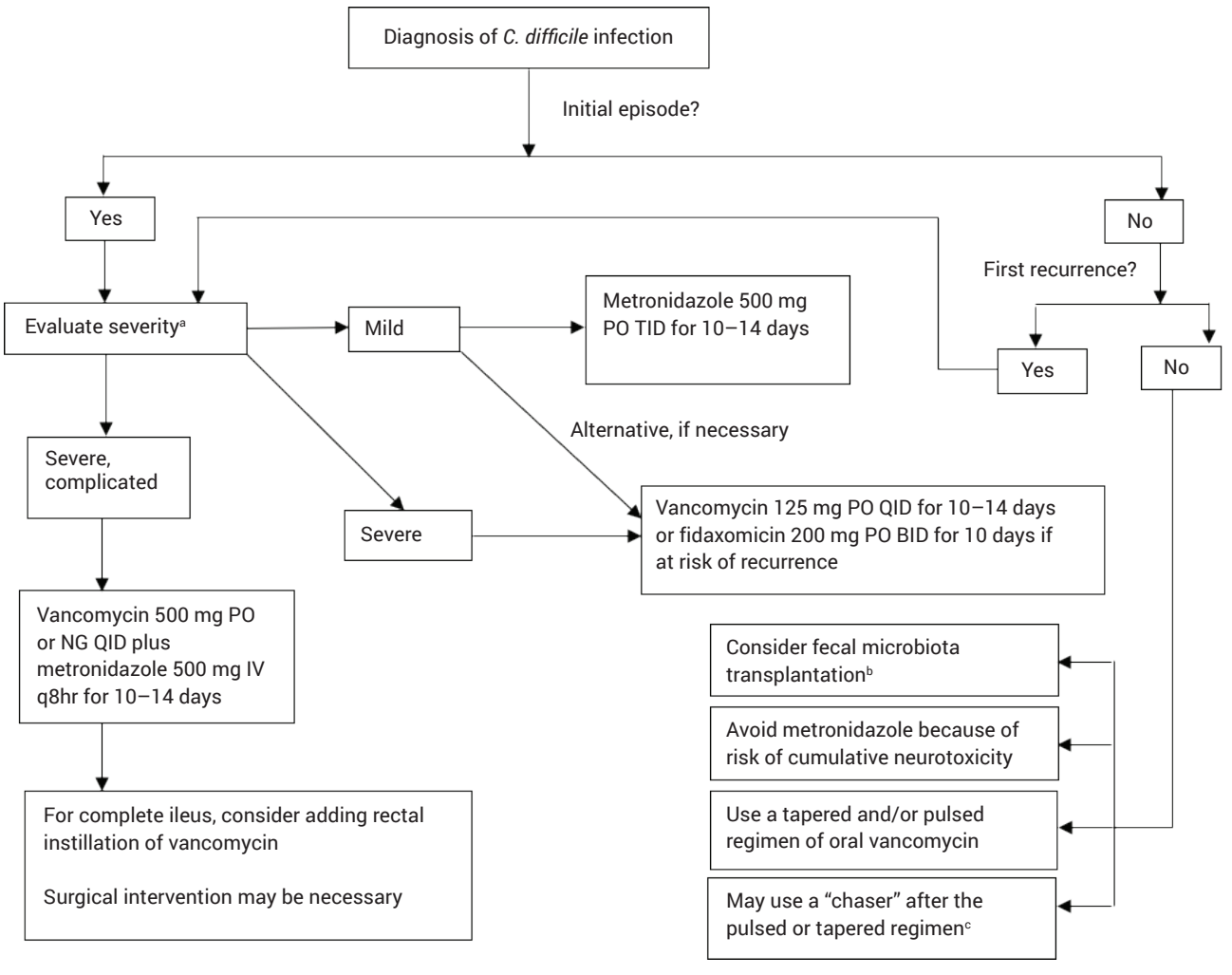

Figure 1-1. Recommended treatment and potential alternatives for *C. difficile* infection.

[a]Severity classification based on IDSA/SHEA definition: severe = WBC ≥ 15 x 10^3 cells/mm^3 or SCr ≥ 1.5 times the pre-illness value. Severe complicated = hypotension, shock, ileus, or megacolon.

[b]Further antibiotics should be avoided after infusion of donor stool if this option is chosen.

[c]Chasers include rifaximin 400 mg PO BID for 14 days or fidaxomicin 200 mg PO BID for 10 days.

BID = twice daily; IV = intravenously; NG = nasogastrically; PO = orally; q = every; QID = four times daily; TID = three times daily.

Information from: Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society of Healthcare Epidemiology of American (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010;31:431-55; and Surawicz, CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment and prevention of *Clostridium difficile* infections. Am J Gastroenterol 2013;108:478-98.

3-day vancomycin regimen followed by one or more fecal microbiota colonoscopy infusions with 19 subjects who received oral vancomycin treatment for 10 days followed by a 3-week pulsed vancomycin regimen (Cammarota 2015). In the FMT group, 90% had resolution of *C. difficile*–associated diarrhea compared with 26% of the vancomycin-only group ($p<0.0001$). This confirmed a previous randomized, placebo-controlled study showing the superiority of FMT to standard of care (van Nood 2013). Guidance on stool donor selection, preparation, and administration by the NIH and the American Gastroenterological Association Fecal Microbiota Transplantation Workgroup has been published (Bakken 2011).

PROCTOCOLITIS AND PROCTITIS CAUSED BY SEXUALLY TRANSMITTED DISEASE

Infectious proctitis, proctocolitis, and enteritis can be associated with sexual transmission of organisms through direct or indirect contact with rectal mucosal surface. The most common sexually transmitted organisms associated with proctitis include *Neisseria gonorrhea*, *Chlamydia trachomatis*, *Treponema pallidum*, and HSV. Causative pathogens for proctocolitis include *Campylobacter* spp., *Shigella* spp., *Entamoeba histolytica*, and lymphogranuloma venereum strains of *C. trachomatis* (serotypes L1, L2, and L3). Symptoms include anorectal pain, discharge, and tenesmus. Additional symptoms of proctocolitis include diarrhea, abdominal cramps, and colonic inflammation.

C. trachomatis is the most commonly reported sexually transmitted infectious disease in the United States, followed by *N. gonorrhea*. Antimicrobial resistance of *N. gonorrhea* is of particular concern, including resistance to fluoroquinolones and cefixime. This concern, as well as the theoretical benefit of using two antimicrobials with different mechanisms of action to increase efficacy and hinder resistance, has prompted the CDC since 2010 to recommend dual therapy with intramuscular ceftriaxone plus either azithromycin or doxycycline, even in the absence of a positive chlamydial test. Although *N. gonorrhea* resistance to ceftriaxone remains less than 1% in the United States, the incidence is increasing, and the CDC has declared drug-resistant *N. gonorrhea* an urgent public health threat.

Current CDC guidelines (2015) recommend presumptive treatment of sexually transmitted disease in people who report receptive anal intercourse and have a presentation consistent with acute proctitis, if no anoscopy or Gram stain is available or when awaiting results from laboratory tests or Gram stain obtained during anoscopy. In addition, men who have sex with men who also present with bloody discharge or perianal or mucosal ulcers and who either have a positive nucleic acid amplification test for *C. trachomatis* or are HIV positive should be offered a 3-week course of doxycycline for presumptive lymphogranuloma venereum infection; if painful perianal or mucosal ulcers are present, presumptive treatment of HSV should be offered as well. Table 1-2 summarizes these recommendations.

Patient Care Scenario

A 72-year-old man (height 70 inches, weight 70 kg) is admitted for treatment of cellulitis of the left thigh. His medical history includes hypertension and diabetes; his home drugs include lisinopril 20 mg daily, hydrochlorothiazide 25 mg daily, and glipizide XL 10 mg daily. The patient has a history of two episodes of mild *C. difficile* disease (9 months ago and 5 months ago) that were treated to resolution with metronidazole. During the present admission, he received ceftriaxone for 2 days with improvement but no resolution of cellulitis. Hospital discharge with oral antibiotics was planned yesterday, but he reported 10 stools per day, and *C. difficile* toxin was positive. He has no other concerns and is hemodynamically stable. His SCr is at his recent baseline of 1.5 mg/dL and WBC is 4 x 10^3 cells/mm^3. The patient is unwilling to consider FMT. What is the best treatment regimen for *C. difficile* in this patient?

ANSWER

This is the second recurrence of *C. difficile* disease. Although FMT is the fastest, most effective therapy for recurrent *C. difficile* disease, the patient would need to consent to instillation of suitable donor stool. Because of concerns for resistance and cumulative neurotoxicity, further metronidazole would be avoided after the first recurrence. Guidelines recommend a pulsed or tapered course of oral vancomycin, such as 125 mg four times daily for 10–14 days, followed by 125 mg twice daily for 7 days, followed by 125 mg daily for 7 days, followed by 125 mg every 2–3 days for 2–8 weeks. Many clinicians would use full-dose oral vancomycin therapy throughout the course of antibiotics for cellulitis. Consideration should be given to switching from a third-generation cephalosporin to a class of antibiotic with less risk of *C. difficile*, such as a penicillin, if possible.

1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society of Healthcare Epidemiology of American (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010;31:431-55.
2. Surawicz, CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment and prevention of *Clostridium difficile* infections. Am J Gastroenterol 2013;108:478-98.

The CDC recommends retesting 3 months after treatment of chlamydia or gonorrhea. To reduce transmission or reinfection, patients and their partners should abstain from sexual contact until both have completed a 7-day treatment and symptoms have resolved. In addition, partners of anyone treated for gonorrhea, chlamydia, or lymphogranuloma venereum should be evaluated, tested, and treated presumptively if sexual contact occurred within 60 days of symptom onset.

BILIARY INFECTIONS

Guidelines from IDSA for management of complicated intra-abdominal infections were published in 2010, including a brief section on biliary infection. These guidelines were based in part on the previous seminal 2007 Tokyo guidelines for acute cholangitis and cholecystitis. The Tokyo guidelines were updated in 2013 with improved clarity of case severity definitions that provide a clear algorithm to select empiric antibiotic coverage (Gomi 2013).

Acute Cholangitis

Acute cholangitis is acute inflammation and infection of the bile duct occurring secondary to biliary obstruction. Gallstones are the most common etiology, followed by malignancy or benign stenosis. Patients often present with right upper quadrant abdominal pain, fever, and jaundice. Diagnosis requires the presence of fever or laboratory evidence of systemic inflammation (increased WBC or CRP); evidence of cholestasis; and biliary dilatation or obstruction on imaging.

Acute cholangitis is classified by severity from grade I (mild) to grade III (severe). Grade III acute cholangitis is diagnosed when dysfunction of at least one organ system occurs, defined by the following criteria: requirement for vasopressor; altered mental status; Pao_2/fraction of inspired oxygen ratio less than 300 mm Hg; oliguria or SCr greater than 2 mg/dL; INR greater than 1.5 because of hepatic dysfunction; or platelet count less than 100,000/mm^3 suggestive of disseminated intravascular coagulation. Grade II (moderate) acute cholangitis is a non-severe case in which two or more of the following factors are present: abnormal WBC (greater than 12 x 10^3 cells/mm^3 or less than 4 x 10^3 cells/mm^3); temperature of 102.2°F (39°C) or higher; age 75 years or older; total bilirubin of 5 mg/dL or higher; or hypoalbuminemia (less than 0.7 times normal). Grade I acute cholangitis is diagnosed when the case does not meet criteria for grade II or III.

Antimicrobial therapy is required for acute cholangitis regardless of severity. Blood cultures should be obtained before antibiotic initiation. Moderate to severe cases require biliary drainage, as do mild cases not responding to antibiotic therapy. When bile is drained, it should be cultured.

The Tokyo 2013 guideline recommendations for both community-acquired and health care–associated acute

Table 1-2. Recommended Treatment of Proctitis and Proctocolitis

Syndrome	Common Organisms Involved	Treatment
Proctitis (rectal pain, discharge, tenesmus)	*Neisseria gonorrhea* *Chlamydia trachomatis* *Treponema pallidum* HSV	Presumptive with ceftriaxone 250 mg IM one time plus doxycycline 100 mg PO BID for 7 days
Proctitis with bloody discharge, perianal ulcers, or mucosal ulcers in MSM with positive rectal *Chlamydia* or positive for HIV	Above organisms, plus LGV strains of *C. trachomatis*	Presumptive with ceftriaxone 250 mg IM one time plus doxycycline 100 mg PO BID for 21 days If painful, perianal ulcers present or mucosal ulcers on anoscopy, include HSV treatment
Proctocolitis (proctitis symptoms with cramps or diarrhea)	*Campylobacter* sp. *Shigella* sp. *Entamoeba histolytica* LGV strains of *C. trachomatis* CMV in immunocompromised	Same presumptive treatment as for proctitis; treat according to organism when results available

BID = twice daily; CMV = cytomegalovirus; HSV = herpes simplex virus; IM = intramuscularly; LGV = lymphogranuloma venereum; MSM = men who have sex with men; PO = orally.

Information from: Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015; 64:1-137.

cholangitis are listed in Table 1-3. The IDSA defines health care–associated cases as occurring in patients more than 48 hours after a hospital admission; or in patients from the community with invasive devices, a history of methicillin-resistant *Staphylococcus aureus*, or a recent history (past 12 months) of surgery, hospitalization, dialysis, or long-term care facility residence.

Empiric antibiotic therapy for biliary infection targets gram-negative enteric bacteria because *Escherichia coli* and *Klebsiella* spp. are the most common causes. For severe community-acquired cases and all health care–associated cases, *Pseudomonas aeruginosa* is a concern. When *Pseudomonas* is not a concern, IDSA recommends against using an antipseudomonal antibiotic if another choice can be made.

Local antibiotic susceptibility patterns must guide empiric antibiotic choice, as well as recent exposure of the patient to antibiotics and the patient's history of colonization with drug-resistant organisms. The IDSA recommends against using an antibiotic empirically when more than 10%–20% of relevant isolates tested are resistant. For example, in some regions, fluoroquinolones may no longer be a reasonable choice for empiric therapy. The IDSA no longer recommends ampicillin/sulbactam and clindamycin for abdominal infections in North America. If susceptibilities become available from blood or bile cultures, antibiotic regimens should be de-escalated to minimize toxicities and the risk of promoting microbial resistance.

Both IDSA and the Tokyo 2013 guidelines recommend covering obligate anaerobes only when a biliary-enteric anastomosis is present. In this case, metronidazole would be added if the principal antibiotic lacks anaerobic coverage. Empiric vancomycin for *Enterococcus* spp. is recommended for all health care–associated biliary infection as well as for grade III community-acquired biliary infection; vancomycin should also be considered for patients with liver transplantation or other immunocompromise. This coverage may be broadened to linezolid or daptomycin in patients with a history or high risk of vancomycin-resistant *Enterococcus*. Therapy duration should be 4–7 days after biliary drainage and removal of obstruction. In patients with gram-positive cocci bacteremia, a 2-week course of therapy should be considered.

Acute Calculous Cholecystitis

Acute cholecystitis is inflammation of the gallbladder, usually caused by gallstone obstruction of the cystic duct (acute calculous cholecystitis). Patients often present with right upper quadrant or epigastric pain and nausea and vomiting. Diagnosis requires the presence of fever or laboratory evidence of systemic inflammation (elevated WBC or CRP); right upper quadrant pain or pain on palpation of the gallbladder; and imaging findings characteristic of acute cholecystitis such as gallbladder wall thickening or pericholecystic fluid.

Acute cholecystitis is classified by severity similarly to acute cholangitis. Grade III (severe) acute cholecystitis is associated with onset of dysfunction of at least one organ system, using the same criteria defined earlier for grade III acute cholangitis. Grade II (moderate) acute cholecystitis is a non-severe case in which one or more of the following factors is present: elevated WBC (greater than 18 x 10^3 cells/mm^3); palpable and tender right upper quadrant mass; duration of symptoms for more than 72 hours; or marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis). Grade I (mild) acute cholecystitis is diagnosed when the case does not meet criteria for grade II or III.

Acute calculous cholecystitis can be complicated by secondary infections, usually caused by Enterobacteriaceae or other enteric gram-negative bacteria. The Tokyo guidelines recommend antibiotics for acute calculous cholecystitis meeting the diagnostic criteria given earlier, regardless of severity, followed in most cases by laparoscopic cholecystectomy. An additional dose of antibiotic should be given within 60 minutes of the surgical incision.

In grade I cases, surgery is typically performed within 72 hours. In other cases, surgery may be delayed until the patient's condition improves, often with a need for gallbladder drainage in the interim. For grade II or III severity, blood cultures should be obtained before antibiotics are initiated, and bile should be cultured.

For antibiotic recommendations for acute calculous cholecystitis, see Table 1-3. The considerations that guide antibiotic choice are similar to those for acute cholangitis and are based on severity, association of the case with a health care history, and presence of biliary-enteric anastomosis. Rare cases of acute cholecystitis unrelated to gallstone obstruction (acute acalculous cholecystitis) require similar empiric antibiotic coverage, but they should always be treated for obligate anaerobes.

Patients with grade I acute cholecystitis should have antibiotics discontinued within 24 hours after cholecystectomy, according to the Tokyo guidelines. If perforation occurs, or if emphysematous changes or necrosis of the gallbladder are found during surgery, antibiotics are extended for 4–7 days after surgery. Duration of antibiotic therapy is 4–7 days after cholecystectomy in patients with grade II or III acute cholecystitis. In contrast, IDSA recommends discontinuing antibiotics within 24 hours after cholecystectomy in all patients unless infection outside the gallbladder wall is evident. If gram-positive cocci bacteremia is present, a 2-week course of therapy should be considered.

PROPHYLAXIS AGAINST INFECTIONS OF THE GI TRACT

Manipulation of the GI tract can result in postprocedural infections because of the high burden of microbes present. Antibiotic prophylaxis can reduce these infections, but it also disrupts the microbiome, leading to complications such as

CDI and antibiotic resistance. Careful balance of these considerations is necessary when selecting antibiotic prophylaxis, and pharmacists are often involved in these decisions.

Abdominal Surgery

General Considerations

When the lumen of the GI tract is entered during surgery, antibiotic prophylaxis is recommended to prevent surgical site infection (SSI). The American Society of Health-System Pharmacists/IDSA/Surgical Infection Society/SHEA guidelines for antimicrobial prophylaxis in surgery have been updated to reflect several important concepts, including the timing of the preoperative dose, redosing during surgery, and duration of prophylaxis.

The preoperative dose should be given such that adequate tissue concentration is achieved at the time of surgery. Adequate antibiotic concentration in tissue is achieved when antibiotics are given even 7–20 minutes before incision, and some studies suggest that a preoperative dose within 30 minutes of incision is ideal to prevent SSI. The IDSA guideline recommends initiating antibiotic infusion within 60 minutes before the first surgical incision. This reflects a change from the prior recommendation to administer at induction of anesthesia. Antibiotics with longer infusion times (e.g., vancomycin, fluoroquinolones) should be initiated within 120 minutes before incision.

Patients with existing infections, those with perforated viscera, and those with traumatic wounds that are no longer fresh should receive full treatment courses of antibiotics instead of prophylaxis. Treatment should begin before surgery, and an antibiotic dose sufficient for SSI prophylaxis should be given within 60 minutes before incision.

Antibiotics with rapid clearance, including many of the β-lactam antibiotics, require redosing during surgery if the procedure takes longer than twice the antibiotic half-life. For example, cefazolin should be redosed every 4 hours during surgery, whereas vancomycin requires no redosing. The updated guideline offers a table of suggested redosing frequencies.

For abdominal surgery, antibiotic prophylaxis should continue no longer than 24 hours after the surgery; in fact, most data suggest that no postoperative doses are required.

A recent retrospective study of appendectomy for nonperforated appendicitis shows the potential benefits of minimizing antibiotic prophylaxis. Of the 728 cases reviewed, 334 patients received postoperative antibiotics and 394 did not. The authors found no baseline difference between the two groups for preoperative morbidity, preoperative antibiotics, operating room time, blood loss, or appendiceal diameter. There was no statistically significant difference in the incidence of postoperative SSI. Statistically significant findings included a 5-fold higher incidence of postoperative diarrhea, a 5-fold higher incidence of UTI, and a doubling in length of

Table 1-3. Empiric Antibiotic Regimens for Acute Cholangitis and Acute Calculous Cholecystitis

	Community Acquired			Health Care Associated
Antibiotic	Grade I	Grade II	Grade III[c]	Any severity[c]
Cefazolin[a,b]	*			
Cefoxitin[b]	*			
Ceftriaxone[a] or cefotaxime[a]	*	*		
Ertapenem	*	*		
Ciprofloxacin[a,b] or levofloxacin[a,b]	*	*		
Moxifloxacin[b]	*	*		
Cefepime[a] or ceftazidime[a]		*	*	*
Piperacillin/tazobactam		*	*	*
Imipenem/cilastatin			*	*
Meropenem or doripenem			*	*
Aztreonam[a]			*	*

[a]Coverage for obligate anaerobes using metronidazole should be added if biliary-enteric anastomosis is present because principal antibiotic lacks sufficient anaerobic coverage.

[b]Local antimicrobial susceptibility patterns should be considered for empiric use.

[c]Add vancomycin for community-acquired grade III and health care–associated infections.

Adapted from: Gomi H, Solomkin JS, Takada T, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci 2013;20:60-70.

stay in the group that received any postoperative antibiotic compared with the group that did not. No CDI was found in the group that did not receive postoperative antibiotics, whereas 1.5% of patients who did receive postoperative antibiotics developed CDI (p=0.02) (Coakley 2011).

In elective, laparoscopic cholecystectomy in patients considered at low risk of SSI, the recommendation is for no antibiotic prophylaxis. High-risk factors include emergency procedure, acute cholecystitis, diabetes, anticipated procedure duration of more than 120 minutes, risk of intraoperative gallbladder rupture, age older than 70 years, risk of conversion from laparoscopic to open procedure, American Society of Anesthesiologists physical status classification of 3 or higher, episode of biliary colic within 30 days prior, reintervention for noninfectious complications of a biliary operation done in the prior 30 days, anticipated bile spillage, jaundice, pregnancy, nonfunctioning gallbladder, and immunosuppression.

Antibiotic Selection

Antibiotic choice for prophylaxis is governed by surgical site and the flora implicated in potential SSI at that site. As with all surgery, skin flora are often implicated. If the GI tract is entered, SSI is commonly caused by enteric organisms, especially the gram-negative organisms *E. coli* and *Klebsiella* spp. Appendectomy, surgery of obstructed small intestine, and colorectal surgery are associated with SSI caused by obligate anaerobes such as *Bacteroides fragilis*.

Cefazolin is therefore recommended as prophylaxis for gastroduodenal surgery, percutaneous endoscopic gastrostomy tube placement, open and laparoscopic biliary tract surgery, and surgery of the small intestine when no obstruction is present. Cefazolin plus metronidazole is recommended for surgery of the small intestine when obstruction is present, for appendectomy, and for colorectal surgery, with cefoxitin or cefotetan as alternatives. For colorectal surgery, adding an oral antibiotic such as neomycin to mechanical bowel preparation on the day before surgery further reduced SSI in some studies.

Prophylaxis for patients with true allergy to β-lactam antibiotics must cover the most common organisms. Clindamycin or vancomycin, each paired with an aminoglycoside, aztreonam, or a fluoroquinolone, is the recommended regimen for gastroduodenal and biliary surgery. Clindamycin or metronidazole, each paired with an aminoglycoside or a fluoroquinolone, is the recommended regimen for colorectal surgery and appendectomy.

Locoregional Therapy for Liver Tumors

Locoregional therapies for hepatocellular carcinoma and hepatic metastases induce tissue ischemia and necrosis and carry a risk of liver abscess. These procedures include transarterial embolization with or without chemoembolization (TACE, TAE), radiofrequency ablation, and chemical ablation. Transarterial chemoembolization is the preferred therapy for treatment of intermediate-stage nonresectable hepatocellular carcinoma in patients whose liver function remains sufficient. The incidence of liver abscess after TACE has been reported as 2%, but patients with intact biliary systems have abscess rates of less than 1% after TACE.

Two similar-sized randomized controlled trials showed a survival benefit for TACE compared with supportive care of hepatocellular carcinoma. One trial used antibiotic prophylaxis before and for 3 days after TACE, whereas the other used no antibiotics. Both trials produced similar reductions in mortality of about 50%, and only one liver abscess was reported (Llovet 2002; Lo 2002). Few studies have assessed whether prophylactic antibiotics are beneficial in preventing abscess formation after locoregional therapy, and none has shown a benefit of prophylactic antibiotics in a general population. Current guidelines suggest no routine antibiotic prophylaxis before or after locoregional therapy (Bruix 2011).

Most abscess formation after locoregional therapy for liver tumors occurs in patients who have undergone prior biliary procedures such as surgery, stenting, or sphincterotomy. Two studies showed a failure of first-generation cephalosporins with or without metronidazole to prevent abscess formation in these patients (Geschwind 2002; Kim 2001). Guidelines do not specifically address these high-risk patients. For these patients, it is reasonable to follow the procedure documented in two small studies in which bowel decontamination coupled with broad-spectrum antibiotics resulted in case series with fewer abscesses than historical rates (Patel 2006; Geschwind 2002). The regimens used were a neomycin-based bowel preparation three times on the day before TACE; plus either piperacillin/tazobactam given for 3 days, starting about 24 hours before TACE, or levofloxacin plus metronidazole, started 2 days before TACE and continued for 2 weeks after TACE. It is unclear whether the preprocedure antibiotic bowel preparation is necessary, and the optimal duration of systemic antibiotics after the procedure is unknown.

Postembolization syndrome including fever and pain is expected after locoregional therapy for liver tumors as a result of tissue necrosis; therefore, a fever lasting 48 hours postprocedure is not reason for concern. Persistent fever, especially in the setting of increased WBC, should prompt investigation for infection, including liver abscess.

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) is a common procedure to visualize and intervene on biliary and pancreatic ducts. Infectious complications after ERCP have been reported to occur in 0.5%–3% of cases. Most infections occur after procedures in which biliary drainage was incomplete.

Past recommendations for antibiotic prophylaxis for ERCP were based in part on an assumption that prophylaxis against

infective endocarditis was needed for ERCP; this is no longer accepted in the latest British and North American GI endoscopy guidelines after a change in guidance from the American Heart Association (Khashab 2015; Allison 2009).

The American Society for Gastrointestinal Endoscopy now states that routine antibiotic prophylaxis is not necessary for patients without biliary obstruction or for whom complete biliary drainage during the ERCP procedure is expected (Khashab 2015). Patients for whom incomplete biliary drainage is anticipated should receive a dose of antibiotic before the ERCP procedure. Other patients for whom pre-ERCP antibiotic prophylaxis is recommended include patients who are post-liver transplantation, patients with an absolute neutrophil count less than 500 cells/mm^3, patients with advanced hematologic malignancy, and patients with pancreatic cyst or pseudocyst. The antibiotic should cover enteric gram-negative bacteria. Fluoroquinolones such as oral ciprofloxacin 750 mg are recommended (Allison 2009).

One quality improvement project limited prophylactic antibiotic use for ERCP to patients with predicted incomplete drainage or immunosuppression. The authors showed a reduction in pre-ERCP antibiotic use from 95% to 26% of all ERCP procedures. The infection rate was 0.48% before the change and 0.23% after (Cotton 2008). A 2010 Cochrane review found reduced risk of bacteremia and cholangitis when prophylactic antibiotics were used before ERCP, but no reduction in mortality (Brand 2010). When the analysis was limited to patients with complete biliary drainage, there was no significant benefit of antibiotic prophylaxis for reducing cholangitis. Another meta-analysis showed no benefit of prophylactic antibiotics for preventing post-ERCP cholangitis or septicemia overall (Bai 2009).

Any patient for whom complete biliary drainage is not achieved should receive a course of post-ERCP antibiotics. The therapy duration is not well defined, but usually it is until definitive therapy for the obstruction is accomplished. Patients with suspected cholangitis at the time of ERCP should be established on an empiric antibiotic course before the ERCP procedure; an additional single dose just before ERCP is not recommended.

Quality Improvement: Infection Secondary to Contaminated Duodenoscopes

More than 500,000 ERCP procedures are performed in the United States each year. Increased surveillance for multidrug-resistant pathogens including carbapenem-resistant Enterobacteriaceae has shown outbreaks of drug-resistant infections linked to ERCP. The FDA received medical device reports regarding 135 patients with possible microbial transmission by duodenoscopes during 2013 and 2014. Several outbreaks have been reported in the literature as well. Infection sites have included bile, blood, abdominal fluid, pancreatic fluid, urine, lung, and wounds.

Duodenoscopes used for ERCP are complex instruments; they have small moving parts and channels and are difficult to decontaminate. One hospital with a carbapenem-resistant Enterobacteriaceae outbreak linked to ERCP has undertaken a program of culturing all duodenoscopes after standard disinfection, followed by quarantine. During a 1-year period, 1.9% of the duodenoscope cultures were positive for pathogens, requiring further decontamination of the endoscopes before reuse (Ross 2015).

The FDA continues to recommend ERCP with thorough cleaning and disinfection of duodenoscopes according to manufacturer instructions between uses. Duodenoscopes suspected of transmitting infection should be decontaminated and verified to be free of pathogens. An FDA advisory panel convened in 2015 to consider whether further measures such as sterilization or instrument redesign should be required, but no final decision was reached. Patients should report fever, chills, chest pain, severe abdominal pain, trouble swallowing or breathing, nausea and vomiting, or black or tarry stools after ERCP. Antibiotic therapy, when post-ERCP infections are diagnosed, should be guided by culture results, when possible. Infections possibly related to duodenoscopes should be reported to the manufacturer and to the FDA.

SELECTED PARASITIC INFECTION OF THE INTESTINE AND LIVER

Invasive Amoebiasis

E. histolytica is the second leading cause of death from parasitic disease worldwide. This protozoan is common in the developing world, including South and Southeast Asia, the Middle East, and Central and South America. Travelers to and immigrants from these areas may become colonized with or infected with *E. histolytica*. In the United States, most cases are reported in the Southwest states among Hispanics.

Invasion of the intestinal lining by *E. histolytica* typically causes dysentery. The most common extraintestinal manifestation is liver abscess, which develops in about 1% of patients with clinically active disease, is 10 times more common in men than in women, and may occur months to years after exposure. Liver abscess typically presents with fever, right upper quadrant abdominal pain, hepatomegaly, and leukocytosis. Imaging reveals a single abscess or coalescing multiple abscesses, often in the right lobe. Stool antigen is often negative, whereas serum antigen and serum anti-amoebic antibodies are often positive. Untreated, amoebic liver abscess is fatal.

Short courses of metronidazole or tinidazole are sufficient for invasive disease such as amoebic colitis and liver abscess (Haque 2003) (Table 1-4). Abscess drainage is rarely necessary but may be necessitated by bacterial coinfection. After completing therapy for invasive disease, the patient should receive the luminal agent paromomycin to eliminate intestinal colonization. Close contacts of the infected person may

be carriers. Asymptomatic carriers should be treated with paromomycin because colonization can progress to invasive disease, and carriers shed infectious cysts.

Intestinal Worms

North America

In the United States, the most common parasitic nematodes are the pinworm (*Enterobius vermicularis*) and the hookworm (*Necator americanus*). Pinworms live in the cecum, and females lay thousands of eggs on the host's perineum at night, causing itching. The eggs are spread by the fecal-oral route, and children are significant hosts. Pinworms are largely innocuous, but restlessness at night in children may be a sign of infection. Hookworm infections are less common but more serious. Transmission is through skin contact with soil contaminated by infected feces. Consumption of blood by hookworms attached to the small intestine may result in anemia, pica, and wasting. Definitive diagnosis of intestinal worms usually requires microscopic observation of eggs in the stool. Eosinophilia also suggests helminth infection.

Treatment of pinworm and hookworm consists of albendazole or pyrantel pamoate (see Table 1-4). Regimens using mebendazole are commonly cited in the literature, but this drug was withdrawn from commercial production in the United States in 2011 and is now only available from compounding pharmacies.

Intestinal Parasites in Refugee Populations

Thousands of other parasitic helminths have been identified, and hundreds are associated with disease throughout the developing world. A recent review limited to fishborne flukes identified almost 60 species that infect humans worldwide. The global burden of GI helminth infection has been estimated at more than 1 billion people. Some governments have instituted mass drug administration programs against common parasites, but for many organisms, the rate of host reinfection is high.

Table 1-4. Oral Drug Therapy for Parasitic Infections

Antiparasitic Agent	Parasite Treated	Adult Dosing	Duration	Additional Notes
Metronidazole	*Entamoeba histolytica* invasive infection	500–750 mg TID	7–10 days	A luminal agent should also be used, after therapy for invasive disease
Tinidazole		2 g/day	3 days (3–5 days for abscess)	
Paromomycin	*E. histolytica* luminal colonization	25–35 mg/kg/day divided TID	7 days	For asymptomatic carriers or after therapy for invasive disease
Albendazole	*Enterobius vermicularis* (pinworm)	400 mg one time	May repeat in 2 weeks if persistent	Take with a fatty meal
	Necator americanus (hookworm)	400 mg one time		Confirm clearance after 2 weeks Use supplemental iron
	Echinococcus spp.	15 mg/kg/day divided BID (maximum 800 mg/day)	Often long term	Monthly treatment interruptions are no longer recommended
	Presumptive treatment of refugees for soil helminths	400 mg one time		See CDC guidelines for which refugees to treat, including advice on pregnancy and children
Pyrantel pamoate	*E. vermicularis* (pinworm)	11 mg/kg one time (maximum 1 g/dose)	May repeat in 2 weeks if persistent	
	N. americanus (hookworm)	11 mg/kg once daily (maximum 1 g/dose)	3 days	Confirm clearance after 2 weeks Use supplemental iron
Praziquantel	*Clonorchis sinensis*, *Opisthorchis* spp.	75 mg/kg/day divided TID	2 days	Take with liquids during meals
Triclabendazole	*Fasciola hepatica*	10 mg/kg one time	May repeat in 12 hours for severe infection	Take with food Available from CDC as an Investigational New Drug

BID = twice daily; TID = three times daily.

Given the high burden of intestinal parasites worldwide, the CDC recommends presumptive treatment of refugees. The program was started in 1999 with a recommendation for single-dose albendazole for refugees from the developing world (see Table 1-4). In the past 10 years, recommendations for praziquantel (for *Schistosoma*) and ivermectin (for *Strongyloides*) have been added for certain groups. Since the start of the CDC program, the prevalence of intestinal parasite infection of refugees arriving in the United States has dropped considerably. *Ascaris*, hookworm, and *Strongyloides* each have a prevalence below 1%. For any nematode infection, the prevalence has fallen from more than 20% to less than 5% (Swanson 2012).

The recommended combination therapy is updated periodically and varies greatly by country of origin; therefore, those encountering refugees should consult the guidelines for overseas management of departing refugees and domestic management of arriving refugees directly on the CDC website. Care must be taken in small children and pregnant women. For a detailed discussion of risk-benefit of antihelminthic drugs in pregnancy and childhood, see the WHO manual on preventive chemotherapy for human helminthiases in addition to the CDC websites. Clinicians who encounter rare parasitic infections should also be aware of the CDC Drug Service, which provides selected drugs by Investigational New Drug application, and the CDC's Parasitic Diseases Hotline (404-718-4745).

Liver Disease Associated with Helminths

Several helminths are strongly linked to liver disease, including *Echinococcus* and the liver flukes. The time from infection to clinical presentation is often prolonged, and therefore these infections may be encountered in immigrants and returning travelers.

Echinococcosis

The liver is the principal organ affected by the tapeworms *Echinococcus granulosus* and *E. multilocularis.* The former causes cystic echinococcosis (CE), also known as hydatid cyst disease, which usually involves a solitary cyst in the liver; *E. multilocularis* causes alveolar echinococcosis (AE), usually involving metacestodes in the liver that may metastasize to other organs. Areas with high endemicity are the livestock farming areas of South America, Eurasia, the Middle East, and East Africa for CE and the rural areas of the Northern Hemisphere for AE. Both forms, but especially AE, may require many years after exposure to manifest clinically.

Diagnosis is based on clinical presentation, travel history, diagnostic imaging, serologies, PCR, and visualization of parasites. Bacterial superinfection can occur. Without adequate treatment, both forms can be fatal, but untreated AE carries an especially poor prognosis.

Drug therapy with albendazole (see Table 1-4) is recommended in all CE and AE cases, except for CE that is classified as "inactive," according to the WHO classification system (Brunetti 2010). Where available, mebendazole is an option for patients who cannot tolerate albendazole. Ideally, drug therapy is paired with a surgical or aspiration procedure for AE and all but certain of the smallest CE lesions. If surgery or aspiration is performed for CE, the first dose of drug should be given before the procedure. For CE, drug therapy is typically continued for 1 month after surgery or aspiration, or for at least 3–6 months if CE is treated only with drugs. For AE, drug therapy is continued for 2 years in those with complete resection of the lesion and lifelong in all other cases.

Monitoring of albendazole sulfoxide concentration is recommended at 1, 4, and 12 weeks after therapy initiation. Albendazole sulfoxide blood concentration 4 hours after the morning dose should be 0.65–3 micromoles/L. Monitoring for leukopenia, thrombocytopenia, and hepatotoxicity is recommended every 2 weeks for the first 3 months of albendazole therapy, then monthly for the first year, then every 3 months. A decrease in WBC to less than 1 x 10^3 cells/mm^3 merits treatment cessation. If transaminases increase above 5 times the upper limit of normal, it is recommended to check drug concentration.

Drug cost can be a limiting factor in the developing world; therefore, drug-minimizing regimens have been described in consensus statements, but these are not ideal. Cost is a growing issue in developed nations as well, especially for patients requiring prolonged courses of therapy. In the United States, the only commercial manufacturer of mebendazole stopped production in 2011. Between 2010 and 2013, the listed average wholesale price for generic albendazole increased more than 1900% (Alpern 2014). The drug manufacturer offers a patient assistance program, and refugees may qualify for the Refugee Medical Assistance Program.

Liver Flukes

Liver flukes include *Fasciola hepatica*, which is endemic in livestock farming areas worldwide; *Clonorchis sinensis*, which is prevalent in Asia and especially China; and *Opisthorchis* spp., which are common in Asia and Eastern Europe. Infection is food- or waterborne. Serious complications of infection can present years after initial exposure because *Fasciola* may have a 10-year life span and *Opisthorchis* can live dozens of years.

Adult *C. sinensis* and *Opisthorchis* worms, which live in the intrahepatic bile ducts, have been implicated in pigmented bile stone formation. The worms themselves cause biliary obstruction and resulting complications (e.g., cholangitis, cholecystitis, abscess, peritonitis, pancreatitis). These liver flukes have been strongly implicated as a risk factor for cholangiocarcinoma, and the International Agency for Research on Cancer classifies *O. viverrini* and *C. sinensis* as group 1 carcinogens. Praziquantel is the recommended treatment (see Table 1-4), and an ERCP will be needed in cases of obstruction.

F. hepatica undergoes both an acute hepatic and a chronic biliary phase of infection. Biliary infection can cause

obstruction and its resulting complications. The presentation may be intermittent. Praziquantel is not effective for *F. hepatica*. The drug of choice is triclabendazole (see Table 1-4), which is not commercially available in the United States but is available through the CDC. When triclabendazole cannot be obtained, nitazoxanide is an option. An ERCP should be performed for biliary fascioliasis because ERCP allows extraction of the worm and biliary drainage.

CONCLUSION

The GI tract and hepatobiliary system are vulnerable to infection caused by viruses, bacteria, fungi, and parasites. Pharmacologic therapy is often essential. Correct identification of the infection is key to selecting an empiric therapy likely to be effective. Therapy choice is often guided by the presenting clinical picture, diagnostic imaging, serology, and cultures of blood, tissue, or fluid. Pharmacists play a role in selecting optimal empiric therapy, determining treatment duration, tailoring antimicrobial therapy to susceptibility results, monitoring for adverse effects, and helping ensure access to drugs.

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

F.H. is a 47-year-old woman with a history of HIV/AIDS (diagnosed 15 years ago), cryptosporidiosis at the time of HIV diagnosis, onychomycosis of toenails (6 years ago), community-acquired pneumonia (3 years ago), and recurrent oropharyngeal and esophageal candidiasis, which was successfully treated with fluconazole five times in the past 2 years. She has poor adherence to her HIV antiretrovirals because of major depression and social issues. Her $CD4^+$ is 5 cells/mm^3 (1%) and HIV RNA is 145,546 copies/mL. Her antiretrovirals include tenofovir/emtricitabine and cobicistat-boosted darunavir. F.H. reports 1 week of painful swallowing but states she has been able to eat, although with some pain and discomfort. The physician reports oropharyngeal thrush on examination.

1. Which one of the following 2-week courses of therapy is best to recommend for F.H.?

   A. Fluconazole tablet, 200 mg by mouth once daily
   B. Itraconazole capsule, 200 mg by mouth once daily
   C. Nystatin oral suspension, swish and swallow four times daily
   D. Voriconazole tablet, 200 mg by mouth twice daily

2. F.H.'s oropharyngeal thrush resolved after 2 weeks of antifungal therapy, but she presents to the ED with continuing odynophagia, failure to thrive, and dehydration because she cannot swallow. Endoscopy reveals erythematous ulcers of the esophagus consistent with cytomegalovirus (CMV) disease, with biopsy results pending. Plasma CMV PCR is 754,675 copies/mL (range 450–5,500,000 copies/mL). Her eye examination is within normal limits. Which one of the following is best to recommend for F.H.?

   A. Initiate intravenous caspofungin for a total of 2–3 weeks of treatment with symptom resolution.
   B. Initiate intravenous ganciclovir and transition to valganciclovir when she can tolerate oral treatment for a total of 3–6 weeks of treatment with symptom resolution.
   C. Initiate intravenous ganciclovir and transition to valganciclovir when she can tolerate oral treatment for a total of 3–6 weeks of treatment; then institute once-daily valganciclovir maintenance until immune reconstitution with HIV antiretroviral therapy.
   D. Initiated intravenous foscarnet for a total treatment of 3–6 weeks with symptom resolution.

3. A patient with esophagitis secondary to CMV is transferred to a skilled nursing facility to continue intravenous ganciclovir therapy initiated in the hospital 1 week ago. The patient's odynophagia has resolved. The skilled nursing facility contacts you because no orders were sent with the patient. The patient has a clinic appointment in 2 weeks. Which one of the following is best to recommend for this patient?

   A. Continue intravenous ganciclovir and monitor CBCs and liver function once per week.
   B. Continue intravenous ganciclovir and monitor renal function, CBC, and serum electrolytes twice per week.
   C. Discontinue intravenous ganciclovir and initiate oral valganciclovir without laboratory monitoring until the follow-up appointment.
   D. Discontinue intravenous ganciclovir and initiate oral valganciclovir while monitoring renal function, CBC, and serum electrolytes twice per week.

Questions 4 and 5 pertain to the following case.

R.D. is a 60-year-old man who resides in a nursing home. He has a history of recurrent hospitalizations and many medical problems, including three episodes of *Clostridium difficile* diarrhea in the past 90 days. One episode was treated with metronidazole and two episodes were treated with oral vancomycin, including a vancomycin taper. Three weeks ago, R.D. was admitted to the hospital with a periorbital abscess, which was treated with clindamycin. He then developed a fourth episode of diarrhea positive for *C. difficile* toxin. He has now completed the course of clindamycin as well as a 2-week treatment with oral vancomycin 125 mg by mouth four times daily with marked improvement in his diarrhea, but without complete resolution.

4. Which one of the following is best to recommend for R.D.?

   A. No further treatment
   B. Fecal microbiota transplantation
   C. Oral metronidazole "chaser"
   D. Oral vancomycin taper

5. R.D.'s clinical examination and laboratory test data at baseline and during his initial *C. difficile* episode are as follows:

Laboratory	At Baseline	At First Episode
Hgb (g/dL)	11.3	11.2
SCr (mg/dL)	1.0	1.9
WBC (x 10^3 cells/mm^3)	3	17.6
BUN (mg/dL)	18	24
Blood pressure (mm Hg)	135/84	120/80

Which one of the following is the best categorization of R.D.'s initial *C. difficile* episode?

A. Mild
B. Moderate
C. Severe
D. Severe complicated

6. An HIV-negative man receives a diagnosis of acute proctitis. He reports having sexual intercourse with a male partner 3 weeks ago. On the basis of the CDC 2015 STI Treatment Guidelines, which one of the following is the best treatment and counseling point regarding how long the patient should abstain from sexual intercourse?

A. Ceftriaxone 250 mg intramuscular plus azithromycin 1000 mg orally one time, abstain from intercourse until 7 days after the patient received the treatment.
B. Ceftriaxone 250 mg intramuscular plus azithromycin 1000 mg orally one time, abstain from intercourse until 7 days after both patient and partner have received treatment.
C. Ceftriaxone 250 mg intramuscular one time plus doxycycline 100 mg orally twice daily for 21 days, abstain from intercourse until the both the patient and partner have completed the 21-day treatment regimen.
D. Ceftriaxone 250 mg intramuscular one time plus doxycycline 100 mg orally twice daily for 7 days, abstain from intercourse until the patient and his partner have completed the 7-day treatment regimen.

7. A 28-year-old man with HIV/AIDS and bipolar disorder is at a clinic for a scheduled follow-up. His laboratory values today are normal except the urine sample, which is positive for *Chlamydia*. The patient reports having sexual activity with both men and women, and regularly is the receptive partner during unprotected anal intercourse. He reports increasing pain on defecation in recent weeks, which he attributes to rough sexual intercourse. Digital rectal examination reveals a palpable rectal fissure or fistula at the 12 o'clock position with no discharge. Anoscopy is not available. Which one of the following is best to recommend for this patient?

A. Ceftriaxone 250 mg intramuscularly one time plus azithromycin 1000 mg orally one time
B. Ceftriaxone 250 mg intramuscularly one time plus doxycycline 100 mg orally twice daily for 7 days
C. Cefixime 400 mg by mouth one time plus doxycycline 100 mg orally twice daily for 21 days
D. Ceftriaxone 250 mg intramuscularly one time plus doxycycline 100 mg orally twice daily for 21 days

8. An 80-year-old man with hypertension and no known drug allergies presents to the clinic from home with right upper quadrant abdominal pain. He has not seen his physician in more than a year. Bile duct dilatation is evident on imaging. His temperature is 103.1°F (39.5°C), total bilirubin is 5.0 mg/dL, ALK is 1000 IU/L, and WBC is 15,000 cells/mm^3. The patient is otherwise clinically stable, and other laboratory values are normal. Acute cholangitis is diagnosed. Which one of the following is the best empiric antibiotic to recommend for this patient?

A. Ampicillin/sulbactam
B. Cefazolin plus metronidazole
C. Ceftriaxone
D. Levofloxacin plus metronidazole

9. A patient with no significant medical history presents to the ED from home with nausea, vomiting, and tenderness over his gallbladder. His temperature is 104°F (40°C), total bilirubin is 4.0 mg/dL, and WBC is 20 x 10^3 cells/mm^3. Diagnostic imaging shows gallbladder thickening and a gallstone obstructing the cystic duct. The patient's blood pressure is 60/40 mm Hg, and respiratory rate is 30 breaths/minute; his mental status is altered. He is admitted to the ICU with a diagnosis of acute cholecystitis. The patient has no known drug allergies. Which one of the following is the best empiric antibiotic to recommend for this patient?

A. Clindamycin plus moxifloxacin
B. Levofloxacin plus metronidazole
C. Linezolid plus piperacillin/tazobactam
D. Meropenem plus vancomycin

10. A 72-year-old woman with a history of diabetes has had intolerable pain from recurrent cholelithiasis. Elective laparoscopic cholecystectomy is planned. She has no known drug allergies. Which one of the following is best to recommend for this patient regarding antibiotic prophylaxis for surgery?

A. No antibiotic prophylaxis
B. A single dose of cefazolin within 60 minutes before surgery
C. Cefazolin within 60 minutes before surgery and for 24 hours after surgery

D. Cefazolin within 60 minutes before surgery and for 48 hours after surgery

11. A 22-year-old patient with no drug allergies or significant medical history presents with acute appendicitis and will have an appendectomy. There is no evidence of perforation of the appendix. A dose of antibiotic will be given for prophylaxis within 60 minutes of the incision. Which one of the following intravenous antibiotics is best to recommend for this patient?

    A. Cefazolin
    B. Ceftriaxone
    C. Cefoxitin
    D. Levofloxacin

12. A retrospective study examined the incidence of *C. difficile* infection (CDI) after appendectomy for nonperforated appendicitis. The CDI occurred in 1.5% of patients who received postoperative antibiotics and in none of the patients who did not receive postoperative antibiotics. For CDI, which one of the following most accurately depicts the number needed to harm for administration of postoperative antibiotics in this study?

    A. 15
    B. 33
    C. 67
    D. 150

13. A patient underwent transarterial chemoembolization (TACE) for hepatocellular carcinoma 8 hours ago. He has no history of hepatobiliary procedures. He has abdominal pain, and his temperature is 100.8°F (38.2°C). The patient otherwise feels well. His laboratory values are significant for a doubling of AST and ALT to 33 IU/L and 25 IU/L, respectively; an increase of total bilirubin from 0.9 mg/dL to 1.5 mg/dL; and an increase in WBC from 5 x 10^3 cells/mm^3 to 9 x 10^3 cells/mm^3. Which one of the following is the best next action to take for this patient?

    A. Conduct ultrasonography of the liver to look for abscess.
    B. Monitor the patient for another day with supportive care.
    C. Initiate empiric antibiotics to treat a suspected infection.
    D. Initiate the post-TACE antibiotic prophylaxis regimen.

14. A 50-year-old man with hyperlipidemia and no known drug allergies is to undergo elective endoscopic retrograde cholangiopancreatography (ERCP). He is asymptomatic, and his laboratory values are significant only for total bilirubin 4.0 mg/dL and ALK 400 IU/L. A biliary stricture has been visualized by magnetic resonance cholangiopancreatography, and the endoscopist expects to achieve complete biliary drainage. Which one of the following is best to recommend for prophylaxis for this patient before ERCP?

    A. No antibiotic
    B. Levofloxacin
    C. Piperacillin/tazobactam
    D. Vancomycin

15. A hospital has an unexpected rise in the number of blood and bile infections caused by carbapenem-resistant Enterobacteriaceae (CRE). An investigation reveals that each infected patient had recently undergone ERCP. The patients were treated for CRE infection with colistin, the only antibiotic that was active. Which one of the following is the best approach to stem the outbreak?

    A. Administer a prophylactic dose of colistin before each ERCP procedure.
    B. Institute a program of gas sterilization of duodenoscopes.
    C. Disinfect contaminated duodenoscopes and verify them to be free of pathogens.
    D. Replace duodenoscopes with instruments from a new manufacturer.

16. A 23-year-old man (weight 60 kg) with no significant medical history presents with fever, abdominal pain, and marked hepatomegaly. Laboratory results include WBC 15 x 10^3 cells/mm^3. Computed tomography reveals several coalescing liver abscesses. Six months ago, the patient spent 2 months in rural Vietnam as a teacher. Serologies are pending. Which one of the following is the best empiric oral antibiotic therapy to recommend for this patient?

    A. Metronidazole 750 mg three times daily for 7 days
    B. Metronidazole 750 mg three times daily for 7 days followed by paromomycin 500 mg three times daily for 7 days
    C. Paromomycin 500 mg three times daily for 7 days
    D. Paromomycin 500 mg three times daily for 7 days followed by metronidazole 750 mg three times daily for 7 days

17. A 2-year-old boy and his mother (weight 70 kg) have both received diagnoses of pinworm (*Enterobius vermicularis*). Which one of the following is the best oral therapy to recommend for the mother?

    A. Albendazole 100 mg one time only
    B. Mebendazole 400 mg daily for 2 days
    C. Praziquantel 1800 mg three times daily for 2 days
    D. Pyrantel pamoate 750 mg one time only

18. A 30-year-old woman has arrived in the United States as a refugee from Burma. She was pregnant at the time of departure overseas, and treatment of parasites was deferred. She lost the pregnancy in transit. Her physician wants to use the CDC guideline for domestic

management of arriving refugees to decide on parasite treatment. Which one of the following would be the best presumptive parasite treatment regimen for this patient?

A. Albendazole plus ivermectin
B. Albendazole plus ivermectin plus paromomycin
C. Albendazole plus ivermectin plus paromomycin plus praziquantel
D. Albendazole plus ivermectin plus praziquantel

19. A 52-year-old farmer came to the United States 6 years ago from Russia. He has echinococcosis secondary to *Echinococcus multilocularis* and has taken albendazole 400 mg twice daily for 1 month. Today, his laboratory results are WBC 2 x 10^3 cells/mm^3, AST 60 IU/L, and ALT 90 IU/L. Albendazole sulfoxide concentration 4 hours after the morning dose is 2.2 micromoles/L. Which one of the following is best to recommend for this patient?

A. Continue albendazole at the current dose.
B. Decrease the albendazole dose.
C. Discontinue albendazole today.
D. Pause albendazole therapy for 2 weeks.

20. A man who emigrated 8 years ago from rural South America to Florida presents with total bilirubin 8 mg/dL, ALK 340 IU/L, and intermittent abdominal pain. During ERCP, a worm identified as *Fasciola hepatica* is removed from a bile duct. The health care provider would also like to treat with a drug. Which one of the following is best to discuss with the provider regarding the preferred drug therapy?

A. The drug concentration should be monitored.
B. The drug must be taken on an empty stomach.
C. The drug should be administered for 7 days.
D. The drug should be requested from the CDC.