Antibiotics, Gastrointestinal
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
fidaxomicin (Dificid®)[1]	Merck Sharp & Dohme	Treatment of *Clostridium difficile*-associated diarrhea (CDAD) in adults and pediatric patients ≥ 6 months
metronidazole (Flagyl®)[2,3]	generic, Pfizer	▪ Symptomatic and asymptomatic Trichomoniasis ▪ Treatment of asymptomatic sexual partners ▪ Amebiasis (acute intestinal amebiasis and amebic liver abscess) ▪ Anaerobic bacterial infections – Oral therapy may be used following intravenous metronidazole therapy in serious infections caused by *Bacteroides* species including intra-abdominal infections, skin and skin structure infections, gynecologic infections, bacterial septicemia, bone and joint infections (as adjunctive therapy), central nervous system infections, lower respiratory tract infections, and endocarditis
neomycin tablet[4]	generic	▪ Suppression of bowel flora – Pre-operative bowel preparation for patients undergoing colorectal surgery in combination with erythromycin ▪ Adjunctive therapy for treatment of hepatic encephalopathy or hepatic coma
nitazoxanide (Alinia®)[5]	Romark	Diarrhea caused by *Giardia lamblia* ▪ Oral tablet is indicated for patients ≥ 12 years old ▪ Oral suspension is indicated for patients ≥ 1 year old Diarrhea caused by *Cryptosporidium parvum* ▪ Oral suspension is indicated for patients 1 to 11 years of age
paromomycin[6]	generic	▪ Amebiasis (acute and chronic intestinal) ▪ Management of hepatic coma as adjunctive therapy
rifamycin (Aemcolo®)[7]	Aeries	▪ Treatment of traveler's diarrhea caused by noninvasive strains of *Escherichia coli* in adults
rifaximin (Xifaxan®)[8]	Salix	▪ Treatment of traveler's diarrhea caused by noninvasive strains of *Escherichia coli (*patients ≥ 12 years of age). Rifaximin should not be used in patients with diarrhea complicated by fever or blood in stool or diarrhea due to pathogens other than *E. coli* ▪ Reduction in the risk of overt hepatic encephalopathy recurrence in patients ≥ 18 years of age ▪ Treatment of irritable bowel syndrome (IBS) with diarrhea in adults
secnidazole (Solosec™)[9]	Lupin	▪ Treatment of bacterial vaginosis (BV) in adult women
tinidazole (Tindamax®)[10]	generic, Mission	▪ Trichomoniasis ▪ Giardiasis (patients > 3 years old) ▪ Amebiasis (patients > 3 years old) ▪ Bacterial vaginosis in adult women
vancomycin (Firvanq Kit†, Vancocin®)[11,12]	generic, Cutis Pharma, Ani	▪ Oral treatment of enterocolitis caused by *Staphylococcus aureus* [including methicillin-resistant *S. aureus* (MRSA)] ▪ *C. difficile* associated diarrhea

† Approved as a New Drug Application (NDA) via the 505(b)(2) pathway. A 505(b)(2) NDA is an Food and Drug Administration (FDA) approval pathway in which at least some of the information required for approval comes from studies not conducted by or for the applicant.[13,14]

OVERVIEW

Organisms causing diarrhea and infections treated by the drugs included in this review are briefly described below. Other conditions treated by drugs in this class include hepatic encephalopathy (HE), bacterial vaginosis, and pre-operative bowel cleansing.

Amebiasis

Entamoeba histolytica is well recognized as a pathogenic ameba, associated with intestinal and extraintestinal infections.[15] Patients can have an asymptomatic infection in mild cases. In severe cases, fulminant colitis and peritonitis or extraintestinal amebiasis can result. Amebia infections are acquired by the fecal-oral route either through person-to-person contact or indirectly through eating or drinking fecally-contaminated food or water. *E. histolytica* can also be transmitted through anal-genital, oral-anal, or digital-anal contact.[16] The parasite initially infects the colon and the incubation period is generally 2 to 4 weeks. Persistent diarrhea is the most common symptom and can worsen to painful, bloody bowel movements, with or without fever (amebic dysentery).[17] The majority of *E. histolytica* infections, morbidity, and mortality occur in Africa, Asia, and Central and South America.

Paromomycin or iodoquinol are the drugs of choice for treatment of asymptomatic infections proven to be caused by *E. histolytica*. For symptomatic intestinal infection, or extraintestinal infections (e.g., hepatic abscess), the drugs of choice are metronidazole (Flagyl) or tinidazole (Tindamax), immediately followed by treatment with iodoquinol or paromomycin.

Giardiasis

Giardiasis is the most frequently diagnosed intestinal parasitic disease in the United States (U.S.) and is caused by *G. lamblia*.[18] Diagnosis is done by the detection of cysts or trophozoites in the feces, trophozoites in the small intestine, or by the detection of *Giardia* antigens in the feces. Patients with Giardiasis may experience mild or severe diarrhea or, in some instances, no symptoms at all. Fever is rarely present. Onset of symptoms is generally 1 to 2 weeks after inoculation. Occasionally, some will have chronic diarrhea over several weeks or months, with significant weight loss. Giardiasis can cause failure to absorb fat, lactose, vitamin A, and vitamin B12. Giardia is passed from the feces of an infected person or animal and may contaminate water or food. *G. lamblia* can also be transmitted through anal-genital, oral-anal, or digital-anal contact.[19] Person-to-person transmission may occur in daycare centers or other settings where hand washing practices are poor.

Effective treatments for Giardia infection include metronidazole, tinidazole, and nitazoxanide (Alinia). Paromomycin is an alternative agent.

Cryptosporidiosis

Cryptosporidiosis is caused by the protozoan, *Cryptosporidium parvum*.[20] Intestinal cryptosporidiosis is characterized by severe watery diarrhea but may also be asymptomatic. Intestinal cryptosporidiosis is self-limiting in most otherwise healthy people. Some infected people are asymptomatic; in others, symptoms may range from mild to profuse diarrhea, with passage of 3 to 6 liters of watery stool per day. In some outbreaks involving daycare centers, diarrhea has lasted from 1 to 4 weeks. Dehydration is a major concern, particularly for pregnant women and young children and immunocompromised people in whom the infection becomes chronic.

Immune status has a strong influence on the severity and duration of symptoms and illness. In people with HIV/AIDS or other immunocompromising conditions, *C. parvum* infections may be severe, lifelong, and may contribute to their death.

The FDA has approved nitazoxanide for the treatment of cryptosporidiosis in immunocompetent people. Nitazoxanide has not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients. A small number of studies reflect administration with azithromycin or paromomycin are also options in this demographic.

Traveler's Diarrhea (non-viral)

Traveler's diarrhea is characterized by more than 2 to 5 loose stools per day.[21] Symptoms can range from mild cramps and urgent loose stools to severe abdominal pain, fever, vomiting, and bloody diarrhea. If untreated, most bacterial illnesses will resolve spontaneously over 3 to 7 days and viral infections in 2 to 3 days. Approximately 10% of traveler's diarrhea is caused by parasitic infections, which can persist for weeks to months, with giardiasis being the most common.[22]

Traveler's diarrhea due to bacterial causes is most often caused by enterotoxigenic *E. coli*, followed by Campylobacter *jejuni*, *Shigella* species, and *Salmonella* species. Ingesting contaminated food or water is the most common mode of acquisition.

Antibiotic chemoprophylaxis for traveler's diarrhea is discouraged for most travelers due to mounting bacterial resistance. Symptomatic self-treatment of traveler's diarrhea includes replacement of fluid losses, although traveler's diarrhea in adults is not usually dehydrating. Symptomatic treatment with bismuth subsalicylate reduces the number of stools by approximately 50%. Other self-treatment options include synthetic opiates, such as loperamide and diphenoxylate.

Antibiotic therapy includes fluoroquinolones (however, increasing microbial resistance may limit their use), azithromycin, and rifaximin (Xifaxan), and rifamycin (Aemcolo). Agents no longer recommended due to drug resistance include neomycin, sulfonamides, ampicillin, doxycycline, tetracycline, and trimethoprim.

Clostridium difficile-associated Diarrhea

Clostridium difficile infection in adults is diagnosed by the presence of symptoms, usually diarrhea, and either a stool test positive for *C. difficile* toxins or toxigenic *C. difficile,* or colonoscopic or histopathologic findings of pseudomembranous colitis.[23] *C. difficile*-associated diarrhea (CDAD) occurs in patients with an alteration in the microflora of the colon or after the exposure and ingestion of spores and vegetative cells.[24] *C. difficile* multiplies in the colon and produces toxins that stimulate a response from the host to release tumor necrosis factor and interleukins, and to recruit neutrophils and monocytes. Colonic epithelial cell junctions widen, and cell death occurs. Additionally, production of hydrolytic enzymes leads to colitis and pseudomembrane formation in some patients. These changes in the colon cause watery and, occasionally, bloody diarrhea.

Risk factors for CDAD include prior antimicrobial use within the preceding 8 to 12 weeks.[25] Nearly all antibiotics have been associated with the development of CDAD. Other risk factors for CDAD include hospitalization, particularly in intensive care units, proton pump inhibitor use, advanced age (> 65 years old), in intensive care, immunosuppression, and gastrointestinal procedures.

A new hypervirulent North American Pulsed Field type 1 (NAP-1/B1/027) strain of *C. difficile* has emerged in North America and Europe.[26] The rapidly increasing numbers of cases and deaths are partly related to the emergence of the NAP-1 strain of *C. difficile.*[27] Unlike other strains, the NAP-1 strain is resistant to fluoroquinolones, so widespread fluoroquinolone use is likely a contributing factor.

Offending antibiotics should be discontinued as soon as appropriate, upon suspected *C. difficile* infection. If possible, avoid the use of antiperistaltic agents, as they may obscure symptoms and precipitate toxic megacolon. The Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) updated their guidelines on *C. difficile* infection in 2017.[28] The guidelines recommend a 10-day course of oral vancomycin or fidaxomicin (over metronidazole) for first-line therapy of an initial *C. difficile* infection in adults (strong recommendation). If access to these is limited, oral metronidazole may be considered in non-severe cases (weak recommendation). Oral vancomycin also remains the drug of choice for a fulminant episode of *C. difficile* infection (strong recommendation). For recurrent *C. difficile* infection in adults, vancomycin as a taper and pulsed course or a 10-day course of fidaxomicin is recommended over an additional 10-day course of vancomycin (weak recommendation); however, a 10-day course of vancomycin is still recommended over a repeat course of metronidazole, if metronidazole was the original agent used for treatment. For those with more than 1 recurrence, options include vancomycin as a tapered and pulsed regimen, 10-day vancomycin followed by rifaximin, or fidaxomicin. For multiple recurrent *C. difficile* infections in adults, fecal microbiota transplantation (FMT) should be strongly considered. In children, while there is a lack of robust data, vancomycin or metronidazole is recommended as first-line treatment for initial and first recurrence of mild-to-moderate *C. difficile* infection. Oral vancomycin is preferred for severe *C. difficile* infection or multiple recurrences in children, and FMT may be considered based on limited data for multiple recurrences in pediatric patients.[29] Fidaxomicin was not FDA-approved to treat pediatric patients with *C. difficile* infection at the time the updated guidelines were published.

Bacterial Vaginosis

Bacterial vaginosis (BV) is a common vaginal infection in which the normal flora, *Lactobacillus* species, are replaced by overgrowth of several other microorganisms.[30] Diagnosis is based on either gram staining of vaginal fluid or presence of at least 3 of the following criteria: vaginal discharge, vaginal pH > 4.5, positive whiff test, and the presence of clue cells. Risk factors for BV include having a new sexual partner or multiple sexual partners, douching, use of an intrauterine device, and lack of condom during sexual intercourse. Some patients do not experience symptoms; if symptoms are present, they can often be confused with those of a yeast infection. All women who have symptomatic disease require treatment. The 2015 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease (STD) Treatment guidelines recommend the following treatment options: oral metronidazole, or intravaginal metronidazole gel or clindamycin cream or ovule.[31] Alternative treatment regimens include oral tinidazole or clindamycin. Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use. Topical clindamycin preparations should not be used in the second half of pregnancy. For this infection, the treatment recommendations have not changed from the previous iteration of the guidelines. Secnidazole (Solosec) was not FDA approved at the time of this guideline development.

Trichomoniasis

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis.* Many infected women have symptoms characterized by a diffuse, malodorous, vaginal discharge with vulvar irritation. Diagnosis of vaginal trichomoniasis is usually performed by microscopy of vaginal secretions. The 2015 CDC STD treatment guidelines recommend a single oral dose of either metronidazole 2 g or tinidazole 2 g.[32] An alternative regimen is metronidazole 500 mg orally twice daily for 7 days. The sexual partner should also be treated at the same time. For this infection, the treatment recommendations have not changed from the previous iteration of the guidelines.

Hepatic Encephalopathy/Coma

Hepatic encephalopathy occurs in patients with cirrhosis and is characterized by altered consciousness, behavior (apathy, irritability, disinhibition), and motor function. Hepatic encephalopathy is caused by accumulation of nitrogenous substances, primarily ammonia, in the blood. In advanced stages, it is referred to as hepatic coma which may be preceded by seizures. The treatment goal is to reduce nitrogen load from the GI tract and to improve central nervous system (CNS) status. Treatment options include lactulose administered orally or by nasogastric tube or enema, non-absorbable antibiotics, such as rifaximin, and protein-restricted diets.[33] Antibiotics are usually second-line therapy.[34] Neomycin or paromomycin can suppress the normal bacterial flora in the intestines that produce urease, an enzyme which breaks down urea to carbon dioxide and ammonia.[35] Rifaximin is minimally absorbed and affects the normal bacterial flora of the intestines.[36] In severe cases of hepatic encephalopathy, combination therapy can be considered. In clinical trials with rifaximin, 91% of patients also received concurrent lactulose therapy for the management of hepatic encephalopathy.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional bowel disorder which can be chronic, relapsing, and often lifelong.[37,38] IBS occurs in up to 15% of the population and is up to 2.5 times more common in women than men. IBS is characterized by symptoms of abdominal pain or discomfort associated with abnormal stool frequency, abnormal stool form, abnormal stool passage, and/or bloating or abdominal distension, which may or may not be relieved by defecation at least 3 days per month in the past 3 months. Patients present with a combination of symptoms that are typically constipation predominant (IBS-C), diarrhea predominant (IBS-D), and/or alternating between both, or mixed (IBS-M). IBS is a chronic condition without a cure. Therefore, treatment of IBS is based on management of the patient's symptoms and may require a combination of modalities to achieve relief. The 2014 American Gastroenterological Association (AGA) guidelines on the treatment of IBS recommend rifaximin (Xifaxan) and loperamide over no drug treatment in patients with IBS-D.[39]

PHARMACOLOGY[40,41,42,43,44,45,46,47,48,49]

The antibiotics in this category treat a variety of different infections and conditions.

Nitazoxanide (Alinia) is a synthetic thiazolide antiprotozoal agent for the treatment of cryptosporidiosis or giardiasis. Nitazoxanide works by interfering with the pyruvate ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction which is essential for anaerobic energy metabolism. The PFOR enzyme from *G. lamblia* directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The PFOR enzyme is similar in *G. lamblia* and *C. parvum*. The PFOR enzyme interference

may not be the only mechanism of action for nitazoxanide. Nitazoxanide and the active metabolite, tizoxanide, are active *in vitro* against the sporozoites and oocysts of *C. parvum* and the trophozoites of *G. lamblia*.

Neomycin and paromomycin are aminoglycoside antibiotics with bactericidal activity. Both agents are poorly absorbed from the GI tract. Neomycin is not used for systemic therapy, as it has been associated with irreversible ototoxicity. Aminoglycosides act by inhibiting bacterial protein synthesis through irreversible binding to the 30S ribosomal subunit of susceptible bacteria. Drug is actively transported into the bacterial cell where it binds to receptors present on the 30S ribosomal subunit. This binding interferes with the initiation complex between the messenger RNA and the subunit. As a result, due to misreading of the bacterial DNA, abnormal nonfunctional proteins are formed, leading to bacterial cell death.

In the adjunctive treatment of hepatic encephalopathy or coma, neomycin and paromomycin are used to suppress growth of bacteria in the gut that produce urease, an enzyme that breaks down urea into carbon dioxide and ammonia. Decreasing the amount of ammonia available for absorption from the gut results in decreased serum and CNS levels and clinical improvement. Organisms susceptible to neomycin and paromomycin include *E. coli*, *Klebsiella*, and other *Enterobacteriaceae*. Like other aminoglycosides, neomycin and paromomycin are ineffective against anaerobic bowel flora.

Metronidazole (Flagyl) is a 5-nitroimidazole agent with excellent anaerobic bacterial activity. It is effective against protozoa such as *T. vaginalis*, *E. histolytica*, and *G. lamblia*. Metronidazole can also be used as a component of multiple regimens to treat *Helicobacter pylori.* Both the parent compound and the metabolite have *in vitro* bactericidal activity against most anaerobic bacteria, including *Bacteroides* species and *Fusobacterium* species; anaerobic Gram-positive bacilli including *Clostridium* species; and anaerobic Gram-positive cocci, including *Peptococcus niger* and *Peptostreptococcus* species.

Tinidazole (Tindamax) is a 5-nitroimidazole anti-protozoal agent similar to metronidazole with similar efficacy to metronidazole against protozoa such as *T. vaginalis*, *E. histolytica*, and *G. lamblia*. Tinidazole has a shorter duration of therapy for some indications. Tinidazole is also effective against anaerobic bacteria and has been used clinically for prophylaxis and treatment of infections due to anaerobic bacteria. The nitro-group of tinidazole is reduced by cell extracts of *Trichomonas*. Free nitro-radicals generated as a result of the reduction may be responsible for the antiprotozoal activity. In addition, chemically reduced tinidazole releases nitrites that cause damage to bacterial DNA. The mechanism of action against *Giardia* sp. and *Entamoeba* sp. is unknown.

Secnidazole (Solosec) is a 5-nitroimidazole with demonstrated *in vitro* activity against many anaerobic Gram-negative and Gram-positive bacteria, while sparing *Lactobacillus* species. Secnidazole is active *in vitro* against most isolates of the following organisms that are associated with bacterial vaginosis *Bacteroides* spp., *Gardnerella vaginalis, Prevotella* spp., *Mobiluncus* spp., and *Megasphaera*-like type I/II.

Rifaximin (Xifaxan) is a non-aminoglycoside semi-synthetic antibacterial derived from rifamycin SV.[50] Rifamycin (Aemcolo) is an ansamycin antibacterial drug. Rifaximin and rifamycin act by binding to the beta-subunit of bacterial DNA-dependent RNA polymerase, resulting in inhibition of bacterial RNA synthesis. Rifaximin and rifamycin are minimally absorbed and concentrated in the GI tract. Rifaximin has a low risk of inducing bacterial resistance with a low incidence of serious adverse effects which makes rifaximin useful in the long-term management of hepatic encephalopathy.

Vancomycin is a glycopeptide antibiotic obtained from *Nocardia orientalis* and is effective only for Gram-positive bacteria. Its bactericidal action against *Staphylococcus aureus* and *Clostridium difficile is* primarily due to inhibition of cell-wall biosynthesis; it also alters bacterial-cell-membrane permeability and RNA synthesis. Vancomycin is poorly absorbed in the GI tract and is administered orally to treat GI infections, such as pseudomembranous colitis, due to overgrowth of *Clostridium difficile*. Resistance to vancomycin can occur. The exact mechanism of *S. aureus* resistance may be due to cell wall thickening and transfer of genetic material. The mechanism that causes *C. difficile* resistance is not fully understood.

Fidaxomicin (Dificid) is a macrolide antibacterial agent that exerts its effects via inhibiting RNA synthesis. This agent is a fermentation product obtained from the actinomycete *Dactylosporangium aurantiacum*. It acts locally in the GI tract on *C. difficile*; it should not be used for systemic infections, nor for infections caused by any organism other than *C. difficile*. Fidaxomicin has little or no activity against organisms other than clostridia, allowing for preservation of normal gastrointestinal flora. Fidaxomicin is bactericidal against *C. difficile*; vancomycin and metronidazole are bacteriostatic. *In vitro* studies indicate a low frequency of spontaneous resistance of *C. difficile* to fidaxomicin and no *in vitro* cross-resistance with other classes of antibacterial drugs.

An *in vitro* study found that fidaxomicin inhibited *C. difficile* spore formation, while vancomycin, metronidazole, and rifaximin did not.[51] This inhibitory effect on *C. difficile* sporulation is thought to lend fidaxomicin its performance in both sustained clinical response and reduced recurrence of infection. In whole genome sequencing of *C. difficile* strains, in recurrence of infection in those patients previously treated with fidaxomicin, both relapse and reinfection with *C. difficile* were reduced with fidaxomicin.[52]

Reports of *in vitro* susceptibility profile of nosocomial and community acquired pathogens should aid prescribers in selecting appropriate antimicrobial drug therapy.

PHARMACOKINETICS[53,54,55,56,57,58,59,60,61,62,63]

Drug	Bioavailability (%)	Half-life (hours)	Metabolites	Elimination (%)
fidaxomicin (Dificid)	minimal systemic absorption	11.7	1 active metabolite	Feces: 92
metronidazole (Flagyl)	nr	8	3 metabolites	Urine: 60-80 Feces: 6-15
neomycin	3	nr	nr	Feces: 97
nitazoxanide (Alinia)	nr	nr	tizoxanide (active); tizoxanide glucuronide	Urine: 33.3 Feces: 66.7
paromomycin	poor oral absorption	nr	nr	Feces: 100
rifamycin (Aemcolo)	minimal absorption	nr	nr	Feces: 86
rifaximin (Xifaxan)	low absorption	5.6-6	nr	Urine: 0.32 Feces: 96.62
secnidazole (Solosec)	completely absorbed	17	*in vitro* via oxidation by CYP450 enzymes; ≤ 1% conversion to metabolites	Urine: 15
tinidazole (Tindamax)	completely absorbed	12-14	significant metabolism; 2-hydroxymethyl metabolite appears in plasma	Urine: 20-25 Feces: 12
vancomycin (Firvanq kit, Vancocin)	poor systemic absorption	nr	nr	Feces

nr = not reported

Nitazoxanide (Alinia) tablets and suspension are not bioequivalent. The relative bioavailability of the suspension compared to the tablet is 70%. Absorption of nitazoxanide is nearly doubled in the presence of food. Nitazoxanide dosage forms should be administered with food. Nitazoxanide's active metabolite tizoxanide is highly protein bound (> 99.9%).

Patients with colitis may develop detectable serum vancomycin (Firvanq, Vancocin) levels following oral administration, especially if they have renal impairment.

CONTRAINDICATIONS/WARNINGS[64,65,66,67,68,69,70,71,72,73,74]

Almost all antibacterial agents have been associated with pseudomembranous colitis (antibiotic-associated colitis), which may range in severity from mild to life-threatening. Systemic use of antibiotics predisposes patients to development of pseudomembranous colitis. Consideration should be given to the diagnosis of pseudomembranous colitis in patients presenting with diarrhea during or following antibacterial therapy. If diarrhea develops during therapy, the drug should be discontinued, and, if diagnosis of pseudomembranous colitis is confirmed, therapeutic measures should be instituted. Drugs inhibiting peristalsis are contraindicated if pseudomembranous colitis exists.

Paromomycin is contraindicated in intestinal obstruction while neomycin is contraindicated in GI obstruction, ileus, or ulcerative bowel lesions, including ulcerative colitis. Absorption may be increased

in the presence of lesions and potentially result in increased adverse effects, such as ototoxicity (sometimes irreversible) and nephrotoxicity, which are more likely to occur with systemic aminoglycoside therapy. Patients receiving oral neomycin and paromomycin should be monitored closely for ototoxicity and nephrotoxicity, as systemic absorption can occur. Nephrotoxicity is evident by decreased creatinine clearance, the presence of cells or casts, oliguria, proteinuria, decreased urine specific gravity, or evidence of increasing nitrogen retention (increasing blood urea nitrogen [BUN] or serum creatinine). Nephrotoxicity is generally reversible. Aminoglycosides are also associated with neuromuscular blockade and respiratory paralysis; neuromuscular weakness can last hours to days. Use with caution in patients with muscular disorders, such as myasthenia gravis or Parkinson's disease. Patients with hypersensitivities to any of the aminoglycosides should not receive neomycin or paromomycin.

Vancomycin (Firvanq, Vancocin) oral preparations are not for the treatment of systemic infections as oral vancomycin is not significantly systemically absorbed. However, patients with inflammation of the intestinal mucosa may have significant systemic absorption; monitoring of serum levels and adverse effects may be appropriate in some, particularly those with renal impairment. Parenteral administration of vancomycin for the treatment of colitis is not effective. Oral vancomycin is contraindicated in patients with a known hypersensitivity to vancomycin.

Nephrotoxicity and ototoxicity have also been reported during and/or following oral vancomycin therapy. Assessment of renal and auditory function may be appropriate in some instances.

Rifaximin (Xifaxan) and rifamycin (Aemcolo) are contraindicated in patients with a hypersensitivity to rifaximin and rifamycin, respectively, or to any of the rifamycin antimicrobial agents. Rifaximin hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis. Rifaximin and rifamycin should not be used to treat patients with diarrhea complicated by fever or blood in the stool or diarrhea secondary to pathogens other than *E. coli* due to a lack of proven effectiveness. Rifaximin and rifamycin have not been shown to be effective in cases of traveler's diarrhea due to *Campylobacter jejuni*, *Shigella* species, or *Salmonella* species and should not be used if one of these organisms may be suspected as the causative pathogen. Rifaximin and rifamycin should be discontinued if diarrhea symptoms worsen or persist more than 24 to 48 hours. Rifaximin and rifamycin are poorly absorbed into the systemic circulation and should not be used to treat systemic infections. In patients with severe hepatic impairment, an increased systemic exposure of rifaximin can occur. Caution should be used for administering rifaximin to patients with severe hepatic impairment (Child-Pugh C). Caution should be used when administering rifaximin along with a P-glycoprotein (P-gp) inhibitor due to the possibility of a substantial increase in exposure to rifaximin.

Nitazoxanide (Alinia) is contraindicated in patients with prior hypersensitivity to nitazoxanide or any of the product components. Nitazoxanide oral suspension contains 1.48 grams of sucrose per 5 mL; diabetic patients and their caregivers should be aware of the sucrose content.

Metronidazole (Flagyl), secnidazole (Solosec), and tinidazole (Tindamax) are contraindicated in patients with a prior history of hypersensitivity to nitroimidazole derivatives. A boxed warning appears in the labeling for metronidazole that its use has been shown to be carcinogenic in mice and rats. While carcinogenicity in animals has not been reported with tinidazole (Tindamax), a similar warning appears in the labeling for tinidazole (Tindamax) as it is structurally related to metronidazole. Use of each agent should be limited to approved indications. Secnidazole does not carry a boxed warning, but the labeling contains a similar warning regarding potential risk of carcinogenicity; however, it is unclear if

this effect would result from a single dose of secnidazole. Chronic use of secnidazole should be avoided.

Metronidazole is contraindicated during the first trimester of pregnancy. Tinidazole is contraindicated in nursing mothers unless breast-feeding is interrupted during therapy and for 3 days following the last dose. Convulsive seizures, encephalopathy, aseptic meningitis, and optic and peripheral neuropathy have been reported in patients receiving metronidazole and/or tinidazole. Therapy should be withdrawn if abnormal neurological signs develop. The manufacturers of metronidazole (Flagyl) recommend caution in patients with existing CNS disorders.

Use metronidazole and tinidazole with caution in patients with blood dyscrasias. Tinidazole may produce transient leukopenia and neutropenia.

Metronidazole and tinidazole may alter reported values of laboratory tests, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose.

The use of metronidazole, secnidazole, or tinidazole may result in vulvo-vaginal candidiasis, which may require treatment with an antifungal agent.

Metronidazole is also contraindicated in the presence of alcohol; do not consume alcohol or products containing propylene glycol during and for at least 3 days after completing metronidazole use. Do not use metronidazole in patients who have taken disulfiram within 2 weeks.

Fidaxomicin (Dificid) is contraindicated in patients with a known hypersensitivity to fidaxomicin or any of its ingredients. There have been reports of acute hypersensitivity reactions (angioedema, dyspnea, pruritus, and rash) with fidaxomicin. In the event of a severe reaction, discontinue use. Do not use for systemic infections. Due to poor systemic absorption, it should not be used for treating infections other than *C. difficile*-associated diarrhea.

Prescribing vancomycin, fidaxomicin, rifaximin, metronidazole, secnidazole, or tinidazole in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

DRUG INTERACTIONS[75,76,77,78,79,80,81,82,83]

Tizoxanide, the active metabolite of nitazoxanide (Alinia), is highly bound to plasma protein (> 99.9%). Therefore, caution should be used when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, such as warfarin. Nitazoxanide and tizoxanide do not have any significant inhibitory effects on the CYP 450 system.

Due to the low systemic absorption of rifaximin (Xifaxan) and rifamycin (Aemcolo), clinically relevant drug interactions with the CYP450 enzymes are not expected. Limited studies with midazolam and oral contraceptives have not shown any drug interactions with rifaximin.[84]

Metronidazole (Flagyl) and tinidazole (Tindamax) can potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolonged prothrombin time and altered international normalized ratio (INR). Anticoagulant therapy may require close monitoring and dosage adjustment for up to 8 days after discontinuation of tinidazole.

Co-administration of drugs that induce CYP450 enzymes, such as phenobarbital and phenytoin, may accelerate the elimination of metronidazole or tinidazole resulting in reduced plasma levels of the antibiotic.

Metronidazole has been shown to decrease the clearance of 5-fluorouracial, cyclosporine, and tacrolimus which can lead to toxicity, and tinidazole is expected to show similar effects. Monitor the toxicities of cyclosporine, tacrolimus, and fluorouracil with concurrent use of metronidazole or tinidazole. Impaired clearance of phenytoin by metronidazole has also been reported.

Inhibitors of the CYP450 system, such as cimetidine, may prolong the half-life of metronidazole and tinidazole.

In patients on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium. Since tinidazole is structurally related to metronidazole, it may have a similar effect. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole or tinidazole to detect any increase that may precede clinical symptoms of lithium toxicity.

Cholestyramine has the potential to decrease the oral absorption of metronidazole and tinidazole. Oral doses should be separated with concurrent use.

Alcoholic beverages should not be consumed during metronidazole or tinidazole therapy and for at least 3 days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur. Metronidazole and tinidazole should not be given to patients who have taken disulfiram within the last 2 weeks as psychotic reactions have been reported with concurrent use.

Neomycin can reduce digoxin absorption by up to 28%. Monitor the clinical response of the patient and consider monitoring serum digoxin concentration with prolonged antibiotic therapy. Oral administration of neomycin inhibits vitamin K-synthesizing intestinal bacteria and can potentiate the effects of warfarin. Neomycin given orally can reduce the bioavailability of methotrexate; and has been shown to reduce the bioavailability of oral penicillin V, oral vitamin B-12, methotrexate, and 5-fluorouracil.

Antibiotics that reduce colonic flora may theoretically interfere with the biological conversion of lactulose to its active, acidic products. Since neomycin is also used in the treatment of hepatic encephalopathy, concurrent use may interfere with the effectiveness of lactulose. Neomycin and lactulose have been used together successfully, as long as the fecal pH remains < 6, and the combination is recommended in patients who respond poorly to therapy with lactulose alone. Patients taking both drugs concurrently should be monitored for the possibility of a decreased response to lactulose.

Fidaxomicin (Dificid) and its active metabolite are substrates of P-gp, and can have slightly higher plasma concentrations in the presence of cyclosporine, as cyclosporine has an inhibitive effect on P-gp transporters. The increased concentration is not significant and no dosage adjustment is necessary.

Drug interaction studies have not been performed for orally administered vancomycin (Firvanq, Vancocin).

There are no reported clinically significant drug interactions reported with secnidazole.

ADVERSE EFFECTS[85,86,87,88, 89,90,91,92,93,94]

Drug	Abdominal Pain	Headache	Diarrhea	Nausea	Metallic Taste
fidaxomicin (Dificid) (reported in adults)	6	nr	nr	11	nr
metronidazole (Flagyl)	reported	reported	reported	reported	reported
neomycin	nr	nr	reported	reported	nr
nitazoxanide (Alinia) oral suspension n=613	7.8	1.1	2.1	< 1	nr
nitazoxanide (Alinia) tablets n=1,628	6.7	3.1	4.3	3.1	nr
paromomycin	reported	reported	reported	reported	nr
rifamycin (Aemcolo)	0.5	3.3	reported	nr	nr
rifaximin (Xifaxan) n=320 with traveler's diarrhea	7 (10)	10 (9)	< 2	reported	loss of taste < 2
rifaximin (Xifaxan) n=140 with hepatic encephalopathy	9 (8)	reported	nr	14 (13)	nr
secnidazole (Solosec) n=197	2 (1.5)	3.6 (1.5)	2.5 (0.7)	3.6 (0.7)	reported
tinidazole (Tindamax) 2 gm single dose – multi-day dose	> 1	0.7-1.3	reported	3.2-4.5	3.7-6.3
vancomycin (Firvanq, Vancocin)	15	7	9	17	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Common adverse effects for vancomycin (Firvanq, Vancocin) also include hypokalemia (13%), vomiting (9%) and pyrexia (9%). Adverse effects such as nephrotoxicity, ototoxicity, neutropenia, and thrombocytopenia are more commonly associated with intravenous (IV) administration of vancomycin.

Prolonged oral neomycin therapy has been associated with a malabsorption syndrome, characterized by steatorrhea, decreased serum carotene, and decreased xylose absorption.

Other common adverse effects experienced with fidaxomicin therapy are vomiting (7%), GI hemorrhage (4%), anemia, and neutropenia (each 2%).

Other common adverse reactions reported with rifaximin include; flatulence, rectal tenesmus, and defecation urgency when used for traveler's diarrhea. When used for HE, peripheral edema, fatigue, ascites, and flatulence have been reported as the most common adverse reactions. When used for IBS with diarrhea, nausea and increased ALT have been reported.

Other adverse reactions with rifamycin include constipation (3.5% versus 1.5% placebo) and dyspepsia (< 2%).

Common adverse effects associated with metronidazole use include vaginitis (15%), bacterial infections (7%), flu-like symptoms (6%), and genital pruritus 5%).

In an additional uncontrolled trial (n=321), vulvo-vaginal candidiasis was reported in 8.4% and dysgeusia in 3.4% of patients treated with secnidazole.

In the phase 3 pediatric (ages 6 months to < 18 years) clinical trials, treatment discontinuation due to adverse reactions occurred in 1% and 2.3% of patients taking fidaxomicin and vancomycin, respectively. The most common selected adverse reactions reported (≥ 5%; versus vancomycin, respectively) were pyrexia (13.3% versus 22.7%), abdominal pain (8.2% versus 20.5%), vomiting (7.1% versus 13.6%), diarrhea (7.1% versus 11.4%), constipation (5.1% versus 2.3%), increased aminotrasferases (5.1% versus 2.3%), and rash (5.1% versus 2.3%).

SPECIAL POPULATIONS[95,96,97,98,99,100,101,102,103,104]

Pediatrics

Fidaxomicin (Dificid) is indicated for the treatment of *C. difficile*-associated diarrhea (CDAD) in patients ≥ 6 months of age. The safety and efficacy in patients < 6 months of age have not been established.

Safety and effectiveness oral vancomycin (Firvanq, Vancocin) in pediatric patients have not been established. The safety and effectiveness of metronidazole (Flagyl) have not been established in pediatric patients, except for the treatment of amebiasis.

Nitazoxanide (Alinia) tablets have not been studied in children < 12 years of age. A single nitazoxanide tablet contains a greater amount of nitazoxanide than is recommended for pediatric patients ≤ 11 years and should not be used in this age group. Nitazoxanide oral suspension has not been studied in children < 1 year of age.

Safety and effectiveness of rifaximin (Xifaxan) for treatment of traveler's diarrhea have not been established in children < 12 years of age. For hepatic encephalopathy, safety and effectiveness of rifaximin have not been established in patients < 18 years of age. For IBS with diarrhea, safety and effectiveness have not been established in patients < 18.

Safety and effectiveness of rifamycin (Aemcolo) for treatment of traveler's diarrhea has not been established in patients < 18 years of age. Safety and effectiveness of neomycin have not been established in pediatric patients. Various drug information sources can provide dosing information for pediatric patients; however, large, well-designed, formal clinical trials have not been performed. Paromomycin is indicated in the pediatric population for treatment of intestinal amebiasis.

Tinidazole (Tindamax) has only been studied in children age ≥ 3 years for the treatment of giardiasis and amebiasis.

Safety and effectiveness of secnidazole (Solosec) have not been established in patients < 18 years of age.

Pregnancy

Metronidazole is contraindicated during the first trimester of pregnancy. It readily cross the placental barrier and enters the fetal circulation rapidly. Available data regarding use of secnidazole in pregnant

women is too limited to advise of drug-related adverse effects to the fetus; however, no adverse developmental outcomes were reported in animal studies.

Oral vancomycin is classified as Pregnancy Category B, paromomycin is Pregnancy Category C, and neomycin is Pregnancy Category D. There are no available data on rifaximin use in pregnant women; teratogenic effects have been observed in some animal reproduction studies. There are no available data on rifamycin use in pregnant women; no malformations have been observed in animal reproduction studies. Due to its minimal systemic exposure, it is unlikely that maternal use of rifamycin will lead to fetal exposure. Product labeling for nitazoxanide, fidaxomicin, and tinidazole has been revised to comply with the current Pregnancy and Lactation Labeling Rule (PLLR) and advises that data for use in pregnant women are inadequate to inform of a drug-associated risk. Previously, nitazoxanide and fidaxomicin were considered Pregnancy Category B, and tinidazole was considered Pregnancy Category C.

Renal Impairment

Pharmacokinetic studies of nitazoxanide, rifaximin, and rifamycin have not been performed in patients with renal insufficiency. Since rifamycin's systemic exposure and renal excretion are minimal, renal impairment is not expected to require a dose adjustment.

If tinidazole is administered the same day and prior to hemodialysis, administer an additional half dose after hemodialysis.

No dose adjustment for metronidazole or fidaxomicin is warranted for patients with impaired renal function.

Since neomycin and paromomycin are excreted renally and are nephrotoxic, caution should be used when administering these agents to patients with renal impairment.

Approximately 15% of a secnidazole dose is excreted unchanged in the urine; dosage adjustments are not recommended for patients with renal impairment.

Hepatic Impairment

Since rifaximin acts locally in the GI tract, no dosage adjustment is necessary in patients with hepatic impairment. However, there is potential for increased systemic exposure of rifaximin with severe hepatic impairment; therefore, caution should be used when prescribing rifaximin to patients with severe hepatic impairment (Child-Pugh C).

Since rifamycin's systemic exposure is minimal, hepatic impairment is not expected to require a dose adjustment.

Elimination of fidaxomicin and its metabolite is not expected to be affected by hepatic impairment. No dosage adjustment is necessary with hepatic impairment.

Pharmacokinetic studies of nitazoxanide and tinidazole have not been performed in patients with hepatic insufficiency. Use caution when administering nitazoxanide and tinidazole to patients with hepatic impairment.

For patients with severe hepatic impairment (Child-Pugh C), the dose of metronidazole (Flagyl) should be reduced by 50%.

Secnidazole is minimally (≤ 1%) metabolized in the liver; dosage adjustments are not recommended for patients with hepatic impairment.

Geriatric Patients

Studies with nitazoxanide, rifaximin for traveler's diarrhea, rifamycin for traveler's diarrhea, secnidazole, and tinidazole did not include a sufficient number of patients aged ≥ 65 years to determine if this age group would respond differently than younger patients. For rifaximin for hepatic encephalopathy, no overall differences in safety or effectiveness were observed between older and younger patients.

The elderly (> 65 years) and patients with dehydration are at an increased risk of toxicity associated with neomycin.

For geriatric patients (> 65 years) on oral vancomycin, regardless of renal status, it is recommended that renal function be monitored during and following treatment in this population to detect possible nephrotoxicity.

There were no differences in safety or efficacy of fidaxomicin between older (≥ 65 years) and younger patients. No dose adjustment is necessary with fidaxomicin in elderly patients.

HIV-infected Patients

According to the prescribing label, nitazoxanide (Alinia) tablets and suspension have not been studied in the treatment of diarrhea caused by *G. lamblia* in immunodeficient patients, including HIV-infected patients. Nitazoxanide has not been shown to be superior to placebo for the treatment of diarrhea caused by *C. parvum* in HIV-infected or immunodeficient patients.

In a manufacturer-sponsored, compassionate-use study based in the U.S., nitazoxanide has been shown to be useful in the management of cryptosporidiosis in patients with AIDS.[105] A total of 365 patients (at least 3 years of age) with documented cryptosporidiosis-positive stools and diarrhea were given nitazoxanide 500 to 1,500 mg twice daily. Therapy duration was a median of 62 days. For the patients (n=357) included in the intent-to-treat analysis, 59% achieved a sustained clinical response while on treatment. Clinical responses correlated with *C. parvum* negative stools ($p<0.0001$). No safety issues were noted.

In a study performed in Mexico, patients with HIV with diarrhea due to *C. parvum* were enrolled in a double-blind trial to investigate the safety and efficacy of nitazoxanide in cryptosporidiosis.[106] Patients were randomized to placebo or nitazoxanide 500 mg or 1,000 mg twice daily for 14 days. Patients then crossed over to the alternative (active drug or placebo) treatment. Both nitazoxanide groups produced cure rates (defined as no identified *C. parvum* oocysts post-treatment stool examinations) superior to placebo of 63% ($p=0.016$) for the low-dose nitazoxanide group and 67% ($p=0.013$) for the high-dose nitazoxanide group. Complete diarrhea resolution occurred in 86% of patients considered to have no *C. parvum* oocysts on stool examination. Both doses of nitazoxanide were well tolerated.

Paromomycin is not FDA-approved but is used for the treatment of cryptosporidiosis in HIV-infected patients.[107]

DOSAGES[108,109,110,111,112,113,114,115,116,117]

Drug	Adult Dosing	Pediatric Dosing	Availability
fidaxomicin (Dificid)	**Diarrhea caused by *C. difficile* (> 18 years):** One 200 mg tablet orally twice daily for 10 days with or without food	**Diarrhea caused by *C. difficile* (≥ 6 months):** Weighing 4 kg to < 7 kg – 80 mg/2 mL orally twice daily Weighing 7 kg to < 9 kg – 120 mg/3 mL orally twice daily Weighing 9 kg to < 12.5 kg – 160 mg/4 mL orally twice daily Weighing ≥ 12.5 kg: 200 mg, as a tablet or oral suspension (5 mL), orally twice daily Duration of therapy is 10 days for all body weight ranges	**200 mg tablet***
metronidazole (Flagyl)	**Trichomoniasis:** 250 mg 3 times daily for 7 days Alternative (tablets); 2 g either as a single dose or in 2 divided doses of 1 g each given in the same day **Amebiasis – intestinal infection**: 750 mg 3 times daily for 5 to 10 days **Amebiasis – liver abscess:** 500 mg or 750 mg 3 times daily for 5 to 10 days **Anaerobic infections:** 7.5 mg/kg IV every 6 hours (~500 mg for a 70 kg adult); do not exceed 4 g in 24-hour period Duration of therapy is 7 to 10 days, depending on severity of infection	**Amebiasis**: 35 to 50 mg/kg/day divided into 3 oral doses for 10 days	375 mg capsule 250 mg, 500mg tablet
neomycin	**Pre-operative bowel preparation:** 1 g at 1 pm, 2 pm, and 11 pm on the day preceding 8 am surgery, as an adjunct to mechanical cleansing of the intestine, in combination with 1 g oral erythromycin; additional dosing recommendations for this indication are detailed in the prescribing information **Adjunctive treatment of hepatic encephalopathy:** 4 to 12 g orally every 4 to 6 hours for 5 to 6 days **Chronic hepatic insufficiency:** 4 g daily for an indefinite period	--	500 mg tablet

* Fidaxomicin (Dificid) 200 mg/5 mL granules for oral suspension have been approved by the FDA, but are not commercially available, as of September 1, 2020.

Dosages (continued)

Drug	Adult Dosing	Pediatric Dosing	Availability
nitazoxanide (Alinia)†	**Diarrhea caused by *G. lamblia* or *C. parvum*** (> 12 years): 500 mg tablet every 12 hours with food for 3 days OR 500 mg (25 mL) of oral suspension every 12 hours with food for 3 days	**Diarrhea caused by *G. lamblia* or *C. parvum* – oral suspension:** **1-3 years**: 100 mg (5 mL) of oral suspension every 12 hours with food for 3 days **4-11 years**: 200 mg (10 mL) of oral suspension every 12 hours with food for 3 days **≥ 12 years**: 500 mg (1 tablet) every 12 hours for 3 days OR 500 mg (25 mL) of oral suspension every 12 hours with food for 3 days	500 mg tablet 100 mg/5 mL oral suspension
paromomycin	**Amebiasis, Intestinal:** 25 to 35 mg/kg/day, administered in 3 divided doses with meals, for 5 to 10 days **Hepatic coma:** 4 g daily in divided doses, given at regular intervals for 5 to 6 days	**Amebiasis, Intestinal:** 25 to 35 mg/kg/day, administered in 3 divided doses with meals, for 5 to 10 days	250 mg capsules
rifamycin (Aemcolo)	**Traveler's diarrhea**: 388 mg twice daily for 3 days taken with or without food; swallow whole, do not crush, break or chew tablets; take with a glass of liquid, do not take concomitantly with alcohol	--	194 mg delayed-release tablets
rifaximin (Xifaxan)	**Traveler's diarrhea**: 200 mg 3 times daily for 3 days taken with or without food **Reduction in risk of overt hepatic encephalopathy**: 550 mg twice daily taken with or without food **Irritable Bowel Syndrome with Diarrhea**: 550 mg 3 times daily for 14 days May repeat course twice more with recurrence for a maximum of 3 treatment cycles	--	200 mg, 550 mg tablets
secnidazole (Solosec)	**Bacterial vaginosis:** 2 g taken orally as a single dose with or without food Sprinkle contents of packet onto applesauce, yogurt, or pudding; consume entire mixture within 30 minutes – may be followed by a glass of water; do not crush or chew the granules	--	2 g oral granules in a unit-of-use foil packet

† Nitazoxanige (Alinia) suspension is not bioequivalent to the tablets.

Dosages (continued)

Drug	Adult Dosing	Pediatric Dosing	Availability
tinidazole (Tindamax)	**Trichomoniasis**: 2 g as a single dose taken with food; treat sexual partners with the same dose and at the same time **Giardiasis**: 2 g as a single dose taken with food **Amebiasis, Intestinal:** 2 g daily for 3 days with food **Amebic liver abscess**: 2 g daily for 3 to 5 days with food **Bacterial vaginosis:** 2 g once daily for 2 days taken with food or 1 g once daily for 5 days taken with food	**Giardiasis** (> 3 years old): 50 mg/kg (up to 2 gm) as a single dose given with food **Amebiasis** (> 3 years old): 50 mg/kg/day (up to 2 g per day) for 3 days with food **Amebic liver abscess** (> 3 years old): 50 mg/kg/day (up to 2 g per day) for 3 to 5 days with food	250 mg *(generic only),* 500 mg tablets
vancomycin (Firvanq, Vancocin)	***C. difficile* associated diarrhea:** 125 mg orally 4 times daily for 10 days **Staphylococcal enterocolitis:** 500 mg to 2 g orally daily in 3 or 4 divided doses for 7 to 10 days	***C. difficile* associated diarrhea**: 40 mg/kg/day given in 3 to 4 divided doses for 7 to 10 days (not to exceed 2 g per day) **Staphylococcal enterocolitis:** 40 mg/kg/day divided into 3 to 4 doses per day for 7 to 10 days (not to exceed 2 g per day)	Oral liquid: kit that contains 3.75 g or 7.5 g (to make 50 mg/mL) or 7.5 g or 15 g (to make 50 mg/mL) vancomycin powder for oral solution and premeasured grape-flavored diluent (Firvanq) 125 mg, 250 mg capsules (Vancocin)

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials published in the last 10 years are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship funding must be considered, the studies in this review have also been evaluated for validity and importance.

Many of the comparative studies in this class are older, potentially limiting their modern applicability; however, the following information has been demonstrated in clinical trials and is included for historical reference.

Recent clinical studies regarding use of paromomycin for the treatment of intestinal amebiasis or hepatic coma are lacking.

In a study comparing pre-operative administration of antibiotics in patients undergoing elective colorectal resection surgery, no difference was found in wound infection, suture dehiscence, urinary infections, pneumonia, postoperative ileus, or intra-abdominal abscess when treated with 1 of the following regimens: multiple doses of neomycin and metronidazole, a single dose of neomycin and metronidazole, or no oral antibiotics.[118] However, both nausea and vomiting were higher in the groups receiving oral antibiotics.

Two trials have assessed the effectiveness of rifaximin (Xifaxan) versus ciprofloxacin (Cipro) in adult travelers to non-U.S. countries who developed traveler's diarrhea.[119,120] Both trials reported a similar median time to passage of last unformed stool with each regimen. One of these trials also included a placebo group, and found that both treatment groups were superior to placebo in this measure. Notably, dosing of rifaximin was higher than the approved dose for this indication in 1 of the trials. Another trial compared the effectiveness of rifaximin to trimethoprim-sulfamethoxazole (Bactrim®) in Americans with acute diarrhea traveling outside the country.[121] No statistically significant difference was found in duration of diarrhea, eradication of enteropathogens, or clinical failure between the 2 agents.

Similarly, no difference was found between treatments in a comparison of tinidazole (Tindamax) and metronidazole (Flagyl) for the treatment of vaginal trichomoniasis.[122]

The efficacy of rifamycin (Aemcolo) was evaluated in two randomized, multicenter, controlled phase 3 clinical trials.[123,124] Trial 1, enrolling 264 patients, provided the primary evidence for the efficacy of rifamycin and was conducted at clinical sites in Guatemala and Mexico. Trial 2, enrolling 835 patients, provided supportive evidence and was conducted in India, Guatemala, and Ecuador. Rifamycin demonstrated superiority to placebo ($p = 0.0008$) and non-inferiority to ciprofloxacin for the primary endpoint of time to last unformed stool ($p = 0.0035$).

Bacterial Vaginosis (BV)

secnidazole (Solosec) versus placebo

The safety and efficacy of secnidazole was evaluated in a phase 3 placebo-controlled trial that included 189 non-pregnant women (ages 18 to 54) with a clinical diagnosis of BV based on Amsel criteria (off-white vaginal discharge, vaginal pH ≥ 4.7, clue cells [epithelial cells with adhering bacteria] ≥ 20% on microscopy of vaginal sample, and positive 10% KOH whiff test) and a Nugent score ≥ 4.[125,126] Patients were randomized (2:1) to a single oral dose of secnidazole 2 g or placebo. The primary efficacy endpoint of clinical outcome response (COR), which was achieved in 53.3% of patients treated with secnidazole versus 19.3% with placebo ($p<0.001$) at days 21 to 30.

secnidazole (Solosec) versus metronidazole

A multicenter, prospective, randomized (1:1), double-blind, double-dummy, phase 3 trial conducted in France was designed according to FDA guidelines to compare the efficacy of secnidazole with

metronidazole in 577 non-pregnant women aged 18 to 65 years with clinical signs of BV.[127] Patients were randomized 1:1 to a single dose of oral secnidazole 2 g or oral metronidazole 500 mg twice daily for 7 days. The primary endpoint of therapeutic response was achieved at similar rates in patients treated with secnidazole or metronidazole, across all analysis populations. Non-inferiority was achieved. Therapeutic success rates found at day 14 were consistent with rates reported at day 28.

C. difficile-Associated Diarrhea (CDAD)

In a review of CDI studies, oral vancomycin was found to have a lower failure rate for the treatment of CDI compared to metronidazole.[128]

fidaxomicin (Dificid) versus vancomycin

Safety and efficacy comparisons between oral fidaxomicin and oral vancomycin were conducted in the US, Canada, and Europe.[129] A randomized, double-blind, multicenter, non-inferiority trial was conducted by enrolling patients between April 2007 and December 2009. Patients enrolled were > 16 years of age and diagnosed with acute, toxin positive *C. difficile* infection. These patients were randomly assigned 1:1 to receive 200 mg of fidaxomicin orally every 12 hours, or 125 mg vancomycin orally every 6 hours for 10 days. The primary endpoint was clinical cure, defined as resolution of diarrhea and no further need for treatment. Of the 535 patients enrolled, 270 were assigned to the fidaxomicin group and 265 to vancomycin therapy. Twenty-six patients were excluded, leaving 509 in the modified intention-to-treat population. A total of 198 (91.7%) of 216 patients receiving fidaxomicin achieved clinical cure compared to 213 (90.6%) of 235 patients who were given vancomycin. This met the criteria for non-inferiority (one-sided 97.5% confidence interval [CI], -4.3%). Subgroup analysis also showed outcomes in the 2 treatment groups did not differ significantly. Occurrences of treatment-emergent adverse events were also found to be similar.

Another study also compared fidaxomicin to vancomycin with the primary endpoint being the rate of clinical outcomes of *C. difficile* infection (CDI) treatment when advancing age is considered.[130] Regression modeling of results from 2 double-blind randomized multicenter studies on treatment outcomes of both primary and first recurrent cases for the effects of age was done. Cure was considered resolution of diarrhea, and recurrence was defined as diarrhea within 4 weeks of successful therapy. Participants were randomized into studies in the US, Canada, and Europe, totaling 999 subjects. Those patients with toxin-positive CDI were randomized to receive fidaxomicin (200 mg twice daily x 10 days) or vancomycin (125 mg 4 times daily x 10 days). The participants were divided into groups of 18 to 40 years and in 10-year increments thereafter. Regression demonstrated a 17% lower cure rate, 17% greater recurrence rate, and a 13% lower sustained clinical response rate would appear by advancing decade in those ≥ 40 years of age ($p<0.01$ each). The results associated fidaxomicin treated patients with a > 50% lower relative risk for recurrence than in those treated with vancomycin ($p<0.001$). Fidaxomicin treatment was associated with a 60% lower risk of recurrence than vancomycin after adjusting for age, concomitant antibiotics, and *C. difficile* strain.

A phase 3, multicenter, investigator-blinded trial compared the safety and efficacy of oral fidaxomicin and vancomycin in pediatric patients 6 months to < 18 years of age with CDAD.[131] A total of 142 patients were randomized 2:1 to fidaxomicin or vancomycin. Patients were stratified by age group as follows: 6 months to < 2 years (n=30), 2 to < 6 years (n=49), 6 to < 12 years (n=40), and 12 to < 18 years (n=29). Other baseline characteristics were similar between the groups. Clinical response for patients < 2 years of age was defined as the absence of watery stools for ≥ 2 consecutive days during therapy and

the patient continued to be well with no further CDAD therapy required through 2 days after completing treatment. Clinical response for patients ≥ 2 to < 18 years of age was defined as < 3 unformed bowel movements for ≥ 2 consecutive days during therapy and the patient continued to be well with no further CDAD therapy required through 2 days after completion of treatment. Sustained clinical response was defined as the percentage of patients with confirmed clinical response and no CDAD recurrence through 30 days after stopping therapy. In the overall population, clinical response was reported in 77.6% and 70.5% of patients in the fidaxomicin and vancomycin groups, respectively (difference, 7.5%; 95% CI, -7.4% to 23.9%). In addition, 68.4% and 50% of patients in each group, respectively, reported sustained response (difference 18.4%; 95% CI, 1.5% to 35.3%). Higher rates of clinical response and sustained response were reported with fidaxomicin compared to vancomycin for all age groups except in patients < 2 years. Regarding clinical response rates across the age groups (fidaxomicin versus vancomycin): < 2 years, 65% versus 90%; ≥ 2 to < 6 years, 78.1% versus 75%; ≥ 6 to < 12 years, 88.5% versus 50%; and ≥ 12 to < 18 years, 75% versus 62.5%. Regarding sustained response rates across the age groups (fidaxomicin versus vancomycin): < 2 years, 55% versus 70%; ≥ 2 to < 6 years, 65.6% versus 50%; ≥ 6 to < 12 years, 84.6% versus 40%; and ≥ 12 to < 18 years, 65% versus 37.5%.

metronidazole (Flagyl) versus vancomycin (Vancocin)

In a randomized, double-blind, placebo-controlled trial, 172 patients with *C. difficile*-associated diarrhea were stratified according to disease severity from mild to severe disease.[132] Patients were randomized to metronidazole 250 mg orally 4 times daily or oral vancomycin 125 mg 4 times daily for 10 days; a placebo was given to all patients in addition to the assigned drug. One-hundred fifty patients completed the trial. For patients with mild disease, treatment with metronidazole (90%) or vancomycin (98%) resulted in clinical cure (p=0.36). For patients with severe disease, metronidazole treatment resulted in clinical cure in 76% of patients compared to 97% of patients receiving vancomycin (p=0.02). Patients were followed up for 21 days to assess cure, treatment failure, relapse, or intolerance. Recurrence of clinical symptoms occurred in 15% and 14% of patients receiving metronidazole and vancomycin, respectively.

nitazoxanide (Alinia) versus vancomycin

In a randomized, double-blind study, a total of 50 patients with CDI were randomized to receive either nitazoxanide (n=23) or vancomycin (n=27) for 10 days.[133] Initial response was the absence of all CDI symptoms between days 11 and 13; final response was the absence of all CDI symptoms by day 31. Time to resolution was similar in both groups in patients who completed therapy. Initial response was reported in 74% in the vancomycin group compared to 77% in the nitazoxanide-treated group (95% CI, -24 to 28). Final response was 87% in the vancomycin group versus 94% of those treated with nitazoxanide (95% CI, -18 to 30). It was concluded that nitazoxanide is as effective as vancomycin in treating CDI; due to the small study sample, conclusions as to noninferiority of nitazoxanide to vancomycin cannot be deduced.

fidaxomicin (Dificid) versus vancomycin

In a phase 3 clinical trial, investigators assessed the efficacy of fidaxomicin versus oral vancomycin in 629 patients, of whom 548 could be evaluated for the per-protocol analysis.[134] Inclusion criteria were acute symptoms of *C. difficile* infection and a positive result on a stool toxin test. Patients were randomly assigned to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily)

orally for 10 days. The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis (15.4% versus 25.3%; p=0.005) and the per-protocol analysis (13.3% versus 24.0%; p=0.004). The lower rate of recurrence was seen in patients with non–North American Pulsed Field type 1 strains. The adverse-event profile was similar for the 2 therapies.

Hepatic Encephalopathy

No significant difference was found in a clinical trial comparing the effectiveness of neomycin to rifaximin (Xifaxan) for the treatment of hepatic encephalopathy due to cirrhosis.[135] However, the total daily dose in this trial was 100 mg higher than the FDA approved total daily dose for this indication.

rifaximin (Xifaxan) versus lactulose

A prospective, double-blind, randomized controlled trial consisting of 120 persons with overt hepatic encephalopathy (HE) were randomized into either Group A: lactulose plus rifaximin (1,200 mg/day; n=63) or Group B: (lactulose plus placebo; n=57).[136] The primary endpoint was complete reversal of HE; secondary endpoints were hospital stay and mortality. A total of 120 patients (mean age 39.4 ± 9.6 years; male/female ratio 89:31) were included in the study. A total of 37 (30.8%) patients were in Child-Turcotte-Pugh (CTP) class B and 83 (69.2%) were in CTP class C. Mean CTP score was 9.7 ± 2.8 and the MELD (model for end-stage liver disease) score was 24.6 ± 4.2. At the time of admission, 22 patients (18.3%) had grade 2, 40 (33.3%) had grade 3, and 58 (48.3%) had grade 4 HE. Of the patients, 48 (76%) in group A compared with 29 (50.8%) in group B had complete reversal of HE (p<0.004). Group B (lactulose) had more deaths than did Group A (23.8% versus 49.1%; p<0.05), deaths due to sepsis were significantly higher in Group B (7/17; p=0.01), with no differences in death due to gastrointestinal bleed or hepatorenal syndrome. Patients in Group A (lactulose and rifaximin) had shorter hospital stays, as well (5.8 ± 3.4 versus 8.2 ± 4.6 days, p=0.001). Therefore, it was concluded that, in cases of HE, the combination of lactulose and rifaximin is more effective than lactulose alone.

Irritable Bowel Syndrome with Diarrhea (IBS-D)

rifaximin (Xifaxan) versus placebo

The efficacy of rifaximin for the treatment of IBS-D was evaluated in 3 randomized, multi-center, double-blind trials.[137] In Studies 1 and 2, a total of 1,258 adults with IBS-D (based on Rome II criteria) received rifaximin 550 mg 3 times a day or placebo for 14 days. Patients were then followed for an additional 10-week treatment-free period. In Studies 1 and 2, adequate relief of IBS symptoms was experienced by 41% of patients in each trial treated with rifaximin and 31% and 32% treated with placebo, respectively. In addition, more patients in both trials experienced at least a 30% decreased in abdominal pain and had weekly mean stool consistency score < 4 (loose stool) for at least 2 weeks during the month after the treatment period. Study 3 included 2,579 adults with IBS-D (according to Rome III Criteria). It included an open-label phase in which patients received rifaximin for 14 days followed by a 4 week observational period. Of the 2,438 evaluable patients, 1,074 (44%) responded to initial treatment in both abdominal pain and stool consistency; these patients were then observed over 22 weeks for continued response or recurrence of IBS-symptoms. A total of 636 patients had symptom recurrence and were randomized to a double-blind phase to receive rifaximin 550 mg 3 times a day or

placebo for 2 additional 14-day courses of therapy that were separated by 10 weeks with no treatment. In the double-blind phase, 17.1% of rifaximin-treated patients and 11.7% of placebo-treated patients responded to the first repeat treatment and did not have recurrence during the follow-up period.

META-ANALYSES

An analysis of randomized controlled trials evaluated the efficacy of antibiotic therapy for CDAD.[138] The analysis also aimed to identify the most effective antibiotic treatment for CDAD in adults and to determine the need for stopping the causative antibiotic during therapy. A total of 15 studies with 1,152 participants with diarrhea who recently received antibiotics for infections other than *C. difficile* were included. Definition of diarrhea varied among studies from 2 loose stools per day with associated fever or at least 6 loose stools in 36 hours. Nine different antibiotics were investigated: vancomycin, metronidazole, fusidic acid, nitazoxanide, teicoplanin (not available in the U.S.), rifampin, rifaximin, bacitracin, and fidaxomicin. No single antibiotic was clearly superior to the others.

Two meta-analyses evaluating the treatment of cryptosporidiosis in immunocompromised individuals were published.[139,140] Nitazoxanide reduced the oocyst burden compared to placebo [relative risk (RR) 0.52; 95% CI, 0.3 to 0.91]. Benefits in the HIV-positive participants were not clear (RR, 0.71; 95% CI, 0.36 to 1.37).

A meta-analysis including 22 studies (n=3,201) in patients with *C. difficile* infection included the following antibiotics: metronidazole, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin, bacitracin, cadazolid, LFF517, surotomycin and fidaxomicin.[141] Of the drugs included in this review, vancomycin was found to be slightly more effective than metronidazole for achieving symptomatic cure (79% versus 72%; RR, 0.9 [95% CI, 0.84 to 0.97]; moderate quality evidence) and fidaxomicin was found to be more effective than vancomycin for achieving symptomatic cure (71% versus 61%; RR, 1.17 [95% CI, 1.04 to 1.31]; moderate quality evidence). Studies including other agents were of low quality.

SUMMARY

A variety of antibiotics are utilized in the treatment of gastrointestinal related infections and bacterial vaginosis.

Rifaximin (Xifaxan) and rifamycin (Aemcolo) have been shown to reduce the duration of loose unformed stool due to traveler's diarrhea compared to placebo. Rifaximin and rifamycin are not systemically absorbed and, therefore, have relatively few systemic adverse effects. Rifaximin and rifamycin have been shown to have similar efficacy compared to ciprofloxacin for treatment of traveler's diarrhea. Rifaximin was approved for use for irritable bowel syndrome with diarrhea in 2015, and current clinical guidelines recommend its use over no drug treatment. Rifaximin and neomycin are approved for hepatic encephalopathy. They have been compared in only 1 small double-blind trial using a rifaximin dosage slightly higher than FDA-approved dosage. Neomycin is additionally indicated for pre-operative bowel preparation.

Nitazoxanide (Alinia) is the only drug approved in this review for the treatment of cryptosporidiosis. Paromomycin, although not FDA approved, is used for treatment of cryptosporidiosis.

Tinidazole (Tindamax) and metronidazole oral are recommended by the CDC for the treatment of trichomoniasis. Tinidazole and metronidazole had similar efficacy in a single-dose study for the

treatment of vaginal trichomoniasis. Tinidazole and nitazoxanide are indicated for the treatment of giardiasis. Tinidazole offers a single-dose regimen, while nitazoxanide is available as an oral suspension for this indication.

Tinidazole and metronidazole (Flagyl) are oral alternatives to vaginal preparations for the management of bacterial vaginosis (BV) and have similar cure rates. Secnidazole (Solosec) has a longer half-life than tinidazole and metronidazole and is available as a single-dose oral preparation for BV. Similar cure rates between secnidazole and metronidazole have been demonstrated.

Metronidazole, tinidazole, and paromomycin are also indicated for the treatment of intestinal amebiasis.

The Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) updated their guidelines on *C. difficile* infection in 2017. The guidelines recommend oral vancomycin or fidaxomicin as first-line therapy for mild-to-moderate *C. difficile* infection in adults. Oral vancomycin is the drug of choice for an initial episode of severe *C. difficile* infection. For recurrent *C. difficile* infection in adults, vancomycin for 10-days is recommended followed by either a taper over several weeks and pulsed course of vancomycin or a 10-day course of fidaxomicin; probiotics are also recommended by the guidelines. In children, vancomycin or metronidazole is recommended as first-line treatment for initial and first recurrence of mild-to-moderate *C. difficile* infection, and vancomycin is preferred for severe infection or multiple recurrences. Fidaxomicin was not FDA-approved to treat pediatric patients with *C. difficile* infection at the time the updated guidelines were published.

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