SUPPLEMENT ARTICLE

Metronidazole Is Still the Drug of Choice for Treatment of Anaerobic Infections

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Metronidazole has been used for the treatment of infections for >45 years and is still successfully used for the treatment of trichomoniasis, amoebiasis, and giardiasis. Anaerobic bacterial infections caused by *Bacteroides* species, fusobacteria, and clostridia respond favorably to metronidazole therapy. Good clinical results in the treatment of vaginosis due to *Gardnerella vaginalis* have also been reported. Rates of resistance to metronidazole are still generally low; however, several studies have reported decreased susceptibility among *Bacteroides* species, as well as different mechanisms of resistance. Metronidazole-resistant *Helicobacter pylori* strains have been described, but combination therapy (eg, metronidazole, amoxicillin, or clarithromycin plus omeprazole) is still recommended for eradication of this pathogen in patients with gastroduodenal ulcers. Metronidazole is considered to be a cost-effective drug because of its low cost, good activity against pathogenic anaerobic bacteria, favorable pharmacokinetic and pharmacodynamic properties, and minor adverse effects. Metronidazole is still the criterion standard for therapy of anaerobic infections, as was described by Tally and colleagues 35 years ago.

Metronidazole is an antimicrobial agent that has been used in clinical medicine for >45 years. It was originally indicated for the management of infection caused by *Trichomonas vaginalis* and was then shown to be effective against other protozoal infections, such as amebiasis and giardiasis. To our knowledge, the first report on the effect of metronidazole for the management of anaerobic infections was published in 1962 by Shinn [1]. In that investigation, acute ulcerative gingivitis was successfully treated by using metronidazole therapy. However, major advances were made by Tally et al [2, 3] at the Wadsworth Veterans Hospital in Los Angeles 10 years later; Tally and colleagues showed that metronidazole is useful in the treatment of systemic anaerobic infections, including those caused by *Bacteroides fragilis*. Later, metronidazole was introduced for the management of *Clostridium difficile* infection and is still recommended as an alternative to vancomycin for treatment of this infection. Treatment regimens for the eradication of *Helicobacter pylori* still include metronidazole in combination with other agents. Metronidazole is also indicated for the treatment of bacterial vaginosis caused by *Gardnerella vaginalis*. Despite 45 years of extensive use, metronidazole remains the criterion standard for the management and prophylaxis of anaerobic infections (Figure 1).

THERAPEUTIC USE OF METRONIDAZOLE FOR ANAEROBIC INFECTIONS

Metronidazole is highly active against gram-negative anaerobic bacteria, such as *B. fragilis,* and gram-positive anaerobic bacteria, such as *C. difficile*. The pharmacokinetic and pharmacodynamic properties of the drug are favorable, and it is available as oral, intravenous, vaginal, and topical formulations. After oral administration, metronidazole is well absorbed, and its peak plasma concentrations occur 1–2 h after administration. Metronidazole is the major component in the plasma, but lower amounts of active metabolites are also present. Protein binding is low; <20% of the circulating metronidazole is bound to plasma proteins.

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Figure 1. Francis P. Tally *(right)* and Carl Erik Nord *(left)* discussing the use of metronidazole for the prophylaxis and treatment of anaerobic infections at Gifu University Medical School in Gifu, Japan, in 1985. Photograph: Professor Kazue Ueno, Gifu, Japan.

Both the parent compound and the metabolite have in vitro bactericidal activity against most strains of anaerobic bacteria, except *C. difficile*, and in vitro trichomonacidal activity. The concentrations of metronidazole in cerebrospinal fluid and saliva are similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses. The major route of elimination of metronidazole and its metabolites is the urine, with fecal excretion accounting for a minor part. Metronidazole is metabolized in the liver, and the simultaneous administration of drugs that increase or decrease the microsomal liver enzyme activity may lead to altered plasma concentrations. Metronidazole potentiates the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. The metabolism of alcohol may be affected by metronidazole in some patients, leading to intolerance.

The safety profile of metronidazole is well known, and adverse effects are considered mainly to be mild to moderate in severity. The most common adverse reactions reported involve the gastrointestinal tract. Rare serious adverse reactions, including convulsive seizures and peripheral neuropathy, characterized mainly by numbness or paresthesia of an extremity, have been reported in patients receiving prolonged metronidazole treatment.

A therapeutic review article published >10 years ago by Freeman et al [4] summarizes the clinical data on the therapeutic use of metronidazole for anaerobic infections. Studies published during 1998–2008 confirm these clinical reports.

METRONIDAZOLE IN CLINICAL PRACTICE

Metronidazole is effective for the management of anaerobic infections, such as intra-abdominal infections, gynecologic infections, septicemia, endocarditis, bone and joint infections, central nervous system infections, respiratory tract infections, skin and skin-structure infections, and oral and dental infections. Metronidazole is also used as prophylaxis before abdominal and gynecological surgical procedures to reduce the risk of postoperative anaerobic infection. For treatment of mixed aerobic and anaerobic infection, metronidazole should be used in combination with other antibacterial agents that are appropriate for the treatment of the aerobic infection, because it is ineffective against aerobic bacteria (Table 1). Metronidazole also produces good clinical results when it is used for treatment of giardiasis, trichomoniasis, and amoebiasis, and it is recommended for the treatment of patients with bacterial vaginosis or nonspecific vaginitis caused by *G. vaginalis*.

In accordance with international guidelines, metronidazole is also a component of multidrug regimens (eg, in combination with omeprazole, clarithromycin, and amoxicillin) for therapy

Table 1. Clinical Uses for Metronidazole

Clinical use
Anaerobic infection
Central nervous system
Oral and dental tissue
Respiratory tract
Intra-abdominal
Gynecologic
Intestinal infection *(Clostridium difficile)*
Endocarditis
Septicemia
Bone and joint tissue
Skin and soft tissue
Surgical prophylaxis
Protozoal infection
Trichomoniasis
Amoebiasis
Giardiasis
Other disease
Stomach and/or intestinal ulcer *(Helicobacter pylori)*
Rosacea
Bacterial vaginosis
Crohn disease

of *H. pylori* infections, such as gastroduodenal ulcers. In addition, metronidazole treatment is considered for patients with Crohn disease that does not respond to sulfasalazine. Topically applied metronidazole has been effective for the treatment of moderate to severe rosacea. In addition, metronidazole gel is used in dentistry for the treatment of periodontitis in patients for whom mechanical debridement is not successful or possible.

Metronidazole therapy for* C. difficile *infection. An increasing number of clinical failures with metronidazole treatment of *C. difficile* infection has been reported during the past few years [5]. The reasons for the diminished effectiveness of metronidazole, compared with vancomycin, are not obvious. Most *C. difficile* strains are still susceptible to metronidazole. Pharmacokinetic and pharmacodynamic properties of metronidazole have been thought to be responsible for the clinical failures. For patients with severe *C. difficile* infection, vancomycin therapy is recommended in North America but has yielded variable clinical responses [6]. Therefore, new agents are being investigated for this indication. Of the antimicrobial agents, fidoxamicin, ramoplanin, and rifaximin have been demonstrated to be active against *C. difficile* [7]. Another approach has been to develop a toxin binder, tolevamer; however, phase 3 studies showed that it is inferior to vancomycin therapy. Monoclonal antibodies and a *C. difficile* vaccine are also undergoing phase 2 trials. Probiotics, such as *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii,* have not produced favorable clinical results. Treatment of patients who experience multiple relapses of *C. difficile* infection has proved to be the greatest challenge. One new approach may be to use metronidazole in various combinations with these new antimicrobials, toxin binders, immunomodulators, nontoxigenic *C. difficile* strains, and/or probiotics. Clinical trials with therapeutic combinations of these agents are recommended.

Metronidazole therapy for intra-abdominal infections. Complicated and serious intra-abdominal infections frequently occur in clinical medicine, and their treatment requires advanced hospital resources. The management of intra-abdominal infections has developed significantly during the past 10 years. Proper use of antimicrobial agents is mandatory. New guidelines for the diagnosis and management of complicated intra-abdominal infections in adults and children have been written by the Infectious Diseases Society of America, the Surgical Infection Society, and the Pediatric Infectious Disease Society and are now under review (J. S. Solomkin, personal communication) (Table 2). These guidelines separate the infections into 2 categories: community-acquired and health care–associated infections. For moderate community-acquired infections in adults, metronidazole in combination with cefazolin, cefuroxime, ceftriaxone, or a quinolone is recommended. Metronidazole together with ceftazidine or cefepime or single-drug therapy with carbapenems and piperacillin-tazobactam is suggested for the management of severe community-acquired intra-abdominal infection. For children, metronidazole in combination with cefuroxime or ceftriaxone is recommended. An alternative agent is cefoxitin. Oral metronidazole in combination with oral second- or third-generation cephalosporin may also be effective. Health care–associated intra-abdominal infections are often caused by more–drug-resistant microorganisms, such as *Staphylococcus aureus,* enterococci, *Pseudomonas aeruginosa, Acinetobacter baumanni, Klebsiella* species, *Enterobacter* species, *Proteus* species, and *Candida* species. Multidrug treatment, based on microorganism susceptibility patterns, is recommended for these infections.

Convalescing patients with complicated intra-abdominal infections can often be treated with oral antimicrobials. For adults, metronidazole in combination with a fluoroquinolone or trimethoprim-sulfamethoxazole may be effective. Oral metronidazole in combination with an oral second- or third-generation cephalosporin can be provided to children.

The favorable efficacy of metronidazole for the management of intra-abdominal infections was recently indicated by Matthaiou et al [8] in a meta-analysis comparing treatment with metronidazole and ciprofloxacin with treatment with broad-spectrum β-lactam antibiotics. The authors found that, for patients with intra-abdominal infections, treatment with metronidazole and ciprofloxacin was associated with greater success than was treatment with β-lactam agents. Recently, Wang et al [9] showed that 1 g of metronidazole given intravenously once daily for treatment of severe intra-abdominal and pelvic infec-

Table 2. Antimicrobial Agents for Intra-Abdominal Infections that Are Recommended by the Infectious Diseases Society of America, the Surgical Infection Society, and the Pediatric Infectious Diseases Society

Treatment	Community-acquired pediatric infection	Community-acquired infection, adult		Health care–associated infections: all forms of intra-abdominal infection
		Perforated or abscessed appendicitis and other infections of mild to moderate severity	Peritonitis and other infections accompanied by severe physiologic disturbance	
Single agents	Meropenem, imipenem-cilastatin, piperacillin-tazobactam, or cefoxitin	Moxifloxacin, ertapenem, tigecycline, or cefoxitin	Meropenem, doripenem, imipenem-cilastatin, or piperacillin-tazobactam	Meropenem, doripenem, imipenem-cilastatin, or piperacillin-tazobactam (each in combination with vancomycin)
Multidrug regimens	Cefotaxime, ceftriaxone, ceftazidime, or cefepime (all in combination with metronidazole or clindamycin)	Cefazolin, cefuroxime, or ceftriaxone (each in combination with metronidazole)	Cefepime or ceftazidime (each in combination with metronidazole); levofloxacin or ciprofloxacin (each in combination with metronidazole)	Cefepime or ceftazidime (each in combination with metronidazole and vancomycin)

tions has pharmacokinetic and pharmacoeconomic advantages over treatment administered every 6–8 h.

MECHANISMS OF ACTION AND RESISTANCE TO METRONIDAZOLE

Metronidazole is active against a variety of protozoa and bacteria. It enters the cell as a prodrug by passive diffusion and is activated in either the cytoplasm of the bacteria or specific organelles in the protozoa, whereas drug-resistant cells are deficient in drug activation. The metronidazole molecule is converted to a short-lived nitroso free radical by intracellular reduction, which includes the transfer of an electron to the nitro group of the drug. This form of the drug is cytotoxic and can interact with the DNA molecule. The actual mechanism of action has not yet been fully elucidated but includes the inhibition of DNA synthesis and DNA damage by oxidation, causing single-strand and double-strand breaks that lead to DNA degradation and cell death. The activated reduced metronidazole molecule binds nonspecifically to bacterial DNA, inactivating the organism's DNA and enzymes and leading to a high level of DNA breakage, with immediate action of the drug but no cell lysis [10, 11]. Aerobic cells lack electron-transport proteins with sufficient negative redox potential; therefore, the drug is active against only bacteria with anaerobic metabolisms, even though the drug is effective against some microaerophils, such as *H. pylori.* In addition, reoxidation can occur in the presence of molecular oxygen and can convert the compound back to its original inactive form [12]. Electron donors involved in the reduction process vary, depending on the organism. In anaerobic bacteria, the electron acceptors flavodoxin and ferredoxin, which receive electrons from the pyruvate-ferredoxin oxireductase complex, play important roles, although other enzymes and electron transfer components may also be involved in the process. Each of these acceptors has a reduction potential lower than that of the metronidazole molecule and will thereby donate its electrons to the drug [12]. In *H. pylori*, a separate mechanism seems to be involved in metronidazole susceptibility that includes a 2-electron transfer step in the reduction of the compound using an oxygen-insensitive nitroreductase (rdxA). Metronidazole-resistant clones are typically mutated in the *rdxA* gene [10, 13].

Several mechanisms of resistance to metronidazole in anaerobic bacteria have been proposed. These mechanisms differ among organisms, but the primary basis for resistance is decreased uptake of the drug or altered reduction efficiency (Table 3). These 2 mechanisms act together; decreased activity of the nitroreductase leads to decreased uptake of the drug. Other mechanisms include active efflux, inactivation of the drug, and increased DNA damage repair [10]. Specific resistance genes *(nim)* conferring resistance to nitroimidazoles have been isolated in different genera of gram-positive and gram-negative anaerobic bacteria, including *Bacteroides* species [14, 15]. Transfer of these genes has been shown to confer resistance to metronidazole in recipients infected with susceptible virus [16]. The *nim* genes encode an alternative reductase that can convert nitroimidazole to a nontoxic derivative, thereby circumventing the toxic effect that causes breakage of the DNA [12, 17]. Thus far, 7 members of the genes—from *nim*A through *nim*G—have been found, although the detection of new variants indicates the existence of an even higher variety of these genes in the anaerobic community than was initially expected. Studies on the prevalence of the *nim* genes have recorded an overrepre-

Table 3. Proposed Mechanisms of Resistance to Metronidazole in Anaerobic Bacteria

Mechanism of resistance
Reduced drug activation
Inactivation of the drug by alternative pathway for drug activation and/or reduction (*nim* genes)
Prevention of entry of the drug or efflux
Altered DNA repair

sentation of *nim*A among anaerobes [15]. The *nim* genes are usually found on low-copy plasmids but have also been located on the bacterial chromosome and have been shown to be transferable by a conjugative process. Specific regulatory elements known as insertion sequences are often associated with the *nim* genes. The insertion sequence elements are mobile and thought to be involved in plasticity of prokaryote genomes. They have been assigned a role in the expression of several resistance genes in *Bacteroides* species, including those for metronidazole, erythromycin-clindamycin, cefoxitin, and carbapenems. These elements can be found on the bacterial chromosome, on plasmids, and in multiple copies [18].

The presence of the *nim* genes is not always associated with resistance, and their actual impact on clinically relevant metronidazole resistance is not yet clear. *nim*-Negative strains, expressing high-level resistance, are sporadically isolated, indicating the importance of additional mechanisms of resistance. Still, the presence of *nim* genes significantly increases the risk of reduced susceptibility to metronidazole [15]. Among >1500 investigated clinical strains in a study by Löfmark et al [15], 2 distinct populations in terms of susceptibility could be recognized according to the minimum inhibitory concentration (MIC) distribution of *nim*-positive and *nim*-negative strains [15]. Thus, a significant relative risk of metronidazole resistance (MIC, $\geqslant$32 mg/L; as defined by the Clinical and Laboratory Standards Institute) among *nim*-positive strains was revealed (odds ratio, 26; 95% confidence interval, 4.6–147), whereas the risk for reduced susceptibility (MIC, $\geqslant$8 mg/L) was even higher among *nim*-positive strains (odds ratio, 53; 95% confidence interval, 19–147). This latter breakpoint divides the normal population of susceptible isolates from those expressing resistance determinants and is also accepted as the European breakpoint for metronidazole resistance [19].

Other mechanisms that may contribute to resistance in *Bacteroides* species include efflux pumps. Few or no data exist on any efflux system in *Bacteroides* species, but overexpression of the efflux pumps is often involved in multidrug resistance in other species and for other antibiotics. Pumbwe et al [20, 21] suggest that efflux overexpression plays a role in metronidazole resistance and can cause low to intermediate resistance to fluoroquinolones and high resistance to β-lactams in clinical *Bacteroides* strains. This mechanism could play an important role in the increased number of isolated clinical multidrug-resistant strains that lack any of the known *nim* genes. Additional investigations are needed. The alteration of DNA repair systems playing a role in metronidazole resistance in *H. pylori* is another incompletely studied mechanism in *Bacteroides* strains. Overexpression of the enzymes involved in the process is correlated with decreased antibiotic susceptibility. A strong candidate is the recA protein; mutants deficient in its expression are sensitive to oxygen stress and to the action of metronidazole. Other genes in the *rec* family have also been suggested for a role in DNA repair, although they have not been as well studied [22].

The mechanism of inducible metronidazole resistance is another feature of the metronidazole drug that could have clinical implications. Reversible and irreversible high-level resistance have been induced in susceptible clinical *Bacteroides* strains with use of subinhibitory concentrations of metronidazole [15, 23]. Subinhibitory concentrations of metronidazole can interfere with the cellular properties of members of the *B. fragilis* group, with implications for their interactions with the host defense [24]. In an in vitro assay, metronidazole resistance was shown to be associated with superior internalization activity of *H. pylori,* providing a protection against antibiotic treatment [25].

METRONIDAZOLE AND THE NORMAL MICROFLORA

Alterations in the bacterial composition and overgrowth of yeasts, as well as selection of resistant strains, have been shown to be associated with metronidazole administration in combination with other agents, such as amoxicillin and clarithromycin [26]. The impact of metronidazole on the normal microflora varies, depending on the body site involved. Concentrations of metronidazole exceeding MIC values of anaerobes are found during treatment in body fluids, such as saliva, which may explain the reduction in the number of oropharyngeal anaerobic bacteria after combination treatment with metronidazole and clarithromycin [27]. In the study by Adamsson et al [27], suppression of the anaerobic flora of the intestine, likely resulting from the administration of clarithromycin, was also recorded. The concentration of active metronidazole in feces is low during administration, because the agent is well absorbed and is excreted primarily by liver metabolism; however, high concentrations have been measured in colon tissue [28]. Only minor changes have been observed in the normal intestinal microflora after oral intake of metronidazole alone. The known clinical efficacy of oral administration of metronidazole in the treatment of *C. difficile* diarrhea and colitis is attributed to a high plasma level combined with enhanced penetration of metronidazole through the damaged colonic mucosa in infected patients [26]. Most of the metronidazole affecting *C. difficile* is thought to reach the gut by diffusion from serum to the intestinal mucosa.

The normal microflora serve as a reservoir of antibiotic-resistance determinants, where some dissemination of resistance can occur [29, 30]. Virtually all genes in *Bacteroides* species that encode resistance to antibiotics, including metronidazole, have been found on transmissible elements

[18, 31]. This transferability may contribute to the spread of resistance; thus far, resistance to metronidazole has remained low.

LEVELS OF RESISTANCE TO METRONIDAZOLE

Resistance among anaerobic pathogens is still generally low; however, the susceptibility patterns of anaerobic bacteria are undergoing changes, and decreases in in vitro susceptibility to various antimicrobials have been reported in recent years. These data are derived predominantly from international and national surveys; individual hospital screenings for susceptibility in anaerobic bacteria remain uncommon (Table 4). The practice in many laboratories of identifying obligate anaerobes by susceptibility to metronidazole is a factor that contributes to probable underestimation of true resistance rates. Growths around disks are presumed to be facultative anaerobes with naturally reduced susceptibility, and these strains have not been investigated further [46]. Consequently, the treatment of anaerobic infections is generally empirical and is based on published reports of susceptibility rates, which emphasizes the importance of reference laboratories providing valid and updated information [47]. A general decrease in susceptibility to metronidazole has been displayed among anaerobes. Most non–spore-forming gram-positive anaerobic bacteria, including isolates of *Actinomyces, Bifidobacterium, Eubacterium, Lactobacillus,* and *Propionibacterium* species, have intrinsically reduced metronidazole susceptibility. Metronidazole resistance in *Sutterella* species has been reported [48]. Susceptibility is still very high in *Fusobacterium, Prevotella,* and *Porphymonas* species; gram-positive anaerobic cocci; and all *Bacteroides* species [34].

Bacteria belonging to the *B. fragilis* group are clinically the most frequently encountered anaerobic pathogens. Metronidazole has been the drug of choice for the treatment of *Bacteroides* infection and remains reliable for this use [49]. The first metronidazole-resistant *Bacteroides* strain was reported in 1978 [50]. Metronidazole resistance among this group is generally lower than 1%, but levels up to 7.5% were reported in the United Kingdom in 1998 [46]. Compared with metronidazole resistance rates of 1.9% in 1995 and 3.8% in 1997, the 7.5% rate could have represented a possible increase in resistance in *B. fragilis* that was achieved with a MIC ⩾32 mg/L, but it might also have represented a selection bias of the material sent to the reference laboratory. The true incidence is difficult to estimate. Low-level metronidazole-resistant strains may be overlooked, because the breakpoint of 32 mg/L that was set by the Clinical and Laboratory Standards Institute is much higher than the 4-mg/L cutoff level for strains isolated in the community. Still, *B. fragilis* resistance to metronidazole is low, according to accepted breakpoints and international data. Reduced susceptibility to metronidazole with MICs of 4–16 mg/L is more frequent (up to 4.5%), indicating the presence of resistance mechanisms [32, 33]. Despite the low levels of resistance to metronidazole, treatment failures attributed to metronidazole resistance have been reported, and multidrug-resistant strains have been identified [51, 52]. In many cases, the infection cannot be associated with a single pathogen be-

Table 4. Selected Published Data on the Distribution of Minimum Inhibitory Concentrations (MICs) to Metronidazole among Clinical Isolates of *Bacteroides fragilis*

Reference	MIC_{50}, mg/L	MIC_{90}, mg/L	Percentage of isolates MIC ⩾8 mg/L	Percentage of isolates MIC ⩾32 mg/L	Number of isolates analyzed	Geographic origin
Hedberg et al [32]	1	2	1.5	0.5	1284	Europe (12 countries)
Snydman et al [33]	ND	ND	<0.5	<0.5	5225	United States
Aldridge et al [34]	1	2	ND	0	542	United States
Tally et al [35]	0.5	1	0	0	753	United States
Fille et al [36]	0.25–0.5	0.5	0	0	87	Austria
Vieira et al [37]	1–2	1–2	ND	0	197	Brazil
Wybo et al [38]	0.5	1	ND	1	238	Belgium
Behra-Miellet et al [39]	1	2	4.5	0.5	359	France
Horn et al [40]	1 (1991), 2 (1997)	2 (1991), 4 (1997)	ND	0.5 (1991), 2 (1997)	200	Canada
Kommedal et al [41]	0.25	0.5	0	0	202	Norway
Koch et al [42]	0.5	0.5	ND	0	44	South Africa
Roberts et al [43]	1	1	0	0	51	New Zealand
Ulger et al [44]	ND	2	ND	0	45	Turkey
Papaparaskevas et al [45]	0.5	1	ND	0	82	Greece

NOTE. Some variations could be seen between species within the group. The breakpoints are in accordance with the Clinical and Laboratory Standards Institute (CLSI; susceptible, ⩽8 mg/L; intermediate, 16 mg/L; resistant, ⩾32 mg/L). MIC_{50}, MIC required to inhibit the growth of 50% of organisms; MIC_{90}, MIC required to inhibit the growth of 90% or organisms; ND, no data.

cause of the lack of identification and susceptibility testing of anaerobes and because of the polymicrobial nature of anaerobic infections, which are also frequently cleared by drainage or surgery. Results of retrospective and prospective studies have correlated clinical failure with antibiotic resistance in anaerobic bacteria [47, 53].

No significant clinical resistance to metronidazole or vancomycin in *C. difficile* strains has been reported. Some metronidazole-resistant *C. difficile* strains have been isolated; however, they have seldom been isolated in toxigenic bacteria. In a study by Wong et al [54] that reported the first well-documented case of a metronidazole-resistant *C. difficile* strain in a patient with *C. difficile*–associated diarrhea, 1 toxigenic-resistant isolate was detected among 100 strains [55]. In a report from the Public Health Laboratory Service Anaerobe Reference Unit in the United Kingdom, no clinical isolate among >10,000 tested strains was resistant, whereas only 1 resistant nontoxigenic strain (of environmental origin) was detected [56]. Treatment failures are not uncommon but have not yet been clearly attributed to drug-resistant strains. In a 10-year prospective study of isolates from patients who experienced treatment failure, all isolates had an MIC of <1 mg/L; thus, a decreased susceptibility of the infecting *C. difficile* strains was not considered to be the cause of the failures [55].

Metronidazole is widely used as a therapeutic agent for *H. pylori* infection in the human gut and is one of the few antibiotics—primarily as part of a combined treatment regimen—that are effective in eliminating the organism. Antibiotic therapy is common for this condition, but failure rates range up to 20% with triple combination therapy in which metronidazole is the cornerstone [57]. Metronidazole resistance is considered to be the main single factor responsible for treatment failure. The high frequency of use of metronidazole may select for resistance not only in *H. pylori* but also in *Bacteroides* species and other intestinal anaerobes. Because of its well-known safety and efficacy in clinical practice, metronidazole is still the cornerstone for the management of anaerobic infections worldwide.

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