WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 13, 130-141. Review Article ISSN 2277– 7105

METRONIDAZOLE: DRUG OF CHOICE FOR ANAEROBIC INFECTIONS - AN OVERVIEW

Virendra Kushwaha, Pooja Agrawal*, Vipul Shukla and Brijesh Pathak

Department of Pharmacology, GSVM Medical College, Kanpur.

Article Received on
26 July 2022,

Revised on 16 August 2022,
Accepted on 06 Sept. 2022

DOI: 10.20959/wjpr202213-25467

***Corresponding Author**
Dr. Pooja Agrawal
Department of Pharmacology, GSVM Medical College, Kanpur.

ABSTRACT

Metronidazole is active against a wide variety of anaerobic bacteria and protozoal infection such as Amoebiasis, Giardiasis, T. Vaginalis etc. It manifests antibacterial activity against all anaerobic cocci, anaerobic gram-negative bacilli and microaerophilic bacteria such as Helicobacter and Campylobacter spp. It is available as oral, intravenous, vaginal, and topical formulations. Metronidazole is contraindicated in patients with documented hypersensitivity to the drug or its components, and it should be avoided in first-trimester pregnancy. Reports of Disulfiram-like reactions in patients drinking alcohol while administered systemic or vaginal Metronidazole. There should be judicious prescribing of Metronidazole by providers only for known indications and high clinical suspicion for needing treatment of anaerobic bacterial infections, protozoal infections, and microaerophilic bacterial infections to avoid the development of resistance against Metronidazole.

KEYWORDS: Metronidazole, Anaerobic infections, Protozoal infections.

INTRODUCTION

Metronidazole is an antimicrobial agent that has been used for more than 45 years in clinical medicine.[1] Metronidazole is active against a wide variety of anaerobic protozoal parasites and anaerobic bacteria; it is indicated for the management of infection that is caused by Trichomonas Vaginalis and is effective against other protozoan infections such as Amoebiasis and Giardiasis. It manifests antibacterial activity against all anaerobic cocci, anaerobic gram-negative bacilli including Bacteroides species, anaerobic spore-forming, gram-positive bacilli such as Clostridium and microaerophilic bacteria such as Helicobacter and Campylobacter spp. It is used to treat intestinal amoebiases, liver amoebiasis, bacterial

septicemia, bone and joint infections, meningitis, brain abscess, endocarditis, endometritis, and bacterial vaginitis, intra-abdominal infections, lower respiratory tract infections, skin structure infections, and surgical prophylaxis colorectal surgeries. Only Nonsporulating gram-positive bacilli, aerobic, and facultative anaerobic bacteria are resistant to metronidazole.[2]

Historical background of metronidazole

The first report on the effect on the management of anaerobic infections was published in 1962 by Shinn.[1] However major advances were made by Tally et al[3,4] at the Wadsworth veteran's 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. Metronidazole has been used in clinical medicine for >45 years. Despite 45 years of extensive use, metronidazole remains the criterion standard for mamanagement prophylaxis of anaerobic infections. Francis Tally discussed the use of metronidazole for the prophylaxis and treatment of anaerobic infections at GIFU university medical school in Gifu Japan in 1985. Metronidazole began to be commercially used in 1960 in France.[5] It is on the World Health Organization's List of Essential Medicines.[6] It is available in most areas of the world. In 2019, it was the 138th most commonly prescribed medication in the United States, with more than 4 million prescriptions.[7]

Mechanism of action of metronidazole

Metronidazole is a prodrug requiring reductive activation of the nitro group by susceptible organisms. Unlike their aerobic counterparts, anaerobic and microaerophilic pathogens (eg, the amitochondriate protozoa. vaginalis, E. histolytica and G.lamblia, and various anaerobic bacteria) contain electron components that have a sufficiently negative redox potential to donate electrons to metronidazole. The single electron transfer forms a highly reactive nitro radical anion that kills susceptible organisms by a radical-mediated mechanism that targets DNA. Metronidazole is catalytically recycled; the loss of active metabolites electron regenerates the parent compound. Increasing levels of O_2 inhibit metronidazole-induced cytotoxicity because O_2 competes with metronidazole for electrons. Thus, O2 can both decrease the reductive activation of metronidazole and increase the recycling of activated drugs. Anaerobic or microaerophilic organisms susceptible to metronidazole derive energy from the oxidative fermentation of ketoacid such as pyruvate. Pyruvate decarboxylation,

catalyzed by PFOR, produces electrons that reduce ferredoxin, which in turn catalytically donates its electrons to biological electron acceptors to metronidazole.[8]

Pharmacokinetic property of metronidazole

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 and its active metabolites are present in a lower amount in plasma. Protein binding is low, and < 20% of the circulating metronidazole is bound to plasma proteins.

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 leading to intolerance in some patients. The most common adverse reactions reporting 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.[9]

Use of metronidazole in clinical practice

Metronidazole is highly active against gram-negative anaerobic bacteria, such as B. fragilis, and gram-positive anaerobic bacteria, such as C. difficile. 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, and 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 aerobic infection, because it is ineffective against aerobic bacteria (Table 1). Metronidazole also

produces good clinical results when it is used for the 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. By international guidelines, metronidazole is also a component of multidrug regimens (eg, in combination with omeprazole, clarithromycin, and amoxicillin) for therapy of Pylori infections such as gastroduodenal ulcers. Metronidazole is also considered for patients with Crohn's disease that does not responds to sulfasalazine. Topically it is effective for the treatment of rosacea. In addition, metronidazole gel is used in dentistry for the treatment of periodontitis in patients for which mechanical debridement is not successful.[10]

Table 1: Clinical uses for metronidazole.[10]

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

Metronidazole therapy for C. difficile infection- Most C. difficile strains are susceptible to metronidazole. The pharmacokinetic and pharmacodynamics properties of metronidazole have been thought to be responsible for clinical failures.[11] One new approach may be to use metronidazole in various combinations with antimicrobials, toxin binder, immunomodulatory, nontoxigenic c.difficile strain, and probiotics.

Metronidazole therapy for intra-abdominal infection for moderate community-acquired infections in adults, metronidazole in combination with cefazolin, cefuroxime, ceftriaxone, or

a quinolone is recommended. Metronidazole together with ceftazidime 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. Oral metronidazole in combination with oral second- or third-generation cephalosporin may also be effective. Convalescing patients with complicated intra-abdominal infections can be treated with oral antimicrobials. For adults, metronidazole in combination with a fluoroquinolone or trimethoprim-sulphamethoxazole may be effective. Oral metronidazole in combination with an oral thirdr generation cephalosporin can be provided to children.[12] In Patients with intraabdominal infections, treatment with metronidazole and ciprofloxacin was associated with greater success than was treatment with beta-lactam agents.[13]

Resistance

Clinical resistance to metronidazole is well documented for T.vaginalis, G.lamblia, and a variety of anaerobic and microaerophilic bacteria resistance correlates with impaired oxygen-scavenging capabilities, leading to higher local O_2 concentrations, decreased activation of metronidazole and futile recycling of the activated drug. Other resistant strains have lowered levels of PFOR and ferredoxin perhaps explaining why they may still respond to a higher dose of metronidazole.[8]

Table 2

Mechanism of resistance[14]
Reduced drug activation
Inactivation of the drug by the alternative pathway for drug activation and/or reduction (nim genes)
Prevention of entry of the drug or efflux
Altered DNA repair

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. 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. 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. Transfer of these genes has been shown to confer resistance to

metronidazole in recipients infected with the susceptible virus. The nim genes encode an alternative reductase that can convert nitroimidazole to a nontoxic derivative, thereby reversing the toxic effect that causes breakage of the DN. 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. The alteration of DNA repair systems playing a role in metronidazole resistance in H. pylori is another incompletely studied mechanism in Bacteroides strains.

Effect of metronidazole on gut flora- Alteration in the bacterial composition and overgrowth of yeasts, as well as a selection of resistant strains have been associated with Metronidazole administration in combination with other agents such as amoxicillin and clarithromycin.[15] The effect of Metronidazole on the normal microflora varies, depending on the body site. Concentrations of metronidazole exceeding MIC values of anaerobes are found during treatment in body fluids, such as saliva, due to which reduction in the number of oropharyngeal anaerobic bacteria after combining treatment with metronidazole and clarithromycin.[16] 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.[17] 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.[18] Metronidazole affecting C. difficile reaches the gut by diffusion from serum to the intestine.

Administration and Dosage

Table 3

Dosing for amoebiasis, both intestinal (acute dysentery) and extraintestinal[19]
• Oral: 500 to 750 mg every 8 hours for 7 to 10 days to be followed up with an intraluminal agent
Dosing for bacterial vaginosis[20]
Oral: 500 mg twice each day for seven days.
Dosing for pelvic inflammatory disease (PID) treatment
• Mild/moderate PID: Oral: 500 mg twice a day for 14 days (may be added to combination therapy) • PID with tubo-ovarian abscess, initial treatment (as an alternative regimen): IV: 500

mg every 8 hours as part of an appropriate combination regimen • PID with tubo-ovarian abscess, oral therapy after clinical improvement on a parenteral regimen: Oral: 500 mg twice daily with doxycycline for at least 14 days
Dosing for trichomoniasis infection
• Initial treatment: Oral: 2 g in a single dose or 500 mg twice daily for seven days (preferred regimen in HIV-infected women) • Persistent or recurrent infection (treatment failure single-dose therapy): Oral: 500 mg twice daily for 7 days for the failure of 2 g single-dose regimen
Dosing for Giardiasis[21]
• Oral: 250 mg 3 times each day or 500 mg 2 times each day for 5 to 7 days
Dosing for intra-abdominal infections[22]
• Oral, IV: 500 mg every 8 hours as in an appropriate combination regimen. Therapy duration is 4 to 7 days following adequate source control, and a longer duration is necessary for uncomplicated appendicitis and diverticulitis managed non-operatively.
Dosing for surgical site infections, incisional (intestinal or GU tract; axilla or perineum), warranting anaerobic coverage
• IV: 500 mg every 8 hours combined with other appropriate agents.
Dosing for *Helicobacter pylori* eradication[23]
• The triple regimen with clarithromycin: Oral: Metronidazole 500 mg 3 times each day combined with clarithromycin 500 mg twice a day and a standard-dose or double-dose proton pump inhibitor (PPI) twice daily; continue regimen for 14 days • Quadruple regimen with bismuth: Oral: Metronidazole 250 mg 4 times each day or 500 mg 3 or 4 times each day in combination with bismuth subsalicylate 300 to 524 mg or bismuth subsalicylate 120 to 300 mg 4 times each day, tetracycline 500 mg 4 times each day, and a standard-dose PPI twice each day; continue regimen for 10 to 14 days • Concomitant regimen: Oral: Metronidazole 500 mg twice each day in combination with clarithromycin 500 mg twice each day, amoxicillin 1 g twice each day, and a standard-dose PPI twice each day; continue regimen for 10 to 14 days
Dosing for *Clostridium difficile* infection (CDI)[24]
• Metronidazole is no longer a first-line antibiotic choice. "Either vancomycin or fidaxomicin are preferred agents over metronidazole for initial episodes of CDI - if access to vancomycin or fidaxomicin is limited, metronidazole is an option for an initial episode of non-severe CDI only at a dose of 500 mg orally three times daily for ten days • Fulminant *Clostridium difficile* infection: Vancomycin administered orally is the regimen of choice; in the presence of ileus, vancomycin can also be administered rectally - IV metronidazole should be administered 500 mg every 8 hours together with oral or rectal vancomycin, particularly if an ileus is present.
Dosing for rosacea
• 1% gel or cream daily, or 0.75% cream or lotion twice a day.

Adverse effects of metronidazole

The primary adverse effects of metronidazole include confusion, peripheral neuropathy, metallic taste, nausea, vomiting, and diarrhea. Adverse events seen in greater than 10% of the population include headache (18%), vaginitis (15%), and nausea (10% to 12%). Adverse

events affecting less than 10% of the population are metallic taste (9%), dizziness (4%), genital pruritus (5%), abdominal pain (4%), diarrhea (4%), xerostomia (2%), dysmenorrhea (3%), urine abnormality (3%), urinary tract infection (2%), bacterial infection (7%), candidiasis (3%), flu-like symptoms (6%), upper respiratory tract infection (4%), pharyngitis (3%), and sinusitis (3%). Rarely, there are reports of transient leukopenia and neutropenia as well.[25,26] Prolonged drug courses can cause severe neurological disturbances due to the risk of cumulative neurotoxicity. Monitor for neurologic sequela and discontinue therapy if any abnormal neurologic symptoms occur.[27]

Contraindications of metronidazole[28]

Metronidazole is contraindicated in patients with documented hypersensitivity to the drug or its components, and it should be avoided in first-trimester pregnancy. Patients should also avoid consuming alcohol or products containing propylene glycol while taking metronidazole and within three days of therapy completion. Metronidazole is likewise contraindicated if there has been recent disulfiram use within the past two weeks.

Toxicity of metronidazole[28,29]

Reports of disulfiram-like reactions in patients drinking alcohol while administered systemic or vaginal metronidazole. A typical disulfiram reaction causes flushing, tachycardia, palpitations, nausea, and vomiting. Alcohol should be avoided during treatment and from up to forty-eight hours to fourteen days after treatment completion, depending on the source; the manufacturer's product information recommends avoiding alcohol ingestion during metronidazole therapy and for at least 48 hours afterward. Ethanol-containing medications such as elixirs and tipranavir, capsules, intravenous (IV) anidulafungin, IV trimethoprim-sulfamethoxazole, and many cough/cold syrups can also lead to a disulfiram-like reaction when ingested with metronidazole.

Comparison of various antibiotic agents against mixed infections

Table 4[29]

	Degree of activity				
		Anaerobic Bacteria		Aerobic Bacteria	
S. no.	Antimicrobials	B-Lactamase producing	Other Anaerobes	Gram + Cocci	Penicillinase
1	Chloramphenicol	0	+++	+	0
2	Chloramphenicol[b]	+++	+++	+	+
3	Cephalothin	0	+	++	+/-

4	Cefoxitin	++	++	+++	Clindamycin
5	Carbapenems	+++	+++	+++	+++
6	Clindamycin[b]	++	+++	+++	0
7	Ticarcillin	+	+++	+	++
8	Amoxicillin + clavulanate[b]	+++	+++	++	++
9	Metronidazole	+++	+++	++	++
10	Metronidazole[b]	+++	+++	0	0
11	Moxifloxacin	++	++	++	+++
12	Tigecycline	++	+++	+++	++

Table 5:[30] Selected published data on the distribution of minimum inhibitory concentrations (MICs) to Metronidazole among clinical isolates of Bacteroides fragilis.

Reference	MIC_{50}, mg/dl	Percentage of isolates MIC_{90},mThe numberMIC> 8 mg/dl		MIC>32, mg/dl	Number of isolates analyzed	Geographic origin
Hedberg et al	1	2	1.5	0.5	1284	Europe
United States	ND	ND	<0.5	<0.5	5225	UnitedStates
Aldridge et al	1	2	ND	0	542	United states
Tally et al	0.5	1	0	0	States	United states
Fille et al	0.25-0.5	0.5	0	0	87	Austria
Vieira et al	1-2	1-2	ND	0	197	Brazil
Wybo et al	o.5	1	ND	1	238	Millet
Behra-Miellet et al	1	2	4.5	0.5	359	France
Hom et al	1 2	2 4	ND	0.5 2	200	Canada
Kommedal et al	0.25	0.5	0	0	202	Norway
Koch et al	0.5	0.5	ND	0	44	South Africa
Roberts et al	1	1	0	0	51	Zealand
New zealand	ND	2	ND	0	45	Turkey
paraskevas et al	0.5	1	ND	0	82	GREECE

CONCLUSION

There should be judicious prescribing of metronidazole by providers only for known indications and high clinical suspicion for needing treatment of anaerobic bacterial infections, protozoal infections, and microaerophilic bacterial infections. To reduce overprescribing, a pharmacy consult is necessary for the prescriber to ensure directed therapy. The documentation already exists regarding increased resistance to metronidazole in the treatment

of Clostridium difficile infections. Doctors, Nurses, and Pharmacists should routinely educate patients to abstain from alcoholic beverages while taking metronidazole, which will help lead to fewer disulfiram reaction symptoms; nursing will play a role in this monitoring and for other potential adverse effects. The patient should also be informed by the health care provider of the possible change in urine color while on this medicine. The team of health professionals, including physicians, physician assistants, nurses, and pharmacists, must work together to provide the best care for these patients when using metronidazole in any formulation.

REFERENCES

1. Shinn DLS. Metronidazole in acute ulcerative gingivitis. Lancet, 1962; 279: 1191.
2. Dawn M.Wetzel and Margaret A.Phillips. Chemotherapy of Protozoal Infections: Amebiasis, Giardiasis, Trichomoniasis, Leishmaniasis, and other Protozoal Infections. In: Laurence, 2018; 991.
3. Tally FP, Sutter VL, Finegold SM. Metronidazole versus anaerobes: invitro data and initial clinical observations. Calif Med, 1972; 117: 22–6.
4. Tally FP, Sutter VL, Finegold SM. Treatment of anaerobic infections with metronidazole. Antimicrob Agents Chemother, 1975; 7: 672–5.
5. D Corey EJ Drug discovery practices, processes, and perspectives. Hoboken, N.J.: John Wiley & Sons, 2013; 27.
6. World Health Organization World Health Organization model list of essential medicines: Geneva: World Health Organization, 2019; 21. ava ilable a t hdl:10665/325771. WHO/MVP/EMP/IAU/2019.
7. Schmid G (28 July 2003). "Trichomoniasis treatment in women". Archived from the original on, 2015; 1: 1.
8. Dawn M.Wetzel and Margaret A.Phillips.Chemotherapy of Protozoal Infections: Amebiasis, Giardiasis, Trichomoniasis, Leishmaniasis, and other Protozoal Infections. In: Laurence L.Brunton, editor. The Pharmacological Basis of Therapeutics, New York: Mc Graw Hill, 2018; 13: 991-92.
9. Freeman CD, Klutman NE, Lamp KC. Metronidazole: a therapeutic review and update of Drugs, 1997; 54: 679–708.
10. Löfmar S, Edlund, C, Nord CE, Metronidazole Is Still the Drug of Choice for Treatment of Anaerobic Infections, Clinical Infectious Diseases, Issue Supplement_1, February, 2010; 50: S16–S23.

11. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile–associated diarrhea, stratified by disease severity. Clin Infect Dis, 2007; 45: 302 – 7.
12. Matthaiou DK, Peppas G, Bliziotis IA, Falagas ME. Ciprofloxacin/metronidazole versus beta-lactam-based treatment of intra-abdominal infections: a meta-analysis of comparative trials. Int J Antimicrobial Agents, 2006; 28: 159–65.
13. Wang S, Cunha BA, Hamid NS, Amato BM, Feuerman M, Malone B.Metronidazole single versus multiple daily dosing in serious intraabdominal/pelvic and diabetic foot infections. J Chemother, 2007; 19: 410–6.
14. 14-.Land KM, Johnson PJ. Molecular basis of metronidazole resistance in pathogenic bacteria and protozoa. Drug Resist Update, 1999; 2: 289–94.
15. Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. Lancet infects dis, 2001; 1: 101-14.
16. Adamsson I, Nord CE, Lundquist P, Sjostedt S, Edlund C. Comparative effects of omeprazole, Amoxycillin plus metronidazole versus omeprazole, clarithromycin plus metronidazole on the oral, gastric and intestinal microflora in Helicobacter pylori-infected patients. J Antimicrobial Chemotherapy, 1999; 44: 629–40.
17. Bergan T, Solhaug JH, Soreide O, Leinebo O. Comparative pharmacokinetics of metronidazole and tinidazole and their tissue penetration. Scand J Gastroenterol, 1985; 20: 945–50. clinicalgate.com[Internet].Metronidazole and Other Antibiotics for Anaerobic Infections; c 2015[updated on 22 March 2015; cited on 06 august 2022]. Available from https://clinicalgate.com/metronidazole-and-other-antibiotics-for-anaerobic-infections/
18. Gonzales MLM, Dans LF, Sio-Aguilar J. Antiamoebic drugs for treating amoebic colitis. Cochrane Database Syst Rev, 2019; 09, 1: CD006085.
19. Van Schalkwyk J, Yudin MH., INFECTIOUS DISEASE COMMITTEE. Vulvovaginitis: screening for and management of trichomoniasis, vulvovaginal candidiasis, and bacterial vaginosis. J Obstet Gynaecol Can, 2015; 37(3): 266-274.
20. Gardner TB, Hill DR. Treatment of giardiasis. Clin Microbiol Rev, 2001; 14(1): 114-28.
21. Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, Chang PK, O'Neill PJ, Mollen KP, Huston JM, Diaz JJ, Prince JM. The Surgical Infection Society

Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt), 2017; 18(1): 1-76.

22. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol, 2017; 112(2): 212-239.
23. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V, Shaklee Sammons J, Sandora TJ, Wilcox MH. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis, 2018; 19, 66(7): 987-994.
24. McKendrick MW, Geddes AM. Neutropenia is associated with metronidazole. Br Med J, 1979; 29, 2(6193): 795.
25. Smith JA. Neutropenia is associated with metronidazole therapy. Can Med Assoc J., 1980; 09, 123(3): 202.
26. Hernández Ceruelos A, Romero-Quezada LC, Ruvalcaba Ledezma JC, López Contreras L. Therapeutic uses of metronidazole and its side effects: an update. Eur Rev Med Pharmacol Sci, 2019; 23(1): 397-401.
27. Finegold SM. Metronidazole. Ann Intern Med, 1980; 93(4): 585-7.
28. Brook I, Wexler HM, Goldstein EJ. Antianaerobic antimicrobials: spectrum and susceptibility testing. Clin Microbiol Rev, 2013; 26(3): 526-46.
29. Brazier JS, Stubbs SL, Duerden BI. Metronidazole resistance among clinical isolates belonging to the Bacteroides fragilis group: time to be concerned? J Antimicrob Chemother, 1999; 44: 580–1.