MEDDOCS Open Access Publisher

ISSN: 2637-4501

Annals of Gastroenterology and the Digestive System

Open Access | Review Article

Rifaximin and Metronidazole Combination in the Management of Diarrhea Associated with Mixed Infection, Irritable Bowel Syndrome, and Inflammatory Bowel Disease

***Corresponding Author(s): Arif A Faruqui**

lClinical Pharmacologist, Opp.K.B.Bhabha Hospital, Bandra West, Mumbai-400050 Maharashtra, India.

Email: drfaruqui@gmail.com

Received: Jun 27, 2022

Accepted: Jul 27, 2022

Published Online: Jul 29, 2022

Journal: Annals of Gastroenterology and the Digestive System

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Diarrhea; Irritable bowel syndrome; Inflammatory bowel disease; Rifaximin; metronidazole.

Abstract

Diarrhoea is usually a symptom of a bowel infection and the etiology of infectious diarrhea is generally mixed. Development of resistance to anti-microbial agents and increased risk of developing clostridium difficile-associated diarrhoea pose a new threat. In combination with metronidazole, rifaximin with its unique properties and broad spectrum activity can be a rational approach for infectious diarrhoea as co-infection is the norm in majority of the patients. *Clostridium difficile*-related post-infectious irritable bowel syndrome develops in about one-third of subjects after an acute bacterial and viral infection or parasitic infestation. Incidence for chronic inflammatory disorders of the intestine such as ulcerative colitis and Crohn's disease has significantly increased in the past years. The etiology for both diseases is complex with diarrhea as the most debilitating symptom. Oral metronidazole is still the first-line treatment option for clostridium difficile infection known to worsen the course of inflammatory bowel disease. However, prolonged administration of antibiotics is limited due to systemic adverse effects. Rifaximin is a broad-range, gastrointestinal-specific antibiotic that demonstrates no clinically relevant bacterial resistance. A combination of rifaximin and metronidazole, each having activity against *Clostridium difficile* infection causing diarrhea, would be a rationale combination for treatment of patients with irritable bowel syndrome and inflammatory bowel disease.

Introduction

Diarrhea is defined as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual). Diarrhea is usually a symptom of an infection in the intestinal tract, which can be caused by a variety of bacterial, viral and parasitic organisms. Infection is spread through contaminated food or drinking-water, or from person-to-person as a result of poor hygiene. Diarrhea can last several days and can leave the body without water and salts that are necessary for survival. In the past, for most people, severe dehydration and fluid loss were the main causes of diarrhea deaths. Now, other causes such as septic bacterial infections are likely to account for an increasing proportion of all diarrhea-associated deaths.

Cite this article: Faruqui AA. Rifaximin and Metronidazole Combination in the Management of Diarrhea Associated with Mixed Infection, Irritable Bowel Syndrome, and Inflammatory Bowel Disease. Ann Gastroenterol Dig Syst. 2022; 5(2): 1063.

Infectious diarrhea presents clinically as one of three major clinical syndromes:

- Acute watery diarrhea – lasts several hours or days and includes cholera
- Acute bloody diarrhea – also called dysentery and
- Persistent diarrhea – lasts 14 days or longer

The most severe threat posed by diarrhea is dehydration. During a diarrheal episode, water and electrolytes (sodium, chloride, potassium and bicarbonate) are lost through liquid stools, vomit, sweat, urine and breathing. Dehydration occurs when these losses are not replaced.

The degree of dehydration is rated on a scale of three.

- **Severe dehydration (at least two of the following signs):**

o lethargy/unconsciousness

o sunken eyes

o unable to drink or drink poorly

o skin pinch goes back very slowly (≥2 seconds)

- **Some dehydration (two or more of the following signs):**

o restlessness, irritability

o sunken eyes

o drinks eagerly, thirsty

- **No dehydration (not enough signs to classify as some or severe dehydration) [1].**

The presence of multiple pathogens in one third of patients with diarrhea has potential implications for treatment and raises several questions. If the various pathogens occurred independently in cases of disease, then each pathogen in a poly microbial infection would be expected to occur in proportion to its presence in all patients with severe diarrhea [2]. Precise information about diarrhoea and its incidence, causation, consequences and trend is necessary for informed policy-making.

Prevalence

Diarrhea is the second leading cause of mortality and morbidity throughout the world. Although diarrhoeal diseases are common among children and older adults, death due to diarrhoea is three times more among older adults and specifically among those who belong in the population above 70 years of age than children under five years of age. It not only causes physical discomfort but emotional distress as well. [3] Even after being one of the leading causes of mortality and morbidity in the world, data associated with diarrheal diseases are limited. Table 1 presents the number of diarrhea deaths and mortality rate in 2019 in India for each age group and sex [4]

Prevalence and comparison of the role of single infection vs. multiple infections on average motions per day

Analyses conducted by Shrivastava *et al*. in Odisha, India presented data on disease severity (only in terms of numbers of liquid motions per day) compared between two groups, i.e., cases with detection of single infection vs cases with detection of more than one infections shown in table 2. [5]

Causes of co-infectious diarrhea and deaths

Poor hygiene and sanitation condition increases the transmission dynamics of diarrheal diseases in community settings. All these diarrheal agents are transmitted either through contaminated food, water, or through the fecal oral route [5].

In India, over 70% of the rural population do not have sanitary toilets and do not practice any method of water purification. The presence of animals in close proximity to human dwellings adds to the risk of transmission of zoonotic infections directly to humans or through the contaminated water [6].

There are 13 etiologies that causes diarrhea in India. Adenovirus is the most prominent pathogen for the cause of diarrhea among children, followed by *Campylobacter* and *Cryptosporidium*. The most pertinent pathogen for the cause of diarrhea for all ages is *Campylobacter* followed by *Cryptosporidium* and *Norovirus*. Table 3 represents etiologies for the cause of diarrhea disease and the number of deaths among under-5 and all ages in India, 2019 [4].

Risk groups for co-infectious diarrhoea

The risk groups prone to acquire infectious diarrhea are listed in Table 4. [7]

Treatment of co-infectious diarrhoea

Treatment of co-infectious diarrhoea includes following measures:

1) General measures (avoid milk and milk products, avoid caffeine, oral intake should consist of boiled starches/cereals, rice, noodles, potatoes)
2) Oral rehydration therapy
3) Antidiarrheal therapy

a. Anti-motility agents (Loperamide, Diphenoxylate + atropine)

b. Antibiotic therapy

Limitations of existing antimicrobial therapy

Resistance to antimicrobial agents

One of the on-going problems in the fight against infectious diseases is the development of resistance to the agents used to control them. The phenomenon of resistance has been known since almost the beginning of antibiotic use.

Antibiotic resistance appears as a result of changes in genes or the acquisition of genes that allow the pathogen to evade the action of antimicrobial drugs. Bacteria have many methods for developing resistance. Alarmingly, many pathogens are simultaneously acquiring resistance to multiple drugs as shown in figure 1 [8].

Antibiotic associated diarrhea (AAD)

Patients with Clostridium Difficile-Associated Diarrhoea (CDAD) stay in hospital 3.6 days longer with additional hospital cost. Clindamycin, penicillins, and cephalosporins are associated with CDAD. Fluoroquinolones like Ciprofloxacin & Levofloxacin are significantly associated with increased risk of developing CDAD infection [10]. A 12 month study also reported 54.8% of CDAD cases with fluoroquinolone use. (ciprofloxacin, levofloxacin & gatifloxacin) [11].

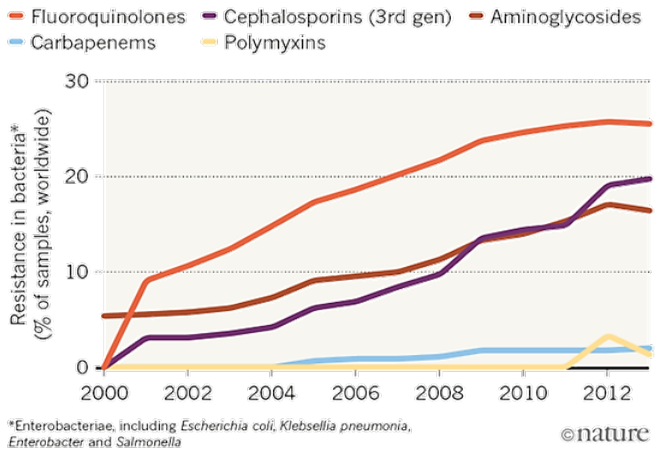

Figure 1: CDDEP (Center for Disease Dynamics, Economics & Policy) Resistance Map [9].

Irritable bowel syndrome and diarrhea

Irritable Bowel Syndrome (IBS) is defined as abdominal discomfort or pain associated with altered bowel habits for at least three days per month in the previous three months, with the absence of organic disease. Altered bowel habits include diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), and mixed presentation with alternating diarrhea and constipation (IBS-M). [12].

IBS can be diagnosed using Rome III criteria and sub classified according to patients' predominant stool pattern using the Bristol Stool Form Scale. Up to 40% of patients with IBS have diarrhea as the predominant bowel symptom (IBS-D subtype). Patients with diarrhea may have the feeling of urgency and incomplete relief after defecation, or may have mucus in the stools. IBS significantly reduces the quality of life of patients, their partners, and caregivers and impairs daily functioning. It places a substantial financial burden on society, owing to impaired work productivity and increased use of health care resources. At least some of the increased costs are related to additional medical tests and medical and non-medical therapies, which are of uncertain value. In a database search of patients with and without IBS, patients with IBS were more likely to undergo standard laboratory blood and stool testing and endoscopic testing than other patients.

The goals of treatment are symptom relief and improved quality of life. Treating IBS can be particularly challenging because symptoms often are recurrent and resistant to therapy. A positive patient-physician interaction is associated with fewer return visits for IBS and is a key component in the treatment of these patients. High-quality clinical trials have been difficult to conduct in patients with IBS; therefore, evidence supporting treatment modalities is often of low quality [13].

Inflammatory bowel disease and diarrhea

Inflammatory Bowel Disease (IBD) is a term used to describe two conditions, Crohn's Disease (CD) and Ulcerative Colitis (UC), which are characterized by chronic inflammation of the gastrointestinal tract [14].

Main types of IBD [14].

	Crohn's Disease	Ulcerative Colitis
Affected Location	May affect any part of the GI tract including mouth, oesophagus, stomach, small intestine, rectum, and anus —Most often it affects the portion of the small intestine before the large intestine/colon	Occurs mostly in large intestine (colon) and the rectum
Inflammation	May reach multiple layers of the walls of GI tract	Present only in the innermost layer of the lining of colon
Damaged Areas	Appear in patches that are next to areas of healthy tissue	Continuous and usually starting at the rectum and spreading further into colon

Although the main cause of the IBD has not yet been fully understood, the comprehensive studies carried out in this regard highlight the role of genetic and environmental factors. Two approaches for the main causes of IBD have been suggested: (a) disruption of the mucous system increases the immunological response rate in the human microbiota; (b) any change in the content of the gut flora or the disruption of the epithelium function stimulates the pathologic response in the normal mucous system. On the other hand, pathogenicity in inflammatory bowel disease depends on factors such as the patient's susceptibility, mucosal immunity and microflora of the intestine [14].

Diarrhea is the hallmark symptom associated with IBD and is seen in almost 80% of the cases. IBD-associated diarrhea is multifactorial and is the outcome of intricate pathophysiological events arising from widespread and sustained mucosal inflammation. Depending upon the site and magnitude of intestinal inflammation the severity of diarrhea varies in IBD patients, ranging from increased bowel frequency to chronic diarrhea requiring electrolyte supplementation and hospitalization. The severity of diarrhea (stool frequency and consistency) is thus considered as an important determinant of the disease activity index. Therefore, the understanding of the molecular mechanisms leading to diarrhea in IBD is crucial for proper diagnosis and management [15].

Fluid loss in diarrhea occurs due to derangements in the equilibrium of electrolyte absorptive and secretory processes. During inflammatory insults in UC and CD the absorptive capacity of the colon is significantly compromised resulting in excessive loss of fluid in the stool. Accordingly, impairment in electrolyte absorption rather than secretion is now proposed as the major ion transport abnormality in diarrhea associated with IBD. The health related quality of life of IBD patients is severely impacted and the fundamental management strategy is aimed at maintenance of remission, control of inflammation, restoration of nutritional deficits and treatment of symptoms like diarrhea [15].

Advances in anti-microbial agents in co-infection diarrhea

A prominent approach should be use of GI specific antibiotic like rifaximin. This approach will conserve other antibiotics for systemic use. Well established indications for combination antimicrobial therapy like anti-protozoal plus GI specific antibiotic include: (a) empirical treatment of life-threatening infections; (b) treatment of poly microbial infections; (c) prevention of the emergence of bacterial resistance; and (d) for synergism [16].

Role of rifaximin and metronidazole in co-infectious diarrhea

Broad spectrum activity of Rifaximin makes it an efficacious regimen for co-infectious diarrhoea treatment. Spectrum of activity includes: Gram positive (ETEC: Enterotoxigenic *E. Coli*, EAEC: Enteroaggregative *E. Coli*, *Salmonella enteritidis*, *Shigella spp*., *C. jejuni*, *Y. enterocolitica*, *Enterobacter spp*., *Klebsiella spp*., *Proteus spp*., *Acinetobacter spp*.) & gram negative (*Staphylococcus aureus*, *S. epidermidis*, *Streptococcus spp*., *Enterococcus faecalis*, *Enterococcus faecium*, *C. difficile*), aerobes & anaerobes [17].

Rifaximin is poorly absorbed & after oral administration bioavailability is less than 0.4% with approximately 97% of the drug being excreted unchanged in feces [18]. Drug and food interaction potential is minimal. Since it is neither metabolized nor absorbed by liver, hence no dose modification is required in patients with liver diseases [17,19].

Metronidazole has shown its clinical efficacy and safety in diarrhoea and CDAD. While targeting pathogens (bacteria plus protozoa) involved in causing co-infectious diarrhoea, logistic approach of combining an antibiotic (rifaximin) with anti-protozoal (metronidazole) will decrease the hospital associated admission, treatment duration, treatment cost and time to recovery of the patients.

In combination with metronidazole, rifaximin with its local action and low bioavailability decreases the chances of developing antibiotic resistance. Moreover its broad spectrum activity makes it useful in treating co-infectious diarrhoea. Rifaximin along with Metronidazole can be a rational approach for gastrointestinal infections where co-infection is the norm in at least one third of the patients (Table 5).

Role of rifaximin and metronidazole in pediatric patients with IBS-D

Pharmacological agents for the management of IBS-D include US FDA approved agents eluxadoline, rifaximin and alosetron, as well as loperamide, smooth muscle antispasmodics, bile acid sequestrants and antidepressants (i.e. tricyclic antidepressants, selective serotonin reuptake inhibitors) [21].

The incidence of Clostridium Difficile Infection (CDI) in pediatric patients continues to rise. Most of the pediatric recommendations for CDI treatment are extrapolated from the literature and guidelines for adults. The American Academy of Pediatrics recommends oral metronidazole as the first-line treatment option for an initial CDI and the first recurrence if they are mild to moderate in severity. Oral vancomycin is recommended to be used for severe CDI and the second recurrent infection [22].

Patients with CDI have a high risk for developing post-infectious irritable bowel syndrome (PI-IBS), particularly those with longer duration of *C. difficile* infection, anxiety and higher BMI. This IBS subtype has been reported following bacterial (*Campylobacter jejuni*, *Salmonella*, *Shigella spp*., *Escherichia coli*) and viral (norovirus) infections, and parasitic (*Giardia duodenalis*) infections [23]. A meta-analysis carried out on more than 20,000 individuals with infectious enteritis reported that more than 10% of patients developed IBS later, at a rate four times higher than that found in non-exposed subjects. [24] It is worth noting that asymptomatic colonization with toxigenic strains of enteric pathogen, *Clostridium difficile* is frequent and more than 20% of patients with a suspected such infection may have alternative etiologies for persistent diarrhea. This pathogen, only in the United States, was responsible for half a million infections and it was associated with approximately 29,000 deaths in 2011 [23].

Therefore, a combination of rifaximin and metronidazole, each having activity against *Clostridium difficile* infection causing diarrhea, would be a rationale combination for treatment of CDI in pediatric patients with IBS-D and for prevention of PI-IBS.

Role of rifaximin and metronidazole in pediatric patients with IBD

The concentration of intestinal bacteria in IBD patients is higher than normal, gradually increasing with the severity of the disease which constitutes a good rationale for the use of antibiotics in IBD. Various meta-analyses have demonstrated that antibiotics such as metronidazole, ciprofloxacin, clofazimine and antibiotic combinations can be successfully employed in the treatment of Crohn's disease and ulcerative colitis. However, prolonged administration of antibiotics is accompanied by systemic adverse effects limiting their use. Rifaximin is virtually unabsorbed after oral administration, is mostly excreted as unchanged drug in the stools in the course of intestinal disorders and is thus devoid of systemic side effects [25].

A prospective, single-blind randomized study comparing metronidazole and rifaximin in the treatment of CDI in pediatric patients with IBD evaluated cure rate after 4 weeks of treatment. The study demonstrated no statistically significant difference in the cure rate between patients treated with metronidazole and rifaximin [26].

Therefore, a combination of rifaximin and metronidazole, each having activity against *Clostridium difficile* infection causing diarrhea, would be a rationale combination for treatment of CDI in pediatric patients with IBD.

Figure 1: The number of diarrhea deaths and mortality rate (per 100,000 populations) in India for each age group and sex [4].

Age	Sex	Number of Deaths	Mortality Rate
All Ages	Male	230,468.8 (142738–482,412.4)	32.31 (20.01–67.64)
	Female	401,876 (166,196.4–793,477.5)	59.31 (24.53–117.11)
	Both	632,344.7 (358561–1,056,036)	45.46 (25.78–75.93)
Under 5	Male	22,392.69 (16,201.54–29,976.6)	36.53 (26.43–48.90)
	Female	32,916.93 (22,665.14–46,353.51)	59.01 (40.63–83.10)
	Both	55,309.61 (39,882.77–73,621.29)	47.24 (34.06–62.88)
5–14 years	Male	6742.824 (3555.182–14,735.31)	4.97 (2.62–10.87)
	Female	9609.717 (3429.244–19,759.56)	7.77 (2.77–15.98)
	Both	16,352.54 (8494.022–27,826.46)	6.31 (3.27–10.74)
15–49 years	Male	22,323.31 (11,883.54–56,059.29)	5.70 (3.03–14.33)
	Female	28,228.08 (9025.635–62,731.19)	7.66 (2.45–17.02)
	Both	50,551.39 (25,651.88–94,949.45)	6.65 (3.37–12.50)
50–69 years	Male	47,983.77 (25,751.48–117,218))	48.59 (26.08–118.71
	Female	76,579.09 (24,773.43–24,773.43)	76.79 (24.84–171.11)
	Both	124,562.9 (62,219.35–234,874.3)	62.76 (31.35–118.35)
70+ years	Male	131,026.2 (78,186.29–271,554.5)	495.20 (295.49–1026.31)
	Female	254,542.2 (98,380.17–506,093.9)	846.84 (327.30–1683.73)
	Both	385,568.3 (204,662.6–646,591.9)	682.21 (362.12–1144.06)

Note: Parenthesis denotes 95% uncertainty interval of lower and upper limits.

Figure 2: Comparison of the role of single infection vs. multiple infections on average motions per day [5].

Pathogen	Prevalence (%)	No. of motions/day (min–max)
Single infection (only bacterial, viral or parasitic)	23.07	2-30
More than one infections (bacterial, parasitic & viral)	33.84	12-25

Figure 3: Etiologies of diarrhea disease and number of deaths among under-5 and all ages in India [4].

Etiology	Number of Deaths	
	Under 5	All Ages
Cholera	308.20 (168.86–529.62)	3832.13 (2241.65–6253.05)
Non-typhoidal Salmonella	2061.21 (315.36–5309.76)	9143.28 (315.36–35,931.43)
Shigella	4962.37 (1679.89–11,247.34)	24,474.21 (8457.54–53,447.86)
Enteropathogenic E coli	1556.12 (684.65–2950.12)	3393.35 (1595.33–6108.74)
Enterotoxigenic E coli	2669.03 (1059.49–5673.76)	22,668.51 (9418.76–48,347.06)
Campylobacter	8435.41 (2991.94–17,552.2)	44,353.98 (10,550.04–116,332.8)
Entamoeba	3347.33 (903.44–8623.98)	11,199.08 (3331.32–28,713.4)
Cryptosporidium	5074.18 (836.74–15,270.26)	36,007.17 (4993.42–125,954.9)
Rotavirus	2059.74 (767.51–4378.68)	4378.68 (17,500.49–91,197.18)
Aeromonas	793.62 (285.88–1673.29)	3025.27 (1340.69–5877.25)
Clostridium difficile	129.76 (62.78–243.66)	1150.95 (724.41–1690.44)
Norovirus	2317.06 (574.28–5613.38)	29,924.36 (3711.67–80,822.81)
Adenovirus	8864.36 (4317.97–16,036.32)	20,916.49 (11,657.05–33,668.17)

Figure 4: Special risk groups for infectious diarrhea [7].

Risk factors	Groups at risk
Age	Infants
	Young children
	The elderly
Non-immune host defense-gastric acid	The elderly Hypo- and achlorhydria patients on acid inhibitory drugs Congenital immunodeficiency
Immunodeficiency	HIV/AIDS
	Cancer and cancer chemotherapy
	Under nutrition
Increased exposure to enteropathogens	Travelers contaminated food and water
Antibiotics	Especially the elderly and cancer patients

Figure 5: Activity of Rifaximin and Metronidazole against pathogens causing diarrhea [20].

Pathogen	Rifaximin	Metronidazole	Rifaximin + Metronidazole
Bacteroides fragilis group	--	√	√
Fusobacterium	--	√	√
Prevotella	--	√	√
Porphyromonas	--	√	√
Peptostreptococcus	--	√	√
Eubacterium	--	√	√
Clostridium perfringens	--	√	√
Giardia lamblia	--	√	√
Entamoeba histolytica	--	√	√

Clostridium difficile	√	√	√
Clostridium spp.	√	--	√
Staphylococcus aureus	√	--	√
Staphylococcus epidermidis	√	--	√
Enterococcus fecalis	√	--	√
Enterococcus faecium	√	--	√
Escherichia coli	√	--	√
Enterotoxigenic E. Coli	√	--	√
Enteroaggregative E. Coli	√	--	√
Enterobacter spp.	√	--	√
Salmonella enteritidis	√	--	√
Yersinia enterocolitica	√	--	√
Vibrio cholerae	√	--	√
Shigella spp.	√	--	√
Campylobacter spp.	√	--	√
Yersinia spp.	√	--	√

Conclusion

Most of the cases of acute diarrhea are mixed in origin wherein both bacteria and protozoa are most commonly responsible. Multiple infections of diarrheal pathogens might cause more severe diarrhea compared to infection with a single pathogen, thereby complicating the treatment procedures. Therefore, management of diarrhea requires eradication of both the causative organisms. Thus, combination of an anti-protozoal and an anti-bacterial serves as a blanket cover for both protozoa and bacteria in diarrhea of bacterial, protozoal or mixed etiology. Limited systemic bioavailability property of rifaximin conserves other potential antibiotic for systemic infection and its excretion via fecal route confers local action of drug i.e.; in intestine where it is meant to act. Also, metronidazole resistance among clinical isolates of luminal protozoa is rare. Use of an anti-protozoal like metronidazole which is being prescribed since decades for GI specific infections along with rifaximin makes it a suitable treatment due to its wide coverage of both bacteria (gram positive/negative, aerobic & anaerobic) and protozoa and also a safe approach with lesser systemic side effects.

High incidence of post-infectious irritable bowel syndrome occurs after *Clostridium difficile* infection with bacterial, viral and parasitic infections. Therefore, a combination of rifaximin and metronidazole having activity against *Clostridium difficile* and mixed infections would be a rationale combination for treatment of IBS-D and for prevention of post-infectious irritable bowel syndrome.

The role of the gut microbiota in the development and maintenance of inflammation in IBD provides the rationale for the use of antibiotics in the medical treatment of both Crohn's disease and ulcerative colitis. Rifaximin, either in monotherapy or as an adjunctive treatment with metronidazole can be successfully employed in the treatment of IBD avoiding long term administration of antibiotics and associated systemic adverse effects.

Acknowledgement

Author acknowledges the contribution of Mr. Rafique Sheikh, M. Pharm (Pharmacology) for his contribution in doing literature search & helping with the preparation of manuscript.

Financial disclosure or funding: Nil

Conflict of interest: Nil

Author contributions: Prepared and reviewed the review article.

References

1. Diarrhoeal disease Fact sheets. World Health Organization. 2022.
2. Lindsay B, Ramamurthy T, Sen Gupta S, Takeda Y, Rajendran K, et al. Diarrheagenic pathogens in polymicrobial infections. Emerg Infect Dis. 2011; 17: 606-611.
3. Srivastava S, Banerjee S, Debbarma S, Kumar P, Sinha D. Rural-urban differentials in the prevalence of diarrhoea among older adults in India: Evidence from Longitudinal Ageing Study in India, 2017-18. PLoS One. 2022; 17: e0265040.
4. Behera DK, Mishra S. The burden of diarrhea, etiologies, and risk factors in India from 1990 to 2019: evidence from the global burden of disease study. BMC Public Health. 2022; 22: 92.
5. Shrivastava AK, Kumar S, Mohakud NK, Suar M, Sahu PS. Multiple etiologies of infectious diarrhea and concurrent infections in a pediatric outpatient-based screening study in Odisha, India. Gut Pathog. 2017; 9: 16.
6. Kattula D, Francis MR, Kulinkina A, Sarkar R, Mohan VR, et al. Environmental predictors of diarrhoeal infection for rural and urban communities in south India in children and adults. Epidemiol Infect. 2015; 143: 3036-3047.
7. Casburn-Jones AC, Farthing MJ. Management of infectious diarrhoea. Gut. 2004; 53: 296-305.
8. Understanding Emerging and Re-emerging Infectious Diseases. NIH Curriculum Supplement Series. 2022.
9. Reardon S. CDDEP Resistance Map. The spread of antibiotic resistance. 2020.
10. McCusker ME, Harris AD, Perencevich E, Roghmann MC. Fluoroquinolone use and Clostridium difficile-associated diarrhea. Emerg Infect Dis. 2003; 9: 730-733.
11. Walbrown MA, Aspinall SL, Bayliss NK, Stone RA, Cunningham F, et al. Evaluation of Clostridium difficile-associated diarrhea with

a drug formulary change in preferred fluoroquinolones. J Manag Care Pharm. 2008; 14: 34-40.

12. Wilkins T, Pepitone C, Alex B, Schade RR. Diagnosis and management of IBS in adults. Am Fam Physician. 2012; 86: 419-426.

13. Lacy BE. Diagnosis and treatment of diarrhea-predominant irritable bowel syndrome. Int J Gen Med. 2016; 9: 7-17.

14. Seyedian SS, Nokhostin F, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. J Med Life. 2019; 12: 113-122.

15. Anbazhagan AN, Priyamvada S, Alrefai WA, Dudeja PK. Pathophysiology of IBD associated diarrhea. Tissue Barriers. 2018; 6: e1463897.

16. Rybak MJ, McGrath BJ. Combination antimicrobial therapy for bacterial infections. Guidelines for the clinician. Drugs. 1996; 52: 390-405.

17. Scarpignato C, Pelosini I. Experimental and clinical pharmacology of rifaximin, a gastrointestinal selective antibiotic. Digestion. 2006; 73: 13-27.

18. Adachi JA, DuPont HL. Rifaximin: a novel nonabsorbed rifamycin for gastrointestinal disorders. Clin Infect Dis. 2006; 42: 541-547.

19. Taylor DN, McKenzie R, Durbin A, Carpenter C, Haake R, et al. Systemic pharmacokinetics of rifaximin in volunteers with shigellosis. Antimicrob Agents Chemother. 2008; 52: 1179-1181.

20. Kucers' the use of antibiotics. A clinical review of antibacterial, antifungal, antiparasitic and antiviral drugs. Ed. Lindsay M Grayson. USA, 2010.

21. Cangemi DJ, Lacy BE. Management of irritable bowel syndrome with diarrhea: a review of nonpharmacological and pharmacological interventions. Therap Adv Gastroenterol. 2019; 12: 17562848-19878950.

22. D'Ostroph AR, So TY. Treatment of pediatric Clostridium difficile infection: a review on treatment efficacy and economic value. Infect Drug Resist. 2017; 10: 365-375.

23. Bassotti G, Macchioni L, Corazzi L, Marconi P, Fettucciari K. Clostridium difficile-related postinfectious IBS: a case of enteroglial microbiological stalking and/or the solution of a conundrum? Cell Mol Life Sci. 2018; 75: 1145-1149.

24. Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, et al. Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: A Systematic Review and Meta-analysis. Gastroenterology. 2017; 152: 1042-1054.

25. Guslandi M. Rifaximin in the treatment of inflammatory bowel disease. World J Gastroenterol. 2011; 17: 4643-4646.

26. Gawronska A, Banasiuk M, Lachowicz D, Pituch H, Albrecht P, et al. Metronidazole or Rifaximin for Treatment of Clostridium difficile in Pediatric Patients with Inflammatory Bowel Disease: A Randomized Clinical Trial. Inflamm Bowel Dis. 2017; 23: 2209-2214.