BEHIND THE SCENE OF DIARRHEA

A MICROBIAL BATTLEFIELD

BIOCODEX
Microbiota Institute

SUMMARY

MICROBIOTA AND INFECTIOUS DIARRHEA:
VIRTUOUS OR VICIOUS CIRCLE?

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Diarrhea is a leading cause of death at all ages, especially among children under five. Most cases of acute diarrhea are due to infectious pathogens: viruses, bacteria or parasites. Usually self-limiting, some cases of severe diarrhea may require diagnostic investigation. The microbiota is doubly involved: as a victim of infectious diarrhea, which is usually accompanied by dysbiotic states; and as a guard, since the intestinal flora might inhibit pathogens.

INFECTIOUS DIARRHEA, ONE OF THE LEADING CAUSES OF INFANT MORTALITY WORLDWIDE

The passage of 3 or more loose or liquid stools per day corresponds to the common definition of diarrhea as set out by the WHO.[1] Both criteria (frequency and consistency) are necessary: frequent passing of formed stools is not diarrhea, nor is the passing of loose stools by breastfed babies (Figure 1). 1.6 million deaths were attributed to diarrhea in 2016.[2] Children are particularly at risk: diarrheal disease is the 3rd leading cause of death in children under 5 years of age. A large part of the mortality used to be attributed to severe dehydration linked to fluid loss but today, **septic bacterial infections account for an increasing proportion of all diarrhea-associated deaths.[1] Malnourished or immunity-impaired** children are the most at risk of life-threatening diarrhea, as well as people living with HIV.[1]

> **"Diarrheal disease, 3rd leading cause of death in children under 5 years of age.[1]"**

1. WHO Fact Sheet. Diarrhoeal disease. March 2024. **2.** GBD 2016 Diarrheal Disease Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis*. 2018 Nov;18(11):1211-1228.

DIARRHEA CLASSIFICATION

There are **3 clinical types of diarrhea** based on its symptoms and duration:[1]

- **acute watery diarrhea**, which lasts several hours or days (up to 14 days) and includes cholera;
- **acute bloody diarrhea** (dysentery);
- **persistent diarrhea,** which lasts 14 days or longer.

Most cases of acute diarrhea are due to infections:[1,3,4] a virus, bacteria or parasites could all be responsible, but rotavirus and *Escherichia coli* are the two most common etiological agents of moderate-to-severe diarrhea in low-income countries.[1] *Rotavirus* and *Shigella* are responsible for the highest number of infectious-diarrhea related deaths;[2] this is giving rise to preventive vaccination strategies (still under development for the latter). Although certain fungal communities have been confirmed to be associated with diarrhea, the role of fungi in diarrhea remains controversial.[5] They could be at work in some clinical settings, especially in immunocompromised patients prone to invasive fungal infections (candidiasis).[6]

PATHOPHYSIOLOGICAL SYNDROMES

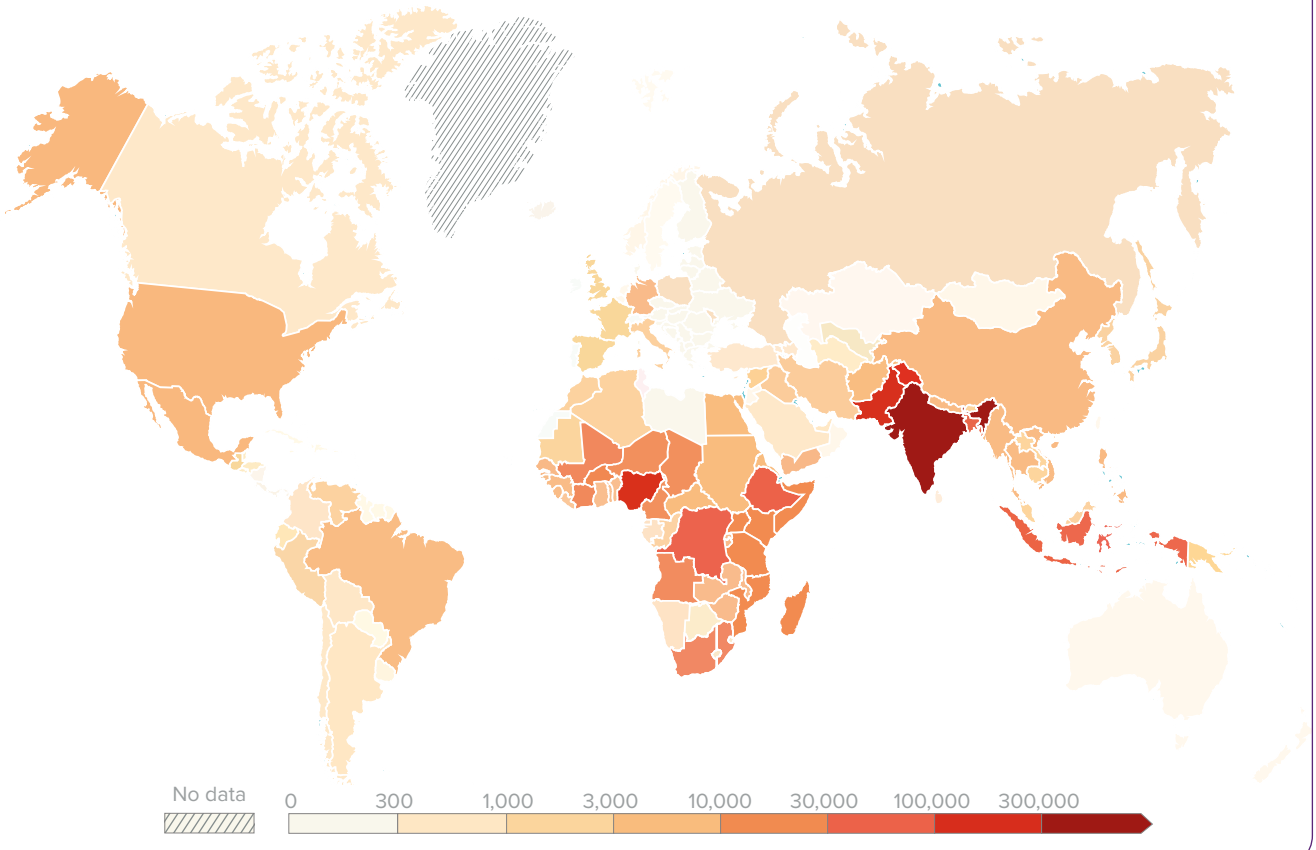
From the clinical perspective, diarrheagenic pathogens can cause 2 pathophysiological syndromes:[4]

- **Noninflammatory diarrhea (NID):** patients present with nausea, vomiting, **watery and voluminous stools,** and abdominal cramping resulting from intestinal secretion (the intestinal mucosa remains intact). This milder course of disease is usually viral (Rotavirus, Norovirus…) but it can also be bacterial (enterotoxigenic *Escherichia coli, Clostridium perfringens*…) or parasitic (*Giardia*, …);

- **Inflammatory diarrhea (ID):** patients present with fever, abdominal pain, tenesmus and **bloody stools** of smaller volume than in NID. This severe course of disease is usually caused by invasive or toxin-producing bacterial strains (*Shigella, Salmonella* species…) that lead to mucosal barrier disruption and tissue destruction.

"Rotavirus and *Escherichia coli* are the two most common etiological agents of moderate-to-severe diarrhea in low-income countries."

FIGURE 1. Diarrheal disease deaths, 2019. Estimated annual number of deaths from diarrheal diseases
(source: https://ourworldindata.org/diarrheal-diseases)



3. Iancu MA, Profir M, Roşu OA, *et al.* Revisiting the Intestinal Microbiome and Its Role in Diarrhea and Constipation. *Microorganisms.* 2023 Aug 29;11(9):2177. **4.** Sokic-Milutinovic A, Pavlovic-Markovic A, Tomasevic RS, Lukic S. Diarrhea as a Clinical Challenge: General Practitioner Approach. *Dig Dis.* 2022;40(3):282-289. **5.** Li Y, Xia S, Jiang X, *et al.* Gut Microbiota and Diarrhea: An Updated Review. *Front Cell Infect Microbiol.* 2021 Apr 15;11:625210. **6.** Lamps LW, Lai KK, Milner DA Jr. Fungal infections of the gastrointestinal tract in the immunocompromised host: an update. *Adv Anat Pathol.* 2014 Jul;21(4):217-27.

BEHIND THE SCENES OF DIARRHEA: THE MICROBIOTA

VICIOUS CIRCLE: WHEN DIARRHEA LEADS TO GUT DYSBIOSIS

Infectious diarrhea is regarded as a **major dysbiotic** event resulting from:

- increased **bowel movements and disruption to mucosal integrity**,[3]
- increased proportion of water in the fecal matter and reduced transit time which contributes to **taxonomic scarcity**,[3]
- and possible oral rehydration, zinc supplements, probiotics and even antimicrobials (in the case of dysentery or bacterial infections) which also contribute to an imbalance in the intestinal microbiota.[7]

Depending of the type of infection, **infectious diarrheas are usually accompanied by dysbiotic states**:[7] **bacteria-induced diarrhea** is generally linked to an elevation in *Escherichia, Streptococcus* and oral bacteria; **viral infections** lead to a less pronounced reduction in anaerobic commensals in the gut (higher abundance in *Bifidobacterium*); **giardia-induced diarrhea** is linked to a decrease in *Gammaproteobacteria* and an enrichment in *Prevotella*.

"The community of microbes that inhabit the gut is as numerous as human cells, with the vast majority of bacteria residing in the colon." [8]

"DYSBIOSIS"	Dysbiosis corresponds to the disruption of a formerly stable, functionally complete microbiota.[9]
"INTESTINAL MICROBIOTA"	The community of microorganisms - bacteria, viruses, fungi (including yeasts) and parasites - that inhabit the gut.[10]

VIRTUOUS CIRCLE: WHEN THE GUT MICROBIOTA OFFERS PROTECTION

Mechanisms by which the gut microbiota provides colonization resistance can be both direct and indirect. The microbiota directly inhibits diarrheal pathogens mainly via competition for nutrients, but also by limiting in a variety of ways the growth of diarrheal pathogens: secreting bacteriocins (antimicrobial peptides), cell contact-dependent inhibitory structures (type VI secretion system), producing molecules that reduce the pathogens' virulence...

The microbiota also indirectly inhibits diarrheal pathogens via its effects on the host: by promoting gut barrier maintenance and by stimulating both the innate and the adaptive immune system.[8]

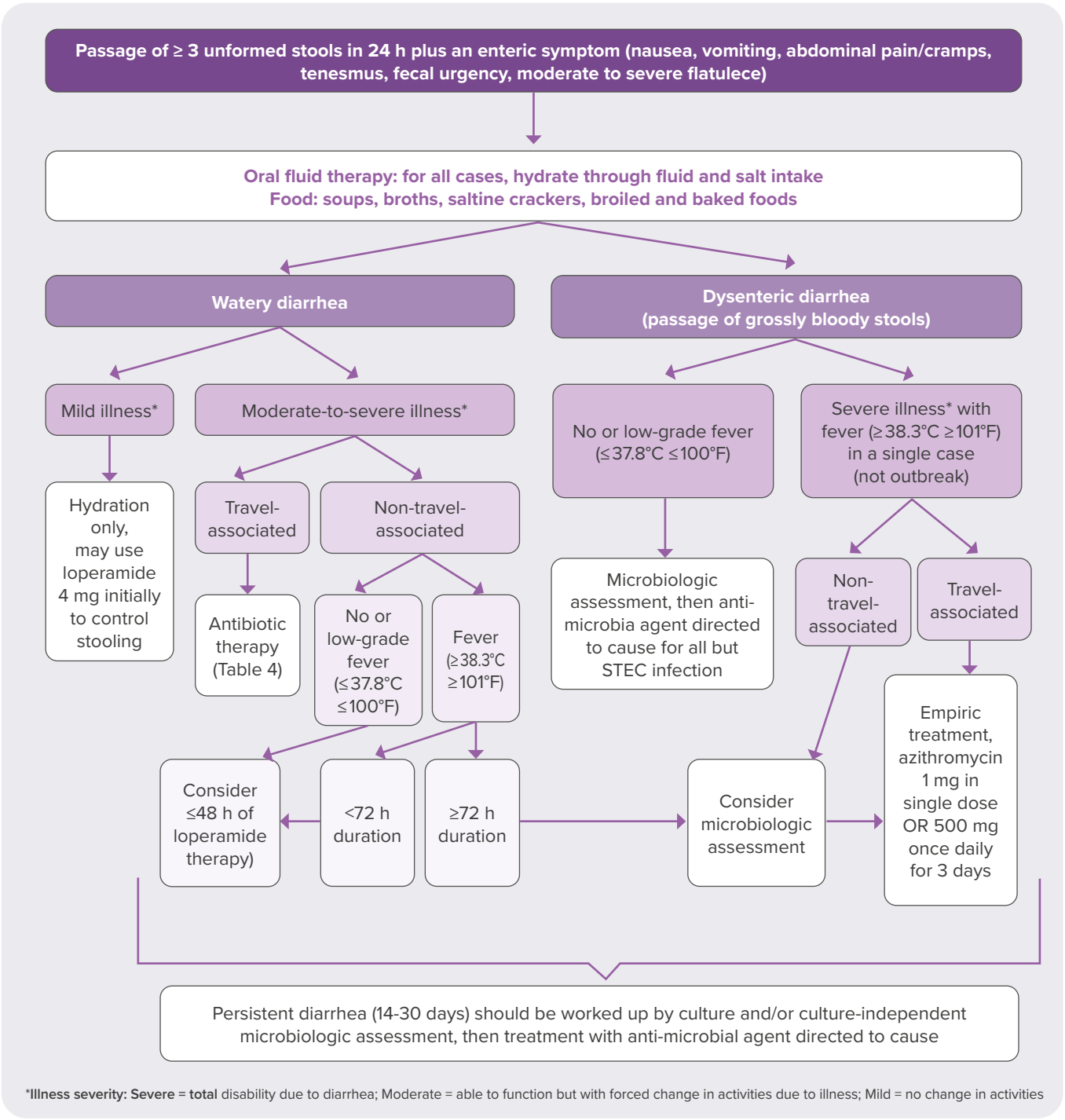
HOW TO MANAGE INFECTIOUS DIARRHEA?

The majority of intestinal infections are self-limiting in immunocompetent individuals. Nevertheless, some patients (with severe dehydration, more severe illness, persistent fever, bloody stools, immunosuppression...) require specific diagnostic investigation. These can include a complete blood count, a creatinine and electrolytes assessment, verification of leukocytes and lactoferrin presence in the stools, stool culture, along with *C. difficile* testing, PCR, ova and parasites search, endoscopy and abdominal imaging[11].

The American College of Gastroenterology (ACG) guideline[12] provides recommendations for the diagnosis and management of adult patients presenting with acute diarrhea of suspect infectious etiology (Figure 2). Clinical investigation in children is based on the same principles.[23] In 2023, World Gastroenterology Organisation Global Guidelines included probiotics in the prevention and treatment of some infectious diarrhea[57].

7. Chung The H, Le SH. Dynamic of the human gut microbiome under infectious diarrhea. *Curr Opin Microbiol.* 2022 Apr;66:79-85. **8.** Vogt SL, Finlay BB. Gut microbiota-mediated protection against diarrheal infections. *J Travel Med.* 2017 Apr 1;24(suppl_1):S39-S43. **9.** Waitzberg D, Guarner F, Hojsak I, Ianiro G, Polk DB, Sokol H. Can the Evidence-Based Use of Probiotics (Notably *Saccharomyces boulardii* CNCM I-745 and Lactobacillus rhamnosus GG) Mitigate the Clinical Effects of Antibiotic-Associated Dysbiosis?. Adv Ther. 2024;41(3):901-914. **10.** Hou, K., Wu, ZX., Chen, XY. *et al.* Microbiota in health and diseases. *Sig Transduct Target Ther* 7, 135 (2022). **11.** Siciliano V, Nista EC, Rosà T, Brigida M, Franceschi F. Clinical Management of Infectious Diarrhea. *Rev Recent Clin Trials.* 2020;15(4):298-308. **12.** Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults. *Am J Gastroenterol.* 2016 May;111(5):602-22.

FIGURE 2. Approach to empiric therapy and diagnostic-directed management of the adult patient with acute diarrhea (suspect infectious etiology).
Sources: Riddle *et al.*, 2016[12]



*Illness severity: **Severe** = **total** disability due to diarrhea; Moderate = able to function but with forced change in activities due to illness; Mild = no change in activities

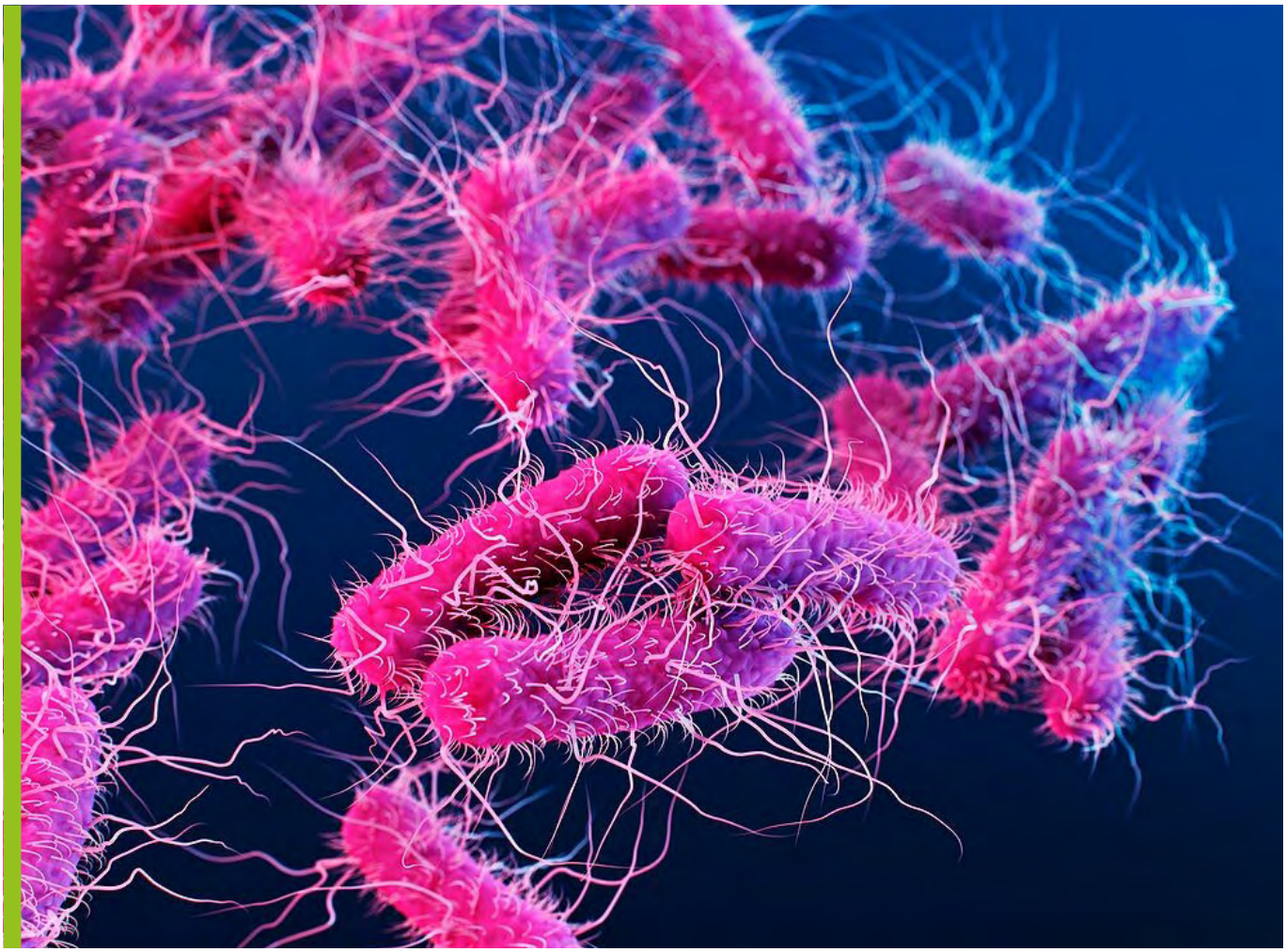
World Gastroenterology Organisation Global Guidelines, 2023 [57]

Treatment of acute diarrhea: *"oral administration [of some probiotic strains]* ***shortens the duration*** *of acute diarrheal illness in children by* ***approximately 1 day.****"*

Prevention of:

- **acute diarrhea:** *"probiotics probably make* ***little or no difference*** *with diarrhea lasting 48 hours or longer."*
- **antibiotic-associated diarrhea:** *"probiotics may provide a* ***moderate effect*** *for preventing antibiotic-associated diarrhea in children, adults, and elderly adults."*
- ***Clostridioides difficile*** **diarrhea:** *"probiotics are* ***effective*** *for preventing C. difficile–associated diarrhea in patients receiving antibiotics."*

BACTERIAL DIARRHEA:
GUT MICROBIOTA, A POTENTIAL VICTIM OR A GUARD AGAINST IT?



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Pathogenic bacteria such as Shigella, Vibrio cholerae, Salmonella, E. coli... lead to bacterial diarrhea, through mechanisms that depend on the bacteria involved. Bacterial diarrheas are accompanied by intestinal dysbiosis. Symmetrically, the gut microbiota exerts effects on the bacterial infection. Since a 'healthy' gut microbiota is more resistant to infection, probiotics could reduce the severity of many bacterial infections.

Underlying how lethal bacterial diarrhea can be, these 8 bacteria were responsible for more than a third of the over 1.65 million deaths from infectious diarrhea recorded worldwide in 2016.[2]

- ***Shigella:*** 212,438 deaths.
- ***Vibrio cholerae:*** 107,290 deaths.
- **Non-typhoidal *Salmonella spp:*** 84,799 deaths.
- ***Campylobacter spp:*** 75,135 deaths.
- **Enterotoxigenic *E. coli:*** 51,186 deaths.
- ***Clostridioides difficile:*** 22,417 deaths.
- ***Aeromonas:*** 16,881 deaths.
- **Enteropathogenic *Escherichia coli:*** 12,337 deaths.

"8 bacteria were responsible for 1 death over 3 from infectious diarrhea in 2016."

FROM INFECTION TO DIARRHEA

The mechanisms that lead to bacterial diarrhea depend on the bacteria involved.
Transmitted via contaminated food, water or by person-to-person contact, ***Shigella*** infests the gastrointestinal tract, produces an enterotoxin and serotype toxin 1, destroying the intestinal epithelium and leading to severe bloody and mucous diarrhea.[3,5]

Pathogenic variants of ***Vibrio cholerae*** produce a cholera toxin that activates anion secretion, inhibits absorption of electroneutral NaCl and destroys the intestinal barrier function, thereby inducing massive fluid secretion in the lumen of the small intestine and the loss of large amounts of water, sodium, chloride, bicarbonate and potassium.[3,5,13]

Different **pathogenic *E. coli*** strains, classified into different pathotypes (Table 1), cause mild to severe diarrhea usually accompanied by fever. *E. coli* adheres to the intestinal epithelial cells through the adherent fimbriae, produces toxins and exerts its pathogenic effects.[3,5]

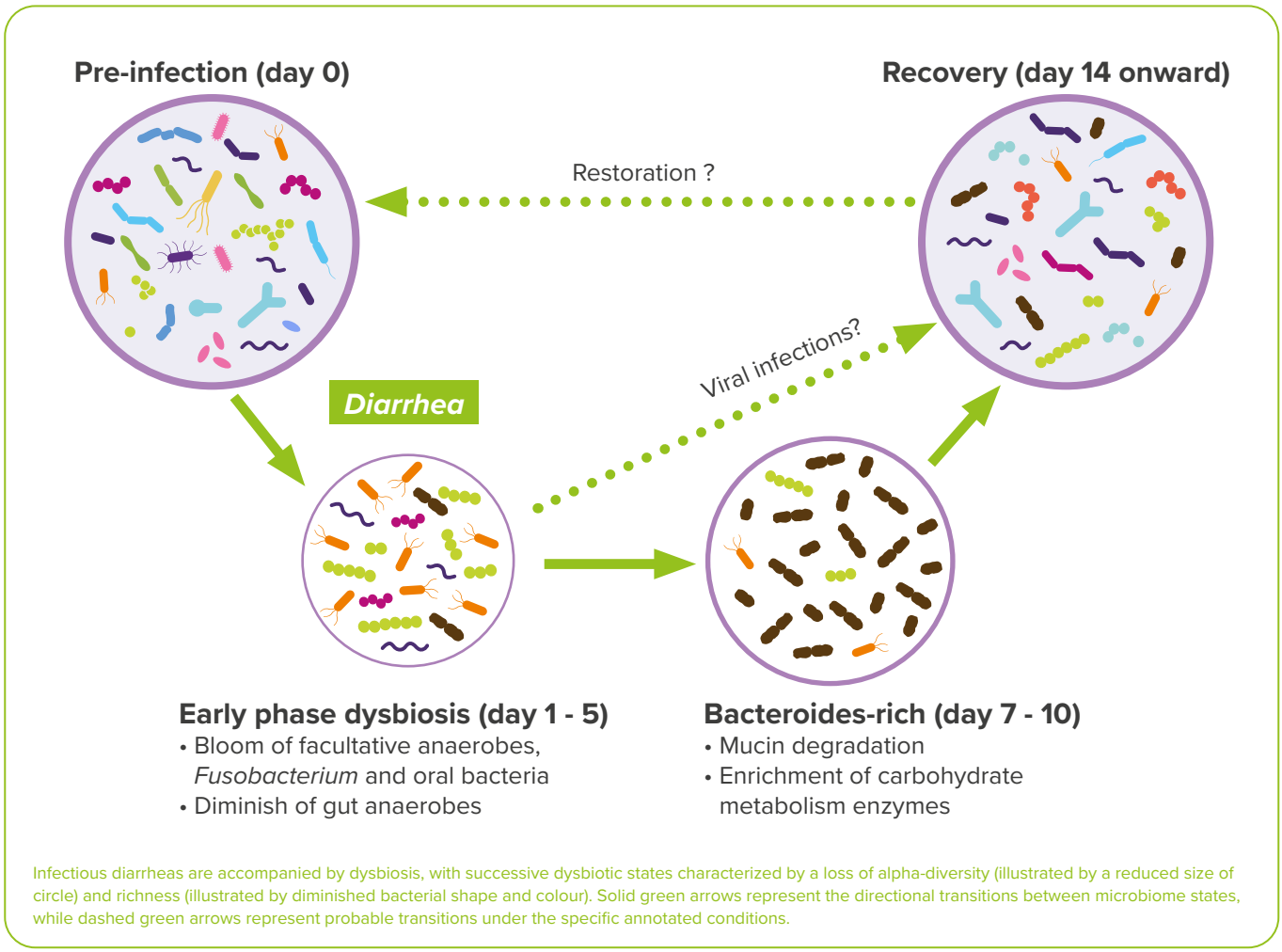
EFFECT OF PATHOGENS AND DIARRHEA ON MICROBIOTA

Bacterial diarrheas are accompanied by dysbiosis, usually with an overabundance of facultative anaerobes (*Escherichia, Streptococcus, Enterococcus*, etc.) in dysenteric diarrhea, and a depletion in bacteria of known immuno-modulatory effects *(Lactobacillus ruminis, Bifidobacterium pseudocatenulatum)*[7] (Figure 3).

TABLE 1. *E. coli* pathotype characteristics
Sources : Iancu *et al.* 2023 [3] ; Li *et al.* 2021 [5]

Pathotype	Diarrhea type	Clinical presentation
Enteropathogenic *E. coli* (EPEC)	Infant diarrhea	Persistent watery diarrhea
Enterotoxigenic *E. coli* (ETEC)	Travelers' diarrhea and infant diarrhea	Watery, non-bloody stool
Enteroinvasive *E. coli* (EIEC)	Dysentery	Diarrhea with blood and mucus
Enterohemorrhagic *E. coli* (EHEC/STEC)	Haemorrhagic colitis and haemolytic uremic disease	Haemorrhagic colitis or watery diarrhea without blood
Enteroaggregative *E. coli* (EAEC)	Travelers' diarrhea and infant diarrhea	Persistent watery diarrhea

FIGURE 3. Schematic representation of gut microbiome dynamic under infectious diarrhea
Sources: adapted from Chung *et al.* 2022 [7]



Infectious diarrheas are accompanied by dysbiosis, with successive dysbiotic states characterized by a loss of alpha-diversity (illustrated by a reduced size of circle) and richness (illustrated by diminished bacterial shape and colour). Solid green arrows represent the directional transitions between microbiome states, while dashed green arrows represent probable transitions under the specific annotated conditions.

13. Ramamurthy T, Kumari S, Ghosh A. Diarrheal disease and gut microbiome. *Prog Mol Biol Transl Sci.* 2022;192(1):149-177. **14.** George S, Aguilera X, Gallardo P, *et al.* Bacterial Gut Microbiota and Infections During Early Childhood. *Front Microbiol.* 2022 Jan 5;12:793050. **15.** Toro Monjaraz EM, Ignorosa Arellano KR, Loredo Mayer A *et al.* Gut Microbiota in Mexican Children With Acute Diarrhea: An Observational Study. *Pediatr Infect Dis J.* 2021;40(8):704-709. **16.** Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem* J. 2017 May 16;474(11):1823-1836.

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For example, in cholera, the gut microbiota is substantially modified both during and after infection, this as a consequence of the removal of the mucus layer along with the residing gut microbial community and of the delivery of toxin by ***V. cholerae***.[13] During recovery, the gut microbiota of cholera patients slowly repopulates via an accumulation pattern similar to that of the maturation of the gut microbiota observed in children.[3]

In the same way, children infected with diarrheagenic ***E. coli (DEC)*** display a distinctive gut microbial composition, with a high fraction of *Bacteroidetes* and *Proteobacteria* and a reduced abundance of *Firmicutes*.[13] Increases in *Proteobacteria* could be partially explained by an increase in *Escherichia/ Shigella* species (as the cause of diarrhea) and in other members of *Enterobacteriaceae*, such as *Citrobacter* and *Enterobacter* (related to histamine production induced by proinflammatory environments and associated with *E. coli* adherence).[14]

Frequent antimicrobial use can also partly explain the observed dysbiosis.[7]

GUT MICROBIOTA PROTECTION AGAINST INFECTIONS

Symmetrically, the gut microbiota has demonstrated effects on bacterial infection. In germ-free animals, their lack of a gut microbiota and the absence of ecological competition results in an immature immune system that renders them highly susceptible to diarrheal pathogens: 10 colony-forming units (CFU) of ***Salmonella*** are enough to cause a lethal infection, whereas to kill 50% of mice with an intact gut microbiota 10^3 –10^9 CFU are required.[8]

In humans, *Prevotella*, *Bifidobacterium* and *Blautia* have been shown to reduce colonization of ***V. cholerae***. Conversely, *Paracoccus* is believed to support the growth of the pathogen.[13]

This is the reason why promoting a 'healthy' gut microbiome has been considered a useful approach in the intervention and prevention of cholera.[13]

"The GI tract encompasses ~1 to 10 times more bacterial cells than the number of cells in the human body." [16]

BACTERIAL AND YEAST PROBIOTICS, PREBIOTICS AND FMT

The severity of several bacterial infections could be reduced by **probiotics**: for example, probiotic ***E. coli*** inhibits the biofilm formation of other *E. coli* strains and likewise those of the pathogenic *Staphylococcus aureus* and *S. epidermidis*.[3] Regarding dysentery, a combination of *Lactobacillus* and *Bifidobacterium* strains and a *Streptococcus* strain reduces both the duration of blood-affected diarrhea and the time spent in hospital.[3]

Numerous mechanisms could explain why probiotics alleviate diarrhea:[3] production of antimicrobial substances, competitive exclusion, competition with cell binding sites, production of acids and metabolites that lower the surrounding pH, strengthening of

the gut mucosal barrier, modulation of gut mucosal immunity and gut microbiota diversity. For example, the probiotic yeast *Saccharomyces boulardii* may facilitate gut microbiota restoration in children with acute diarrhea.[15]

Prebiotics can also have a positive impact on diarrhea: by increasing **the bacterial production of short-chain fatty acids (SCFAs) such as butyrate**, which contribute to the gut barrier integrity; and by antagonizing the adherence of pathogens to epithelial cells, thus inhibiting colonization and promoting gut pathogen elimination.[3]

Fecal microbiota transplantation (FMT), which aims to restore a healthy gut microbiota, has proven effective and is only indicated in the treatment of recurrent *C. difficile* in both adults and children.[14]

CLINICAL CASE *by Pr. Aldo Maruy*

- A 2-year-old boy presented with fever, abdominal pain and diarrhea with mucus and blood. He had history of two similar episodes in the last six months, treated solely with antibiotics.
- In order to prevent a relapse, it was decided to treat him with antibiotics and probiotics. The diarrhea ceased within 48 hours, the antibiotic was suspended at the 5th day while the probiotic was continued for two weeks; a diet rich in complementary food and prebiotics was prescribed.
- In addition to treating the infection with antibiotics, it is recommended in order to prevent a new diarrheal episode that the composition of the gut microbiota be restored via the diet together with the administration of prebiotics and probiotics.

PR. ALDO MARUY
Paediatric Gastroenterologist, Hospital Cayetano Heredia, Lima (Peru)

EXPERT OPINION

Throughout one's life, a healthy microbiota plays an important role in the prevention and treatment of bacterial diarrhea. Specific species have demonstrated protective effects against diarrhea: *Lactobacillus* taxa are protective against *Shigella spp.*-induced diarrhea; the presence of *Sutterella sp., Prevotella copri* and *Bacteroides vulgatus* predict resistance to enterotoxigenic *E. coli* (ETEC).

On the other hand, microbial intervention, through modifying the diet and using prebiotics, probiotics and FMT, can regulate the composition of gut microbiota to prevent and treat diarrhea. Future research should expand our knowledge of the microbiome as it relates to infectious diarrhea, thereby assisting in the design of improved preventative and managerial interventions.

CONSEQUENCES OF TRAVELERS' DIARRHEA

When visiting medium- and high-risk destinations, 10–70% of travelers from low infectious disease-risk countries experience diarrhea. Travelers' diarrhea is predominately caused by bacteria (≥80%–90% of cases), with intestinal viruses accounting for a minimum of 5%–15% of the cases.[52] Infections by protozoal pathogens might account for approximately 10% of diagnoses mostly in those traveling for extended periods.

The microbiota of travelers who experienced diarrhea show greater variation throughout the length of their stay than those of healthy travelers, associated with a lower baseline diversity, which has been linked to an increased susceptibility to infection.[51]

Moreover, diarrhea reduces the capacity of microbiota restoration (large increase of the rate of divergence from baseline) and leads to the acquisition of multidrug-resistant organisms.[51] Thus, according to a study including 267 Americans travelling outside the United States, a third returned with diarrhea, 61% with intestinal dysbiosis and 38% with antibiotic-resistant bacteria (most of them an *E. coli*), contributing to the global spread of antimicrobial resistance.[58]

During travelers' diarrhea, a dysbiotic microbiota[51] has been observed, marked by the enrichment and depletion of several taxa.
Source: adapted from Boolchandani *et al.*, 2022[51]


OXA 30
AK 30
DOR 10
CO 10

ANTIBIOTIC ASSOCIATED DIARRHEA (AAD)

Antibiotics are a powerful tool in the fight against bacterial infections, however they also disrupt the protective intestinal microbiota and this can lead to unintended consequences including antibiotic-associated diarrhea (AAD) in as much as 35% of patients.[17,18,19] **The incidence of AAD depends on several factors**:[17,18,19] **age** (among children this percentage can reach up to 80%) [15], **setting, type of antibiotic, etc.** Most of the time, AAD is caused by antibiotic-induced dysbiosis, is of mild intensity and is self-limiting, lasting between 1 and 5 days.

"Diarrhea occurs in as much as 35% of patients who receive antibiotics."[17,18,19]

While the etiologies for AAD are diverse, approximately one-third of AAD cases are attributed to *C. difficile*. Under certain conditions, *C. difficile* will trigger an inflammatory response leading to a range of clinical outlooks, from mild diarrhea to pseudomembranous colitis, toxic megacolon and/or death.[17]

CLINICAL CASE *by Pr. Aldo Maruy*

- A 10-year-old patient came to the clinic with a seven-day history of diarrhea. From the onset, the child had been producing each day two or three liquid stools with mucus, though without blood. The mother said there had been neither fever nor vomiting. On clinical examination, the child seemed well and appeared to be adequately hydrated.
- The doctor requested a stool culture and OVA & parasite checks; these were negative.
- An antecedent had not initially been considered: six weeks before, the child had had a respiratory infection which was treated with antibiotics.
- Late-onset Antibiotic Associated Diarrhea (AAD) was then suspected. The patient received probiotics and improved within a week.
- **AAD can take anywhere from 2 hours to 8-10 weeks to develop after antibiotic use.**

ESPGHAN 2023 RECOMMENDATIONS

In 2023, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Special Interest Group on Gut Microbiota and Modifications set out updated recommendations for the use of probiotics in the management of selected paediatric gastrointestinal disorders:[20]

"If the use of probiotics for preventing antibiotic-associated diarrhea (AAD) is considered because of the existence of risk factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, or previous episodes of AAD, healthcare professionals may recommend ***high doses (≥5 billion CFU/day) of S. boulardii or L. rhamnosus GG started simultaneously with antibiotic treatment to prevent AAD*** *in outpatients and hospitalized children (certainty of evidence: moderate; grade of recommendation: strong)."*

EXPERT OPINION

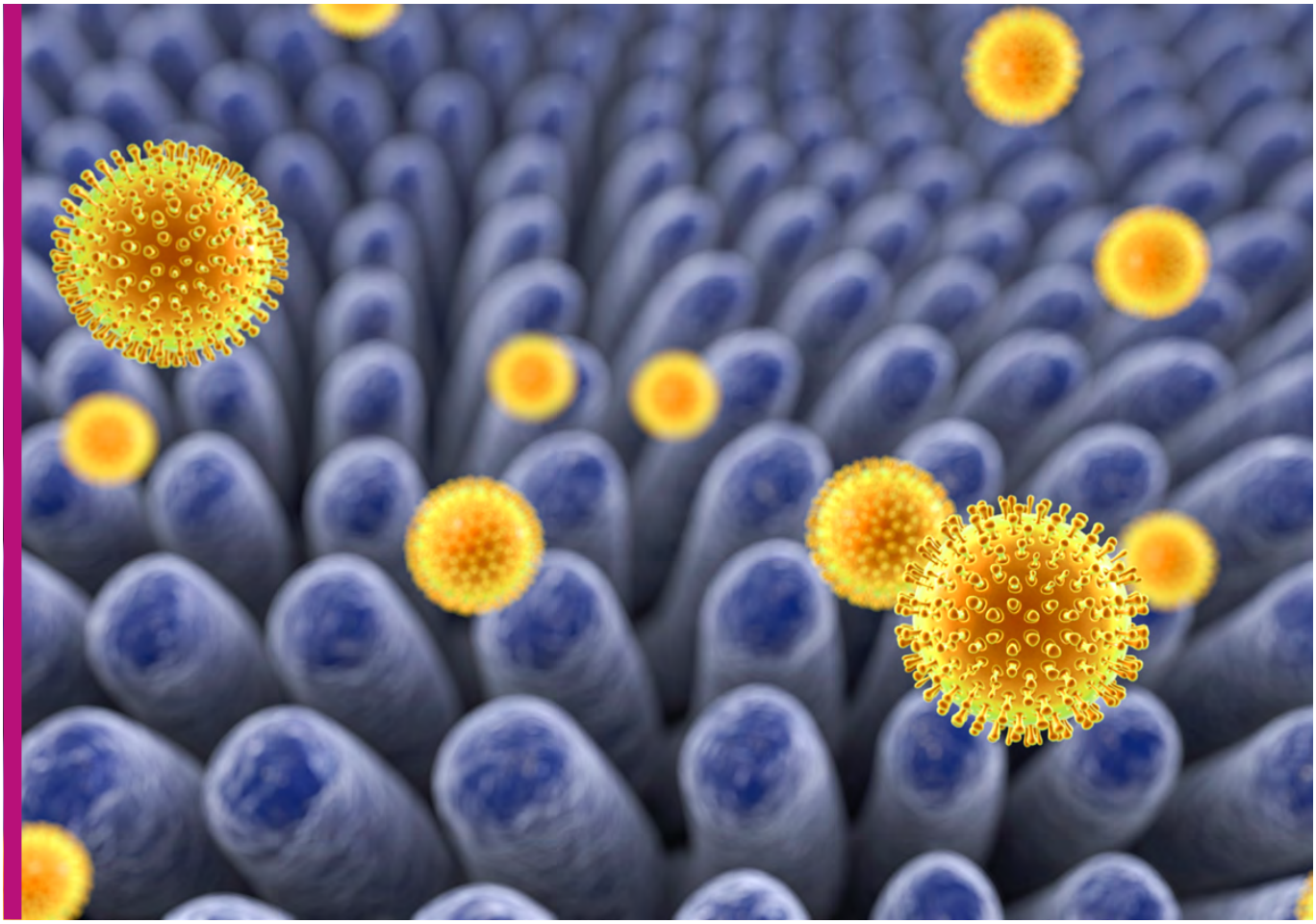
PR. ALDO MARUY

Paediatric Gastroenterologist, Hospital Cayetano Heredia, Lima (Peru)

Antibiotic Associated Diarrhea (AAD) is a common side effect of antibiotics. Age, spectrum of antibiotics used, underlying illness and recent surgery have been identified as risk factors. Recent evidence shows a new one: composition of the microbiota. In patients treated with β-lactams, higher relative abundances of *Bacteroides* were inversely associated with AAD while higher baseline abundance of *Bifidobacterium* species and *Lachnospiraceae* and amino acid biosynthesis pathways (AABP) were associated with AAD. Relative abundances of potentially protective taxa and levels AABP may distinguish children who did and did not experience AAD.
Further studies are needed to investigate whether similar trends are observed across different antibiotic types. The identified potentially protective taxa may inform the development of preventive approaches for AAD.

17. McFarland LV, Ozen M, Dinleyici EC *et al.* Comparison of pediatric and adult antibiotic associated diarrhea and Clostridium difficile infections. *World J Gastroenterol.* 2016;22(11):3078-3104. **18.** Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. *N Engl J Med* 2002;346:334-9. **19.** Theriot CM, Young VB. Interactions Between the Gastrointestinal Microbiome and Clostridium difficile. *Annu Rev Microbiol.* 2015;69:445-461. **20.** Szajewska H, Berni Canani R, Domellöf M *et al*; ESPGHAN Special Interest Group on Gut Microbiota and Modifications. Probiotics for the Management of Pediatric Gastrointestinal Disorders: Position Paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications. *J Pediatr Gastroenterol Nutr.* 2023 Feb 1;76(2):232-247.

VIRAL DIARRHEA:
WILL VACCINES CHANGE THE GAME?



Usually presenting as watery diarrhea, viral diarrheas are caused by 5 main types of virus. Among them, rotavirus remains the leading cause of diarrhea-related mortalities in children under 5 years of age, this despite the availability of vaccines since 2006. Composition of the gut microbiota, implicated in viral infection outcomes, and rotavirus vaccine efficacy, could play a key role in strategies aimed at reducing the burden of viral diarrhea.

Rotaviruses, norovirus, sapovirus, astrovirus, and adenovirus: five virus types are currently recognized as the main causes of viral diarrhea.[21] Of the 2 billion plus episodes of diarrheal disease that occur across the world each year, as estimated by the 2016 Global Burden of Disease (GBD) Study,[2] almost **900 millions of the moderate-to-severe episodes were** attributed to just three of these viruses: rotavirus, norovirus and adenovirus[22].

ROTAVIRUS, THE NUMBER ONE DIARRHEAL KILLER IN CHILDREN

Despite the development and availability of **rotavirus vaccines** since 2006,[22] this virus, which causes more severe symptoms than most other enteric pathogens,[22] was still responsible for over **228,000 deaths** worldwide in 2016, of which over 128,000 occurred in children below the age of 5[2] – **making rotavirus the leading cause of diarrhea-related mortalities among this segment of the population** (Figure 4).

WATERY DIARRHEA

Whatever the virus that triggers an episode of diarrhea, the process of infection is broadly the same: the virus infects the epithelial cells of the small intestine and causes damage that hampers the absorption of fluid.[21] Viral diarrhea usually manifests itself in **the form of a watery (non-bloody) diarrhea.** It can be accompanied by other symptoms, i.e. nausea, abdominal cramps, vomiting and fever,[22] resulting in what is known as viral gastroenteritis.

21. Iturriza-Gómara M, Cunliffe NA. 34 - Viral Gastroenteritis. Editor(s): Edward T. Ryan, David R. Hill, Tom Solomon, Naomi E. Aronson, Timothy P. Endy, *Hunter's Tropical Medicine and Emerging Infectious Diseases (Tenth Edition)*, Elsevier, 2020, Pages 289-307. ISBN 9780323555128. **22.** Bányai K, Estes MK, Martella V, Parashar UD. Viral gastroenteritis. *Lancet.* 2018 Jul 14;392(10142):175-186.

REHYDRATION... AND PROBIOTICS

Just as for the other etiologies (bacterial or parasitic) of infectious diarrhea, **management of viral diarrhea relies on oral or intravenous fluid replacement therapy,** depending on the degree of dehydration.[21] In addition, according to the latest conclusions of the ESPGHAN committee (2023),[20] healthcare professionals may recommend **some probiotic strains (*L. rhamnosus, S. boulardii* and *L. reuteri*) for the management of acute gastroenteritis in children,** since there is some evidence (certainty of evidence: low; grade of recommendation: weak) of reduced duration of diarrhea, and/or length of hospitalization, and/or and stool output.

IMPROVING ROTAVIRUS VACCINE EFFICACY, A CHALLENGE YET TO OVERCOME

Regarding prevention, the usual preventive measures apply (ensuring safe drinking water, adequate sanitation and frequent handwashing, limiting contact with infected people, etc.). Given the considerable burden of rotavirus diarrheal disease, **rotavirus vaccines are another important preventive measure**.[22,23]

Among all diarrheal pathogens, and despite vaccine availability, rotavirus remains the number one killer of children under five years of age.[2]

SARS-COV-2: NEW MEMBER OF THE DIARRHEAL VIRUSES CLUB

Alongside the viruses long recognized as principal causes of viral diarrhea, infection with the **SARS-CoV-2**, responsible for the greatest pandemic in recent times, **COVID-19, may also give rise to diarrhea.** In clinical studies, **the incidence rate of diarrhea ranges from 2% to 50% of cases**.[27] As with the respiratory tract, the angiotensin-converting enzyme 2 (ACE2) receptors are highly expressed on intestinal cells, serving as an important site of entry for the virus in the gut. The putative mechanisms leading to the development of diarrhea mainly involve angiotensin-converting enzyme 2 dysregulations following virus entry into enterocyte, which could trigger an inflammatory response, ionic imbalance and increased permeability. Furthermore, the spike protein of SARS-CoV-2 acts as an enterotoxin, with a mechanism similar to the rotavirus enterotoxin NSP4.[28] Alteration of gut microbiota and side effects of medications (antiviral and antibiotics) are also thought to be involved.[29]

FIGURE 4. Which pathogens are responsible for deaths from diarrheal disease in children?
Sources: Our world in data, from Cohen *et al.* 2022[26]

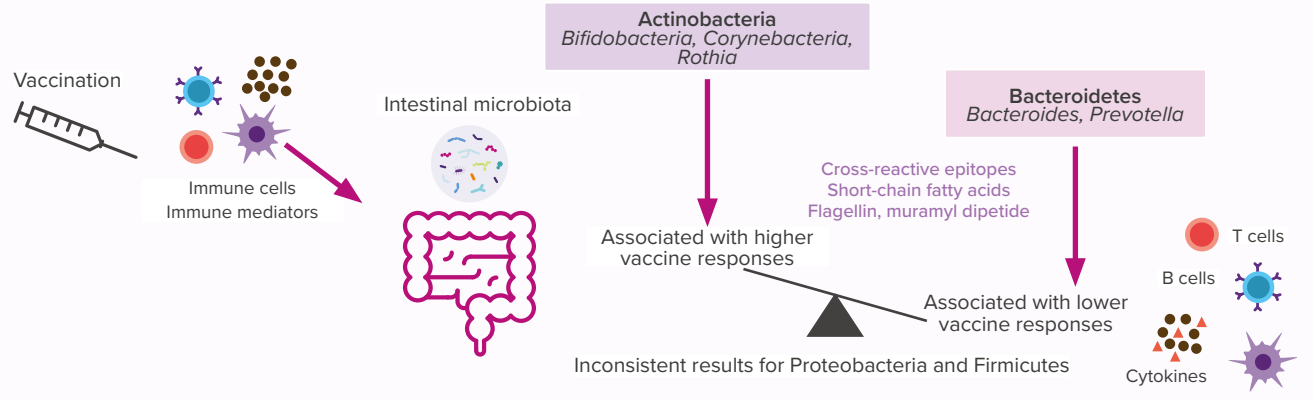
Viruses account for more than 50 % of diarrheal deaths in children under five.

23. Florez ID, Niño-Serna LF, Beltrán-Arroyave CP. Acute Infectious Diarrhea and Gastroenteritis in Children. *Curr Infect Dis Rep.* 2020 Jan 28;22(2):4. **24.** Clark A, Mahmud S, Debellut F, *et al.* Santosham M, Sanderson C. Estimating the global impact of rotavirus vaccines on child mortality. *Int J Infect Dis.* 2023 Dec;137:90-97. **25.** Sohail MU, Al Khatib HA, Al Thani AA, *et al.* Microbiome profiling of rotavirus infected children suffering from acute gastroenteritis. *Gut Pathog.* 2021 Mar 29;13(1):21.

Microbiota: a key role in rotavirus vaccination efficacy

Since their introduction in 2006, oral rotavirus vaccines (ORVVs) have at a global level led to a significant drop in the number of hospitalisations and deaths due to rotavirus diarrhea.[30] However, the efficacy of the vaccines has been varied, with low-income countries suffering from lower performance compared to the remarkably high efficacy (>90%) observed in higher income countries.[31] Reasons for this disparity are thought to be multi-factorial (host immunity, perinatal outcomes, genetics, nutritional status, stress, tobacco and alcohol use, rural versus urban location, family size, etc.). Just as for other vaccines, the composition and function of the gut microbiota is considered to be a key factor that regulates the immune response to vaccination[30,32,33] (Figure 5).

FIGURE 5. Interplay between vaccination and the intestinal microbiota
Sources: Zimmermann *et al.,* 2023[34]



The composition of the intestinal microbiota is thought to modulate vaccine immunogenicity through cross-reactive epitopes between microbes and vaccine antigens, modulation of B cell responses by microbial metabolites such as short-chain fatty acids (SCFAs), and the provision of natural microbial adjuvants (flagellin...). Vaccination might itself alter the composition of the intestinal microbiota through immune mediators triggered by vaccination reaching the intestine after having joined the blood flow.

These were estimated to have prevented 139,000 deaths from rotavirus among under-fives during the period 2006 to 2019, and to have prevented 15% of under-five rotavirus deaths in 2019.[24] However, **vaccine efficacy is region-specific and displays poor seroconversion in low-and middle-income countries.** Human clinical trial data have suggested a possible link between **the gut microbiota** and the enteric immune system's response to rotavirus vaccine[25] (Figure 5).

MICROBIOTA: FRIEND OR FOE IN THE ONSET OF VIRAL DIARRHEA?

In cases of viral diarrhea, as with infectious diarrhea in general, the outcome of the confrontation between pathogen and host depends on complex balances that in large part involve the microbiota.

The gut microbiota **displays bidirectional interactions with rotavirus and norovirus infections:**[14] **it can either protect against or predispose the host to infection;** in turn, an infection can alter the gut microbiota. Some bacteria seem able to inhibit viral infection. For example, one study shows **segmented filamentous bacteria** preventing and curing rotavirus infection in mouse colonies[35] (Figure 6). On the other hand, *in vitro* and *in vivo* studies indicate the **gut microbiota's involvement in facilitating viral infection:** certain gut microbes (e.g. *Enterobacter cloacae*) stimulate

Each gram of human gut content is estimated to contain at least, 10^8–10^9 virus-like particles, the vast majority of which are phages.[14]

26. Cohen AL, Platts-Mills JA, Nakamura T *et al.* Aetiology and incidence of diarrhea requiring hospitalisation in children under 5 years of age in 28 low-income and middle-income countries: findings from the Global Pediatric Diarrhea Surveillance network. *BMJ Glob Health.* 2022 Sep;7(9):e009548. **27.** D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and Management. *Clin Gastroenterol Hepatol.* 2020 Jul;18(8):1663-1672.

the ability of human norovirus to infect human B cells *in vitro*; microbiota elimination by antibiotics delays infection, reduces infectivity and/or viral titer of norovirus and rotavirus in mice.[8,36]

Therefore, **any invasive pathogens might have different effects depending on the state of the gut microbiota**.[3] The optimal microbiota profile and microbiota-targeting strategies that would lower the risk of infection and the following viral diarrhea remain to be characterized.[37]

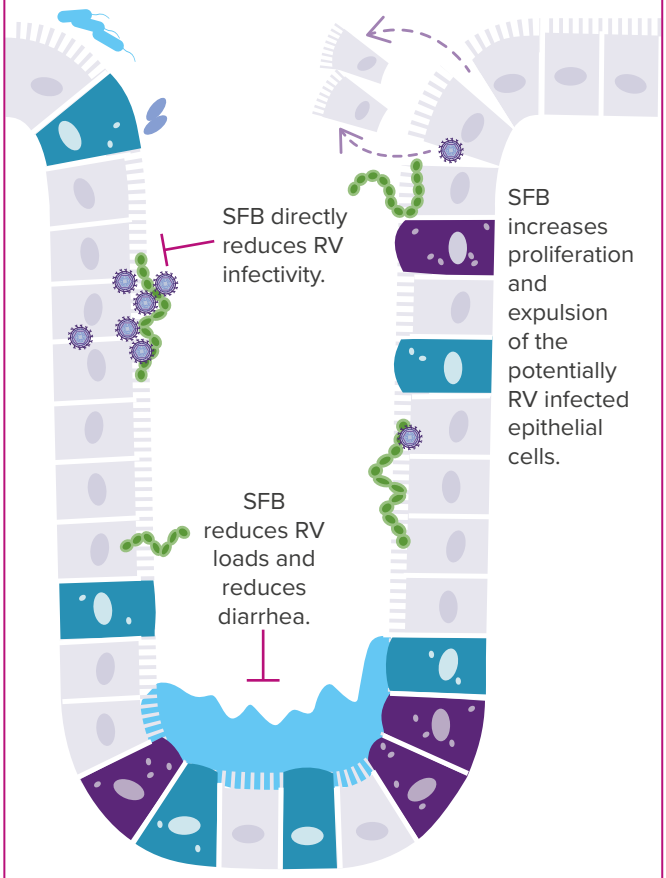
As to the effect of viral infection on gut microbiota composition, numerous studies have documented specific patterns of dysbiosis in patients suffering from viral diarrhea compared to healthy controls[25,38]. A reduction of microbiota (alpha) diversity is often reported, but specific taxa increases or decreases vary widely across the studies.[14] And one question remains: **does the dysbiosis observed during viral diarrhea reflect a prior disposition that might have facilitated the infection, is it a state caused by the virus, or is it a combination of both?**

CLINICAL CASE *by Dr. Marco Poeta*

- A 4-year-old girl presented to the paediatric emergency room with fever, diarrhea, vomiting and severe dehydration.
- Since the child needed intravenous rehydration, she was admitted to the hospital.
- The nasopharyngeal swab returned positive for SARS-CoV-2 infection, despite the absence of respiratory symptoms.
- Stools were negative for rotavirus, norovirus, adenovirus, bacteria and parasites but positive for SARS-CoV-2.
- Following the administration of probiotics, her stool frequency and consistency both recovered.
- The intravenous hydration was discontinued after four days, and the child was discharged.
- Diarrhea can be the only clinical manifestation of the SARS-CoV-2 infection. SARS-CoV-2 should therefore be added to the list of enteric pathogens.
- The efficacy of probiotics against Covid-associated gastroenteritis observed in this clinical case has already been demonstrated via in vitro studies.

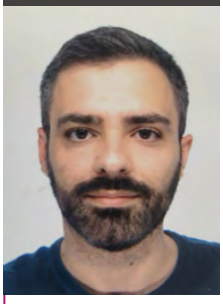
FIGURE 6. The protective role of segmented filamentous bacteria (SFB) in rotavirus (RV) infection

Source: Shi *et al.*, 2019[35]



DR. MARCO POETA

Paediatric Infectious Diseases Unit, University of Naples Federico II (Italy)

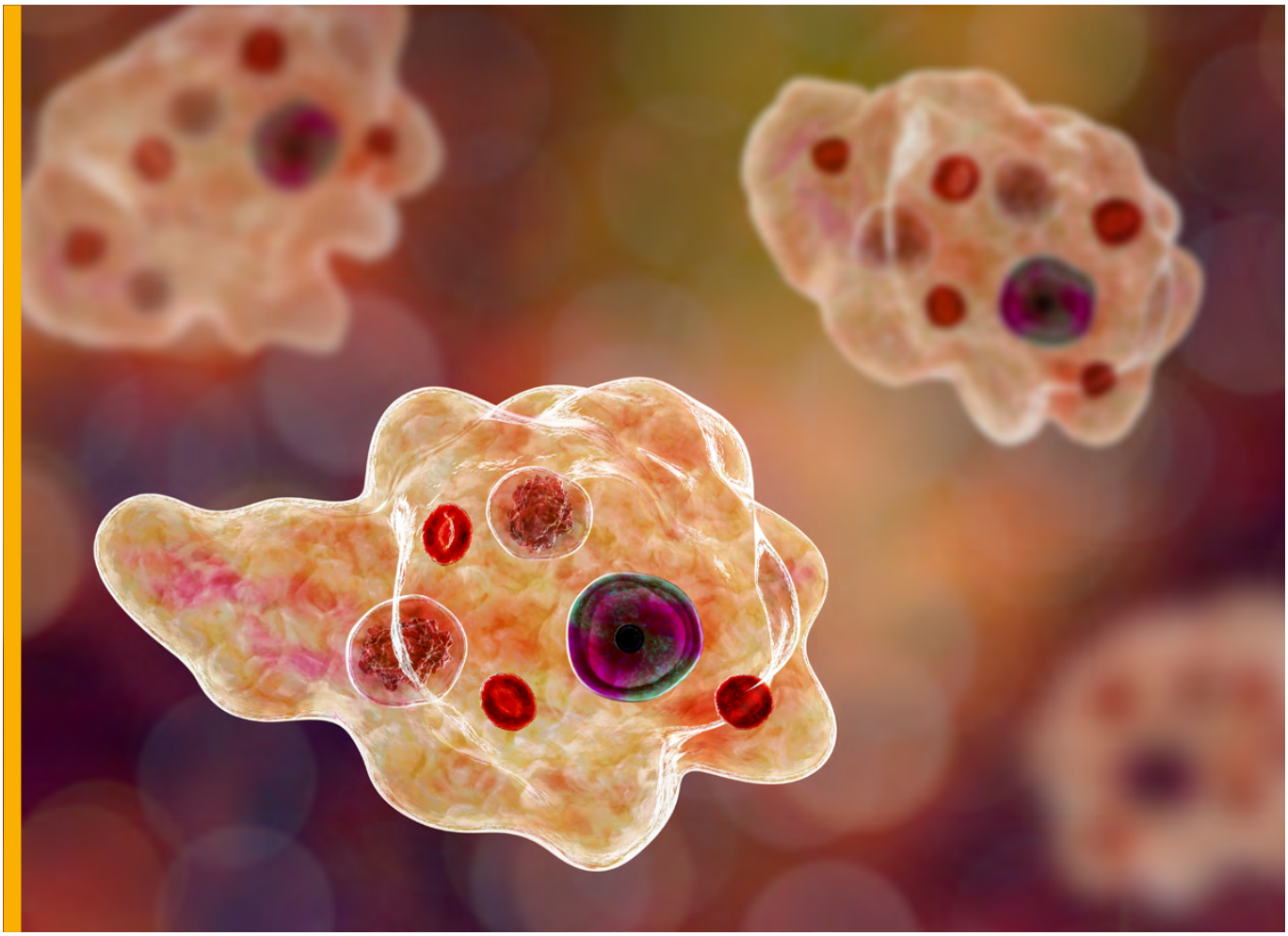


EXPERT OPINION

Probiotics are recommended as an active means of treating of viral diarrhea in children, exerting an antidiarrheal effect that restores microbiota composition from its altered state. In clinical trials, some probiotic strains reduce secretory diarrhea in a very short time, measurable within hours after the start of probiotic administration. Considering that several days are normally required to establish changes in the composition of the microbiota, the rapid efficacy of probiotics implies that there are additional positive effects. Molecules secreted by the bacteria that act directly on intestinal cells can inhibit secretory diarrhea through an antioxidant mechanism. This is defined as the "postbiotic effect". The metabolites produced by probiotics have pharmacological-like action and could represent innovative therapies for the management of viral diarrhea.

28. Poeta M, Cioffi V, Buccigrossi V, *et al.* SARS-CoV-2 causes secretory diarrhea with an enterotoxin-like mechanism, which is reduced by diosmectite. *Heliyon*. 2022 Aug;8(8):e10246. **29.** Juthi RT, Sazed SA, Sarmin M, *et al.* COVID-19 and diarrhea: putative mechanisms and management. *Int J Infect Dis.* 2023 Jan;126:125-131. **30.** Magwira CA, Taylor MB. Composition of gut microbiota and its influence on the immunogenicity of oral rotavirus vaccines. *Vaccine*. 2018 Jun 7;36(24):3427-3433. **31.** Lee B. Update on rotavirus vaccine underperformance in low- to middle-income countries and next-generation vaccines. *Hum Vaccin Immunother.* 2021 Jun 3;17(6):1787-1802. **32.** Huang B, Wang J, Li L. Recent five-year progress in the impact of gut microbiota on vaccination and possible mechanisms. *Gut Pathog.* 2023 Jun 12;15(1):27. **33.** Lynn DJ, Benson SC, Lynn MA, Pulendran B. Modulation of immune responses to vaccination by the microbiota: implications and potential mechanisms. *Nat Rev Immunol.* 2022 Jan;22(1):33-46. **34.** Zimmermann P. The immunological interplay between vaccination and the intestinal microbiota. *NPJ Vaccines*. 2023 Feb 23;8(1):24. doi: 10.1038/s41541-023-00627-9. **35.** Shi Z, Zou J, Zhang Z, Zhao X, Noriega J, Zhang B, Zhao C, Ingle H, Bittinger K, Mattei LM, Pruijssers AJ, Plemper RK, Nice TJ, Baldridge MT, Dermody TS, Chassaing B, Gewirtz AT. Segmented Filamentous Bacteria Prevent and Cure Rotavirus Infection. *Cell.* 2019 Oct 17;179(3):644-658.e13. doi: 10.1016/j.cell.2019.09.028.

PARASITIC DIARRHEA:
CAN THE MICROBIOTA SHAPE CLINICAL OUTCOMES?



Not all individuals respond to intestinal infections of parasites in the same way: while some develop no symptoms at all, others experience more or less severe diarrhea, which can lead to death. The gut microbiota is increasingly cited as a key factor in explaining this variability.

Intestinal parasites can be broadly **classified into protozoa (single cell organisms) and helminths** (multicellular, known as worms).[39] Globally, there are an estimated **895 million people infected with soil transmitted helminths** (STH). Intestinal protozoa (IP) have a lower overall prevalence rate, but still, over 350 million people are believed to be infected with 3 of the most common protozoan parasites[40]. Protozoan infections are common in low and middle income countries (LMICs). Food-chain globalisation, international travel and migration are leading to an increase in protozoan infections in high income countries, where they are more common than intestinal helminth infections.[39]

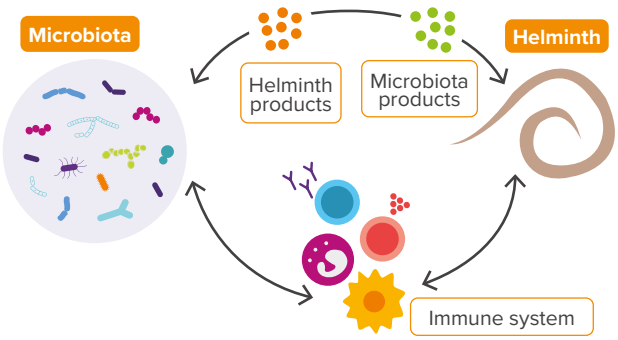
***Giardiasis*, the most common parasitic diarrhea worldwide, affects 280 million people each year.** [41]

DIARRHEAS CAUSED BY PROTOZOAN PARASITES

The most common intestinal protozoan parasites are *Giardia intestinalis (Giardia duodenalis or Giardia lamblia), Entamoeba histolytica, Cyclospora*

36. Lv Z, Xiong D, Shi J, Long M, Chen Z. The Interaction Between Viruses and Intestinal Microbiota: A Review. *Curr Microbiol.* 2021 Oct;78(10):3597-3608. doi: 10.1007/s00284-021-02623-5. **37.** Soorneedi AR, Moore MD. Recent developments in norovirus interactions with bacteria. Curr Opin Food Sci. 2022; 48:100926. https://doi.org/10.1016/j.cofs.2022.100926. **38.** Mizutani T, Ishizaka A, Koga M, Tsutsumi T, Yotsuyanagi H. Role of Microbiota in Viral Infections and Pathological Progression. *Viruses.* 2022 May 1;14(5):950. doi: 10.3390/v14050950. **39.** Ahmed M. Intestinal Parasitic Infections in 2023. *Gastroenterology Res.* 2023 Jun;16(3):127-140. *et al.* **40.** Wong LW, Ong KS, Khoo JR, *et al.* Human intestinal parasitic infection: a narrative review on global prevalence and epidemiological insights on preventive, therapeutic and diagnostic strategies for future perspectives. *Expert Rev Gastroenterol Hepatol.* 2020 Nov;14(11):1093-1105. **41.** Mauriello A, Mari A, Nseir W, *et al.* Diarrhea due to parasites: a short, updated point of view from the clinical setting. *Minerva Gastroenterol (Torino).* 2022 Dec;68(4):463-469.

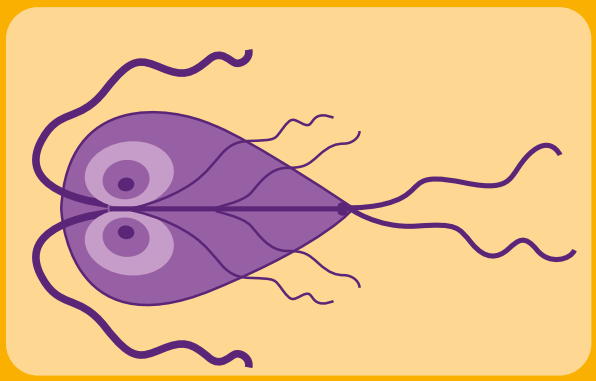
FIGURE 7. Helminths and Microbiota interactions
Source: adapted from Llinás-Caballero *et al.*, 2022[50]



The microbiota is involved in the regulation of gut colonization by helminth parasites. In turn, upon infection, helminth parasites alter the diversity and composition of the human microbiota. Both interact with the immune system.

cayetanensis, and *Cryptosporidium* spp. Diarrheal diseases caused by these pathogens are known respectively as giardiasis, amebiasis, cyclosporiasis and cryptosporidiosis.[41]

- ***Giardia intestinalis*** infects the upper small intestine altering its barrier and permeability. Between 6 and 15 days after infection, it can cause acute, watery diarrhea associated with abdominal cramps, bloating, nausea and vomiting. Giardiasis, **the most common parasitic diarrhea worldwide, affects 280 million people annually**.[41]
- ***Entamoeba histolytica*** infections are usually asymptomatic but can produce an invasive disease of the large bowel (notably in immunocompromised patients) and *amebic dysentery can develop*. The acute phase lasts 3 weeks, with abdominal pain, bloody diarrhea and mucus in the stools. Accounting for over 26 000 deaths annually,[2] **amebiasis is the third leading cause of death from parasitic** infections worldwide; it particularly affects people in LMICs.[41]
- ***Cyclospora cayetanensis*** is the only species of the genus Cyclospora that can infect humans. After an incubation period which may vary from 2 to 12 days, **it typically manifests as voluminous watery acute diarrhea,** abdominal cramps, nausea, low grade fever, fatigue and weight loss.[41]
- ***Cryptosporidium spp.*** infection symptoms appear after one or two weeks of incubation: the most common clinical symptoms are **acute watery diarrhea,** abdominal cramps, malabsorption, nausea, vomiting and fever, lasting for approximately 5 to 10 days.[41] An estimated 64 million cases of cryptosporidiosis are reported each year.[40]



TRAVELERS' DIARRHEA: PARASITIC INFECTION IS COMMONLY ASSOCIATED WITH PI-IBS

While the majority of travelers' diarrhea cases are acute and resolve spontaneously, a subset of individuals will experience persistent gastrointestinal (GI) symptoms potentially extending for weeks, months, or even years, after the initial cause has been effectively treated.[52] A recent publication suggests that nearly **10% of patients experiencing travelers' diarrhea develop persistent symptoms** consistent with post-infectious irritable bowel syndrome (PI-IBS). Parasitic infection, particularly giardiasis, is commonly associated with PI-IBS.[53]

Helminth parasites and the microbiota have coexisted within their hosts, for millions of years.[50]

DIARRHEAS CAUSED BY SOIL-TRANSMITTED HELMINTHS

Globally, the principal soil-transmitted helminths are **the roundworm *(Ascaris lumbricoides)*, the whipworm (*Trichuris trichiura*) and hookworms *(Necator americanus* and *Ancylostoma duodenale)*.** Symptoms experienced following helminth infection are related to the number of worms harboured: people with infections of light intensity (few worms) do not usually experience discomfort, whereas **heavier infections can cause a range of symptoms including some that manifest in the intestine (diarrhea and abdominal pain)**, malnutrition, general malaise and weakness, and impaired growth and physical development. Soil-transmitted helminths contribute to the burden of diseases by impairing the nutritional status of the people they infect in a variety of ways: they feed on

42. World health organisation. Soil-transmitted helminth infections. Fact Sheet. 2023. **43.** Center for Disease Control and Prevention. Parasites -Ascariasis. Last update : June 2023. **44.** Center for Disease Control and Prevention. Parasites - Trichuriasis (also known as Whipworm Infection). Last update : June 2023. **45.** Center for Disease Control and Prevention. Parasites – Hookworms. Last update: May 2023. **46.** Burgess SL, Gilchrist CA, Lynn TC, Petri WA Jr. Parasitic Protozoa and Interactions with the Host Intestinal Microbiota. *Infect Immun.* 2017 Jul 19;85(8):e00101-17. **47.** Carey MA, Medlock GL, Alam M, *et al.*. Megasphaera in the Stool Microbiota Is Negatively Associated With Diarrheal Cryptosporidiosis. *Clin Infect Dis.* 2021 Sep 15;73(6):e1242-e1251. **48.** Berry ASF, Johnson K, Martins R, *et al.* Natural Infection with Giardia Is Associated with Altered Community Structure of the Human and Canine Gut Microbiome. *mSphere*. 2020 Aug 5;5(4):e00670-20. **49.** Fekete E, Allain T, Siddiq A, *et al. Giardia spp*. and the Gut Microbiota: Dangerous Liaisons. *Front Microbiol.* 2021 Jan 12;11:618106.

host tissues, cause intestinal blood loss and hamper the absorption of nutrients.[42]

- ***Ascaris lumbricoides*** is the most common intestinal nematode that infects humans, with an **estimated 807 - 1,221 million people infected each year**.[43] Infection commonly occurs without symptoms. **The symptomatic form** is characterized by an early lung phase followed by a later intestinal phase, which is characterized by diarrhea, mild abdominal pain, anorexia, nausea and vomiting.[41]
- An estimated 604-795 million people in the world are infected with ***Trichuris trichiura***. People with heavy infections can experience frequent painful bowel movements that contain a mixture of mucus, water and blood.[44]
- An estimated 576-740 million people in the world are infected with ***hookworms***, usually without symptoms. Few people, especially those infected for the first time, experience gastrointestinal symptoms. The most common and serious effects of hookworm infection are intestinal blood loss leading to anaemia, in addition to protein loss.[45]

CLINICAL CASE *by Pr. Stephen Allen*

- During her holiday in Asia, 36-year-old company executive develops non-bloody, slimy, smelly diarrhea with abdominal cramps and bloating.
- In the second week of the illness, stool microscopy revealed giardiasis and she takes a 10-day course of metronidazole.
- Over the course of the following year in the UK she experiences frequent episodes of similar symptoms, each lasting for a few days and forcing her to stay off work.
- After other illnesses are ruled-out by further investigations and a clinical review, she is diagnosed with post-infectious, diarrhea-predominant, irritable bowel syndrome (IBS-D), a condition that develops in 10% of patients following an acute episode of gastroenteritis.[54]
- She finds that dietary changes and treatments for IBS-D have little effect and wants to know if she should send a stool sample abroad for microbiome analysis and whether a fecal transplant might help.
- The role of persistent dysbiosis in post-infectious IBS due to parasitic infection and/or drugs used for treatment is poorly understood. More research is needed before this woman's questions can be answered with any confidence.

MICROBIOTA: A ROLE IN THE MARKED CLINICAL VARIABILITY OF PARASITIC DIARRHEA?

Parasitic protozoan infections are characterized by marked variability in their clinical presentation: they can be asymptomatic or cause diarrhea, abdominal pain, weight loss, *etc.* Recent studies have highlighted the **potential contribution of the intestinal microbiota to this clinical variation:** for instance, an abundance of *Prevotella copri* in the gut microbiota predicted diarrhea in the context of *Entamoeba histolytica* infection;[46] low *Megasphaera* abundance prior to and at the time of *Cryptosporidium* detection was associated with parasitic diarrhea in infants in Bangladesh, suggesting that the gut microbiota may play a role in determining the severity of a *Cryptosporidium* infection.[47] In turn, infection by protozoan parasites alters the gut microbiome.[48,49] Regarding helminths, the complex interactions between worms and the microbiota *("two of humans' old friends"*[50]*)* are currently under study[50] (Figure7). Authors agree on the existence of a **complex and dynamic interplay between parasite(s), the host microbiota and host immunity, capable of shaping the clinical outcomes of parasitic infections**.[46,48]

PR. STEPHEN ALLEN
Professor of Paediatrics, Liverpool School of Tropical Medicine (UK)

EXPERT OPINION

Gut parasite infection is a common cause of disease worldwide, predominantly diarrhea with protozoans such as giardia, *Entamoeba histolytica* and *Cryptosporidium,* and anaemia with helminths. Equally, gut parasites occur as commensals and may even bring health benefits such as improving resistance to other enteropathogens and preventing allergic and auto-immune diseases. The challenge is to gain a better understanding of the complex inter-relationships between different parasites, the intestinal mucosa, gut immune cells and the gut microbiota in order to be able to exploit the benefits while at the same time ameliorating adverse effects of intestinal parasitic infection.

50. Llinás-Caballero K, Caraballo L. Helminths and Bacterial Microbiota: The Interactions of Two of Humans' "Old Friends". *Int J Mol Sci.* 2022 Nov 1;23(21):13358. **51.** Boolchandani M, Blake KS, Tilley DH, *et al.* Impact of international travel and diarrhea on gut microbiome and resistome dynamics. *Nat Commun.* 2022 Dec 5;13(1):7485. **52.** Connor B. Travelers' Diarrhea. CDC Yellow Book 2024 https://wwwnc.cdc.gov/travel/yellowbook/2024/preparing/travelers-diarrhea **53.** España-Cueto S, Oliveira-Souto I, Salvador F, *et al.* Post-infectious irritable bowel syndrome following a diagnosis of traveller's diarrhea: a comprehensive characterization of clinical and laboratory parameters. *J Travel Med.* 2023;30(6):taad030. **54.** Lupu VV, Ghiciuc CM, Stefanescu G, Mihai CM, Popp A, Sasaran MO, Bozomitu L, Starcea IM, Adam Raileanu A, Lupu A. Emerging role of the gut microbiome in post-infectious irritable bowel syndrome: A literature review. *World J Gastroenterol.* 2023 Jun 7;29(21):3241-3256. **55.** Our World in data. Diarrheal diseases. *(latest estimate from the IHME's Global Burden of Disease study).* **56.** World health organization. Rotavirus vaccines: WHO position paper - July 2021. *Weekly Epidemiological Record*, 96 (28): 301 – 219. **57.** Guarner F, Sanders ME, Szajewska H. *et al.,* World Gastroenterology Organisation Practice Guideline. Probiotics and Prebiotics. February 2023. https://www.worldgastroenterology.org/guidelines/probiotics-and-prebiotics. **58.** Worby CJ, Sridhar S, Turbett SE *et al.* Gut microbiome perturbation, antibiotic resistance, and Escherichia coli strain dynamics associated with international travel: a metagenomic analysis. *Lancet Microbe.* 2023 Oct;4(10):e790-e799.

KEY TAKE AWAYS

The high burden of infectious diarrheas

- Diarrhea kills around 1.5 million people every year.[55] It is the third cause of death in children under 5.[1]
- **Most cases of acute diarrhea are due to infectious pathogens, i.e. viruses, bacteria, parasites.** *Rotavirus* and *Escherichia coli* are the two most common etiological agents of moderate-to-severe diarrhea in low-income countries.[1]

The complex interplay between infectious agents and the microbiota

- Whatever the etiological agent of infectious diarrhea, the outcome depends on **complex interplays between the pathogen and the gut microbiota.**
- The composition of the **gut microbiota can shape the outcome of an infection** by a diarrheal pathogen, and be either a protective or a facilitating factor. In turn, the diversity and composition of **gut microbiota can be severely altered by infectious diarrhea** and a return to a "healthy microbiota" may require several weeks after diarrhea has resolved.[14]

A significant proportion of preventable cases

- A significant proportion of diarrheal disease can be prevented through **safe drinking-water and adequate sanitation and hygiene.**[1]
- **Rotavirus vaccination** is another important preventive strategy, which the WHO recommends be included in all national immunization programmes and considered as a priority.[56]

Patient monitoring and management

- The majority of infectious diarrheas are self-limiting in immunocompetent individuals. Nevertheless, some patients (with severe dehydration, more severe illness, persistent fever, bloody stools, immunosuppression...) require specific diagnostic investigation.[11]
- **The most important complication of infectious diarrhea is dehydration**, which may require oral or intravenous fluid replacement therapy, depending on the degree of dehydration.[1]

Gut microbiota targeting strategies, essential in diarrhea prevention and management

- Both the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the World Gastroenterology Organization (WGO) consider that **some probiotic strains** can be recommended by HCP:
  - for the **prevention of antibiotic-associated diarrhea;**
  - **for the treatment of acute (viral) diarrhea in children, as they may shorten diarrhea duration.**

Promising research paths involving microbiota

- Future research should expand microbiome knowledge in the context of infectious diarrheas, in order to improve their prevention and management.
- **The optimization of microbiota profile** in order to shape infectious outcomes[5] and improve rotavirus vaccine efficacy[29] represents a promising research path.

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