DYSBIOSIS OF THE GUT MICROBIOTA

Multiple clinical consequences

Disorders associated with imbalances of the gut microbiota caused by antibiotics intake or gastrointestinal infections

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Editorial

Gut microbiota and dysbiosis: what are we talking about?

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The gut microbiota consists of around 10^{13} bacteria, which is about the same as the number of eukaryotic cells in the body[1]. It is a stable ecosystem living in symbiosis with the host individual. The gastrointestinal tract of every adult harbors 500 to 1,000 different bacterial species. In humans, there is a core set of species that are both dominant and prevalent[2]. Its composition is influenced by many intrinsic and environmental factors.

The gut microbiota plays an essential role in several physiological processes. It limits the growth of pathogenic microorganisms by competing for nutrients, by providing a barrier effect or by producing bactericidal substances. Beyond the intestinal mucosa, the microbiota helps to maintain a functional immune system. It also has a housekeeping role by renewing the intestinal epithelium and it also plays a role in metabolism through the production of vitamins (vitamin K for example) and the transformation of complex sugars.

The equilibrium of the gut microbiota can however be durably "disrupted". A number of factors come into play, including **intestinal infections** (viral, bacterial, parasitic), drugs (**antibiotics in particular**), changes in diet, stress, to name a few.

What follows is a **reduction in bacterial diversity** and a weakened resistance to pathogenic microbes like toxinogenic *Clostridioides difficile* (*C. difficile*, formely *Clostridium difficile*). **Dysbiosis can be thought of as a rupture of the symbiosis between the microbiota and the host.** But by the way, what is dysbiosis? Can we today define a «healthy» microbiota as we would define a normal blood ionogram? Can we say by analyzing the bacteria that populate our intestines if our microbiotic organ is doing well like a heart whose ventricular ejection fraction would be evaluated on ultrasound? The answer today is «no» and we have some clues that it will remain negative. Two recently published studies confirm this.

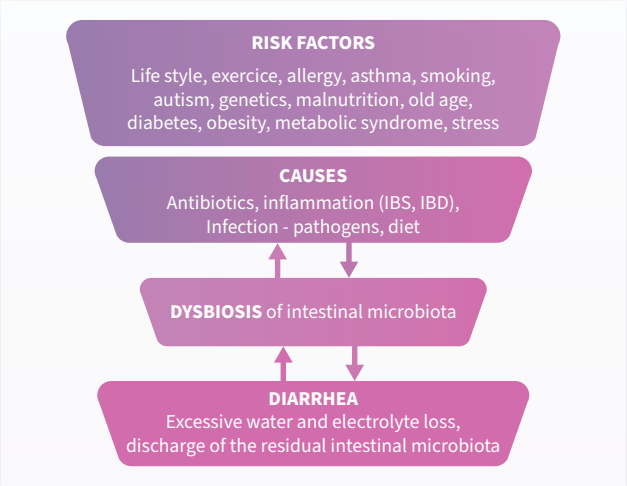


Figure 1. Dysbiosis risk factors and causes during diarrhea. Adapted from MoréMI & Swidsinski A. *Clin Exp Gastroenterol.* 2015;8:237-255; Levy *et al. Nat Rev Immunol.* 2017;17(4):219-232; Ortiz-Alvarez *et al. Clin Transl Gastroenterol.* 2020 Feb; 11(2): e00126; Robless *et al. Br J Nutr.* 2013;109 Suppl 2:S21-S26; Iebba *et al. New Microbiol.* 2016;39(1):1-12.

In the first study, the intestinal microbiota of more than 7000 individuals (these are Chinese living in the same province but in 14 different districts) was analyzed[3]. As expected, each individual had his/her own intestinal bacterial composition. But what factor did vary the most about this composition? Quite simply his/her place of residence, much more than his/her food, or his/her way of life. More specifically now, let's look within the same district, if the microbiota of people with type 2 diabetes (T2D) is different from those who don't have it. Yes, indeed, by analyzing the microbiota of individuals in this district, we can separate T2D individuals or not with a probability of around 75%. But if we apply this method to individuals living in the district next door, the prediction drops to 50%, as much as to say that we no longer predict anything. This means that the «dysbiosis» associated with T2D identified in one district is not the same in the next district. Imagine then wanting to describe a «universal» dysbiosis for all individuals from different regions and countries.

In the second study, the microbiota of 2 individuals (A and B) was analyzed daily for one year[4]. For A., the microbiota is stable for months and then changes radically during a trip abroad, returning a few days later to its previous state. He, therefore, had an «acute» dysbiosis which his microbiota - resilient - corrected on his own. For B., we see that his microbiota also remains sandy for months and then changes greatly during an infectious episode and then returns to a stable state but different from its previous state. This time, the infection-induced dysbiosis was not corrected identically but led to another stable composition of the gut microbiota. Can we speak of «chronic» dysbiosis? In fact, everything depends on the health of B. If he is in good health, it will be said that he has a 'normobiosis' different from the previous one. But, if, on the other hand, he develops a post-infectious irritable bowel syndrome, for example, we can talk about 'chronic' dysbiosis that we can try to correct with modifiers of intestinal flora such as pre- or pro-biotics.

We, therefore, see in the light of the analysis of these 2 examples taken from recent publications that **« dysbiosis » is not universal and is defined for each individual, according to their state of health.**

Contents

In this document, we will focus on the clinical consequences following dysbiosis induced by antibiotics and intestinal infection only. Other causes of dysbiosis are sometimes well characterized but clinical consequences are less obvious.

Dysbiosis in infants and children: clinical consequences

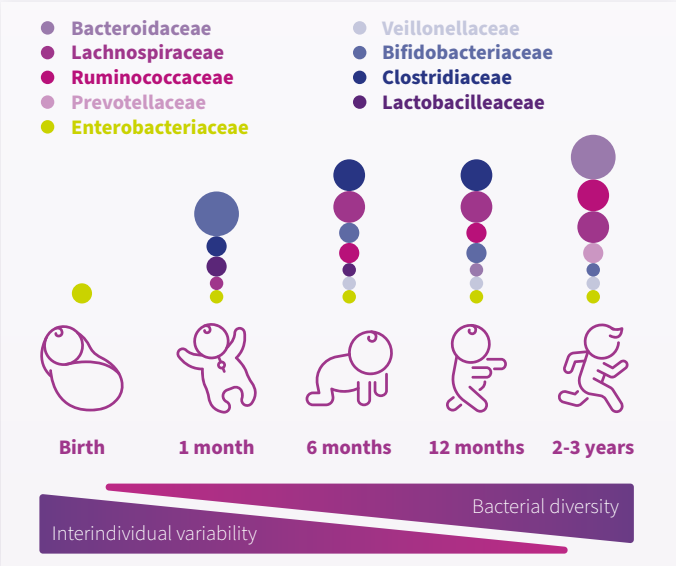


Figure 2. Stages of microbial colonization of the infant and child intestine. Adapted from Arrieta *et al. Front Immunol.* 2014; 5: 427.

Common factors inducing a dysbiosis in children are **infectious diarrhea** and **antibiotic treatment.** One the one hand, infectious diarrhea causes **abrupt changes in the gut ecosystem,** affecting its abiotic conditions (rapid transit, looser stools, etc.) and the gut microbiota by introducing one or more pathogens[5] as bacterial, viral and parasitic organisms[6]. **In acute diarrhea,** there is a loss of the barrier effect and a reduction in the diversity of gut bacteria[7,8]. **Diarrhea is usually a warning signal of a disturbance in the gut ecosystem**[6]. To treat acute diarrhea, WHO recommends rehydration with oral rehydration salts solution. Probiotics, as adjuvant therapies, have also been recommended[9] to prevent and treat acute diarrhea.

On the other hand, antibiotics have been saving many lives over the past century and are a common prescription for children in westernized countries[10]. Beside their role in eradicating a specific infection, they also will disrupt the intestinal microbial ecosystem. Even in a healthy adult, we do know that the **recovery** of the previous bacterial composition could be only **partial up to 6 months after an antibiotic course**[11]. The resilience of the ecosystem is mostly due to the gut microbiota basal composition of the individual[12], highlighting the **importance of shaping a healthy microbiome from birth.** The time of the perturbation is also very important: an antibiotic-induced disruption of the gut microbiota early in life – when the microbiota is still immature and unstable - might have **long term consequences on its composition later in life**[13]. For example, just a single dose of intrapartum antibiotic prophylaxis to the mother may have consequences on the gut microbiota composition of the offspring up to the age of 1 year[14]. In the same way, a single antibiotic course in early life disrupts the gut microbiota composition up to 3 months later[15]. Therefore, it is not surprising that antibiotic-induced **dysbiosis in infants and children may have short-term but also long-term clinical consequences**[16].

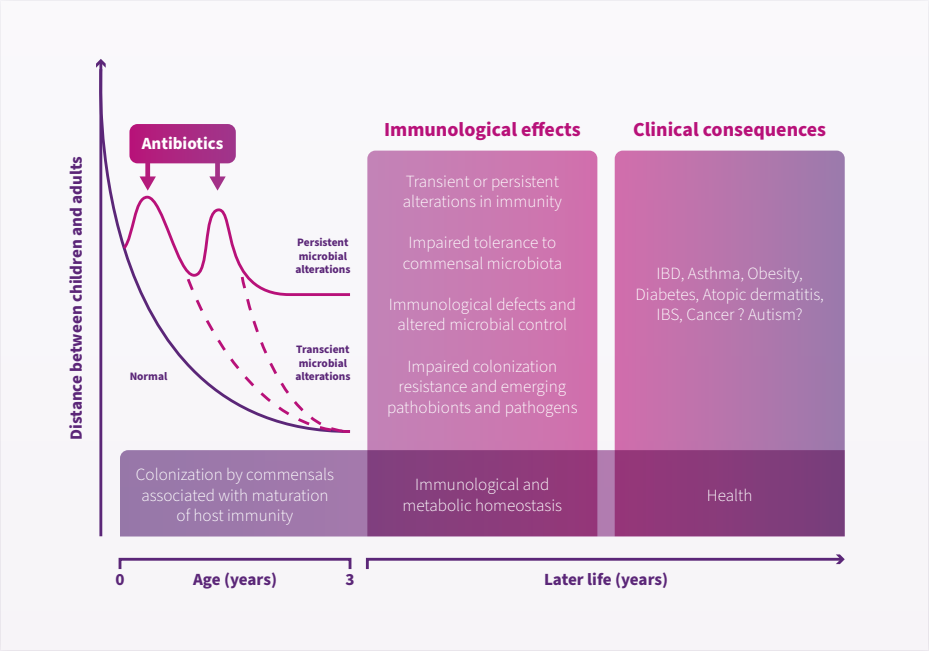


Figure 3. Microbial colonization, development of the immune system and their perturbation by treatment with antibiotics early in life. Microbial colonization during early postnatal development represents a dynamic process, which evolves toward an adult-like configuration within 3 years after birth. Adapted from Zeissig *et al. Nat Immunol.* 2014;15(4):307-310.

Next subchapters will present dysbiosis triggered in childhood and potential clinical consequences for health.

Antibiotic-Associated Diarrhea (AAD)

Antibiotic-associated diarrhea is defined as diarrhea which occurs in conjunction with antibiotics administration[17]. AAD has been recognized as a clinical concern since the 1950s, when antibiotic use increased significantly. Prevalence of AAD can differ with antibiotic prescribed and extreme age of life (elderly or young children). Its mean duration is 7 days[18].

Treatment for uncomplicated cases of AAD is to discontinue or change the antibiotic if possible. For more serious cases of AAD (as *C. difficile* disease) other treatments are needed like specific antibiotic, probiotic therapy, fecal microbiota transplant[18].

In a study conducted over an 11-month period in 650 children aged 1 month to 15 years treated with antibiotics for an infection, 11% had an episode of diarrhea. The **incidence of AAD was especially high after the administration of certain antibiotics** (amoxicillin alone or in combination: **+ 23 %;** p = 0.003 compared with other antibiotics[19] (Figure 4).

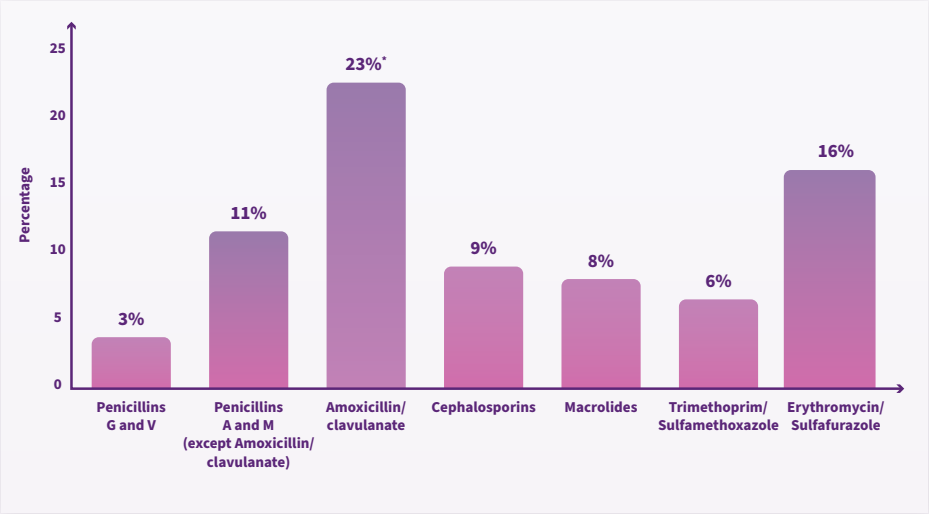


Figure 4. Indidence of episodes of diarrhea according to antibiotics prescribed versus all other antibiotics taken together *p=0,003. Adapted from Turck *et al. J Pediatr Gastroenterol Nutr.* 2003;37(1):22-26.

Early antibiotic exposure in infants is associated with an increased rate of diarrhea during childhood. Exclusive breastfeeding during the first six months of life may have a protective effect[20]. As antibiotic exposure in children can lead to AAD, simultaneous use of a probiotic not sensitive to antibiotic may be an effective prophylactic strategy[18].

Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome is defined by the World Gastroenterology Organisation (WGO) as a functional bowel disorder in which abdominal pain or discomfort (like bloating) is associated with defecation and/or a change in bowel habit[21].

In children, association between IBS development and gastrointestinal infection and antibiotic administration are observed[22].

Children with IBS have significantly higher percentage of the class γ-proteobacteria in their gut[23]. Moreover, levels of *Veillonella*, *Prevotella*, *Lactobacillus*, and *Parasporo bacterium* were increased in children diagnosed with IBS, whereas members of *Bifidobacterium* and *Verrucomicrobium* were less abundant in those individuals[24]. Increasing visceral sensitivity, altered gastrointestinal transit and increase in permeability of the intestine is reported in experimental studies using germ free animals receiving gut microbiota of patients with IBS, indicating a **potential pathogenic role of gut microbiota**[25]. Some other studies have reported an association between differences in short chain fatty acid (SCFA) production by colonic bacteria and the development of symptoms in diarrhea predominant IBS[26]. Interactions between the gut microbiota and food (fermented protein products, generation of gases) are potential sources for cell damage, altered barrier function as well as symptoms such as bloating and distension[27].

Figure 5. Management options for children with irritable bowel syndrome. Adapted from Devanarayana *et al. World J Gastroenterol.* 2018 Jun 7; 24(21): 2211–2235.

In addition, **gut microbiota may influence other patho-physiological factors** such as intestinal permeability, brain function, enteric nervous system, gastrointestinal motility and visceral pain, contributing to the patho-physiology of FGIDs[28]. **However, further clinical studies are needed to confirm the role of gut microbiota in IBS.**

Inflammatory Bowel Disease (IBD)

IBD (Crohn's disease and ulcerative colitis) are chronic disorders characterized by gastrointestinal inflammation. Etiology of IBD is multifactorial with genetic and environmental risk factors. Gut microbiota composition is also an important contributor[29].

Dysbiosis occurring during inflammatory bowel disease is increasingly well characterized and might play a role in inflammation[30].

The deleterious effects of post-antibiotic dysbiosis have been demonstrated in several studies:

- A prospective study found a **strong association between antibiotic exposure during childhood and inflammatory bowel disease**[31], but this relationship decreases with age[32] (Figure 6)
- **Antibiotic exposure appears to increase the probability of being diagnosed with Crohn's disease but not ulcerative colitis**[33]

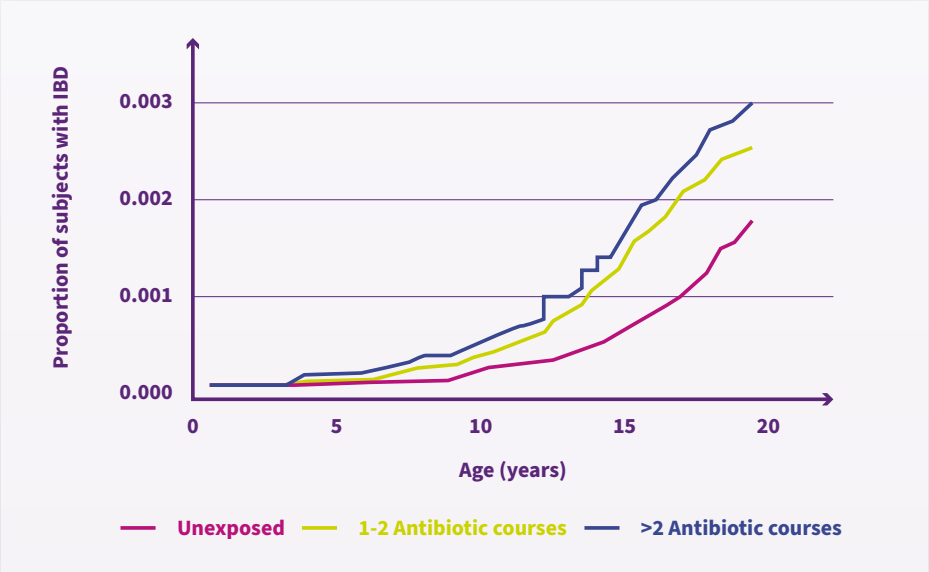


Figure 6. The proportion of subjects developing IBD according to age and anti-anaerobic antibiotic exposure level. P < 0.001 for the difference among groups by using the log-rank test. Adapted from Kronman *et al. Pediatrics.* 2012 Oct; 130(4): e794–e803.

Obesity

In recent years, a great deal of research has focused on the relationship between the gut microbiota and obesity, revealing that **dysbiosis occurs during obesity** and associated comorbidities[34]. Pioneering experiments with flora transfer in rodents have shown that the gut microbiota plays a role in regulating weight, illustrating the involvement of the microbiota in energy storage[35].
Regarding **post-antibiotic dysbiosis in early life,** numerous studies have described its **impact on obesity:**

- A meta-analysis of 15 studies found a small association between use of antibiotic before 24 months and overweight or obesity in childhood. Particularly, boys seem to be more inclined than girls[36]
- Repeated exposure to broad spectrum antibiotics before the age of 2 may be associated with childhood obesity[37] (Figure 7) or higher body weight at 5 years[38]

In addition, post-antibiotic dysbiosis during pregnancy seems associated with childhood weight. Prenatal exposure to antibiotics increases the risk of overweight and obesity in children between 7 and 16 years[39].

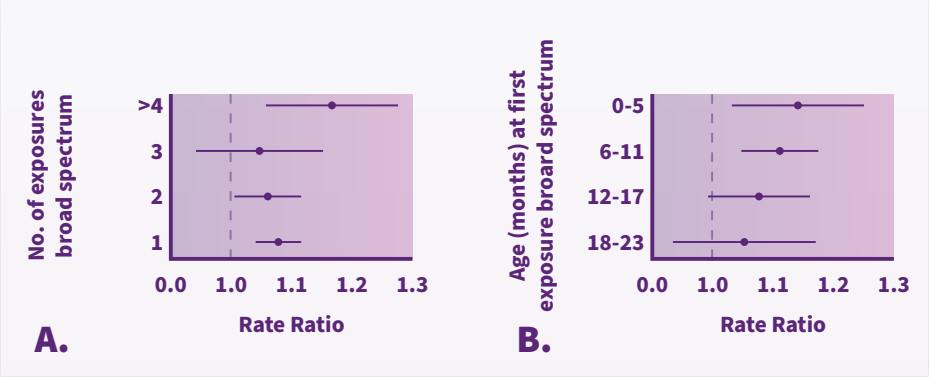


Figure 7. Impact of antibiotic class, frequency and timing on the risk of obesity. Points indicate rate ratios, with 95% CIs shown by lines, derived from multivariate models examining number of exposures (A) or timing of first antibiotic exposure at 0 to 23 months (B). Adapted from Bailey *et al. JAMA Pediatr.* 2014;168(11):1063-1069.

A Allergy

The microbiota plays a role in immunity and changes in the gut microbiota have been detected in allergic individuals, sometimes even before any allergic symptoms[40]. **Low microbiota diversity** during the first weeks of life has been associated with a **higher risk of allergic sensitization and allergic rhinitis**[41]. **Asthma** is also associated with a **lower diversity** of the intestinal microbiota[42]. Another study found an association between microbiota composition and asthma, allergic sensitization and atopic dermatitis. Particularly, *Lachnospiraceae* family, *Faecalibacterium* and *Dialister* genus were found to be associated with a reduced risk of atopy[43].

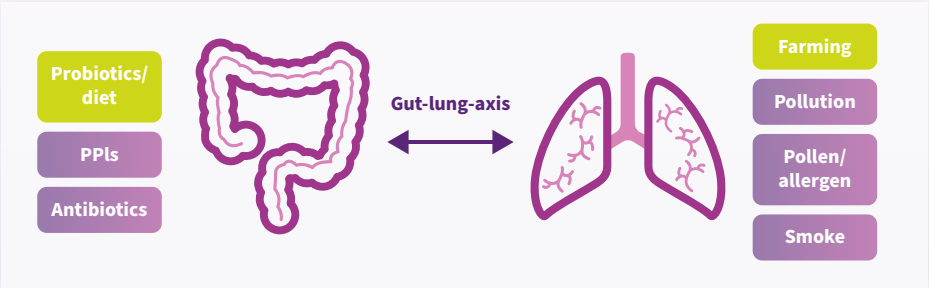


Figure 8. Environmental factors associated with asthma and their influence on the gut-lung axis. Adapted from Hufnagl *et al. Semin Immunopathol.* 2020; 42(1): 75–93.

Studies have shown a **relationship between post-antibiotic dysbiosis and risk of allergic disease:**

- Antibiotic exposure in the first week of life increases the risk of allergic rhinitis at school age. This increased risk is also observed with parental allergic rhinitis, food allergy first year, eczema first year and male gender[44]
- A study of longitudinal data on 30,060 children up to 7 years of age who had three or more antibiotic prescriptions found a greater probability of milk allergy, non-milk food allergy and other allergies compared with children with no antibiotic prescriptions[45]

Several studies have highlighted the **important role played by early life dysbiosis** in the development of childhood **asthma:**

- Antibiotic use during the third trimester of pregnancy was associated with an increased risk of asthma in preschool children[46]. However, another study adjusted their analysis considering family factors and found that this risk is no longer significant[47]
- During the first year of life antibiotic use was associated with an increased risk for development transient wheezing and persistent asthma[48] (Figure 9), with adjustment for familial factors only antibiotics to treat respiratory infections are responsible for increased risk of asthma[47]

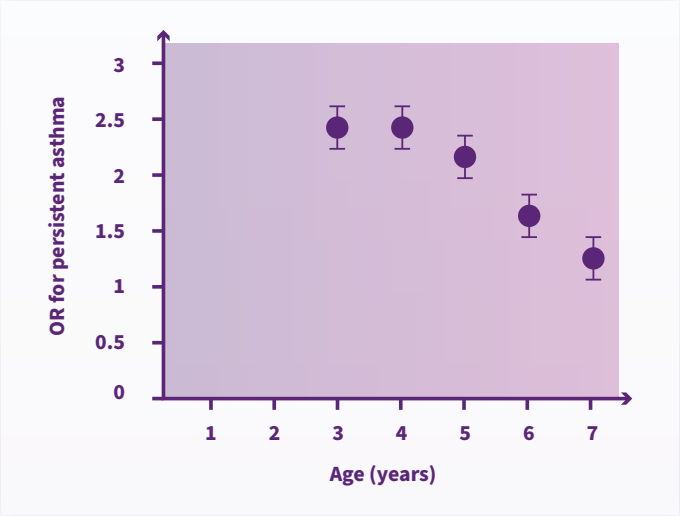


Figure 9. Association between antibiotic exposure in infancy and persistent asthma at 3 to 7 years of age. The odds ratios achieved statistical significance at all ages (P < 0.001). Adapted from Ong *et al. Ann Allergy Asthma Immunol.* 2014;112(5):441-445.e1.

Psychiatric disorders (anxiety, depression)

Several studies suggest that **dysbiosis is observed in central nervous system disorders such as anxiety and depression.** Also, alteration in the "gut-brain axis" can be observed, due to dysbiosis[49]. There is increasing evidence of the effects of the gut microbiota on mood.

Three case-control studies were conducted in cohorts of patients with depression, anxiety and psychosis[50]. The primary variable of interest was antibiotic therapy prescribed more than one year before diagnosis. After adjustment, antibiotic exposure was associated with a significantly higher risk of depression. This risk increased with the number of courses of antibiotic treatment. Similarly, the risk of anxiety was significantly increased[50].

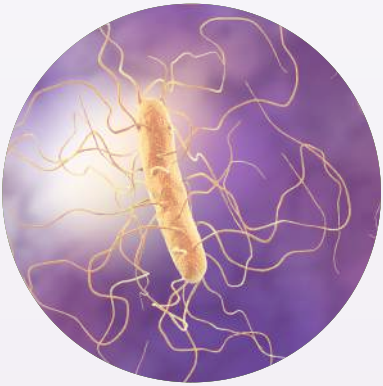
A study in 871 European mothers and their children antibiotic use during the first year of life and between 1 year and 3.5 years of age was collected. Children who had received antibiotics had more behavioral difficulties and more symptoms of depression at follow-up[51].

Moreover, as **gut microbiota impacts central nervous system development**[52], a dysbiosis induced in the first years of life could then increase the risk of psychological disorders.

Dysbiosis in adults: clinical consequences

Next subchapters will present dysbiosis triggered in adult and potential clinical consequences for health.

Antibiotic-Associated Diarrhea (AAD) and *C. difficile* disease



AAD is a major side effect of antibiotic treatment in children but also in adults. **Antibiotic treatment disturbs the gut microbiota, leading to dysbiosis and can lead to diarrhea.** Commonly used antibiotics lead to a 25% reduction in microbial diversity[53] and **up to 35% of patients taking antibiotics will experience antibiotic-associated diarrhea**[18]. Persistence of gut microbiota alterations (sometimes up to 3 months) may explain susceptibilities to AAD. The **reduced diversity of gut microbiota can subsequently allow the growth of pathogens** such as *C. difficile* (almost one-third of AAD cases), *Clostridium perfringens*, *Staphylococcus aureus* and other pathogens[54].

C. difficile is a gram-positive, spore-forming anaerobic bacillus that can be associated with gastrointestinal manifestation from uncomplicated diarrhea, to nonspecific colitis or pseudomembranous colitis[55]. *C. difficile* toxins can be found in the stool of 15% to 25% of patients with AAD[55] and is the most commonly reported pathogen in hospitals[56]. **Recurrence is one of the most challenging complications of *C. difficile*-associated disease (CDAD)** with 12% to 24% of patients developing a second episode of CDAD within 2 months of the initial diagnosis[55].

These findings suggest that **strategies to reinforce the ability of the gut microbiota to resist and prevent modifications caused by antibiotics would be of major clinical interest.**

Irritable Bowel Syndrome (IBS)

Intestinal microbiota dysbiosis can also be a potential trigger for IBS. Potential cause of microbiota disruption and IBS development are gastrointestinal infection and antibiotic administration[22]. Approximately 10 to 30% patients with IBS believes that this disorder began after an episode of acute diarrhea[57].

Studies have shown that 3 to 36% of enteric infections cause persistent symptoms suggestive of IBS. The incidence depends on the causal microbe. While gastroenteritis caused by a virus seems only to have short-term effects, bacterial gastroenteritis is more likely to be followed by IBS[58].

Two meta-analysis show that risk of IBS after an episode of infectious enteritis was increased at 6 months[59], 12 months (by 10.1%[60]) and more than 12 months (by 14.5%[60]) post-infection. The risk of IBS was 4 times higher in patients who experienced infectious enteritis in the past 12 months than in those without such infections. Risk also increases with antibiotic exposure associated or not with gastroenteritis[60].

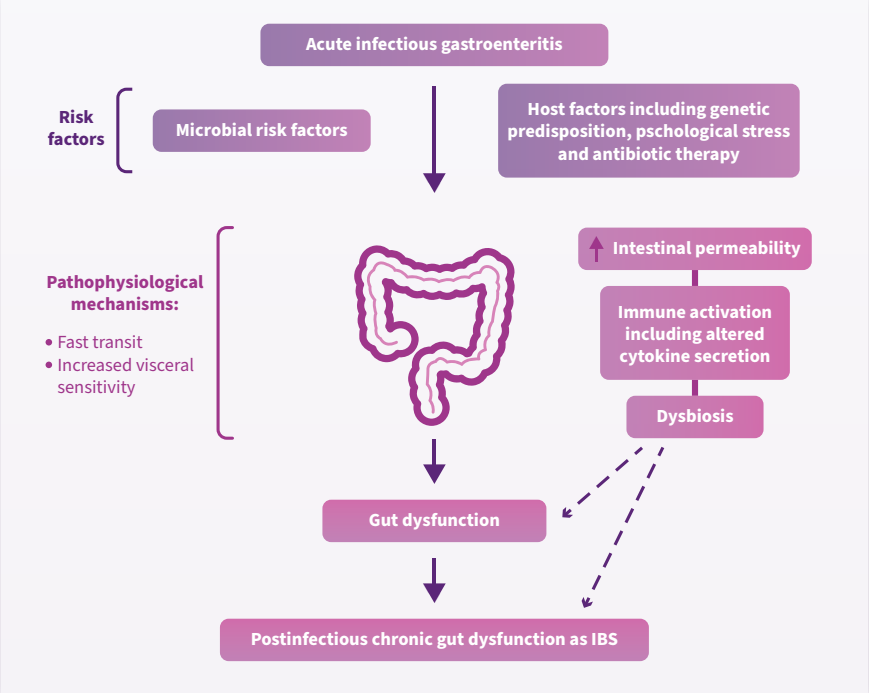


Figure 10. Postinfectious chronic gut dysfunction: risk factors and pathophysiological mechanisms. Adapted from Cocciolillo *et al. Curr Opin Gastroenterol.* 2016;32(1):1-6.

Dyspepsia

Gut microbiota dysbiosis can be implicated in functional dyspepsia. Also, **post infectious, acute gastrointestinal infections and antibiotic use, known to be associated with dysbiosis, can trigger functional dyspepsia in susceptible patients**[61].

A meta-analysis of six studies found an increased risk of post-infectious functional dyspepsia six months after the initial infectious episode[62]. Another meta-analysis of nine studies showed an increased risk of functional dyspepsia 12 months after an episode of acute infectious gastroenteritis. After 12 months the risk decreased but is still significant[63].

Inflammatory Bowel Disease (IBD)

A possible association between acute infectious episodes and first onset or relapse of inflammatory bowel disease has been described since the 1990s[66]. The mechanism basis of this risk association is not elucidated but we can assume an impact of gut microbiota dysbiosis induced by infectious episode.

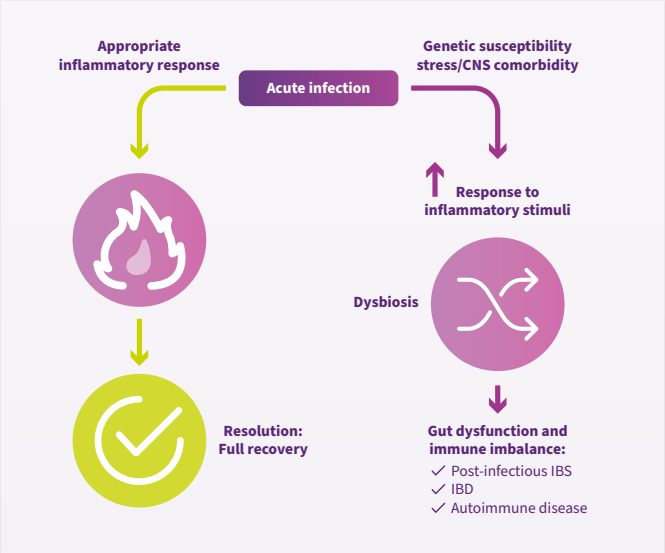


Figure 11. Acute infection and chronic consequences in the gut. Adapted from Verdu *et al. Am J Gastroenterol.* 2012;107(7):981-989.

A previous episode of infectious gastroenteritis was associated significantly with an increased odd of IBD, with Crohn's disease slightly higher than ulcerative colitis. The risk was greater during the first year after the infective episode[67].
It was recently shown that dysbiosis caused by enteric bacterial infection with *Yersinia* leads to immunological alterations in the gut, fostering the development of chronic inflammatory disease[68]. Also, an episode of *Salmonella/Campylobacter* gastroenteritis increased the risk of IBD[69].

Dysbiosis occurring after gastroenteritis may promote the development of IBD.

Type 2 diabetes

Metabolic inflammation is a crucial factor associated with the development of insulin resistance and type 2 diabetes. Several studies reported alterations in gut microbiota, referred as dysbiosis and a special microbiota signature in type 2 diabetes. The **gut microbiota contributes to its development**[34].
In a case-control study of incident type 2 diabetes in Denmark, risk associated with type 2 diabetes after exposure to antibiotics of any type was increased. Although no individual group of antibiotics was specifically associated with type 2 diabetes risk, the relative risk was slightly higher with narrow-spectrum and bactericidal antibiotics compared with broad-spectrum and bacteriostatic antibiotics[64]. Also, the **risk of diabetes increases with the number of antibiotic courses**[65].

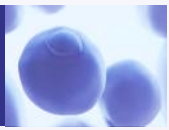
The role of probiotics in gut microbiota balance*

*** This part must be adapted to your local regulatory constraints (drug, food supplement or medical device status)**

Gut microbiota is a stable ecosystem in symbiosis with the host and is sometimes referred to as an organ itself. Homeostasis of gut microbiota plays an important role in host health.

As described previously, perturbation of this homeostasis by antibiotics or intestinal infection can lead to dysbiosis and subsequently further disorders. Strategies to modulate gut microbiota include probiotics, aiming at restoring a balance.

***Saccharomyces boulardii* CNCM I-745**



As an example, *S. boulardii* CNCM I-745 is a probiotic that holds several marketing authorizations around the world, has clinically demonstrated efficacy **to prevent antibiotic-associated diarrhea (AAD), treat acute infectious diarrhea and also to recover from dysbiosis.**

To prevent diarrhea in children and adults

Several studies provided evidence of *S. boulardii* CNCM I-745 efficacy in preventing antibiotic-associated diarrhea, recurrence of *C. difficile* disease (CDD) combined with standard antibiotics and digestive side effects during *Helicobacter pylori* eradication therapy.

Prevention of antibiotic-associated diarrhea

A meta-analysis performed by Szajewska *et al.* in 2015[70], using 21 randomized controlled trials with 4780 participants, **confirms that *S. boulardii* is effective in reducing the risk of antibiotic-associated diarrhea by 57% in children and by 51% in adults.**

In children treated with antibiotics[71], *S. boulardii* CNCM I-745 significantly reduces the prevalence of antibiotic-associated diarrhea by 78%. In adults treated with antibiotics[72], *S. boulardii* CNCM I-745 decreases antibiotic-associated diarrhea from 9% in placebo group to 1.4% in study group ($p<0.05$).

As *S. boulardii* is a yeast naturally non susceptible to antibiotics[73] it can be taken at the same time as antibiotics. Also, *S. boulardii* CNCM I-745 does not alter the efficacy and pharmacokinetic parameters of antibiotic (amoxicillin)[74]. Those results highlight the potential of *S. boulardii* CNCM I-745 to prevent diarrhea during antibiotic treatment without interfering with it.

Prevention of recurrence of *C. difficile* disease

The meta-analysis by Szajewska *et al.*[70] in 2015 also analyses the risk of *C. difficile* associated diarrhea and has shown that *S. boulardii* is effective in reducing the risk of *C. difficile*-associated diarrhea in children receiving antibiotics by 75%.

In addition, a meta-analysis of 25 trials studied several probiotics for their prevention of AAD and 6 trials for the recurrence of *C. difficile* disease. **Only *S. boulardii* showed significant reduction in recurrence of CDD combined with standard antibiotics[75].**

In patients with recurrent *C. difficile*, high dose of vancomycin were given with or without *S. boulardii* CNCM I-745. Adding *S. boulardii* CNCM I-745 was 67% more effective ($p = 0.05$) in preventing further CDD recurrences than treatment with high-dose of vancomycin alone[76].

Prevention of digestive side effect of *H. pylori* eradication therapy

A meta-analysis with **18 trials in adults and children shows that *S. boulardii* supplementation on standard *H. pylori* eradication therapy significantly reduced the incidence of gastrointestinal adverse effects, especially diarrhea[77].**

In adults with confirmed *H. pylori* infection, *S. boulardii* CNCM I-745 added to standard sequential antibiotic therapy significantly decreases the incidence of side effects and specially therapy-associated diarrhea compared to placebo (2.0% vs. 46.4%; $p = 0.02$)[78].

International recommendations to prevent diarrhea in children and adults

Children		
Disorders	**Society**	**Recommendation**
Antibiotic-associated diarrhea	European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[79]	*S. boulardii* and LGG are probiotics recommended to prevent AAD
	World Gastroenterology Organisation[9]	
	Recommendations for the management of gastrointestinal disorders in children in the Asia-Pacific region[80]	
	Latin-American Experts Consensus Group for the use of probiotics in paediatric Gastroenterology[81]	
	Groupe Francophone of Hepathology-Gastroenterology and Pediatric Nutrition[89]	
C. difficile	European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[79]	*S. boulardii* recommended to prevent *C. difficile*-associated diarrhea
Helicobacter pylori	World Gastroenterology Organisation[9]	*S. boulardii* CNCM I-745 and *Lactobacillus casei* DN-114 001 in fermented milk reduce risk of *H. pylori* therapy-related side effects
	Recommendations for the management of gastrointestinal disorders in children in the Asia-Pacific region[80]	*S. boulardii* CNCM I-745 is recommended to prevent *H. pylori* therapy-related side effects in children

Tableau 1. International recommendations for the use of *Saccharomyces boulardii* CNCM I-745 and other probiotics in children to prevent diarrhea.

Adults		
Disorders	**Society**	**Recommendation**
Antibiotic-associated diarrhea	World Gastroenterology Organisation[9]	*S. boulardii* CNCM I-745 is one of the probiotics recommended to prevent AAD in various clinical settings
C. difficile	World Gastroenterology Organisation[9]	*S. boulardii* CNCM I-745 is one of the probiotics recommended to prevent recurrences of *C. difficile* disease
Helicobacter pylori	World Gastroenterology Organisation[9]	*S. boulardi*i CNCM I-745 is one of the probiotics recommended to prevent gastrointestinal *H. pylori* therapy-related side effects
	Maastricht V/Florence Consensus Report[82]	Some probiotics, as *S. boulardii*, are effective in reducing gastrointestinal side effects caused by *H. pylori* eradication therapies

Tableau 2. International recommendations for the use of *Saccharomyces boulardii* CNCM I-745 and other probiotics in adults to prevent diarrhea.

To treat acute diarrhea in children and adults

A meta-analysis including 23 trials in children with acute gastroenteritis has confirmed the efficacy of ***S. boulardii* to treat acute diarrhea by reducing the duration by -1.06 days** compared to placebo or no treatment[83].

In children with watery diarrhea, the duration of diarrhea was approximately 24 hours shorter with *S. boulardii* CNCM I-745 administration ($p<0.001$)[84] which may be resolved as early as 48h following treatment. Also, in adults with acute diarrhea ***S. boulardii* CNCM I-745 can reduce the score for stool frequency and stool quality therefore reducing the clinical symptoms of acute diarrhea** compared to placebo ($p = 0.035$)[85].

International recommendations to treat acute diarrhea in children and adults

Children

Disorders	Society	Recommendation
Acute diarrhea	European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[85]	LGG and *S. boulardii* CNCM I-745 with the best level of evidence for the management or treatment of acute gastroenteritis, as adjunct treatment to oral rehydration therapy
	World Gastroenterology Organisation[9]	
	Recommendations for the management of gastrointestinal disorders in children in the Asia-Pacific region[80]	
	Latin-American Experts Consensus Group for the use of probiotics in paediatric Gastroenterology[81]	
	Groupe Francophone of Hepathology-Gastroenterology and Pediatric Nutrition[90]	

Tableau 3. International recommendations for the use of *Saccharomyces boulardii* CNCM I-745 and other probiotics in children to treat acute diarrhea.

Adults		
Disorders	**Society**	**Recommendation**
Acute diarrhea	World Gastroenterology Organisation[9]	*S. boulardii* CNCM I-745 is recommended to treat acute diarrhea

Tableau 4. International recommendations for the use of *Saccharomyces boulardii* CNCM I-745 and other probiotics in adults to treat acute diarrhea.

To recover from diarrhea in children and adults

In a healthy human, ***S. boulardii* does not alter microbiota composition**[87]. Following a dysbiotic situation, as diarrhea or antibiotic treatment, ***S. boulardii* CNCM I-745 can restore diversity and composition of human gut microbiota**[87,88]. In several human studies, *S. boulardii* CNCM I-745 can also support a faster reestablishment of the diversity and composition of gut microbiota, thus restoring intestinal balance[87].

Conclusion

There are no more doubts today that the gut microbiota plays an important role in human health and disease. **Protecting this ecosystem during aggressions like gastrointestinal infections or antibiotic treatment is of major importance**. In infancy, the gut microbiota is unstable and under an ongoing process of maturation. Growing evidence suggest that perturbing this process may explain in part the impairment of the 'education' of our immune and metabolic systems, leading to an increase susceptibility to develop 'non-communicable' diseases (like obesity, allergy, autoimmune diseases, etc.) later in life. In adults, post-infectious or antibiotic driven dysbiosis could have harmful consequences on subject well-being like functional disorders, susceptibility to infections (eg. *C. difficile*) or even IBD.

To mitigate these risks, we need robust clinical evidence that demonstrate the benefit of specific gut microbiota modifiers. To date, ***Saccharomyces boulardii* CNCM I-745**, is one of the most studied probiotics that is **able to restore diversity and composition of human gut microbiota**[87,88]. It has accumulated evidence of **efficacy in preventing AAD**[70,71,72], **recurrences of *C. difficile* disease**[70,75,76], as well as gastrointestinal *H. pylori* therapy-related side effects[77,78]. It also **reduces the duration of acute diarrhea illness**[83,84,85].

Nonetheless, the world of the gut microbiota science is still growing, and we all expect that in the next few years, our arsenal for treating gut microbiota linked disorders will amplify.

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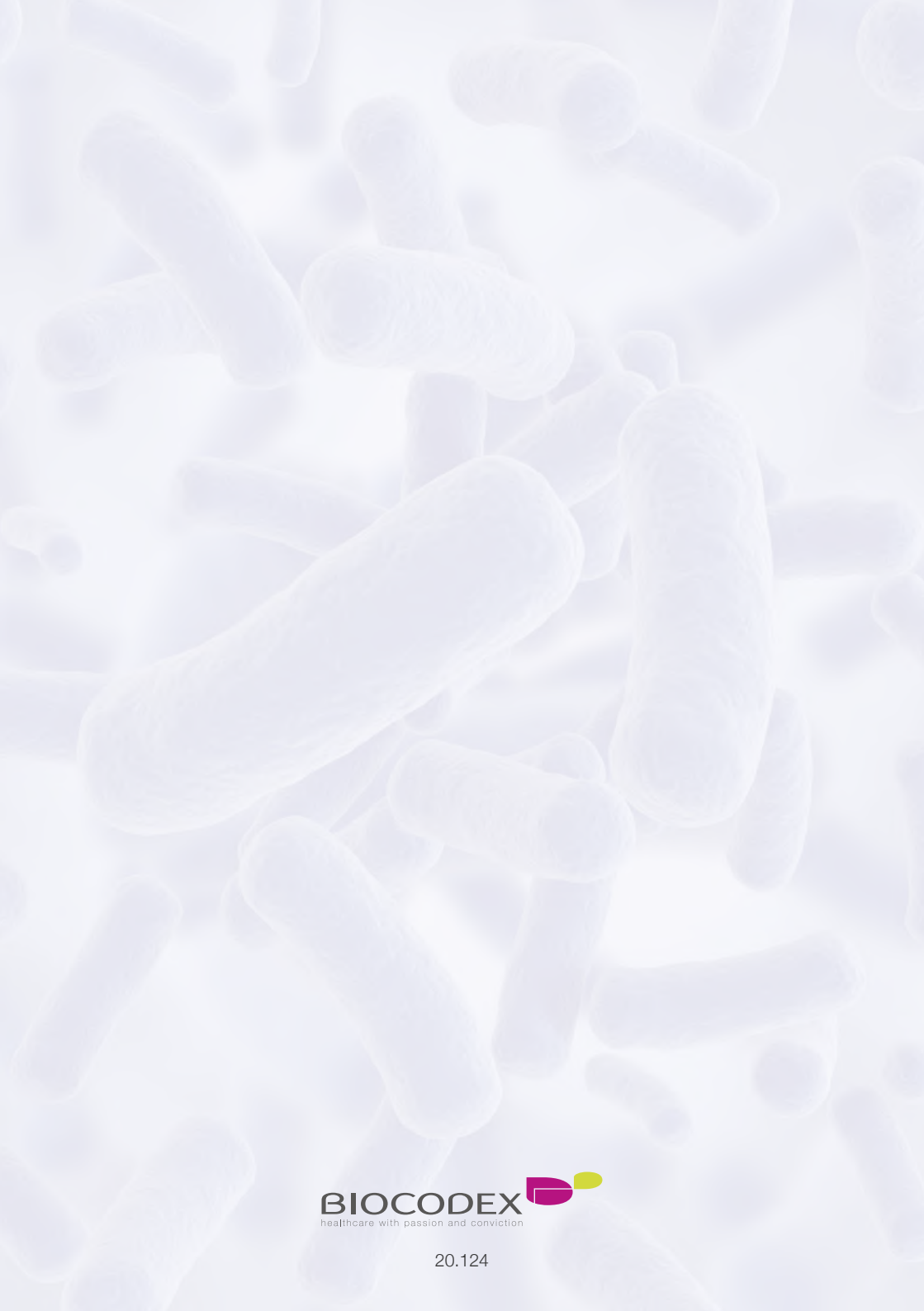
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