

Gastroenteritis

AND OTHER TYPES OF INFECTIOUS DIARRHEA

When your microbiota is struggling

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1 • HOW TO ACT ON THE MICROBIOTA TO COMBAT DIARRHEA?



Viruses, bacteria, parasites: causes behind gastrointestinal infections are varied. The main associated symptom is diarrhea, which dehydrates your body. In most cases, these infections are acute, resolve spontaneously within five days with symptomatic treatment, and do not relapse. However, in other cases, they can be severe from the start or they can last longer, and thus require a specific treatment. This may be due to the virulence of some microorganisms or their toxic substances, but also to their interactions with the gut microbiota¹, which is unique to each individual. What can we do then? Acting on our gut microbiota could open the way to effective preventive and curative treatments and help us face the public health issue posed by infectious diarrhea.

Diet: a key factor

The primary step in the treatment of any acute diarrhea is to counter-balance water and sodium losses, and slow down the intestinal transit (except in case of hemorrhagic diarrhea or high fever). It is also important to make sure that the amount of protein and calorie intake as well as micronutrient supplements are adequate.

Drink salty fluids^{2,3}!

This rehydration process can be carried out either through diet, combining an increased consumption of drinks containing glucose, sodium, potassium and bicarbonates (still or sparkling water, some soft drinks) and salty high-glucose food (rice, pasta...), or through the intake of commercially available oral rehydration solutions

(ORS) in case of nausea. Tap water should be avoided, as well as chicken broth, apple juice and most soft drinks. Special caution should be paid with older people who are less sensitive to thirst: in case of severe dehydration, intravenous rehydration may be required. In newborns, breastfeeding should be encouraged whenever possible. For formula-fed babies, the use of lactose-free milk is not recommended because it could jeopardize treatment effectiveness once an antibiotic is given.



¹ Non-pathogenic microorganisms (bacteria, viruses, fungi, parasites) living in our intestines.

² Beaugerie L, Sokol H. *Acute infectious diarrhea in adults: epidemiology and management*. Presse Med. 2013 Jan

³ Crawford SE et al. *Rotavirus infection*. Nat Rev Dis Primers. 2017 Nov 9

DIARRHEA IN A NUTSHELL

In practice, diarrhea is defined as the passage of three or more loose or liquid stools per day. According to the WHO, there are three clinical types of diarrhea:

- ❖ Acute watery diarrhea (lasts several hours or days, and includes cholera-induced diarrhea)
- ❖ Acute bloody diarrhea (also called dysentery)
- ❖ Persistent diarrhea (last 14 days or longer)

Zinc for malnourished children

The World Health Organization recommends the daily use of zinc supplements for two weeks in malnourished children over six months; unfortunately, this recommendation is seldom applied in low-income countries where meat consumption (source of zinc) is low⁴. In the GI tract, zinc restores the integrity of the gut barrier and stimulates immunity against microorganisms responsible for gastrointestinal infections. This twofold benefit has been confirmed in animal studies concluding that a chronic zinc deficit alters the composition and function of the gut microbiota and increases the risk of gastrointestinal infections. More specifically, giving zinc dietary supplements to children with severe diarrhea

decreases the duration of the episode. However, according to scientists, this approach is of little use in children under five years old with severe diarrhea but no zinc deficit, especially considering that this supplementation may increase the risk of vomiting following the initial dose.

⁴ Lazzarini M. Oral zinc provision in acute diarrhea. Curr Opin Clin Nutr Metab Care. 2016 May

- ❖ **2nd** leading cause of death in children under five years old (525,000 deaths per year)
- ❖ **1.7** billion children affected every year
- ❖ **>90%** of lethal infections occur in poor countries

Probiotics as a potential therapeutic tool^{5,6}



Although they are not part of the standard treatment for gastroenteritis, probiotics⁷ could play a role in the treatment of patients with acute diarrhea, provided the strain(s) used had been proven effective to alleviate symptoms.

In the past several years, the use of probiotics has grown significantly. The increasing number of works on these “beneficial” microorganisms have largely contributed to this trend. But not all microorganisms can be called “probiotics”: they need to be able to survive in the GI tract, resist to gastric acid and digestive enzymes, temporarily populate the intestines and they must have proven effective. The term can only

⁵ Szajewska H et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Use of probiotics for management of acute gastroenteritis: a position paper by the ESPGHAN Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr. 2014 Apr

⁶ Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, Shamir R, Vandenplas Y, van Goudoever JB, Weizman Z. ESPGHAN Working Group for Probiotics/Prebiotics. Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children. J Pediatr Gastroenterol Nutr. 2016;62:495-506

⁷ According to the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO), probiotics are “live microorganisms which, when administered in adequate amounts, confer a health benefit to the host”.

1 • HOW TO ACT ON THE MICROBIOTA TO COMBAT DIARRHEA?

be applied to microorganisms that resist degradation, are harmless to the human body, and are able to alleviate symptoms. They are generally marketed as dietary supplements or drugs, depending on their efficacy to alleviate symptoms and their degree of safety. They are composed of one or several strains or a mix of several species, and are available in many forms: capsules, powders for oral solution, orally dispersible powders, tablets...

Two leading species

A review of scientific literature to assess the use of probiotics in the prevention and treatment of pediatric gastrointestinal disorders showed that the benefits are specific to each strain and depend on the type of infection⁸. At this time, two microorganisms seem to efficiently act on gastroenteritis symptoms by re-

ducing their duration: *Saccharomyces boulardii* yeast as well as *Lactobacillus rhamnosus* GG (LGG) bacteria. More generally, these probiotics seem to improve symptoms, and even more so if they are administered at an early stage of the infection, and if the latter is of viral origin. In case of antibiotic-induced diarrhea, *S. boulardii* and *L. rhamnosus* GG could also have a beneficial effect. However, to prevent relapses of *Clostridium difficile* infections and traveler's diarrhea, it seems that only *S. boulardii* has an effect on symptoms.

Quicker recovery!

In case of rotavirus-induced gastroenteritis, these probiotics reduce the duration of the episode by a day or two². They lower the levels of molecules that improve the inflammatory process, by stimulating the immune response and

promoting proliferation and/or migration of intestine cells responsible for the transport of nutrients, thus facilitating glucose—and consequently water—absorption. Beyond the prevention of diarrhea in children receiving antibiotics or hospitalized children, these strains (*S. boulardii* among others) prevent 85% of diarrhea episodes related to the consumption of contaminated food or water⁹ (traveler's diarrhea). To be effective, these treatments must be taken a few days before departure and during the entire journey, and even after.

⁸ Hojsak I. Probiotics in Children: *What Is the Evidence?* *Pediatr Gastroenterol Hepatol Nutr.* 2017 Sep

⁹ Mc Farland LV. *Are probiotics and prebiotics effective in the prevention of travellers' diarrhea: A systematic review and meta-analysis.* *Travel Med Infect Dis.* 2018 Sep 29. pii: S1477-8939(18)30258-8



Traveler's diarrhea¹⁹

Traveler's diarrhea (TD) is caused by the consumption of food or drinks infected mainly by enteropathogenic bacteria. Taking into account the gut microbiota in the assessment of TD could lead to more efficient prevention and treatment.

❖ Symptoms

Diarrhea, abdominal cramps, nausea, fever

❖ Duration of the episode

4 to 5 days with no treatment

❖ Responsible bacteria/viruses/parasites

Escherichia coli, norovirus and rotavirus, *Salmonella*, *Campylobacter jejuni*, *Shigella*, *Giardia lamblia*...

❖ Prevention

Standard hygiene measures (washing fruits and vegetables, drinking bottled water)

❖ Treatment

Consumption of water or ORS, symptom relief, antibiotic therapy in some cases

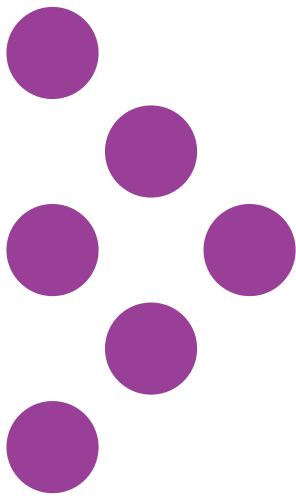
❖ Possible complications

Dysentery, post-infectious irritable bowel syndrome (3 to 17% of patients), chronic gastrointestinal symptoms

❖ Incidence

10 to 40% during a 2-week trip to a high-risk country (South Asia, West Africa, Central Africa, for instance)

2. WHO IS RESPONSIBLE?



What causes these disorders? Among all infectious agents responsible for viral gastroenteritis, two viruses stand out as the most virulent and draw the most attention: rotavirus and norovirus. The composition of the gut microbiota—that will end up being altered by these viruses—, as well as each person's genetics probably play a role in individual susceptibility to these infections.

Rotavirus and norovirus are to blame

Taking all ages together, the main cause of gastroenteritis is norovirus. However, in children under five, rotavirus-induced infections are the first cause of severe and acute diarrhea worldwide. Poor countries are the most affected, despite vaccines and antiviral drugs.

Rotavirus was identified in 1973 and owes its name to its distinctive wheel-like structure³. There are ten different species of rotavirus, the most common one being species A. Besides diarrhea, which is non-bloody and short term, contrary to bacterial diarrhea, the infection causes vomiting that contributes to the patients' dehydration and may hamper treatment efficacy. Rotavirus-induced infection is generally more severe than diarrhea caused by other infectious agents: fever, dizziness, fatigue are defensive reactions to the infection. If it persists for over a week or if diarrhea/vomiting worsen, medical consultation and specific treatment are required. Rotavirus transmission is possible year-long and mainly occur through direct or indirect contact with infected people. Complications are rare but possible: if it enters the blood stream, the virus can cause extraintestinal infections, mainly neurological (meningitis, encephalitis, encephalopathy). The introduction of vaccination in 2006 throughout the world had two consequences in rich

countries: people infected are older (teenagers or people over 70), and outbreaks have become seasonal.

Pay attention to diet and close contact¹⁰!

Norovirus is extremely contagious, highly infectious and relatively resistant to disinfectant agents. As such, it is mainly transmitted through the intake of infected food or water, or through contact with contaminated objects or people. Airborne contamination is also possible. Simple isolated cases can quickly lead to epidemics in confined spaces (cruise ships, health care facilities, hospitals...) and acute forms can cause severe intestinal complications (postinfectious irritable bowel syndrome, life-threatening dehydration...). Usually, norovirus-induced gastroenteritis lasts between one and four days and is associated to the same symptoms as rotavirus-induced gastroenteritis: abdominal pain, nausea, vomiting and non-bloody diarrhea. It generally resolves spontaneously, but several months may be needed to eradicate the virus in healthy carriers (infected but without any symptom), or sometimes even years in people with a weakened immune system; and since they become chronically ill, they probably also become disease reservoirs.



Rotavirus.

¹⁰ Baldrige MT et al. *Norovirus Regulation by Host and Microbe*. Trends Mol Med. 2016 Dec

❖ **20** million norovirus-induced gastroenteritis per year in the US (cost: 60 billion USD)

❖ **42%** decrease in mortality rate since the launch of the anti-rotavirus vaccine (2006)

What about the gut microbiota?

The gut microbiota is a mix of micro-organisms (bacteria, viruses, fungi...) making up a complex environment that interacts with the viruses responsible for gastroenteritis. Since each individual has a unique microbial ecosystem, these interactions, as well as the nature and severity of the symptoms, vary from person to person¹¹.

No matter what virus is responsible, viral gastroenteritis leads to a decrease in diversity of species composing the gut microbiota and impacts the abundance of three species¹² : *Prevotella*, *Staphylococcus* and *Atopobium*. The resulting imbalance (called “intestinal dysbiosis”) is the source of several symptoms observed in patients. For instance, abundant diarrhea that characterizes rotavirus-induced gastroenteritis is the result of disorganization of the microbiota that leads to the destruction of microbial barrier.

Is the gut microbiota a frenemy?

Dysbiosis alone cannot explain the whole story: for example, the norovirus can merge with “commensal” bacteria (i.e. beneficial and naturally present in the microbiota) or act together with “harmful” bacteria (pathogens) and cause inflammation³. The body therefore produces natural antiviral substances, such as interferons. However, as a result of strong stimulation, these substances turn against the body and attack it, thus causing severe intestinal lesions. The underlying mechanisms ruling over the interactions between these agents are still poorly understood and are the subject of many research studies. But relations between norovirus and gut microbiota can also be beneficial: experiments in mice have shown that intestinal dysbiosis caused by antibiotics may prevent or mitigate norovirus infection.



The role of genetics

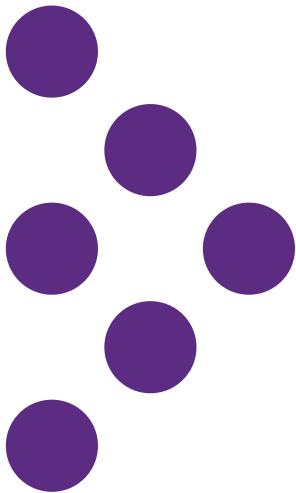
These findings give us an overview of the complex relations existing between viruses originating from our environment and microorganisms living in our intestines. In fact, they seem to depend on a third player: our genes. Based on studies carried out in rodents, we are

not equal when it comes to fighting norovirus infections: there is an individual susceptibility which depends on our genetic makeup, our gut microbiota and the presence of concomitant infections, that leads to a great variety of symptoms and long-term effects.

¹¹ Dinleyici EC et al. *Time series analysis of the microbiota of children suffering from acute infectious diarrhea and their recovery after treatment*. Front Microbiol. 2018 Jun 12

¹² Chen SY, Tsai CN, Lee YS, Lin CY, Huang KY, Chao HC et al. *Intestinal microbiome in children with severe and complicated acute viral gastroenteritis*. Sci. Rep. 7:46130. doi: 10.1038/srep46130. 2017

3. OTHER TROUBLEMAKERS



Viruses are not the only causes of diarrhea: there are other enteric pathogens (microorganisms infecting the gastrointestinal tract). Bacteria such as *Salmonellae* and *Escherichia coli*, or unicellular organisms (protozoans) such as *Giardia lamblia*, are able to colonize the GI tract, to disrupt the gut microbiota, and to cause short- and long-term consequences¹³. There are other factors: some drugs, such as antibiotics that disrupt the microbiota, impair its functioning and promote colonization by pathogens, of which *Clostridium difficile* is the most frequent.

When bacteria and parasites attack the gut microbiota

Why are some people particularly sensitive when others are more resistant? “It depends on the microbiota”, answer the researchers, whose studies underline the impact of interactions between invasive pathogens and microorganism living in our intestines.

An uphill battle

To understand the infectious process of enteropathogenic bacteria, researchers reviewed the mechanisms employed by the body to fight the colonization of the digestive tract by *Salmonella typhimurium*¹⁴, a bacterium causing food poisoning with diarrhea, that is sometimes severe although short-lived. The first mechanism comes into play in the stomach where the acid environment destroys between 95 and 99% of ingested bacteria (through food). For bacteria that are able to reach the intestines, it is too early to claim victory: they can only grow if the level of resistance to colonization allows it. But the latter depends on the composition of the gut microbiota, specific to each person, that has an arsenal of tools to fight this colonization: secretion of components blocking the invader's growth and virulence, competition for



the same binding sites, creation of an oxygen-poor environment that is unfavorable to its growth...

A fierce fight

And our defenses have not said their last word: bacteria must be present in sufficient amounts to trigger diarrhea, and it only happens between 12 to 36 hours (sometimes 72 hours, depending on the number of ingested bacteria) after they cross the intesti-

nal barrier. Based on animal models, *S. typhimurium* accomplishes this by secreting toxic substances, thus allowing it to reach the mucosa and then the submucosa. The body reacts by expelling infected intestinal cells—

¹³ Fink MY et al. *The Intersection of Immune Responses, Microbiota, and Pathogenesis in Giardiasis*. Trends Parasitol. 2017 Nov

¹⁴ Wotzka SY et al. *Salmonella Typhimurium Diarrhea Reveals Basic Principles of Enteropathogen Infection and Disease-Promoted DNA Exchange*. Cell Host Microbe. 2017 Apr 1



thus dividing the number of pathogenic bacteria in the tissues by 100—and sets off a massive inflammatory response which affects the enemy in two ways: by reducing the bacterial load in the body, while serving as fuel to the remaining bacteria.

Long-term consequences

There is another enemy: *Giardia lamblia*. This protozoan infects humans through the consumption of contaminated water or food. Although the frequency of giardiasis does not exceed 7% in developed countries, it can reach 30% in developing countries. In most cases, the infection takes a few

weeks to resolve but it can sometimes last several months and become chronic. There is currently no vaccine and available treatments have different levels of effectiveness. Giardiasis is often asymptomatic, but it can cause diarrhea, cramps and nausea. In newborns, disease severity hinges on its long-term consequences: at the age of two, they show a significant growth deficit. And some people may develop post-infectious syndromes several years after the elimination of the parasite, such as irritable bowel syndrome or chronic fatigue. According to several papers, *Giardia lamblia* could act by decreasing the immune response and causing dysbiosis.

Diarrhea and use of antibiotics: case study

Diarrhea is a common side effect of antibiotics, and it may compromise their efficacy, especially if the treatment is prematurely withdrawn. Antibiotic-induced diarrhea is usually benign, but it may mask a more serious intestinal infection.

Antibiotics not only eradicate pathogenic microorganisms responsible for infection, but they can also destroy some bacteria that are beneficial to the gut microbiota. They always cause a more or less significant imbalance within this ecosystem. This ecosystem becomes less rich and less diversified, and is no longer able to properly carry out its protective functions².

Antibiotics are not automatic anymore¹⁵!

Between 10 and 30% of patients treated with antibiotics experience a change in their intestinal transit within 3-5 days of treatment, most often in the form of diarrhea¹⁶. Most of the time, this diarrhea is purely functional, caused by the antibiotic-induced dysbiosis. It usually presents without fever, it is short lived, not severe, and in most cases, it regresses once antibiotics are discontinued, or in the

following weeks. However, dysbiosis starts in the first 24 hours of antibiotic treatment and lasts up to six weeks after its conclusion. New microorganisms, close to the initial strains but not necessarily identical, slowly re-colonize the intestines and create a new balance, although it often remains incomplete.



A new route for pathogens

But sometimes, the mucus layer, true line of defense of our intestines, has been so weakened that the body becomes more vulnerable to pathogens. In 10 to 20% of cases, diarrhea results from the colonization of the microbiota by *Clostridium difficile*. This bacterium is very widespread in hospitals and nursing homes, and elderly people are particularly vulnerable: in these facilities, up to 20% of residents

(50% in cases of long-term stay) can host this bacterium in their intestines without showing any symptom (asymptomatic carriers). Although most cases of *C. difficile* diarrhea resolve once the antibiotics are discontinued, most severe forms could occur (pseudomembranous colitis and fulminant colitis, especially in people over 65 years old¹⁷). In the US, for instance, this infection is responsible for around 30,000 deaths/year¹⁸. The families of antibiotics that are often blamed are penicillins, some generations of cephalosporins, fluoroquinolones and clindamycins. To stop this vicious circle, stool transplant (transplant of healthy microbiota into the GI tract of a patient) could be a therapeutic alternative to antibiotics in order to repopulate the microbiota and restore the gut barrier.

¹⁵ Piche T. Diarrhée associée aux antibiotiques. Hépatogastro & Oncologie Digestive. 2002;9(5):339-44

¹⁶ Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. N Engl J Med 2002;346:334-9. Cited in Beaugerie L, Sokol H. Acute infectious diarrhea in adults: epidemiology and management. Presse Med. 2013 Jan

¹⁷ Castrillon B et al. Infections à *Clostridium difficile* : spécificités chez le sujet âgé. Rev Med Suisse. 2013; 9 : 2044-8

¹⁸ Lessa FC et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015 Jun 11



Collective food poisoning²⁰

Collective food poisoning occurs when there are at least two clustered cases with identical symptoms (usually gastrointestinal) and caused by the same contaminated food.

❖ Symptoms

Abdominal pain, diarrhea (bloody or not), nausea, vomiting, headache, fever, muscular pain

❖ Duration of the episode

Quick recovery if hygiene is adequate

❖ Responsible bacteria

Salmonella spp., *E. coli*, *Shigella* spp., *Yersinia* spp., *Listeria monocytogenes*, *Staphylococcus aureus*, *Clostridium* spp., *Bacillus cereus* and fungal toxins (mycotoxins)

❖ Possible complications

Meningitis in case of *Listeria monocytogenes* infection in vulnerable or weakened subjects (newborns, pregnant women, elderly, immunocompromised individuals)

❖ Incidence

Has been rising since the 1980's because of the increase of fresh produce consumption; decrease of serious cases thanks to a better management of hygiene conditions in food production, transformation and distribution processes.

High-risk foods

FOR FOOD POISONING OR INTESTINAL INFECTION⁸



❖ Pastries, raw egg products



❖ Unpasteurized dairy products



❖ Meat: processed meat, raw beef (especially minced meat), pork (cold cuts, salami...), undercooked (pinkish) chicken or rotisserie chicken



❖ Rice, soya stored at ambient conditions



❖ Readymade dishes



❖ Raw or cooked shellfish



❖ Raw fresh produce (vegetables, fruits...)



❖ Nuts: walnuts, hazelnuts...

¹⁹ Steffen R et al. *Traveler's diarrhea: a clinical review*. JAMA. 2015 Jan 6

²⁰ Yeni F et al. Most Common Foodborne Pathogens and Mycotoxins on Fresh Produce: A Review of Recent Outbreaks. Crit Rev Food Sci Nutr. 2016 Jul 3



Dr. Julie Lemale is a Pediatric Gastroenterologist at the Armand Trousseau Hospital (AP-HP, Paris) and a member of the Board of Directors of the Francophone Group of Pediatric Hepatology, Gastroenterology and Nutrition (GFHGNP). She explains how important it is to consider and preserve the gut microbiota in children with diarrhea.

Modulation of the gut microbiota: prevention and treatment at the same time?

It is highly probable: beyond standard hygiene and dietary measures and especially rehydration, two probiotics (*Saccharomyces boulardii* yeast and *Lactobacillus rhamnosus GG* bacterium (LGG)) seem to prevent antibiotic-associated diarrhea in high risk patients (newborns, children with concomitant diseases...) and are recommended for this purpose by experts of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN). They could also prevent the onset of nosocomial diarrhea in hospitalized

children or in community facilities: according to encouraging data which still needs to be confirmed, they could reduce the risk by 15%, in some studies. As add-on treatment for gastroenteritis, *S. boulardii*, and some concentrations of *Lactobacillus rhamnosus GG* (LGG), could reduce the duration of diarrhea by a day and decrease the risk that it lasts more than four days. As for fecal microbiota transplant, it is only indicated in cases of *Clostridium difficile* drug-resistant or recurrent infection, which is rare in children.

Is the microbiota of a child treated with antibiotics impacted in the long term?

It is difficult to say at the moment since there is currently no scientific evidence of this. But the question needs

cules in young children compromises the organization of intestinal microbiota and the immune system, it could very well have long-term consequences on the intestinal flora and increase vulnerability to some diseases later in life.

What is the outlook in terms of prevention and treatment?

Oral vaccination, undoubtedly. It has allowed to considerably reduce the number and severity of cases of rotavirus-induced diarrhea. In this area, one of the perspectives is to extend this vaccination to all babies under 6 weeks old (for the first injection). Beyond this age, its efficacy seems to decrease. Researchers are also trying to develop more effective vaccines and identifying more effective probi-

“ **THE INTAKE OF ANTIBIOTICS IN YOUNG CHILDREN COULD VERY WELL HAVE LONG-TERM CONSEQUENCES ON THE INTESTINAL FLORA.** ”

to be asked: after an antibiotic treatment, the gut microbiota is disrupted for two to three months. Then a normalization process, that tends to give the patient its previous microbiota back, although the restored version is not the exact copy of the original microbiota. Because the repeated and/or prolonged intake of these mole-

otic strains: according to some scientific data, our body's immune response seems to depend, among others, on our “bacterial profile”. Our gut microbiota, when modulated and/or boosted by probiotics, could allow us to better respond to vaccination against rotavirus.



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