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Intestinal MIcrobiota, Antibiotics and Neutropenic Colitis

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ABSTRACT *Neutropenic colitis is a complication for patients receiving chemotherapy; it has been considered that the use of antimicrobial agents to treat it is essential. Some studies have shown that the use of these agents modifies the habitual microbiota, and others have revealed that intestinal dysbiosis produces biological alterations that have an impact on the intestinal environment and on the subjects' health state. In neutropenic colitis, the interaction of multiple factors interferes with the identification of a sole factor as responsible for this complication.*

The interaction between antibiotics, microbiota and chemotherapy establishes conditions that favor microenvironmental alterations that should be taken into account when treating neutropenic colitis.

Introduction

The microbiota, considered an essential component of the intestinal environment, is always present as part of its structure (1); its metabolism has a decisive impact in the maintenance of the host's homeostasis, in such a way that in metabolic terms, the human/gut microbiota interaction is catalogued as a supra- or super-organism (2) forming a complex ecosystem that comprises more than 400 bacterial species. Most of these bacteria are not harmful and many are beneficial. It is estimated that only 100 can become harmful when and if the conditions that allow the expression of their pathogenicity come together (3).

From the point of view of health strategies, the use of antimicrobial agents has historically been a tool that has proven effective when it is properly used and the precise indications that warrant its success are followed (4) In children with cancer, using antimicrobials aims to reduce the risk of infections by pathogenic microorganisms that might complicate the evolution of the disease (5) These include among others: beta-lactamase-producing bacteria, Pseudomonas, anaerobic bacteria and Enterococcus (6).

From a biological point of view, it has been shown that the use of antimicrobials is a determinant that favors intestinal dysbiosis and alters metabolic pathways (7) unfortunately the criteria for the use of antimicrobial agents in the treatment of ailments where the pathogenic role of bacteria is an assumption have not been clearly defined (8) for example pancreatitis and serious traumas illustrate this: it has been shown that the administration of antibiotics in these cases is based on an inflammatory symptomatology rather than on the evidence of an infectious process.(9) Conditioning factors are similar in children with cancer and neutropenic fever. (10)

Antibiotics and neutropenic colitis

The main concern is that any antimicrobial prescription will have an impact on the intestinal microenvironment whose balance is necessary for an adequate progress (11) in this context, there is a group of subjects with hemato-oncological diseases who, after receiving chemotherapy, present neutropenia, fever, abdominal pain, mucositis, diarrhea or constipation with alterations in the ultrasonography (USG) or computed tomography (CT) images that show an intestinal wall thickening > 4 mm known as neutropenic colitis (NC) (12,13) According to its pathogeny, neutropenic colitis is a direct consequence of the damage produced by chemotherapy and neutropenia on the intestinal mucosa, i.e., an intestinal inflammatory necrotizing illness to which an infectious process is usually added,(14) not the other way around.

So, the main hypothesis is that when antibiotics are used, susceptible colonizing bacteria die, and, in an environment swollen due to chemotherapy, this brings about the loss of the fermentative activity and the acidification that symbiotic bacteria carry out in the intestine. This, in turn, enhances the increase of pathogenic microorganisms not sensitive to the antimicrobial agent (15) (Figure 1 about here).

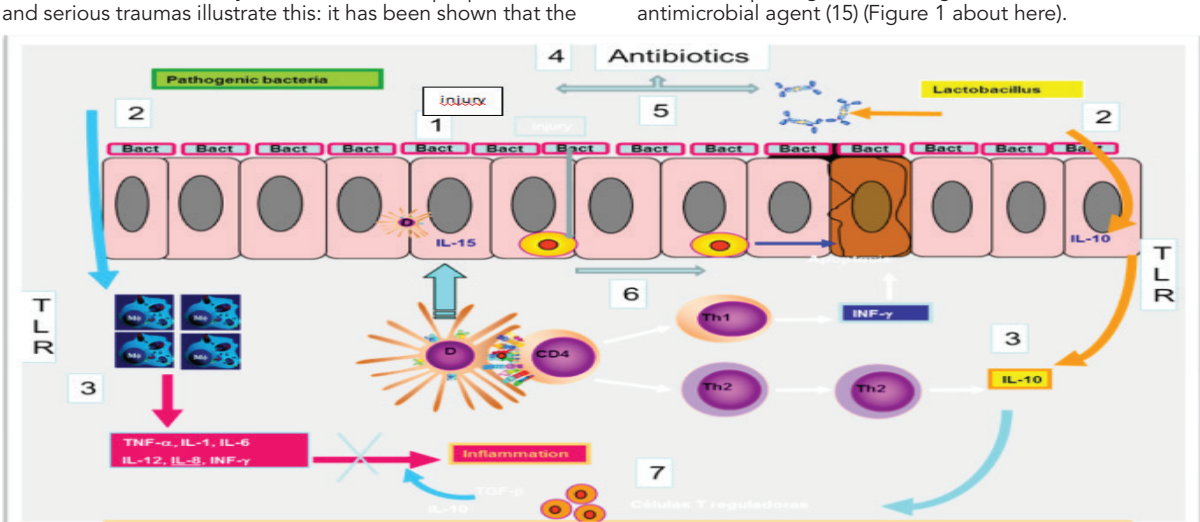

Figure 1. The immune response in the intestinal environment comprises 1) the integrity of the epithelial barrier and the

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mucus layer. 2) In this environment, habitual and pathogenic bacteria bind to TLRs triggering the activiaton of NFkB and 3) liberation of proinflammatory and anti-inflammatory cytokines, the microbiota has the capacity to influence the inflammatory process and the intestinal permeability. 4 y 5) Bacterias with fermentative activity. 6) In an environment that already presents chemotherapy-induced inflammation. 7) The increase of pathogenic microorganisms that are not sensitive to the antimicrobial agents. (38-40)

Chemotherapy also causes damage to the mucosa, submucosal hemorrhage, and parietal necrosis of the cecum, colon, small intestine, rectum and esophagus. (13) In an important percentage of subjects this will encourage the administration of broad-spectrum antibiotics, when the invasion of the bloodstream by microorganisms has not actually taken place. (Figure 2 about here'.)

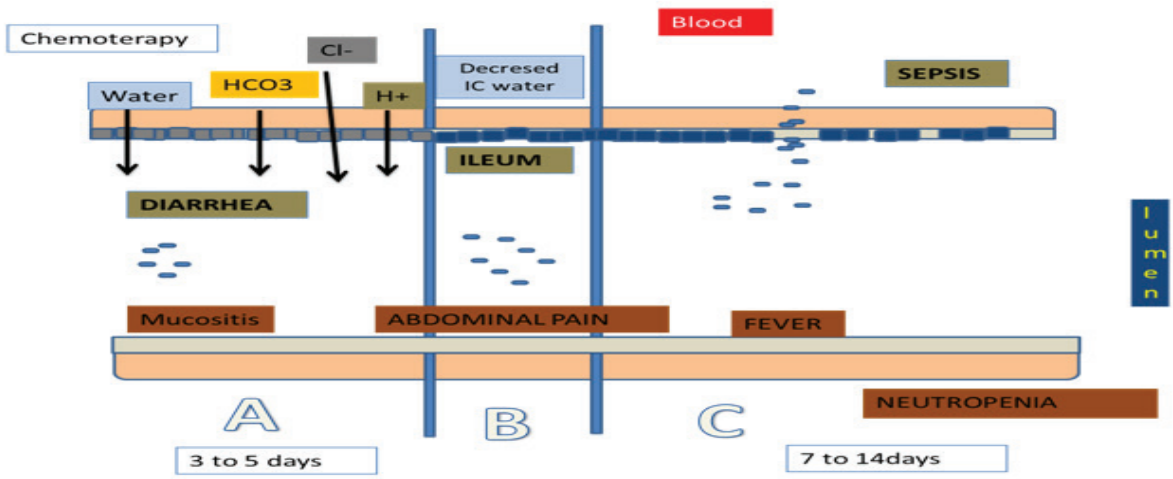

Figure 2. A) During chemotherapeutic treatment, sphacelation and inflammation of the intestinal mucosa (mucosytes) takes place. There is an outflow of monovalent electrolytes towards the intestinal light and due to the inflammation, water absorption decreases; this provokes mucous diarrhea (secretory and exudative). B) After the use of chemotherapy, there can be constipation, although the rate is lower than that of diarrhea. Inflammation perpetuates and it provokes abdominal pain. Bacterial proliferation increases as does the metabolism of sugars, which entail an increase of intestingal gas, more abdominal bloating and hence, nausea and vomit. C) Seven to 14 days after chemotherapy, and if the conditions persist, there is an increase in ischemia and necrosis; ulcerations are produced, and they allow the flow of bacteria into the bloodstream of an individual with neutropenia; this favors the appearance of severe systemic infections. Although there are reports that show a direct impact of active toxic metabolites of certain chemotherapeutic agents produced by the microbiota on the intestinal mucosa, apparently this does not play a leading role in the production of mucositis, but it does constitute an issue in terms of the production of sepsis secondary to bacterial translocation in phases III and IV of a host with neutropenia.

Origin of bacteria isolated from blood in Children with cancer

It is clear that isolated bacteria in blood come from two particular environments among children with neutropenic colitis**:** (8) the hospital, associated to the loss of natural barriers, (Bone) the intestine, whose microorganisms include colonizing bacteria such as *Escherichia coli*, *Clostridium* sp., enterococci, *Klebsiella* sp. and *Pseudomomas* sp, (16) However**,** is accepted that bacterial isolation in children with neutropenic colitis is a consequence rather than a trigger and that it occurs after the appearance of neutropenia and harm to the intestinal mucosa due to chemotherapy and alterations of the intestinal metabolic pathways then there exist the conditions that favor intestinal dysbiosis.(17,18)

The exact incidence of neutropenic colitis is unknown, since many patients survive without ever having been diagnosed**.** A study of autopsies of children treated for hematological ailments reported a prevalence of 24%. Another study reported a prevalence of 33% in children treated for acute myelogenous leukemia**.** (19) More recent data point to an approximate incidence of 6% and a prevalence between 1 and 15%. (20)

Moreover, balance depends on a complex range of physiological factors (21) when these factors are modified; the microbiota undergoes changes making way for the development of pathogenic microorganisms in a favorable environment. The colonizers of the biological niche will change, but it will never be left empty. The new microorganisms will evidently change the role played in relation to the host, and in consequence, there will be a shift from normobiosis to dysbiosis. (1,3,22)

Changes of intestinal microbiota with antimicrobial agents use.

The evaluation of the impact of antimicrobial agents on animal models has established that the number of copies of 16S rRNA decreases in the ileum and the cecal appendix, where ischemia is most often observed in children with neutropenic colitis. Depending on the antibiotics and their combination, different bacterial species can undergo changes. **(**23) Several studies have reached similar results, establishing the increase of the intestinal load of 16S rRNA of bacteria from the following families: *Enterococcaceae*, *Enterobacteriaceae*, and *Clostridiaceae*, and the decrease of bacterial phyla Firmicutes and Bacteroidetes, as a consequence of using ampicillin, vancomycin, (24). a combination of amoxicillin, metronidazole and bismuth or cefoperazone alone (25**)** ciprofloxacin (26,27**)** and vancomycin (28) The changes in the composition of the microbiota, specially due to *Bifidobacterium* and *Lactobacillus*, could in principle favor the increase of resistant colonizing bacteria in the intestine (29,30)**.** For instance**,** nonfermentative bacteria such as *Pseudomonas* use glucose and other carbohydrates in an oxidative way, and they are characterized by the production of pyocyanin and pyoverdin, as well as by the use of enzymes like arginine dihydrolase, the hydrolysis of acetamide and the reduction of nitrates. (31)

The impact of antimicrobials has been assessed in animal models without cancer, where it has been established that the number of 16S rRNA copies decreases in the ileum and the cecal appendix. Coincidentally, this is where ischemia is more frequently observed in children with NC (32)**.** Depending on the antibiotics and their combination, the species of bacteria can experience modifications (33).

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Particularly among cancer patients, *C. difficile* has emerged as an important pathogen in patients with diarrhea and colitis, so attention should be paid to the early liberal use of antibiotics such as vancomycin (34)**,** but others antibiotics are used in neutropenic patients like Piperacillin/ tazobactam (41.9%), imipenem (25.7%), cefepime (17.5%) and ciprofloxacin (2.7%) (28) increasing risk of intestinal disbiosis.

Recent studies represents a merely associative, not causal, approach to considering the risk of using antibiotics to prevent diseases deemed as serious in a hospital setting. This practice could be seen as a risk factor, along with others that have been described as determinants for the development of NC. Limiting the use of antimicrobials in children with cancer and in those with neutropenia and fever is likely to be difficult when facing risk of death and that of serious infection with low bacterial inocula. Nevertheless, some strategies can be implemented with previous risk-benefit assessments.

The consensuses with respect to the management of the patient with neutropenia and fever, and particularly with neutropenic colitis, recommend that once the diagnosis has been established, treatment should begin with the replenishment of liquids and electrolytes and the prescription of broad-spectrum antibiotics. Nevertheless, there are enough arguments to establish that using the latter can enhance the selection of the pathogenic strains of the intestinal flora and the infection of the wall, (35,36) emphasizing the prompt reestablishment of the numbers of neutrophils.

On perspective, it has been shown that the use of probiotics plays an important role when treating gastrointestinal ailments, since the microbiota can be thus reestablished and the performance of the different functional mechanisms improved.(37) Still, there is not enough evidence to support the use of probiotics for the prevention and treatment of neutropenic colitis, although some animal models with colitis have undergone improvement with their use. In humans, the scarce availability of data on the safety of the probiotics in immunocompromised patients with loss of the defensive intestinal barrier is one of the main problems. Some studies have informed that probiotics are safe in immunocompromised patients, but others have reported lactobacillus bacteremia and *Saccharomyces* fungemia occurring after probiotics were given particularly to immunocompromised patients; among them are included subjects that did not receive the probiotics directly but were in the same hospital unit as the individual that got them.(37,38)

As in the case of sepsis, neutropenic colitis is considered a dynamic process, the physiological alterations of which establish the severity of the sickness. It is likely that the early use of antibiotics could enhance the selection of pathogenic strains and increase the risk of serious complications such as intestinal perforation and peritonitis. Notwithstanding, once that microbial participation has been established regarding the severity of the systemic symptoms, the use of antimicrobial agents becomes necessary. Establishing the ideal moment when these medicines should be used is probably the capstone of the treatment of patients with neutropenic colitis.

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