**Bacterial-host interactions (PARACORREGIR)**

**Bacterial translocation (BT)**

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| The BT is the passage of viable bacteria from the intestinal lumen to the mesenteric nodes with the possibility of dissemination and causing bacteremia 2 |

There is a functional natural barrier but the microorganisms of the intestinal microbiota, even in healthy individuals, are capable of migrating. This is accentuated in subjects with some underlying problem.

It is important to note that endotoxin can migrate to the ganglia, as demonstrated by Wageha et al in 20173.

Bacterial DNA and endotoxin are capable of triggering a cytochemical response that, through certain effectors such as nitric oxide, can aggravate the homeostatic balance and alter hemodynamic parameters.

How the bacteria can leave the intestine and reach other organs has remained largely unexplored. However, researchers have observed that there may be different variables or populations of the same species of bacteria, as occurs with *Enterococcus faecalis*. These populations behave differently, which would explain why not all of them translocate.

The study of BT has not been in-depth but it is logical to think that there are factors that condition it, and especially in intestinal areas with greater microbial density such as the ileocecal area.

Philpott, D.J. and cols7 propose three mechanisms to explain its pathogenesis:

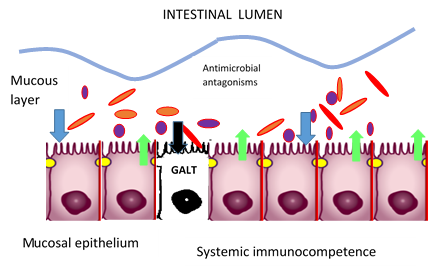
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| ***A-intestinal bacterial overgrowth (IBS),***  ***B-local and systemic immunological alterations***  ***C-increased intestinal permeability***  ***A-Intestinal bacterial overgrowth*** |

It may be due to an overgrowth of the entire microbiota as well as that of a particular species. These alterations are due to multiple factors ranging from the type of diet, presence of an underlying disease that requires medication that influences the microbiota, use of antimicrobials that are eliminated through the intestine, and metabolic or hormonal alterations1, 2.

**B-Local and systemic immunological alterations**

The intestine has endocrine and immunological functions, in addition to the usual digestion, metabolism and absorption of nutrients. Let us remember that there is a true immune complex in the intestinal mucosa called GALT (gut associated lymphoid tissue)14 as can be seen in figure 1.

**Figure 1.** Intestinal barrier and immune system

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It is estimated that 25% of the intestinal mucosa is lymphoid tissue and that between 70%-80% of the immunosecretory cells are located in the intestine.

Basically one can mention:

* **Peyer's patches:** are analogous to lymph nodes. Specialized epithelial cells, M cells, line Peyer's patches and act as afferent lymphatics7.
* **Lymphoid cells of the lamina propria:** They include T and B lymphocytes, plasma cells, eosinophilic macrophages, and mast cells.
* **Intraepithelial lymphocytes.** They are located within the lamina propria in a proportion of one lymphocyte for every 6 epithelial cells.

The alteration of this intestinal immune system can be due to various factors but the most important are, according to . Nava, P et al (12), Otamiri, T. (13) the following:

***1-cellular hypoxia***

***2-tissue injury induced by mediators, such as oxygen free radicals, NO, cytokines and other molecules*12*.***

***3-the toxic effect of some bacteria on the intestinal lumen* 16*.***

The final result is the appearance of episodes of ischemia, reperfusion and changes in flows in different intestinal areas. This results in: edema and peeling of the enterocytes, interruption of the lamina propria with hemorrhagic foci and ulcerations and, occasionally, the presence of bacteria crossing the mucosa.

**C-Increased intestinal permeability7**

As we already mentioned, there are functional components in the intestinal barrier such as mucin. Intercellular junctions that have the ability to select the passage of substances are also important (figure 2).

**Figure 2.** Union of epithelial cells of the intestinal mucosa and types of translocation (adapted from 3)

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JAM = Junctional adhesion molecule; CAR = Coxsackie virus and adenovirus receptor, ZO = Zonula occludens.

**How do pathogens influence?**

The interaction between different unusual microorganisms and the intestinal barrier produces a different degree of virulence. The most common form of violation and subsequent penetration is through the union of epithelial cells, due to a decrease in their resistance; such is the case of *Escherichia coli*, *Salmonella* or *Bacteroides*.

In tables 1, 2, 3 and 4 you can see the interaction of relevant pathogens with the structures that bind the cells of the intestinal mucosa.

**Table 1.** Interaction of EPEC with intestinal mucosal cell junctions (adapted from3)

|  |  |  |  |
| --- | --- | --- | --- |
| Pathogen/Mechanism | *In Vivo/In Vitro* | Effects | References |
| EPEC dephosphorylates and dissociates occludin | *in vitro* | periadhesion actmyosin that increases paracellular permeability and disturbs the barrier | Simonovic et al. 4 |
| EPEC redistributes occludin | *in vivo* | disruption of ion transport and disturbs the barrier | Shifflet et al.5 |
| EPEC induces redistribution of ZO-1 and occludin  ECEP alters the distribution of the TJ protein ZO-1 | *in vivo*  *in vitro* | increases translocation and changes the junctional structure  alteration of barrier and transport functions | Zhang et al.6  Philpott et al.7 |

**Table 2**. Interaction of *Salmonella* with the junctions of the cells of the intestinal mucosa (adapted from 3)

|  |  |  |  |
| --- | --- | --- | --- |
| Pathogen/Mechanism | *In Vivo/In Vitro* | Effects | References |
| *Salmonella enteritidis* compromises the intestinal epithelial barrier | *in vitro* | depression of transepithelial ion transport | Awad et al.8 |
| *Salmonella* Typhimurium depresses the production of claudin-1, claudin-4, and the mRNA that allows the expression of occludin | *in vivo* | disruption of epithelial function | Shao et al.9 |
| *Salmonella* Typhimurium disruption of epithelial function | *in vivo* | alteration of the barrier function of the intestinal mucosa | Zhang et al.10 |
| *Salmonella* Typhimurium depresses ZO-1 and occludin mRNA expression, causes redistribution of TJ epithelial proteins claudin-1 and ZO-2 | *in vitro* | damage to the intestinal barrier, facilitates the translocation of pathogenic and non-pathogenic microorganisms | Koehler et al.11 |

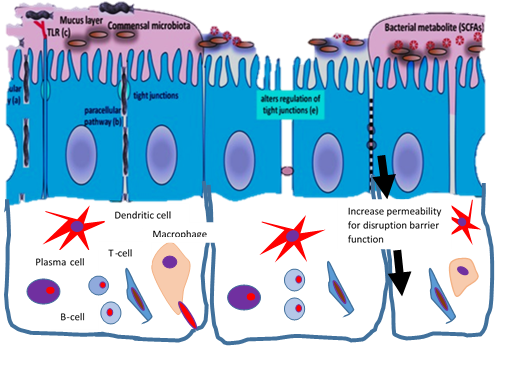
**Table 3.** Interaction of *Clostridium perfringens* with the junctions of the cells of the intestinal mucosa (adapted from 3)

|  |  |  |  |
| --- | --- | --- | --- |
| Pathogen/Mechanism | *In Vivo/In Vitro* | Effects | References |
| *C. perfringens* type C causes redistribution of the epithelial TJ proteins, occludin and claudin-3 | *in vitro* | depresses transepithelial electrical resistance | Nava and Vidal12 |
| *C. perfringens* disrupts the TJ barrier through phospholipase activation | *in vivo* | perturbation of TJ by increasing intestinal permeability | Otamiri 13 |
| *C. perfringens* decreases claudin-1 and occludin mRNA expression | *in vivo* | alteration of the intestinal barrier by increasing intestinal permeability | Collier et al.14 |

**Table 4**. Interaction of *Campylobacte*r with the junctions of the cells of the intestinal mucosa (adapted from 15)

|  |  |  |  |
| --- | --- | --- | --- |
| Pathogen/Mechanism | *In Vivo/In Vitro* | Effects | References |
| *C. jejuni* (NCTC 12744) disrupts epithelial barrier function | *in vivo* | TJ perturbation by increasing permeability | Awad et al.15 |
| *C. jejuni* 81116 induces occludin redistribution | *in vitro* | decrease in transepithelial electrical resistance | Dodson16 |
| *C. jejuni* 81–176 induces the translocation of commensal bacteria through a transcellular process mediated by lipid transporters | *in vivo* | promotes the translocation of non-invasive bacteria through the intestinal epithelium | Kalischuk et al.17 |
| *C. jejuni* RM1221 alters claudin-4 distribution | *in vitro* | Increases transepithelial permeability | Lamb-Rosteski et al.18 |
| *C. jejuni* (NCTC 12744) interferes with intracellular Ca2+ signaling | *in vivo* | alteration of the barrier and transport and facilitates the translocation of *E.coli* | Awad et al.19 |

**Figure 3.** Pathophysiology of *Campylobacter* in chickens: translocation via transcellular (a) and paracellular (b) pathways (adapted from 1)



**a**

**b**

**Figure 3b:** Paracellular transmigration of C. jejuni through tight junctions and adherens junctions of intestinal epithelial cells (adapted from 20)

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In experimental studies, BT has been widely reproduced, but results in clinical studies have been very limited. Evidence of mesenteric lymphatic contamination (and the role of IL-2) may be important for the demonstration of BT according to some authors15, and inconclusive for others, since it represents a normal immune response in serious situations21.

It has been seen that increased intestinal permeability causes a higher incidence of multi-organ failure (MOF).

Intestinal permeability and episodes of infection are two situations related to the severity of the injuries in the critically ill patient, but not consequential.

The set of measures aimed at reducing the intensity and duration of the injury, such as reducing periods of hemodynamic instability, the early use of vasoactive medication and the early administration of substrates, can reduce episodes of hypoperfusion (ischemia/repercussion), which in turn would decrease the extent of intestinal permeability and the time for its repair 22.

Anti-inflammatory medication reduces or blocks the proinflammatory response triggered by immune activation, as demonstrated by several studies, such as the one carried out with flavonoids, which induces a decrease in the production of nitric oxide synthase (NOS) and cyclooxygenase 2 (COX-2) both in vivo in rats as in cell line (BV-2 or Caco-2)23, 24.

***The concept that BT contributes to morbidity remains an attractive line of research*4.**

The role of the liver and lung in modulating the inflammatory response must be investigated. Studies should also be carried out on changes in colonic permeability, in the lymphatic pathway of BT in release of inflammatory mediators by mesenteric lymph nodes22.

That is, the intestinal barrier must be reestablished to limit the translocation of microorganisms capable of causing distant infections, sepsis or aggravating existing clinical problems with secondary infections.

There are several types of secretion apparatus in bacteria. Some use the type III for injecting virulence proteins (effectors) into the host cell and thus counteract innate immunity. The ribosomal protein S3 (RPS3) guides NF-κB subunits to specific κB sites and plays an important role in the innate response to bacterial infection25.

**What happens in other mucous membranes?**

The epithelium of the vaginal mucosa acts as a physical barrier and as an immunological mediator, providing the first defense against possible infections.(2)

Mucosal epithelia generally comprise multiple layers of rarely keratinized stratified squamous epithelium resting on a *lamina propria* where the apical layers lack tight junctions . and therefore different from what occurs in the intestinal epithelium.

These layers are permeable to water, soluble proteins, viruses, and penetrable by the vaginal microbiota, as well as cellular (e.g., CD4+ T cells and macrophages) and molecular mediators of the immune system (e.g., cytokines)

***This is permeability and the question: is it a translocation?*** If it constitutes a translocation, systemic pathologies should be observed from this mucosa.

The vagina and endocervix provide immunological defenses by conferring tolerance to microbes, maintaining epithelial integrity, and recruiting and supporting immune cells.

As the first line of immune defense, epithelial cells express pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), which respond to microbes or pathogen-associated molecular patterns (MAMPs/PAMPs) by secreting cytokines and chemokines, antimicrobial peptides and other molecules.

The proinflammatory response elicited by pathogens is normally required to control infections.

However, inflammation of the vaginal mucosa can promote the transmission of viral STIs, such as HIV, by compromising the integrity of the epithelium and by recruiting and activating HIV target cells.

Epithelial cell-derived immune mediators have critical roles in cell recruitment, immune regulation, and tissue repair

Given the intimate contact of the microbiota and its acid metabolites with the vaginal epithelium, it is important to study how these interactions modulate the immunity of these mucous membranes and whether this is enough to avoid a true translocation26.

The stability of the vaginal microbiota depends on several factors and we know that the bacteria of the vaginal microbiota, which normally maintain a pH <4.5, have the opportunity to migrate towards the uterus through the cervix since they are adjacent. The communication of microorganisms between these two sites is still unclear and the mechanisms underlying the modulation of the microbiota in the uterus and the induction of diseases when vaginal bacteria move to the upper reproductive system remains obscure27.

It can be assumed that, in addition to the canalicular route, there may be a true translocation through the tissues of the genital tract.

**Translocation across the outer membrane of Gram-negative bacteria**

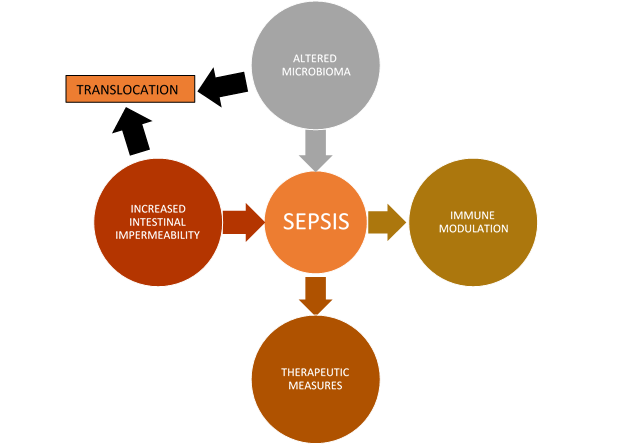
Until now we have talked about bacterial translocation through epithelia, but there is **another translocation and it is the one that occurs in Gram-negative bacteria through their external membrane**28.

**Clinical importance of bacterial translocation in the intestine** **in the initiation of sepsis and multiorgan failure (MOF)**

As we have already expressed, the intestinal mucosa provides a functional barrier between the microbiota microorganisms and the host. When this is altered, the passage of microorganisms to the lymph nodes and from there to the bloodstream can occur and systemic dissemination appears. Let us remember that sepsis is a potentially fatal organ dysfunction and is one of the main causes of MOF in critically ill patients29.

Both microorganisms and host factors can contribute to bacterial translocation and trigger sepsis.

**Figure 4.** Contribution of BT to sepsis and multiorganic failure



The figure 4 shows how the alteration of the microbiome caused by multiple factors such as the use of antimicrobials, unbalanced diet, immune alterations and other causes, can contribute to the increase in intestinal permeability that will allow microbial passage.

During the initial stage of sepsis, as demonstrated by Shimizu K et al (30), there is a decrease in *Bifidobacterium* and *Lactobacillus* spp, which are usually protective and modulate the normal intestinal microbiota. On the contrary, there is an increase in *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

**Antibiotics in sepsis have a double function that can be risky.** On the one hand, they contribute to eliminating the causative microorganisms, but they also accentuate the intestinal imbalance that increases intestinal permeability.

Azithromycin has been studied as an antibiotic that regulates the activity of the microbiota by reducing protein synthesis and biofilm formation.

In chronic inflammatory disorders, it exerts an immunomodulatory effect on epithelial cells and cells of the immune component through modulatory activity on the NF-κB inflammatory pathway, mucin release, expression of surface receptors, macrophages and autophagy31.

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| In summary we can say that in the pathogenesis of systemic processes such as sepsis, microorganisms and their virulence factors are as important as those dependent on the host. These findings provide new challenges and new targets for therapeutic management since treatment has not changed drastically in recent years and other strategies are required to reduce the morbidity and mortality caused by this pathology. |

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