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Ulcerative Colitis and Microorganisms

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1. Introduction

The gut, due to its anatomical and functional characteristics, forms the largest area of contact with the outside world. Unlike skin that acts as a defensive barrier, digestive and absorptive processes in the intestine require a certain amount of permeability. This facilitates and creates an optimal niche for the development of a large community of microorganisms that maintains, ideally, a commensal relationship with the host. This ecosystem, known as microbiota, is essential for the digestion of certain carbohydrates, the production and metabolism of nutrients necessary for life and for proper development and maturation of the immune system.

The aim of this chapter is to offer a thorough review of recent publications and scholarly work in order to explain, and somehow clarify, the always complex interaction between humans and microorganisms, as well as the implications that the later have in Ulcerative Colitis.

1.1 The human microbiota

Should we consider the number of microorganisms that live in the mucous linings of human beings, we should be considered merely as the base that supports and nourishes a large microbial ecosystem. Indeed, the total amount of bacteria that colonize our gut reaches about 100 trillion, while the number of cells in our body is no more than 10 trillion. The physiological and environmental differences of each part of the body determine the existence of many different niches, each with its unique microflora adapted to the nutritional resources, pH and presence of antibacterial substances. The capabilities inherent to the colonizing organisms such as the presence of pili or fimbriae which facilitate adherence to epithelial cells, the specific metabolic pathways that each genus is able to develop or the cell wall components that confer increased resistance to the environment are also vital.

The large intestine is by far the location with the greatest number of microorganisms which establish a symbiotic relationship that is broadly beneficial to the host. Over 98% of the microbiota that is found past the ileocaecal valve consists of strict anaerobes, outnumbering aerobic bacteria in a ratio of 1/1,000- 1/10,000. Numerous studies performed hitherto describe microbiota as having between 200 and 1,000 different species of bacteria in healthy subjects any given time, with horizontal transmission of genetic material between species. This means that there is great diversity among the microbiota of different people, and that there is no common core related to all humans, since no particular species is more than 1%

of the total. Only about 50-100 bacteria were found in most individuals regardless of their number. On the other hand, it has been observed that the changes that occur over the lifetime of a healthy person are minimal, the most dramatic being at the beginning of life, since initial colonization after birth until weaning, when the microbiota begins to transform and becomes gradually very similar to that of an adult. These changes are determined by the geographic location with their characteristic eating habits, by the type of birth (caesarean versus vaginal delivery), and the type of feeding after birth (breast vs. bottle). Eventually, the microbiota is composed mostly (> 90%) by bacteria of the genera *Bacteroides* and *Bifidobacterium*, and the rest by *Eubacterium*, *Lactobacillus*, coliforms, *Streptococcus*, *Clostridium*, and a variable number of yeasts.

As an indirect consequence of the large number and variety of microorganisms, the balance achieved between the components of the microbiota and the competition for nutritional resources exert a protective effect on the host by preventing colonization and proliferation of potential pathogens.

This huge set of microorganisms contains approximately three million of unique genes, i.e. 150 times more genes than our own genome. This metagenome or microbiome is essential for proper homeostasis and good health, as it provides metabolic pathways that allow implementations that we would be unable to perform without the assistance of the intestinal microbiota, like digestion of some sugars, production of vitamins or removal of hydrogen in the distal intestine. Recent studies have demonstrated a common set of around 500,000 unique genes shared by the microbiota of different subjects, in other words, a common metagenome. For all this, it has been suggested that the microbiota serves as an organ for human beings (Zhu et al., 2010).

In addition to these functions, the intestinal epithelium requires intestinal flora and the substances excreted by it in order to develop properly, given that these metabolic by-products promote growth and epithelial differentiation.

1.2 Microbiota and immune system

The intestinal lumen is comparable to a battlefield; there is a continuous struggle even when the host does not show any type of pathology. Indeed, the intestinal epithelium is extensively infiltrated by lymphocytes with defensive functions. More profoundly, in the lamina propria, dendritic cells are responsible for monitoring the presence of pathogenic antigens and activate surrounding lymphocytes if necessary. It has been established that there is a continuous exchange of information and regulation between epithelial and immune cells present in the intestinal mucosa, mainly through Toll-like receptors on the cell membrane and the Nucleotide-binding oligomerization domains in the cell cytosol, but also, by other substances that need further investigation so their functioning is utterly understood. The end result of this cross-talk is the development and maturation of lymphocytes Th 1, Th 2, Th 17 (a type of lymphocyte abundant in the intestine but scarce elsewhere in the body), regulatory T cells, IgA-secreting plasma cells and the release into the intestinal lumen of bactericidal substance like the defensins (Tanoue et al., 2010; Sansonetti , 2010). All this leads to the subsequent inflammatory response or tolerance reaction; but also to systemic immune defence maturation, as neutrophils, in the absence of intestinal flora, lack the necessary priming to be effective (Takeshi et al., 2010).

Several studies have shown that a plural and abundant microbiota is essential to maintain a balance between defensive immune responses and tolerance towards commensal bacteria

(Salzman, 2010; Tanoue et al., 2010; Lidar et al., 2009). But some bacteria seem to have a more significant role than others:

- Segmented Filamentous Bacteria, a Gram-positive bacteria related to *Clostridium*, also known as *Candidatus arthromitus*, is capable by itself of stimulating the differentiation of Th 17 cells, which by producing IL-17 attracts neutrophils and macrophages to the gut mucosa. But on the other hand, these bacteria also stimulate the IgA-producing plasma cells, an antibody that blocks bacterial antigens in the intestinal lumen and prevents the possible infiltration and local inflammation while regulating the ecological balance of the commensal flora. This bacterium is not found in the mucus above the epithelial layer, instead, it attaches intimately to the epithelial cells (Takeshi et al., 2010).
- A Gram-negative bacterium, *Bacteroides thetaiotaomicron*, whose presence down-regulates inflammation by activation of the nuclear export of RelA, subunit of Nuclear Factor kappa B, a substance with inflammatory properties that enhances gene transcription when located inside the nucleus (Takeshi et al., 2010). This protein complex is related to the receptor responsible for the anti-inflammatory properties of 5-aminosalicylic acid.
- Two species of Gram-positive rods, *Lactobacillus* spp. and *Bifidobacterium* spp., and a Gram-negative rod, *Bacteroides fragilis*, induce the maturation of regulatory T cells in the lamina propria, stimulating the production of IL-10, an immunosuppressive interleukin (Danase, 2011; Takeshi et al., 2010).

1.3 Microorganisms as causative agents in ulcerative colitis

Since the description of inflammatory bowel disease as an independent clinical entity, attempts have been made to associate it with a particular microorganism as an aetiological agent, as happened with *Helycobacter pylori* and gastric ulcer. Several studies have shown some involvement of a number of pathogens in the onset of Ulcerative Colitis flares, but to date, no study has concluded a positive relation between a microorganism and this disease:

- *Cytomegalovirus* and *Clostridium difficile* are able to develop a condition similar to Ulcerative Colitis, precipitate a relapse or worsen the course (Lawlor et al., 2010; Sonnenberg, 2010). In addition, it has been found a linear geographical relationship between Ulcerative Colitis cases and colitis due to *C. difficile*.
- *Escherichia coli*, *Campylobacter jejuni*, *Salomonella enterica* and *Shigella* spp. have been associated with this disease because of their ability to disrupt the intestinal epithelium, promote a displacement of commensal flora and trigger an excessive inflammatory response (Gasull et al., 2007; Phalipon & Sansonetti, 2003; Siegel et al.,2005).
- *Mycobacterium avium paratuberculosis* has been associated with Crohn's disease, but some studies suggest it may have some relevance in patients with impaired intracellular bacteria destruction by a continuous augmented state of inflammation.

The most recent lines of research point to the dysbiosis as the cause of up-regulated inflammation. Several studies have discovered that the microbiota of Ulcerative Colitis patients is significantly different from that of healthy controls (Danase, 2011; Scarpa et al., 2011). Although, a causal relationship was not establish because these changes in the microbiota could be either the cause or the consequence of the alterations observed in the intestinal epithelium. Thus far, this hypothesis is to some extent supported by some other studies that point toward the transplant of healthy microbiota as a solution to the disease, with very promising results (Do et al., 2010; Kahn et al., 2011; Ng et al., 2010).

The main theories that try to explain Ulcerative Colitis aetiopathogenesis by means of an infectious agent can be summarized as follows:

- Dysbiosis hypothesis which implies that an imbalance between beneficial versus detrimental resident intestinal bacterial species may incite chronic inflammatory responses (Friswell et al. 2010).
- Persistent infection hypothesis which proposes that Ulcerative Colitis may arise as a result of persistent infection with enteric pathogens (Khan et al., 2011).
- Luminal antigen translocation hypothesis which indicates that defects in the intestinal barrier function or impaired mucosal clearance facilitate increased translocation of luminal antigens, including intestinal commensal bacteria, across the intestinal barrier where they may prime mucosal immune responses that lead to loss of immunological tolerance toward the luminal antigens (Fava & Danes, 2011).
- Hygiene hypothesis which postulates that helminthic colonization of the gut shifts immune response towards Th 2 and Th 3, i.e., humoural and regulatory pathways. Thus, prevention of parasitic helminths by means of improved hygiene, may be one factor leading to Ulcerative Colitis through a excessive Th 1 immune response (Weinstock & Elliot, 2008).

In summary, the relationship between the microbiota and its host is very complex and studies to date suggest that the aetiology of Ulcerative Colitis is equally complex. Beyond the characteristics of the patient, a myriad of microorganisms capable of modulating the inflammatory response come into play. To find a single responsible among them challenges conventional models of infectious disease, and small variations in the concentration or location of commensal microorganisms may be the key.

2. Immunosuppressive therapy in ulcerative colitis

Immunosuppressive drugs are used increasingly and earlier for the treatment of Ulcerative Colitis. This implies an important risk factor for these patients since they become partially defenceless against possible microbiological pathogens. Moreover, the degree of immunosuppression may be exacerbated by factors such as older age (Cottone et al., 2010), severity of symptoms and comorbidities, recent surgery or malnutrition. In addition, more severe conditions or those that do not respond to treatment involve a greater degree of immunosuppression due to the fact that the combination of two or more drugs is required (Koutroubakis, 2010). Table 1 summarizes immunosupression impairments and the most common microorganisms associated.

2.1 Corticosteroids

Corticosteroids suppress the Th 1 response by inhibiting the transcription of genes encoding pro-inflammatory interleukins, chiefly IL-2; thereby reducing the proliferation and activation of T cells. However, the Th 2 response is also altered, given that B lymphocytes express fewer IL-2 receptors and consequently, there is a reduction in the production of antibodies (Elenkov, 2004).

This reduction in pro-inflammatory cytokines tampers the chemotactic migration of neutrophils to the inflammatory focus, diminishing also its ability to adhere and its phagocytic function.

Phagocytosis of opsonised microorganisms is also disturbed as the expression of FC receptors in macrophages is down-regulated too (Franchimont, 2004).

Immune response impairment	Microorganisms
Neutropenia	*Staphylococcus aureus*, Gram-negative rods, *Aspergillus*, *Candida*
Phagocytic function	*Streptococcus pneumoniae*, *Haemophilus influenzae*
Chemotaxis	*Sataphylococcus aureus*, *Mucor*
T lymphocytes (Th 1 response)	*Mycobacterium*, *Nocardia*, *Legionella*, *Aspergillus*, *Candida*, *Cryptococcus neoformans*, *Pneumocystis jiroveci*, Cytomegalovirus, *Herpes simplex virus*, *Varicella-Zoster virus*, respiratory viruses, *Strongyloides*, *Toxoplasma*, *Leishmania*
B lymphocytes (Th 2 response)	*Staphylococcus aureus* , *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pneumocystis jiroveci*, *Enterobacteriaceae*

Table 1. Immune System impairment and most common associated microorganisms

2.2 Purine analogues: Azathioprine and 6-mercaptopurine

Azathioprine is a pro-drug that is converted into 6-mercaptopurine by human metabolism. 6-thioguanine nucleotides, the resulting metabolites, accumulate in tissues where they exert their cytotoxic effects by inhibiting purine synthesis and consequently, DNA and RNA. Therefore, a decrease in the production of T and B lymphocytes is achieved; they also promote apoptosis of activated T lymphocytes. Thus, both the Th 1 and Th 2 immune responses are impaired (Sahasranaman et al., 2008; Tiede et al. 2003).

The therapeutic effects of these drugs are achieved within 2-3 months from administration, and duration of treatment depends on adverse effects and patient's tolerance, so that the time period of immunosuppression that the patient will face can be considerable (Maltzman & Koretzky, 2003).

2.3 Calcineurin inhibitors: Tacrolimus and cyclosporine

Calcineurin inhibitors decrease the cellular immune response by inhibiting T-dependent antibody production and several cytokines, chiefly IL-2 but also IL-3, IL-4, IL-5, Tumour Necrosis Factor alpha and beta. A reduction in the number of activated T lymphocytes is achieved with a significant decrease in the Th 1 response. Numerous studies have shown that calcineurin inhibitors can be effective for short-term clinical improvement in patients with refractory disease, but also could be used in situations that require an early and powerful response as in fulminant Ulcerative Colitis. The use of these drugs requires careful assessment of risks and benefits, and close surveillance of adverse effects.

2.4 Biological therapies

Biological drugs block the action of Tumour Necrosis Factor alpha, a pro-inflammatory cytokine, and promote apoptosis of activated T cells, inhibiting Th 1 immune response and local inflammation. Monoclonal antibodies anti-Tumour Necrosis Factor alpha mechanism

of action includes the neutralization of both soluble and transmembrane portion of this molecule; also neutralizes Tumour Necrosis Factor alpha-producing (Sandborn, 2010; Smolen, 2011). Monoclonal antibodies anti-Tumour Necrosis Factor alpha were first used in the treatment of Crohn's disease but have been used successfully in severe, unresponsive to treatment Ulcerative Colitis or as rescue therapy (Hoentjen & van Bodegraven, 2009; Lees et al. 2007).

3. Ulcerative colitis and infection

Patients suffering from Ulcerative Colitis may develop infections just like any healthy person. However, there are a number of situations and conditions that make these infections critical; hence they must be addressed as soon as possible in order to avoid unwanted or unexpected complications.

On the one hand, these patients present an altered immunity, which predisposes them to face a number of opportunistic microorganisms that seldom cause disease in healthy people. Second, they are challenged with infections from typical and common pathogens, but in their state of immunosuppression this microorganisms may have a more aggressive course and a worse prognosis (Harbaum et al., 2010; Nagasaki et al., 2010). Local disorders in the digestive tract result in another source for potential complications, allowing the displacement of bacteria from the normal microbiota which are harmless otherwise (Sahuquillo-Arce et al., 2008). Finally, these patients may need surgical treatment, aggravating local immunosuppression as well as increasing susceptibility to infection (Scarpa et al. 2011).

Although large studies of patients with Ulcerative Colitis show a low prevalence of opportunistic infections, there are numerous articles about specific cases reports or short series of such infections, which confirm the severity that these infections can acquired in Ulcerative Colitis patients (Aoyagi et al., 1999; Chuang et al., 2010; Escher et al., 2010; Kudo et al., 2010; Rodríguez-Peláez et al., 2010).

An early suspicion of these complications is essential to enhance prognosis in this group of patients, so physicians must improve their knowledge and be aware about these infections. The management of immunocompromised patient is difficult; therefore, an early diagnosis and a prompt establishment of an adequate therapeutic regimen remain the two fundamental pillars that will determine the course and outcome of infection.

3.1 Management of the patient before infection

The infectious and immunological history of the patient should be defined when Ulcerative Colitis is first diagnosed, and whenever possible, before starting immunosuppressive therapy (Viguet et al., 2008). This will require a thorough knowledge about the patient and a systematic record of every detail (Rahier et al., 2009) in order to assess:

- The history of past infections and travels to areas with endemic infections, even if those travels are distant in time.
- A methodical review of systems, including regular dental and gynaecological evaluation.
- A serological screening to evaluate the immune status against the following viruses: rubella, measles, mumps, *Varicella-Zoster*, *Cytomegalovirus*, *Epstein-Barr*, hepatitis B, hepatitis C, HIV, poliovirus; and against tetanus, diphtheria and *Toxoplasma gondii*.

- Any contact with *Mycobacterium tuberculosis* by means of a chest X-ray and tuberculin skin test (with a booster if negative) or interferon-gamma release assays (Schoepfer et al. 2009), in patients who have not suffered from tuberculosis in the past. These tests should always be performed, but they are mandatory before initiating therapy with anti-Tumour Necrosis Factor alpha drugs.

The use of vaccines is another important step in managing these patients. Besides the recommended vaccinations for the general population, the following should also be considered (Aberra & Lichtenstein, 2005):

- *Varicella-Zoster* in seronegative patients, preferably before starting immunosuppressive therapy since this vaccine contains attenuated viruses. Passive immunization should be considered in seronegative high risk immunosupressed patients after exposure to the virus.
- Pneumococcal vaccination with booster after 3-5 years.
- Hepatitis B, which may require a booster due to immunosuppressive therapy.
- *Influenzavirus* annually.
- *Papillomavirus* in young women, according to national guidelines.
- Travel vaccines; the practitioner must bear in mind that vaccines which contain live viruses should be avoided.

3.2 Management of patients with suspicion of infection

The diagnosis of infection begins with a thorough anamnesis, which should reflect the degree and time length of immunosuppression of the patient, concomitant diseases, use of antineoplastic or antimicrobial treatments, presence of catheters, previous infections and any possible exposure to nosocomial, occupational or unusual pathogens, such as travels to endemic areas of histoplasmosis, coccidioidomycosis, etc. These factors will be crucial in establishing an empirical treatment (Gómez Gómez & Gobernado, 2011).

A systematic physical examination will be the next step. Given that very often the symptoms that immunosuppressed patients present are scarce or absent, and that fever can be the only one, the physician's attitude should be aggressive in order to locate the source of infection. To describe all the necessary tests for the diagnosis of these patients is beyond the scope of this chapter, but there are a number of important considerations that must be taken into account:

- A CT yields better performance than X-ray in pulmonary infections (Sahuquillo-Arce & Menéndez-Villanueva, 2010).
- Infections of the digestive tract can be misleading and may be interpreted as an Ulcerative Colitis relapse. It may require tissue biopsy for microbiological and histopathological studies, as well as all the usual non-invasive tests such as stool culture, study of parasites or detection of *C. difficile* toxins.
- Central nervous system infections may require a MRI or even a biopsy, especially if space-occupying lesions are observed.

3.3 Opportunistic microorganisms and common infectious agents

The following is a brief description of the most frequent opportunistic microorganisms found in immunosuppressed patients; but we will also discuss about typical pathogens that may have a ominous prognosis chiefly due to the poor immune system of the host (Murray et al., 2003; Rahier et al., 2009).

3.3.1 Bacteria

These microorganisms constitute the commonest group of infectious agents in both gastrointestinal and other systems infections. Three different groups can be distinguished:

- Nosocomial infections by pathogens that may present antimicrobial multi-resistance such as *Pseudomonas aeruginosa*.
- Community-acquired microorganisms which, in these patients, may be more devastating and with greater tendency to spread, such as *Streptococcus pneumoniae*.
- Endogenous microorganisms which were under control before immunosuppression (Qu et al., 2009).

The following are the most relevant of bacterial pathogens, both common and opportunistic. Recommended treatments for opportunistic and common bacterial pathogens are shown in table 2.

- *Pseudomonas aeruginosa* is a Gram-negative rod found in nature, which colonizes the hospital setting. Among the many virulence factors it has, adhesion to the epithelium, toxin production, biofilm formation and quorum sensing are essential for its great adaptation and survivability. This bacterium is associated with nosocomial infections, mechanical ventilation infection, wound infections and community-acquired pneumonia, chiefly in immunosuppressed patients who have been in contact with the hospital environment. The most challenging infection is pneumonia, as it is rapidly progressive and radiographically indistinguishable from other pyogenic infections. Patients present with productive cough, fever, dyspnoea, micro-abscesses and focal haemorrhage. Mortality is very high among immunosuppressed patients because of its rapid course, it reaches up to 40%, and this ratio increases if there is bacteraemia. Antimicrobial treatment is problematic because of its intrinsic resistance to many broad-spectrum antibiotics, especially considering that hospital-acquired strains present a greater number of resistances due to selection in a hostile antimicrobial environment.
- *Staphylococcus aureus* is a Gram-positive coccus that colonizes the skin and is a major nosocomial pathogen. Between 10-40% of people are nasal carriers. It has several virulence factors, including toxin production and antibiotic resistance. Methicillin resistant strains (MRSA) vary in proportion between countries (2% in the Netherlands, 28% in Spain, 54% in Portugal). It is more frequent in hospitals and health-care associated settings. This pathogen is very versatile and can produce different clinical syndromes ranging from conditions like skin or surgical wound infection to bacteraemia, meningitis, or a highly aggressive type of pneumonia that occurs after an Influenzavirus infection.
- *Streptococcus pneumoniae* is a Gram-positive coccus that can be found in the nasopharynx of healthy carriers. It is an important agent of community-acquired pneumonia, but it can also emerge as sinusitis, otitis, bacteraemia or meningitis.
- *Nocardia* spp. is a Gram-positive partially acid-fast branched rod. Ubiquitous in the environment, it is acquired primarily by inhalation. Pulmonary nocardiosis supposes over 40% of all forms, and *Nocardia asteroides complex* is responsible for up to 90%. It can follow an acute course, but chronic forms are more likely, presenting as a recurrent suppurative process with or without abscess formation, cavitation, or fistula. Other types include surgical wound infection or disseminated forms that can affect the central nervous system. The prognosis depends on the patient's immunosuppression level and bacterial dissemination.

Microorganism	Treatment	Alternative treatment
Empirical treatment	Amikacin + piperacillin-tazobactam, imipenem or meropenem	Empirical treatment should be adapted to more likely microoganisms, local antimicrobial resistance patterns and prior infections.
Pseudomonas aeruginosa	Ceftazidime; cefepime; aztreonam; Piperacillin-tazobactam or carbapenem Associate aminoglycoside + ciprofloxacin or colistin in severe systemic infection.	
Staphylococcus aureus	Methicilin susceptible *S. aureus*: Cloxacillin + gentamicin. Methicilin resistant *S. aureus*: glycopeptide. If vancomycin MIC is > 1 mg/l then linezolid or daptomycin.	MSSA: amoxicillin-clavulanate; ampicillin-sulbactam; 1st-2nd generation cephalosporins; clindamycin; levofloxacin or moxifloxacin. MRSA: Linezolid; tigecycline or minocycline
Listeria monocytogenes	Ampicillin alone or associated with gentamicin	Cotrimoxazole alone or associated with ampicillin or rifampicin. Clarithromycin, doxycycline, rifampicin, moxifloxacin, levofloxacin, meropenem, linezolid and vancomycin are also active
Nocardia spp.	Cotrimoxazole + amikacin, cefotaxime, ceftriaxone or imipenem.	Linezolid; levofloxacin; moxifloxacin, tigecycline; doxycycline; minocycline or amoxicillin-clavulanate
Stenotrophomonas maltophilia	Cotrimoxazole + minocycline, tigecycline, moxifloxacin, levofloxacin, aztreonam, ceftazidime, rifampicin or colistin.	Tigecycline; fluorquinolone or ceftazidime
Acinetobacter baumannii	Imipenem + sulbactam or amikacin	Associate two or more of the following according to antibiogram: Tigecycline, colistin, doripenem, ceftazidime, doxycycline, minocycline piperacillin-tazobactam, tobramycin, rifampicin and levofloxacin

Microorganism	Treatment	Alternative treatment
Enterobacter spp.	Carbapenem or fluoroquinolone	Cefepime; Piperacillin-tazobactam; aminoglycosides; tigecycline; cotrimoxazole or colistin.
M. tuberculosis	Isoniazid+rifampicin+pyrazinamide for two months, then 4 months on isoniazid + rifampicin. Add ethambutol the first two months if high suspicion of Multi-drug resistance.	Ethambutol or streptomycin instead of pyrazinamide. Ethambutol + levofloxacin or moxifloxacin instead of isoniazid. isoniazida + pyrazinamide + ethambutol for 12 months if rifampicin is not possible. Levofloxacin o moxifloxacin can be added the first two months.
M. kansasii	Isoniazid + rifampicin + ethambutol	Amikacin; clarithromycin; streptomycin; fluoroquinolone or ethambutol if rifampicin resistance. Sulfamethoxazole; linezolid or cycloserine can be used instead of ethambutol
M. avium complex	Macrolides (azithromycin or clarithromycin) + ethambutol + rifampicin or rifabutin three times a week, or dialy if cavitation or dissemination	Streptomycin or amikacin + ethambutol + rifampicin or ribabutin if macrolide resistance. Consider addition of moxifloxacin. Consider surgical excision in antimicrobial therapy failure.
M. xenopi	Isoniazid + rifampicin + ethambutol and/or streptomycin	

Table 2. Recommended treatments for bacterial pathogens in immunocompromised patients (Mensa et al., 2011)

- *Listeria monocytogenes* is a Gram-positive rod widely distributed in the environment, circumstance that facilitates its incorporation into food production and processing. Moreover, it can grow at 4ºC and become a food-borne disease. Typically, it causes meningitis, encephalitis and sepsis in cell-mediated immunocompromised patients. It has also been linked to intestinal lesions in Ulcerative Colitis patients.
- *Legionella pneumophila* is an intracellular Gram-negative rod widely distributed in aquatic environments. Pneumonia by this pathogen in immunocompromised patients can be severe and life threatening. Corticosteroid treatment is a major risk factor.
- Nonfermentative Gram-negative bacilli and *Enterobacteriaceae* such as *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* or *Enterobacter* spp. are increasingly becoming relevant as nosocomial pathogens which endanger the lives of patients during the

immediate postoperative period. Furthermore, these bacteria have multiple acquired and intrinsic antimicrobial resistances that complicate treatment.

Microorganism	**Treatment**	**Alternative treatment**
Escherichia coli	Aminopenicillin + betalactamase inhibitor; 2nd- 3rd generation cephalosporin or aztreonam. Fosfomycin or nitrofurantoin can be used in urinary tract infections. Enteritis: fluoroquinolone or cotrimoxazole (Patients with enterohaemorrhagic *E. coli* who are treated can develop HUS)	Carbapemen; tygecycline or colistina if Extended-Spectrum Betalactamase *E.coli*.
Shigella spp.	Ciprofloxacin	Cotrimoxazole, ceftriaxone, cefixime or azithromycin
Salmonella enterica	Typhoid fever: ceftriaxone; cefixime or azithromycin. Enteritis: fluoroquinolone. Bacteraemia: 3rd generation cephalosporin; aztreonam or ciprofloxacin for a month.	Typhoid fever: ciprofloxacin; aminopenicillin; chloramphenicol or cotrimoxazole. Bacteraemia: Aminopenicillin.
Yersinia spp. (other than *Y. pestis*)	Ciprofloxacin 3rd generation cephalosporin + gentamicin for systemic infection	Doxycycline or Cotrimoxazole
Campilobacter jejuni	Erithromycin or azithromycin	Imipenem or aminopenicillin + betalactamase inhibitor
Clostridium difficile	Mild course: metronidazole p.o. More aggressive forms: vancomycin Consider association with metronidazole i.v. or gammaglobulin in severe forms	Teicoplanin; fusidic acid; nitazoxanide; rifampicin p.o. or tygecycline i.v.

Table 3. Recommended treatments for enteric bacterial pathogens in immunocompromised patients (Mensa et al., 2011)

- *Mycobacterium tuberculosis* presents a low incidence around 2%, despite the fact that the risk of active tuberculosis in immunosuppressed patients is 30-50 times higher than in the general population. The main risk factor is reactivation of latent infection, thus

screening for tuberculosis before initiating therapy is required, in particular in those who will receive anti-Tumour Necrosis Factor alpha antibodies. In immunocompromised patients, *M. tuberculosis* is often more rapidly progressive and disseminates more frequently. Multi-drug resistant isolates are a worldwide concern that jeopardizes the final outcome.

- Other mycobacteria such as *M. kansasii*, *M. avium complex* or *M. xenopi*, can appear as opportunistic pathogens primarily affecting the lung. They all have, in immunocompromised patients, an incidence similar to that of *M. tuberculosis*. Diagnosis is difficult because it requires the presence of symptoms, isolation of the microorganism in at least three respiratory samples and radiological signs or response to antimicrobial treatment.

Recommended treatments for enteric bacterial pathogens are shown in table 3.

- *Campylobacter jejuni* is a Gram-negative curve-shaped rod and the most common cause of community-acquired acute bacterial diarrhoea. It is normally accompanied by fever and abdominal pain. Campylobacter diarrhoea may contain blood or mucous. The majority of patients with Campylobacter diarrhoea have some component of segmental colitis, usually beginning in the small bowel and progressing distally to the caecum and colon.
- *Shigella* spp. is a Gram-negative rod belonging to the *Enterobacteriaceae* family. It causes bacillary dysentery in humans, an acute recto-colitis that reflects the capacity of the microorganism to invade, and cause the inflammatory destruction of the intestinal epithelium barrier, which will disrupt the homeostatic balance that protects the gut against inflammation in the presence of its commensal microbiota. The activation of pro-inflammatory molecules can initiate an Ulcerative Colitis-like process or trigger a relapse (Sansonetti, 2006).
- Adherent and invasive *Escherichia coli*, *Salmonella enterica* and *Yersinia* spp. all have the same potential as Shigella spp. to cause disease, although some serotypes of the *Escherichia* genus seem to have a healing capacity in Ulcerative Colitis patients, similar to that of 5-ASA drugs, by restoring mucosal homeostasis (Sartor & Muelhbauer, 2007). All three can cause life-threatening disease, but *E. coli* is much more frequent and versatile.
- *Clostridium difficile* is a Gram-positive anaerobic rod that produces two toxins -named A and B- with cytopathic effects. It has been associated with Ulcerative Colitis onset and can also worsen its clinical manifestations or mimic an acute flare. Unlike healthy persons, colitis in immunocompromised patients is mostly community-acquired.

3.3.2 Fungi

This group represents a constellation of opportunistic pathogens associated with high mortality. One of the main reasons is that they are often overlooked due to its difficult and intricate diagnosis. Recommended treatments for fungi are shown in table 4.

- *Aspergillus* spp. is a filamentous fungus present in the environment and generates high concentrations of spores in the air. It is not a common pathogen in healthy people since the inhaled spores are eliminated by the mucociliary apparatus of the respiratory tract, alveolar macrophages or neutrophils. But, it poses a serious challenge to neutropenic patients. Neutropenia and impaired cellular immunity are predisposing factors for

colonization and development of invasive pulmonary aspergillosis. The most frequently isolated species in humans are *A. fumigatus* (73%) and *A. flavus* (15%), followed to a lesser extent by A. niger, *A. terreus*, and so on. The incidence of this disease in immunosuppressed patients varies between 1-15%, and although there are limited data in patients with Ulcerative Colitis, case reports do exist that reflect its severity. The classic symptoms of invasive pulmonary aspergillosis are dyspnoea, chest pain and haemoptysis, even though 25% of patients may be asymptomatic at the time of diagnosis. A chest radiograph may be normal in up to 10% of cases, so CT is essential for diagnosis. Initially, one or more nodules with or without cavitation are detected. The presence of halo sign indicates vascular invasion by the microorganism, but other fungi such as *Fusarium* or diseases such as carcinomatous metastases can produce similar patterns. The aetiological diagnosis is based on direct examination and culture of non-invasive or invasive respiratory specimens such as sputum, bronchial aspirate or bronchoalveolar lavage, and the detection in blood or bronchoalveolar lavage of DNA or galactomannan, an antigen from the cell-wall of *Aspergillus*. Treatment is based on the administration of antifungals, the reconstitution of the immune status and surgery if it presents with severe haemoptysis, persistence of the organism despite treatment, or committed major vascular structures.

- *Pneumocystis jiroveci* is a non-filamentous fungus that colonizes the respiratory epithelium of humans and is transmitted by air from person to person. Recent studies suggest that the reservoir comprises young children and immunocompromised patients. In all cases, over 90% of patients have received continued treatment with corticosteroids. The typical presentation is the emergence of non-productive cough, fever, dyspnoea and tachypnoea in a one-week period time. X-ray shows a bilateral interstitial pattern, but may be normal in up to 20% of cases, CT being more sensitive. The most informative samples for diagnosis are the bronchoalveolar lavage and transbronchial biopsy, but induced sputum, nasopharyngeal washings or biopsies are also useful. Prophylaxis is not as clear as in HIV-positive patients, but is recommended in subjects who have received prolonged treatment with corticosteroids, or who have received anti-T cell therapy, those suffering from a prolonged neutropenia or have a CMV lung infection, and those with prior P. jiroveci or other opportunistic pathogens pneumonia.
- *Cryptococcus neoformans* is a yeast widely distributed in nature which is acquired by inhaling small dried forms of the microorganism. In immunosuppressed patients, it is capable of a rapidly progressive pulmonary infection with spread to other organs, with great predilection for central nervous system. The most common symptoms are fever, pleurisy, dyspnoea, chronic cough, haemoptysis and weight loss. Neurological manifestations such as sub-acute meningitis with possible development of hydrocephalus may precede pulmonary symptoms. Chest X-rays shows calcified nodules, bilateral infiltrates and hilar or mediastinal lymphadenopathy, cavitation and pleural effusion may also be observed. The aetiological diagnosis is done through the vision of encapsulated yeasts in respiratory samples or cerebrospinal fluid, cultivation and identification by biochemical tests. Detection and titration of capsular antigen in cerebrospinal fluid, blood or respiratory specimens facilitate an early diagnosis, but it is also useful to acknowledge the disease prognosis and progression.

Prophylaxis with fluconazole is not recommended because of the low incidence of this disease.

- *Candida* spp. is a yeast that frequently colonizes the respiratory and gastrointestinal tracts of immunosuppressed patients or of those who have received broad spectrum antibiotics. It seldom causes disease but it may arise as oral mucositis, colonization of catheters and surgical wounds, and even as haematogenous dissemination. Diagnosis may be difficult in some cases because it is necessary to distinguish between colonization and infection. Prophylaxis with fluconazole in different immunocompromised patients has led to increasing numbers of antifungal resistant strains of Candida other than *C. albicans*, such as *C. glabrata* or *C. krusei*.
- *Histoplasma capsulatum* is endemic along the Ohio, Mississippi and St. Lawrence rivers, but it can be found throughout the world. Histoplasmosis can reactivate years after primary infection and may mimic tuberculosis or neoplastic disease chiefly in the nervous central system and mucocutaneous surfaces.

Microorganism	**Treatment**	**Alternative treatment**
Empirical	Caspofungin or voriconazole	Amphotericin B lipid formulation
Aspergillus spp.	Voriconazole Combination with equinocandine is recommended Withholding immunosuppressive treatment and surgical excision should be considered	Caspofungin; amphotericin B lipid formulation or the combination of both.
Pneumocystis jiroveci	Cotrimoxazole	Pentamidin; clindamycin + primaquine; dapsone + trimethoprim; atovaquone 750 mg/8 h.
Cryptococcus neoformans	Amphotericin B + flucytosine	Fluconazole + flucytosine
Candida spp.	Equinocandine (except for *C. parapsilosis* and *C. guilliermondii*); fluconazole (except for *C. krusei* or *C. glabrata*)	Voriconazole or amphotericin

Table 4. Recommended treatments for fungal pathogens in immunocompromised patients (Mensa et al., 2011)

3.3.3 Viruses

Viruses are a group of pathogens whose incidence is increasing and may have a high morbidity and mortality. Disease in these patients may be community-acquired, but reactivation of latent viruses such as Herpesviridae is more characteristic and challenging. Recommended treatments for common viruses are shown in table 5.

- *Cytomegalovirus* is a herpes virus that remains in a latent form after primary infection. The disease is acquired by infection from another person or by reactivation after immunosuppressive therapy. CMV colitis can imitate an Ulcerative Colitis flare. Symptoms range from fever and abdominal pain to haemorrhagic diarrhoea or fulminant colitis. Moreover, it has been associated with steroid-resistant Ulcerative Colitis (Ayre et al., 2009). Pneumonitis is also a major complication; radiologically, it shows interstitial or bilateral reticulonodular infiltrates. CT shows bronchial wall thickening and ground-glass opacification. In addition to infectious conditions, CMV produces local immunosuppression that promotes super-infection with other opportunistic pathogens. The presence of CMV in the lung is a risk factor for infection with *Aspergillus* or *Pneumocystis jiroveci*. The etiological diagnosis is complicated by the presence of co-infection and similarity with other pathogens. Interestingly, the histopathological detection of CMV means infection, but not necessarily disease. The most predictive diagnosis is achieved with the detection of CMV in blood either by cell cultures (shell vial + immunofluorescence staining), detection of pp65 antigen in peripheral blood leukocytes, or detection of viral load with molecular biology techniques (PCR, real-time PCR).

Microorganism	**Treatment**	**Alternative treatment**
Citomegalovirus	Ganciclovir	Foscarnet or cidofovir
Varicella-Zoster virus	Valaciclovir; acyclovir or famciclovir	Foscarnet
Herpes simplex virus	Acyclovir	Foscarnet or cidofovir
Herpes 8 virus	Unknown	Foscarnet; cidofovir; adefovir; valaciclovir or ganciclovir
Epstein-Barr virus	Acyclovir or ganciclovir	
Respiratory sincitial virus	Inhaled ribavirin Consider association with palivizumab	
Influenzavirus	Oseltamivir or zanamivir	Amantadine or ribavirin (in severe pneumonia by B or C serotypes)

Table 5. Recommended treatments for viral pathogens in immunocompromised patients (Mensa et al., 2011)

- *Respiratory syncytial virus* is a seasonal pathogen that affects mostly in winter and spring. It may cause pneumonitis on its own or alonside other opportunistic microorganisms with similar clinical and radiological findings (CMV, *P. jiroveci*). Thus, suspicion is essential for diagnosis. Prevention is the best therapeutic tool because, although there are treatments with ribavirin or monoclonal antibodies, the results are yet inconclusive.

- *Herpes simplex virus*, immunosuppressed patients frequently develop symptomatic HSV disease which can be life-threatening. Undoubtedly, disseminated HSV with pulmonary, hepatic, colonic or brain involvement have a very high mortality rate. Early treatment reduces mortality and morbidity.
- *Varicella-Zoster virus* primary infection in immunocompromised patients can develop pneumonia or encephalic complications. Reactivation of the virus presents the risk of disseminated zoster, with mortality rates similar to those for varicella.
- *Epstein-Barr virus* can reactivate in patients on immunosuppressive therapy and, although the clinical relevance has not yet been established, its capability to produce lymphomas demands careful attention. Cessation of immunosuppressive agents often leads to lymphoma spontaneous regression.
- *Herpes* 8 is not a very common pathogen, although colonic Kaposi's sarcoma that required total colectomy has been described in an Ulcerative Colitis patient under immunosuppressive therapy.
- There is little evidence about **Hepatitis C virus** and Ulcerative Colitis, but immunotherapy does not seem to have any adverse effect on its course. Nevertheless, liver function and viraemia must be monitored as well as patient's immunosuppression level in order to make a decision on treatment.
- Corticosteroids and anti-Tumour Necrosis Factor alpha appear to have a deleterious effect on **Hepatitis B virus**-positive patients. Consequently, prophylactic antiviral treatment should be started prior to immunosuppressive therapy.
- **HIV**-positive patients on immunosuppressive therapy should be closely observed due to their underlaying condition. Although the interactions between these diseases fall beyond the scope of this chapter, doctors should be very cautious and suspend immunosuppressive therapy if concomitant opportunistic infections arise or there is no response to Highly Active Anti Retroviral Therapy.
- Other respiratory viruses such as *Influenza*, *Parainfluenza*, *Metapneumovirus* and *Adenovirus*, are a growing cause of morbidity and mortality in immunocompromised patients, reaching 10-20% of all pulmonary infections in some studies. The course of infection may also be aggravated by *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Staphylococcus aureus* bacterial pneumonia (Sahuquillo-Arce & Menéndez-Villanueva, 2010).

3.4 Parasites

They are a group of rare lung infections, but physicians must be observant due to its remarkable clinical relevance. Recommended treatments for common parasites are shown in table 6.

- *Strongyloides stercoralis* is an intestinal nematode of tropical and subtropical climates. The larvae penetrate the skin and migrate via the blood to the lungs, from where they will reach the intestine. In immunosuppressed patients, it can produce Ulcerative Colitis-like colitis but also hyperinfestation which implies very poor prognosis since diffuse bronchopneumonia and alveolar bleeding can be present. The diagnosis is done by observing larvae in faecal extensions, but also in the sputum or bronchoalveolar lavage from hyperinfestation cases.
- *Toxoplasma gondii* is a parasite of cats. It rarely causes disease in healthy patients, but it remains dormant and can reactivate in immunosuppressed patients. Toxoplasmosis is

usually due to reactivation, and commonly causes central nervous system disease which is uniformly fatal if untreated, but also interstitial pneumonia, haemorrhagic pneumonia, lung consolidation, myocarditis or chorioretinitis. The high mortality observed is related to diagnosis delay. The diagnosis of choice is the direct view of the parasite by histological staining or isolation in cell cultures.

- *Leishmania* spp. are obligate intracellular protozoa transmitted to humans from infected sandflies. In visceral leishmaniasis, the parasite migrates to the internal organs such as liver, spleen and bone marrow. Signs and symptoms include fever, weight loss, malaise, anaemia, substantial swelling of the liver and spleen, and frequently, diarrhoea. Visceral leishmaniasis is a zoonosis rare in Western Europe, but life-threatening in immunocompromised patients. The course of infection depends on the type of the patient's immune reaction; patients with Th 1 response often present an asymptomatic or oligo-symptomatic disease, and after recovery they are immune to re-infection (Badaró et al., 1986; Hagenah et al., 2007). The disease can relapse after treatment in immunocompromised patients.

Microorganism	**Recommended treatment**	**Alternative treatment**
Toxoplasma gondii	sulfadiazine + pyrimethamine + folinic acid Pregnant woman: spiramycin until delivery	Cotrimoxazole; clindamycine + pyrimethamine + folinic; pyrimethamine + folinic acid + dapsone, atovacuona or clarithromycin; sulfadiazine + atovaquone, dapsone or clarithromycin.
Strongyloides stercoralis	Ivermectin for 5-7 days Consider addition of albendazole in hyperinfestation	Albendazole (once every month during 3 months after therapeutic success) Thiabendazole or mebendazole
Leishmania spp.	Amphotericin B liposomal on days 1, 5, 10, 17, 24, 31 and 38	Pentamidine; meglumine antimoniate; amphotericin B deoxycholate or paramomicin

Table 6. Parasitic infections treatment in immunocompromised patients (Mensa et al., 2011)

4. Conclusions

The relationship between the microbiota and its host is based on a very delicate equilibrium. Recent research has enlarged our knowledge about the interactions between humans and microbiota to an extent that admiration is the only possible reply at the sight of all the associations and its connotations. Trillions of microorganisms live and interact inside our bodies, and they are not only useful, but valuable for us.

Immune responses are modulated in such a fine way as to differentiate beneficial microorganisms from pathogens, and this happens at every moment without even noticing. As we have seen, in normal circumstances different bacteria play different roles; some have pro-inflammatory faculties, others protect from inflammation and at least one, *Candidatus arthromitus*, can have both. In the end, the microbiota and the immune system achieve a balance that preserves intestinal homeostasis. But, when the barrier between the two worlds

fails, this cross-talk between bacteria and immune cells is disturbed and inflammation reactions take place.

The involvement of bacteria in Ulcerative Colitis is not yet utterly understood, but unquestionably, microorganisms found in gut microbiota have the potential to induce and maintain inflammatory processes. Needless is to say that more research is needed, but the picture drawn so far brings to light that, interestingly, the human microbiota could be both the cause and the solution to this disease.

While a total comprehension of the aetiopatholgy is found so an accurate cure may be developed, Ulcerative Colitis patients are treated with immunosuppressive drugs. This fact involves that their immune response against challenging microorganisms are impaired. Thus they are exposed to infectious diseases with a worst course and prognosis, but also to opportunistic pathogens. A better knowledge and awareness about this scenario is necessary by both doctors and patients for a correct and early management of infection. On the other hand, specialist in gastroenterology, internal medicine, microbiology and infectious diseases need to collaborate for a successful management of these patients.

In conclusion, Ulcerative Colitis, due to the intrinsic characteristics of the patient and immunosuppressive therapies, features a multifaceted relationship with microorganisms which we are just beginning to unveil.

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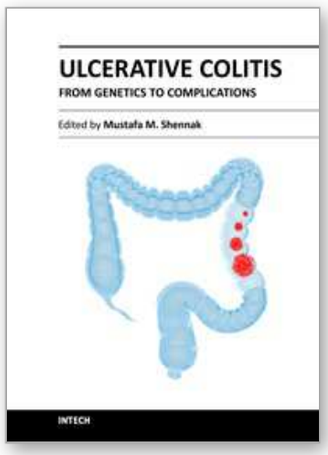
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Ulcerative Colitis (UC) is a rapidly evolving medical field, and will continue to be very exiting in the next few decades. Although the underlying cause of this disease is still unknown, results in research dealing with various issues related to this disease are published every day. Chapters included in this book review the most recent literature on related advancements in regard to this chronic disease, which is controllable but not curable. Aspects like epidemiology, pathophysiology, genetics, incriminated etiologies, clinical aspects, complications, and disease management, including advancements in the diagnostic and therapeutic options, were documented by well known clinicians, researchers, and world wide authorities in their fields. This book on UC will be a valuable addition to each doctor's library interested in this subject, or for physicians dealing with patients suffering from this disease. Authors have also included figures and diagrams to depict their point, and to easily reach the minds of the readers in the simplest way.

How to reference

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