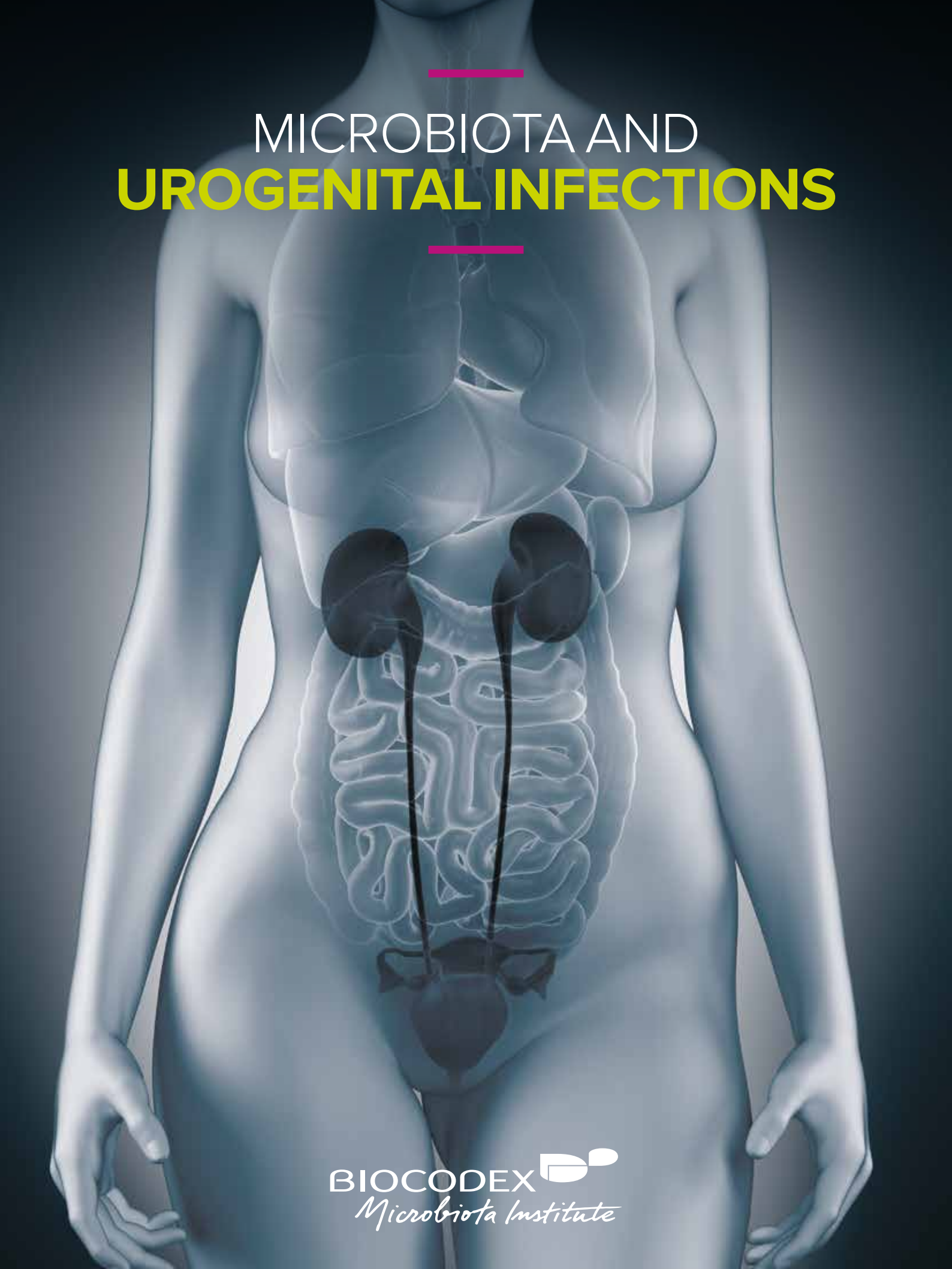


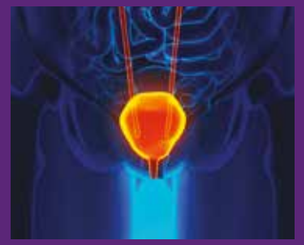
# MICROBIOTA AND UROGENITAL INFECTIONS

BIOCODEX
Microbiota Institute

**Lower urogenital tract infections are extremely common amongst women and appear to be closely related to a dysbiosis of the urinary or vaginal microbiota.** Contrary to a still widely held belief, urine is never sterile; it is instead home to a unique microbiota. And a loss of diversity in this microbiota is a risk factor for urinary tract infections. On the other hand, the vaginal microbiota, when balanced, has low diversity and is dominated by a small number of lactobacilli.

A loss of this dominant flora is associated with infections of the lower urogenital system. Hence the efforts of science to regulate vaginal and urinary microbiomes using probiotics (bacteria, yeasts) or even vaginal microbiota transplants.

# CONTENTS



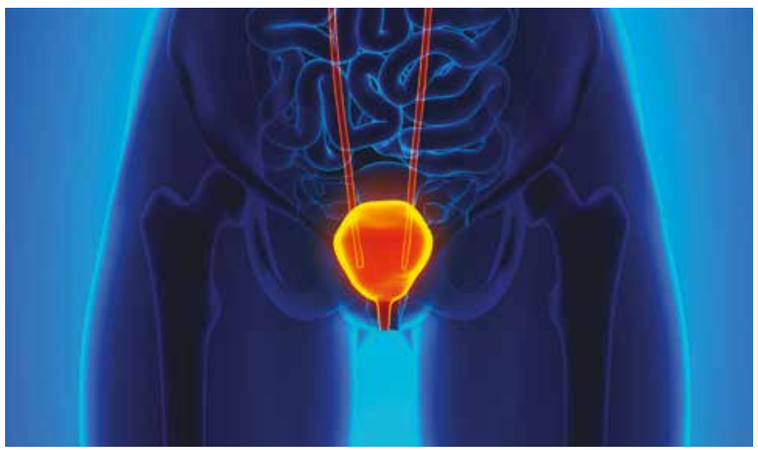
1

# INFECTIONS OF THE LOWER UROGENITAL TRACT

Infections of the lower urogenital tract are extremely common amongst women: **seven out of ten women** will suffer at least once from a urogenital infection or vulvovaginal candidiasis, while an even greater number will develop bacterial vaginosis at one point in their life.

## Urinary tract infections

**Uncomplicated lower urinary tract infections are much more common amongst women than amongst men. Rarely linked to a structural abnormality, they occur when a pathogen from the digestive system–often *Escherichia coli*–travels up the urinary tract and colonizes it.**



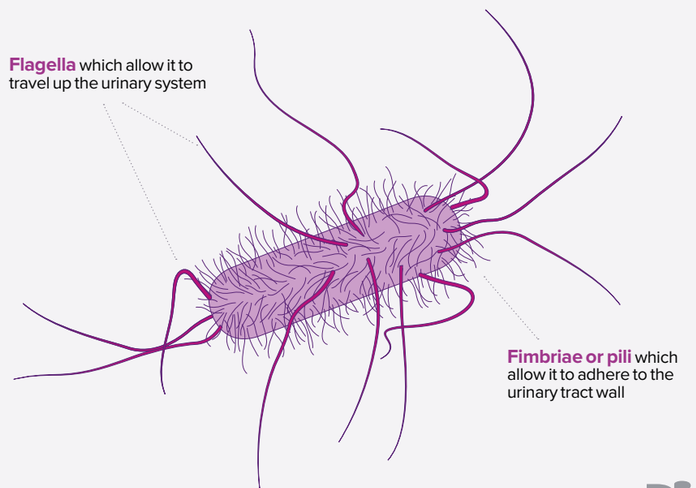
### SEVEN OUT OF TEN WOMEN

With 150 million new cases each year, urinary tract infections (UTIs) are a global health problem. A gender imbalance is evident in the case of UTIs, with women twice as susceptible as men in the same age group. One in three women is diagnosed before the age of 24, one in two before the age of 35, and up to seven out of ten once in their lifetime (30% on a recurrent basis[1]). The frequency of UTIs increases with age and following two key events, the commencement of sexual activity and the menopause[2]. Distinguishing complicated UTIs from uncomplicated cases is clinically important, since this will determine the duration and type of treatment. In general, uncomplicated UTIs are found in patients with no anatomical or functional abnormalities of the urinary tract, whereas complicated UTIs are more common alongside factors such as urinary tract obstructions, pregnancy, immunosuppression, fever, catheterization, renal failure, or diabetes mellitus. Prolonged symptoms (>1 week), non-response to treatment and bacteria that persist despite treatment are also characteristic of complicated UTIs[1].

### COLONIZATION BY DIGESTIVE SYSTEM PATHOGENS

Urinary tract infections are rarely the result of an underlying structural abnormality and are instead usually caused by a colonization of the vagina and periurethral area by uropathogens from the digestive tract which travel up the urinary tract. The virulence of pathogens, particularly *E. coli*, is mainly due to their adhesion capacity, which enables them to colonize the urinary system up to the point where biofilms form inside the urothelial barrier, protecting the pathogens from the host's immune system[1].

*E. COLI* **HAS A NUMBER OF APPENDAGES:**




[1] Abou Heidar NF, et al. Management of urinary tract infection in women: A practical approach for everyday practice. Urol Ann. 2019 Oct-Dec;11(4):339-346.



## Vaginal infections

**Bacterial vaginosis and vulvovaginal candidiasis are two very common gynecological infections. The first is a bacterial infection while the second is due to the spread of a fungus.**

### BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) is the most frequently reported microbiological syndrome amongst women of reproductive age. The Amsel criteria, although controversial, remains the standard method for diagnosing bacterial vaginosis and is based on the presence of at least three of the following clinical criteria: (1) thin, homogeneous vaginal discharge; (2) vaginal pH > 4.5; (3) amine (fishy) odor on adding potassium hydroxide to a vaginal smear; (4) presence of clue cells (cells of the vaginal epithelium to which a large number of bacteria adhere) on microscopy of vaginal secretions[3]. The Nugent score, a microscopic examination of a Gram stain of vaginal secretions, is also used in many countries and classifies the bacterial flora into three groups: healthy if the score is between 0 and 3, intermediate if the score is between 4 and 6, and indicative of bacterial vaginosis if the score is greater than 6.
Some authors believe that BV may actually be a set of common clinical signs and symptoms caused by a wide range of pro-inflammatory bacteria, coupled with a host-dependent immune response. As a result, some experts prefer to refer to it as polymicrobial vaginosis[3].

### VULVOVAGINAL CANDIDIASIS

Vulvovaginal candidiasis (VVC), so called because it is linked to the spread of fungi (more specifically, yeasts) of the *Candida* genus, is considered the second most common vaginal infection after BV: 70%-75% of women are thought to have been affected at least once in their lifetime, 50% twice, and

[1] Abou Heidar NF, et al. Management of urinary tract infection in women: A practical approach for everyday practice. Urol Ann. 2019 Oct-Dec;11(4):339-346.
[2] Infections urinaires de l'adulte / Connaître les particularités de l'infection urinaire au cours de la grossesse (UE6 n°157 / UE2 N°27). In : *ECN.PILLY 2020 – 6e édition. Maladies infectieuses et tropicales – Préparation ECN – Tus les items d'infectiologie.* Éditions Alinéa Plus. 320 pages.
[3] Onderdonk AB *et al.* The Human Microbiome during Bacterial Vaginosis. *Clin Microbiol Rev.* 2016 Apr;29(2):223-38.

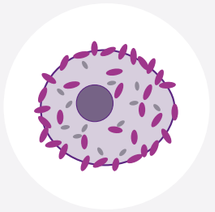
5%-10% suffer from recurrent cases. The symptoms and signs of vulvovaginal candidiasis are not clear, especially since colonization by the fungus is not a good indicator, with some women remaining asymptomatic despite colonization[4]. The most common clinical signs are vulvar pruritus, a burning sensation accompanied by vaginal pain or irritation that may lead to dyspareunia or dysuria, and sometimes vulvar or vaginal erythema, edema, or lesions[4].

Risk factors include pregnancy (and other situations where estrogen levels increase), diabetes mellitus, immunosuppression and the use of systemic antibiotics. Incidence increases with the commencement of sexual activity, but the links with different types of contraceptive remain unclear[5]. Lastly, many *Candida* yeasts alternate between a unicellular phase and a much more virulent filamentous phase. The filamentous forms offer greater mechanical resistance, which assists the colonization and invasion of host tissues and confers increased resistance to phagocytosis[4].

**CLINICAL CRITERIA FOR VAGINAL INFECTIOUS DISEASES**

**Bacterial vaginosis (BV)**
***(Gardnerella vaginalis)***

- Thin, homogeneous, fishy odor vaginal discharge
- No inflammation



- Vaginal pH>4,5
- Positive to amine odor test (whiff test)
- Clue cells

*« clue cells »*

**Vulvovaginal candidiasis (VVC)**
***(Candida albicans)***

- Whitish, pasty leukorrhea, adherent to vaginal wall
- Vulvar pruritus and burning sensation
- Vulvar erythema +/- edema with scratching lesions
- Ulcerations, fissures
- Dyspareunia and dysuria

- Acid pH (3,8 – 4,2)
- Spores and mycelial filaments

*C. albicans*

[4] Gonçalves B *et al.* Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. Critical *Reviews in Microbiology.* 2015 42(6):905–927.
[5] Martin Lopez JE. Candidiasis (vulvovaginal). *BMJ Clin Evid.* 2015 Mar 16;2015. pii: 0815.



# 2

# PATHOPHYSIOLOGY OF DYSBIOSIS-RELATED INFECTIONS OF THE LOWER UROGENITAL SYSTEM

The microbiota seems to play an important role in infections of the lower urogenital system, whether it is the urinary microbiota (urine is not sterile) in the case of urinary tract infections, or the vaginal microbiota, in the case of bacterial vaginosis and vulvovaginal candidiasis. However, there is a difference: while diversity is favorable in the first case, it is unfavorable in the latter.

## Dysbiosis-related urinary tract infections

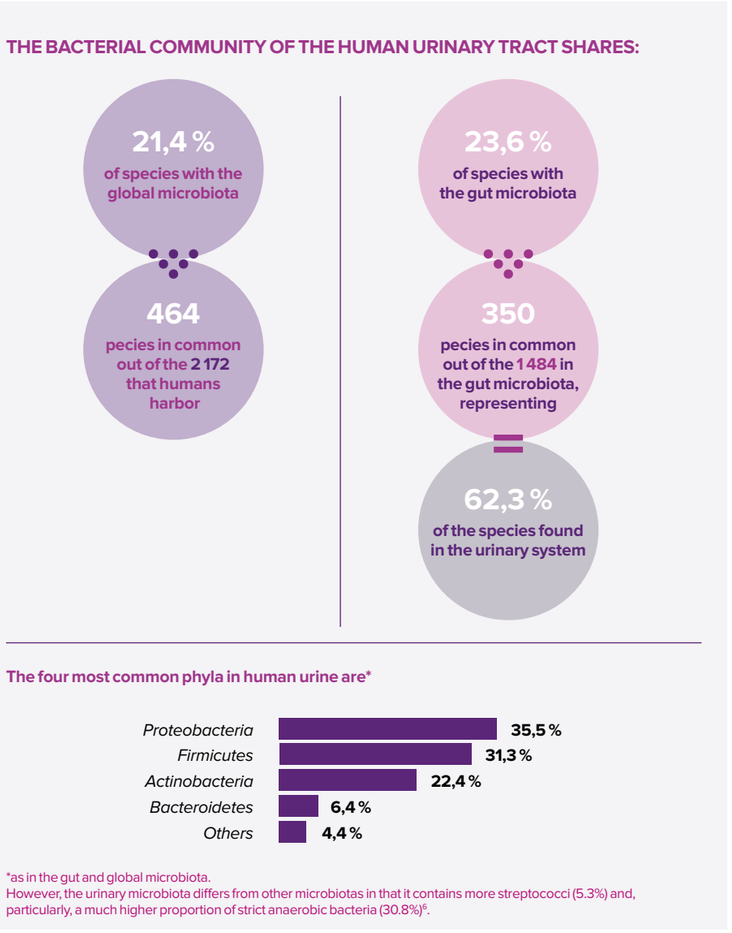
**Although long considered sterile, the urinary tract is actually home to a microbiota containing over 500 bacterial species. A loss of diversity in this microbiota seems to be a risk factor for urinary tract infections.**

### URINE IS NOT STERILE

Historically, urine was considered sterile but recent scientific discoveries have shown that this is not the case: 562 bacterial species have been identified in the human urinary microbiota[6]. Of these, 352 species (62.6%) have been linked to at least one report of infection among humans, including 225 (40.0%) described as the causal agent of urinary tract infections. The eight bacteria most commonly implicated in UTIs are *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Chlamydia trachomatis, Neisseria gonorrhoeae, Klebsiella pneumoniae, Proteus mirabilis* and *Enterococcus faecalis*[6]. Conversely, bacteria that secrete lactic acid, namely *Lactobacillus* and *Streptococcus*, are believed to play a protective role against pathogens[7]: lactic acid lowers the pH of urine (≃ 4.5), resulting in a microenvironment that is unfavorable to most pathogenic bacteria, while lactobacilli produce antibacterial metabolites (hydrogen peroxide and bacteriocins).

[6] Morand A *et al.* Human Bacterial Repertoire of the Urinary Tract: a Potential Paradigm Shift. *J Clin Microbiol.* 2019 Feb 27;57(3). pii: e00675-18.
[7] Aragón IM *et al.* The Urinary Tract Microbiome in Health and Disease. *Eur Urol Focus.* 2018 Jan;4(1):128-138.

## GLOBAL, GUT AND URINARY MICROBIOTAS




*as in the gut and global microbiota.
However, the urinary microbiota differs from other microbiotas in that it contains more streptococci (5.3%) and, particularly, a much higher proportion of strict anaerobic bacteria (30.8%)[6].

### WHEN DYSBIOSIS OPENS THE DOOR TO PATHOGENS

Studies published to date have demonstrated the clear role played by the urinary microbiota in urinary tract infections and responses to treatment[7]. Several mechanisms have been put forward[6], for example, commensal bacteria acting as a barrier against uropathogens (secretion of inhibitory or bactericidal molecules), with a loss of diversity in the urinary microbiota leading to a urinary tract infection. Therefore, while most microorganisms colonize the human body without causing infection, they may become pathogenic under certain conditions (immunosuppression, antibiotic resistance, etc.). A urinary tract infection may therefore develop due to the action of commensal bacteria when a dysbiosis exists. Other potential factors include disorders of a traumatic (catheter), biochemical (acidity, etc.), hormonal (pregnancy), mechanical (constipation), or alimentary (food pathogen that reaches the urinary tract from the digestive system) nature[6]. On the other hand, certain eating habits (consumption of fermented dairy products containing probiotic bacteria or of cranberry juice) may help reduce the risk of recurrent urinary tract infections by regulating the microbiota[6,7].

# Dysbiosis-related infections of the lower genital tract

**Unlike the urinary microbiota and many other microbiotas, the vaginal microbiota, when healthy, has low diversity and is mostly dominated by a few lactobacilli. A dysbiosis where lactobacilli lose their predominance has been linked to infections of the lower genital tract (bacterial vaginosis, vulvovaginal candidiasis).**

### A HEALTHY VAGINAL MICROBIOTA: LOW DIVERSITY AND DOMINATED BY LACTOBACILLI

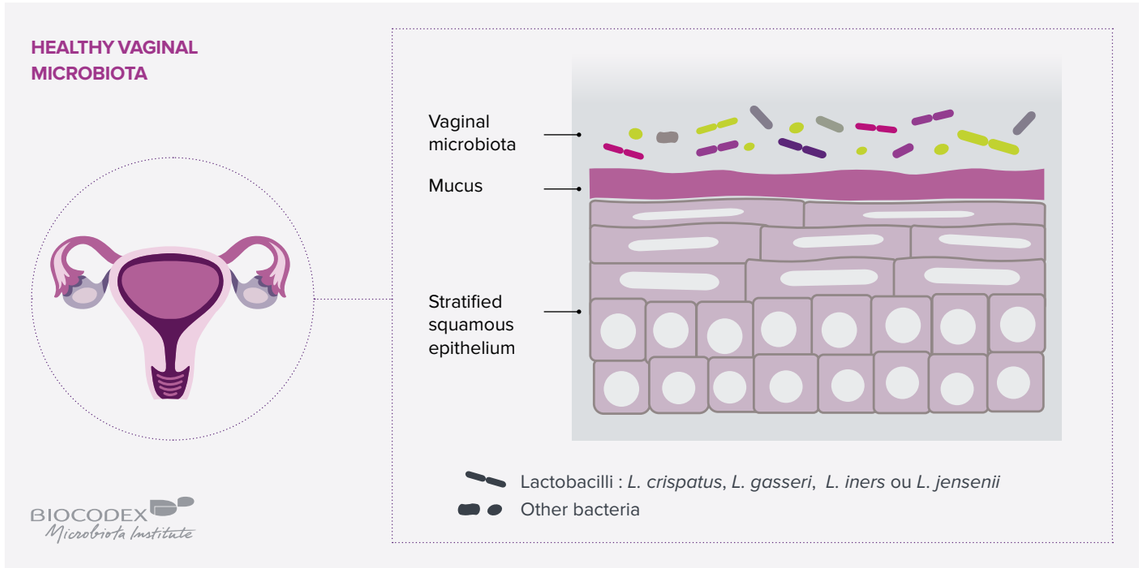
The vaginal microbiota consists mainly of lactobacilli with a protective role. Despite considerable variability among women, in general, five types of community have been categorized, depending on whether they are dominated by *L. crispatus, L. gasseri, L. iners* or *L. jensenii*, or have few or no lactobacilli and a significant quantity of strict anaerobic bacteria (*Megasphera, Prevotella, Gardnerella* and *Sneathia*) known to be characteristic of bacterial vaginosis[8].

Therefore, while a high number of microbial communities is usually an indicator of health for several microbiotas (digestive microbiota, etc.), the vaginal microbiota is balanced when it has low diversity and is dominated by one or a few species of lactobacilli.

In women of childbearing age, hormones promote the proliferation of lactobacilli. Estrogen levels induce the deposition of large amounts of glycogen, the main source of energy for lactobacilli, on the vaginal walls[8]. From adolescence to the menopause, high estrogen levels promote colonization of the vagina by lactobacilli which metabolize glycogen, produce lactic acid and maintain intravaginal health by lowering the pH level.

### BACTERIAL VAGINOSIS: WHEN *G. VAGINALIS* DRIVES OUT LACTOBACILLI

Despite more than sixty years of research, the etiology of BV remains unknown. Nevertheless, research seems to point more and more to the dysbiosis theory according to which dominant lactobacilli are replaced by polymicrobial flora derived from numerous bacterial genera (*Gardnerella, Atopobium, Prevotella*, etc.). *G. vaginalis* is in effect present in 90% of symptomatic subjects and 45% of normal subjects, whereas *Lactobacillus sp*. is found in 70% of apparently healthy subjects and 40% of symptomatic subjects[9]. Consequently, *G. vaginalis* has been suspected of being the main pathogen in BV. However, there is long-standing disagreement in this regard[10], since this virulent bacterium has also been found




[8] Gupta S *et al.* Crosstalk between Vaginal Microbiome and Female Health: A review. *Microb Pathog.* 2019 Aug 23;136:103696.
[9] Onderdonk AB *et al.* The Human Microbiome during Bacterial Vaginosis. *Clin Microbiol Rev.* 2016 Apr;29(2):223-38.

in virgin girls and in sexually active women with normal vaginal microbiota; in other words, colonization by *G. vaginalis* does not always lead to BV.
An explanation recently put forward may settle the debate: there is not one, but at least thirteen, different species of the genus *Gardnerella*, some of which may not be pathogenic. A mechanism for the development of the dysbiosis has even been suggested[10]: *G. vaginalis*, transmitted sexually, spreads itself among healthy vaginal lactobacilli, such as *L. crispatus*, initiating the formation of a biofilm, a structure that further protects the pathogen from the hydrogen peroxide and lactic acid secreted by the lactobacilli. By reducing the redox potential of the vaginal microbiota, *G. vaginalis* gradually reduces the lactobacilli population in favor of strict anaerobic bacteria such as *P. bivia* and *A. vaginae*. *G. vaginalis* and *P. bivia* seem to facilitate each other's development, the former providing amino acids to the latter and the latter ammonia to the former. Lastly, both pathogens produce an enzyme that destroys the mucus in the vaginal epithelium, facilitating the adhesion of different bacteria associated with BV, such as *A. vaginae*, and potentially causing a polymicrobial infection.

*Chlamydia tractomatis*

## VULVOVAGINAL CANDIDIASIS: A PROLIFERATION OF *CANDIDA*

Vulvovaginal candidiasis could be linked to an imbalance of the vaginal microbiota together with a proliferation of the fungus *Candida*, including *C. albicans* in 80%-92% of cases[11], and to a lesser extent *C. glabrata, C. tropicalis, C. parapsilosis* and *C. krusei*[12]. Exposure to antibiotics, whether local or systemic, is thought to be one of the main factors leading to vulvovaginal candidiasis[13]. The reduction of certain bacterial species, lactobacilli or not, that control the replication and virulence of *Candida* yeasts apparently allows the fungi already present in the vagina to multiply and induce infection. Future studies involving new sequencing technologies are needed to characterize in further details the interaction between vaginal microbiota, these yeasts and the occurrence and recurrence of vulvovaginal candidiasis.

## HEALTHY VAGINAL MICROBIOTA: A SAFEGUARD AGAINST STIS

The vaginal microbiota also plays an important role in maintaining vaginal health and protecting the host against the acquisition and transmission of sexually transmitted infections. Vaginal microbiota with a small number of bacterial communities and dominated by lactobacilli (in particular *Lactobacillus crispatus*) are those most associated with vaginal health, whereas increased diversity seems to be associated with lower resilience to imbalances and higher susceptibility to STIs such as herpes (BV increases the risk of herpes and vice versa), papillomavirus (increased prevalence and likelihood of contracting HPV, delayed elimination, increased severity of cervical intraepithelial dysplasia), HIV (increased risk of acquisition and transmission), and other infections (gonorrhea, chlamydia and trichomoniasis)[14].

*Candida albicans*

[10] Muzny CA *et al.* An Updated Conceptual Model on the Pathogenesis of Bacterial Vaginosis. *J Infect Dis.* 2019 Sep 26;220(9):1399-1405.
[11] Ceccarani C. *et al.* Diversity of vaginal microbiome and metabolome during genital infections. *Scientific Reports – Nature research.* 2019 9:14095
[12] Gonçalves B *et al.* Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. *Critical Reviews in Microbiology.* 2015 42(6):905–927.
[13] Shukla A, Sobel JD. Vulvovaginitis Caused by *Candida* Species Following Antibiotic Exposure. *Curr Infect Dis Rep.* 2019 Nov 9;21(11):44.
[14] Lewis FM *et al.* Vaginal Microbiome and Its Relationship to Behavior, Sexual Health, and Sexually Transmitted Diseases. *Obstet Gynecol.* 2017 Apr;129(4):643-654.



# 3

# REGULATING THE MICROBIOTA TO PREVENT AND CURE

Since lower urogenital infections seem closely related to a dysbiosis of the urinary or vaginal microbiota, treatments attempt to regulate the microbiota in order to prevent or even cure these conditions.

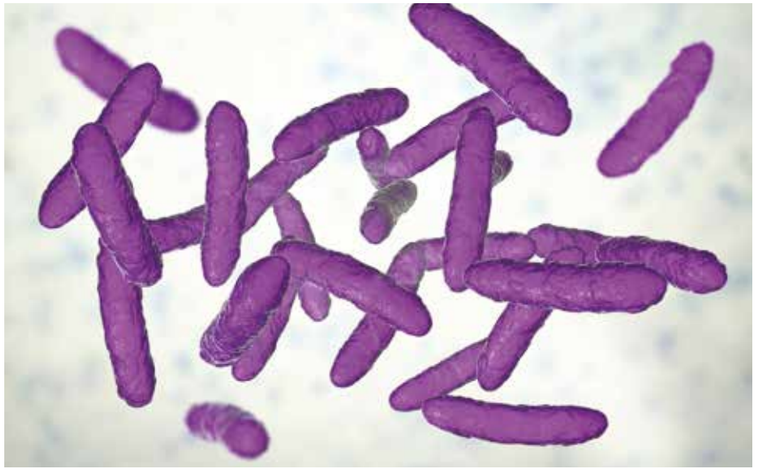
## Urinary area: efficacy to be confirmed in clinical trials

**In order to endow the urinary microbiota with the diversity it requires to be in equilibrium and reduce the development of bacterial resistance to antibiotics, the use of probiotics and cranberry has also been considered. Different strains of lactobacilli have demonstrated their potential, although further clinical trials are expected.**

Canneberge *Vaccinium macrocarpon*

Popular with patients, alternative treatments to antibiotics aim to prevent recurrence and antibiotic resistance. They are in line with the recommendations of health authorities, including the Haute Autorité de Santé (HAS) in France, which works to *"encourage the appropriate use of antibiotics in order to reduce bacterial resistance that can lead to therapeutic deadlock"*[15]. Cranberries, in the form of a 36 mg/day dose of proanthocyanidin, can be used to prevent the recurrence of UTIs linked to *E. coli*[16].
The depletion of the urinary microbiota in women susceptible to UTIs has raised the question of whether an intake of microorganisms via probiotics can reduce UTI rates. An ideal probiotic should have the ability to adhere to cells, prevent and reduce the adhesion of pathogens, secrete acids (e.g. lactic acid), hydrogen peroxide and bactericides capable of reducing the growth of pathogens, be free of adverse side-effects (they should not be invasive, carcinogenic or pathogenic) and be capable of forming clumps to produce

[15] https://www.has-sante.fr/jcms/c_2722827/en/acute-simple-cystitis-cystitis-with-risk-of-complication-or-recurrent-cystitis-in-women, consulté le 23/01/2020
[16] Caron F, *et al.* Practice guidelines for the management of adult community-acquired urinary tract infections. *Med Mal Infec.* 2018 Aug;48(5):327-358.



*Lactobacillus*

normal, balanced flora[17].
According to the literature, probiotics have proven effective in the treatment and prevention of urogenital infections[17]. Certain lactobacilli (*L. rhamnosus, L. fermentum* and *L. reuteri*) have been shown to have a beneficial effect in treating urinary tract infections[18]. An inhibitory effect on *E. coli* has been demonstrated *in vitro*, with certain strains of lactobacilli (*L. rhamnosus* and *L. plantarum*) possessing antimicrobial properties against this bacterium[19]. Therefore, the data increasingly suggests that probiotics may be used as a first step in the regulation of urinary microbiota in order to reduce the risk of, or treat, certain urinary infections, particularly since they are safe, better tolerated than antibiotics and frequently requested by patients[17]. However, further clinical trials involving large numbers of patients will be required to obtain clear evidence on the preventive and curative role of probiotics in urinary tract infections[17].

# Vaginal area: efficacy confirmed

**In order to maintain a lactobacilli-dominated protective flora, the use of topical or oral probiotics to prevent or treat vaginal infections, as well as a first clinical trial focused on vaginal microbiota transplants, have been initiated. Results are positive.**

## PROBIOTICS: IMPORTANCE OF BACTERIA AND YEASTS

Since a vaginal microbiota dominated by lactobacilli is considered optimal, vaginal probiotics unsurprisingly contain strains of this genus, which vary depending on the probiotic in question (*L. acidophilus, L. crispatus, L. reuteri, L. rhamnosus*). A review of 22 commercially available topical vaginal probiotics carried out in early 2019[20] highlighted their potential for the prevention and treatment of BV, but much less so for the prevention and treatment of vulvovaginal candidiasis. None of the studies reported any major safety concerns. Probiotic strains have never been detected in the vagina beyond the period of administration, suggesting they do not colonize

the environment in a sustained manner. In addition to probiotics for local use, oral probiotics have gained considerable importance. Four strains (*L. crispatus, L. gasseri, L. jensenii* and *L. rhamnosus*) out of 127 vaginal lactobacilli studied are noteworthy for their ability, *in vitro*, to acidify the environment, inhibit the growth of *G. vaginalis* and *C. albicans* and survive gastrointestinal transit[21]. But what about *in vivo*? Consumed in the form of a yoghurt drink by patients suffering from BV (twice a day for four weeks), these same four strains led to a 100% recovery (Amsel criteria), compared to a 65% recovery in the placebo group[22].
In addition to bacteria, certain yeasts may also be of interest, particularly against *C. albicans*. *Saccharomyces boulardii*, already used in the prevention and treatment of intestinal infections, naturally secretes capric acid, which modifies the structure of *C. albicans*, reducing its adhesion capacity, inhibiting its filamentation and hindering its ability to form biofilms[23].

## VAGINAL MICROBIOTA TRANSPLANTS: PROMISING FIRST CLINICAL TRIALS

In October 2019, the results of a first exploratory trial testing the transplant of vaginal microbiota from donors as a therapeutic alternative in five patients with symptomatic, untreatable and recurrent BV were published in *Nature Medicine*[24]. Four patients showed a full long-term remission (sometimes requiring several transplants or even a change of donor) up to the end of the follow-up period (5 to 21 months after the transplant), with a marked improvement in symptoms, Amsel criteria and the microscopic appearance of vaginal fluids, as well as the reconstitution of lactobacilli-dominated vaginal microbiota. The remaining patient is still in incomplete remission, while no adverse side-effects were observed. Accordingly, the researchers recommended further trials evaluating the therapeutic efficacy of vaginal microbiota transplants.

[17] Akgül T et Karakan T. The role of probiotics in women with recurrent urinary tract infections. *Turk J Urol.* 2018 Sep;44(5):377-383.
[18] Aragón IM *et al.* The Urinary Tract Microbiome in Health and Disease. *Eur Urol Focus.* 2018 Jan;4(1):128-138.
[19] Mogna L *et al.* Assessment of the in vitro inhibitory activity of specific probiotic bacteria against different *Escherichia coli* strains. *J Clin Gastroenterol.* 2012 Oct;46 Suppl:S29-32.
[20] van de Wijgert J et Verwijs MC. Lactobacilli-containing vaginal probiotics to cure or prevent bacterial or fungal vaginal dysbiosis: a systematic review and recommendations for future trial designs. *BJOG.* 2019 Jul 12.
[21] Domig *et al.* Strategies for the evaluation and selection of potential vaginal probiotics from human sources: an exemplary study. *Benef Microbes.* 2014 Sep;5(3):263-72.
[22] Laue C *et al.* Effect of a yoghurt drink containing Lactobacillus strains on bacterial vaginosis in women – a double-blind, randomised, controlled clinical pilot trial. *Benef Microbes.* 2018 Jan 29;9(1):35-50.
[23] Krasowska A *et al.* The antagonistic effect of Saccharomyces boulardii on *Candida albicans* filamentation, adhesion and biofilm formation. *FEMS Yeast Res.* 2009 Dec;9(8):1312-21.
[24] ev-Sagie A *et al.* Vaginal microbiome transplantation in women with intractable bacterial vaginosis. *Nat Med.* 2019 Oct 7.

DR JEAN-MARC BOHBOT

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# COMPLETE THERAPEUTIC ARSENAL: THE ONE THAT WILL ALSO TARGET MICROBIOTA

**Do we not overestimate the importance of microbiota in the urogenital area?**

In recent years we have come to understand the urogenital microbiota more clearly. We now know that it can be a factor in infections, in urinary disorders related to the menopause and even in tumors. The urogenital microbiota and its disruptions must be taken into account in patient management and probiotics must be part of the therapeutic arsenal. Although probiotics are obviously not our only weapon, they are indispensable, since anti-infectious treatments do not treat the cause of recurrence, i.e. the dysbiosis.

**What role do you think probiotics can play today against urinary tract infections?**

Urinary tract infections are closely linked to imbalances in three microbiomes: the urinary microbiota, since urine is not sterile; the vaginal microbiota, with which the urinary microbiota shares many similarities; and the gut microbiota, from which the pathogens involved in urinary tract infections originate (e.g. *E. coli*, which passes from the anus to the vulvar vestibule and then to the bladder).

**« Less balanced the vaginal microbiota, the greater the risk of acquiring a sexually transmitted infection (STI) »**

Conventional antibiotic treatment is justified for single UTI episodes. On the other hand, for recurrent UTIs (more than four episodes per year), it is essential, after having ruled out functional causes (e.g. a tumor of the bladder), to question the patient about possible disorders of the gut microbiota (constipation, etc.) and/or vaginal microbiota, the latter acting as a protective barrier between the digestive and urinary systems. The prevention of recurrence involves treatment for three to six months with intestinal probiotics administered orally, if a dysbiosis of the intestinal microbiota is present, and/or vaginal probiotics, ideally administered vaginally. These treatments may be combined with the use of cranberry, which reduces the level of *E. coli* in the bladder.

**What about vaginal infections?**

There are two types of vaginal infections: endogenous infections resulting from changes in endogenous microorganisms (bacteria or fungi) and exogenous infections contracted during sexual intercourse.

For endogenous infections, in the case of a single episode, an antimycotic vaginal suppository or antibiotic treatment may suffice. However, where there is a risk of recurrence, the dysbiosis must be treated for several months with gynecological probiotics.

Probiotics also have a role to play in exogenous infections, since the less balanced the vaginal microbiota, the greater the risk of acquiring a sexually transmitted infection (STI), and the higher the risk of an unfavorable outcome. For example, the papillomavirus is four to five times more likely not to be completely eliminated, and progresses more rapidly to potentially cancerous forms, when a dysbiosis exists. It is therefore important to test for an imbalance of the vaginal microbiota in infected women through a simple measurement of acidity (the pH should be between 3.5 and 4.5) and then by vaginal sampling where the pH is above 4.5. Where there is an imbalance, laboratory-tested and clinically approved probiotics should be prescribed.

A vaginal dysbiosis also increases the risk of contracting HIV. Although the acidity of lactobacilli helps destroy the virus, an inflammatory state increases the presence of lymphocytes, the cells targeted by HIV.

**Lastly, what can we expect from vaginal microbiota transplants?**

The results of just over twenty cases of vaginal microbiota transplants have been published. Although these results are interesting, they are not yet conclusive. The idea of treating recurrent bacterial vaginosis through a microbiota transplant still raises concerns as regards the criteria for selecting donors–particularly since the absence of symptoms does not mean that the donor's flora is balanced–and the indications for the recipient. It will most likely be known within a year or two whether vaginal microbiota transplants can be used as a last resort. ●

## Microbiota and urogenital infections

Urinary tract infections, bacterial vaginosis and vulvovaginal candidiasis, which are widespread in women, are the most common types of lower urogenital tract infections. In the urinary area, infections are due to the colonization by a pathogen originating in the gastrointestinal tract, most frequently Escherichia coli, that travels up the urinary tract. In the gynecological area, infections are related to bacterial (bacterial vaginosis) or fungal (vulvovaginal candidiasis) proliferation. These female urogenital disorders are largely caused by urinary or vaginal dysbioses. The urinary tract has long been considered a sterile environment, but it actually hosts a specific microbiota. Its imbalance is a risk factor for UTIs, allowing opportunistic bacteria to colonize the bladder. On the contrary, a healthy vaginal microbiota displays low diversity and is dominated by one or several species of lactobacilli. While vulvovaginal candidiasis seems to be associated to an imbalance in the vaginal microbiota, the exact etiology of bacterial vaginosis is still unknown. However, the hypothesis that dysbiosis promotes colonization by a polymicrobial flora (*Gardnerella*, *Atopobium*, *Prevotella*...) seems to be the most plausible.
How can a protective microbiota be restored and kept healthy? What challenges tomorrow's therapies must overcome? Is it already conceivable to prevent, or even treat, some lower genital infections by modulating microbial ecosystems? The objectives of this paper are to explain the current state of knowledge, and to question and clarify the value of probiotics (bacteria, yeasts) in the urogenital field.

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