Review

Urinary and genital infections in patients with diabetes:
How to diagnose and how to treat

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Abstract

Diabetes is a predisposing factor for urinary tract and genital infections in both women and men. Sodium–glucose cotransporter-2 (SGLT2) inhibitors constitute a novel therapeutic class indicated for type 2 diabetes (T2D) patients, and are already on the market in a few countries in Europe. They decrease glycaemia mainly by enhancing glucose excretion in urine by reducing renal glucose reabsorption via the action of SGLT2 in the kidneys. In general, they are well tolerated, but their mode of action results in specific side effects as well as an increased risk of genital (vulvovaginitis and balanitis) and urinary tract infections, for which T2D patients are already at high risk, reported within the first 6 months of treatment. Usually these infectious events are successfully treated with standard therapies, but diabetologists are not accustomed to dealing with them. The aim of this review is to describe the different types of lower urinary tract and genital infections, and the treatment strategies currently available for patients with diabetes.

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1. Introduction

Patients suffering from type 2 diabetes (T2D) are prone to a higher occurrence of certain infections compared with the general population [1]. Indeed, diabetes is considered a risk factor for urinary and genital tract infections, particularly in the setting of uncontrolled hyperglycaemia [1,2]. The true prevalence of urinary tract infection (UTI) in this population remains controversial, depending on whether or not asymptomatic bacteriuria is included [2–4]. Beyond frequency considerations, the severity of infection may also be increased in such patients. In male diabetics, for instance, UTI is associated with increased rates of complications, including perinephric and testicular abscesses, emphysematous pyelonephritis and perineal gangrene [5]. Diabetes also portends adverse outcomes in the management of genital infection, with higher incidences of treatment failure and prolonged hospital stays [6].

Sodium–glucose cotransporter-2 (SGLT2) inhibitors constitute a new and promising therapeutic approach in diabetes patients. They enable urinary glucose excretion by blocking renal SGLT2 and, as a consequence, reduce hyperglycaemia. However, their mechanism of action results in specific side effects, such as an increased risk of genital and urinary tract infections. Thus, the aim of this review is to provide an overview of the diagnosis and management of genital and lower urinary tract infections in both the general and diabetic population.

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2. Diabetes and male genitourinary tract infections

In contrast to female UTIs, which are subject to clear guidelines, specific recommendations for the management of UTI in diabetic men are less documented [7]. In men, it is considered that infections limited to urine do not happen, as the parenchyma (urethral glands, prostate, seminal vesicles, vas deferens, epididymis) is always infected (whether symptomatic or not). One difficulty is to precisely pinpoint the site of infection, and to differentiate between infection of the seminal vesicles (often ignored by physicians) and prostatitis [8]. Types of infection and recommended treatments are summarized in Table 1.

2.1. Male urethritis

Inflammation of the urethra usually presents as a urethral discharge, burning sensations and symptoms affecting the lower urinary tract. Infection is generally spread by sexual contact. Pathogens include Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium, Trichomonas vaginalis and Ureaplasma urealyticum. From a therapeutic and clinical point of view, gonorrhoeal urethritis needs to be differentiated from non-gonococcal urethritis (NGU). Two points are notable: up to 50% of NGU cases have no defined aetiology; and the frequency of the different species involved is highly variable [9,10]. In a recent US study, the distribution of pathogens in NGU was; C. trachomatis, 22.3%; M. genitalium, 12.5%; T. vaginalis, 2.5%; and U. urealyticum, 24.0%. Multiple pathogens were detected in 9.5% of cases [10]. The pathogenicity of Mycoplasma hominis and Ureaplasma spp. in urethritis remains controversial, as these are found in asymptomatic patients.

In all patients with urethritis and when sexual transmission is suspected, the aim should be to identify the pathogenic organisms. Diagnosis of pyogenic urethritis is based on a Gram stain of the urethral discharge or a urethral smear that shows more than 5 leucocytes per high power field (×1000) and, for gonococci, the discovery of intracellular Gram-negative diplococci. Laboratories should also use validated nucleic acid amplification tests (NAATs) to detect chlamydial and gonorrheal infections [11]. When using an amplification system for identifying pathogens, the first voided urine specimen may be taken instead of a urethral smear. N. gonorrhoeae and Chlamydia cultures are mainly restricted to evaluating treatment failures. Trichomonas spp. can usually be identified by microscopy.

First-choice treatment is a single dose of ceftriaxone 1 g intramuscularly or intravenously, plus azithromycin 1.0–1.5 g (3 tablets at 0.5 g) orally as a single dose. Alternative regimens such as oral cefixime 400 mg as a single dose, or oral azithromycin 1.0–1.5 g as a single dose, may be considered if susceptibility is established.

2.2. Bacterial prostatitis

Prostatitis represents one of the more predominant causes of urological complaints in men aged <50 years. It affects 11–16% of American men over the course of their lifetimes [12,13]. In the 1999 US National Institutes of Health (NIH) consensus statement on prostatitis, four categories were defined. Type 1 prostatitis refers to acute bacterial prostatitis. Although rare, it has the highest potential for mortality and morbidity, and should be considered a true urological emergency [14]. Type II encompasses chronic bacterial prostatitis, and accounts for 5–15% of
all prostatitis cases [14]. Type III is the most common manifestation of the syndrome, and is characterized by chronic pelvic pain in the absence of detectable infection. Finally, type IV refers to asymptomatic prostatitis, found incidentally at the time of surgery, biopsy or autopsy. The use of this classification system from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIH is recommended, as it clearly distinguishes bacterial prostatitis from chronic pelvic pain syndrome [15].

The diagnosis of bacterial prostatitis is made clinically and biologically by evidence of infection localized to the prostate. According to the duration of symptoms, bacterial prostatitis is described as either ‘acute’ (Type I) or ‘chronic’ (Type II). Presentation is also different between the both groups. Men with acute bacterial prostatitis have obvious signs and symptoms of a UTI, including dysuria and frequency, and often present with suprapubic pain, fever and discomfort [14,16]. In these cases, although a gentle rectal examination can be performed, prostatic massage is inadvisable because of the risk of bacteraemia or even sepsis. On the other hand, chronic bacterial prostatitis classically presents as recurrent UTI, usually with the same organism. Patients do not look ill, but will often complain of irritative symptoms on voiding and perineal discomfort.

Acute bacterial prostatitis always has a causative pathogen detectable by routine methods, which therefore makes antimicrobial therapy a rational choice. The most important investigation in the evaluation of patients with acute prostatitis is urine culture. In contrast, for chronic bacterial prostatitis (CBP), diagnosis has hinged on the gold standard four-glass test, initially described by Meares and Stamey [17]. This involves the collection of distinct specimens, each designed to localize inflammation and infection to a discrete portion of the urinary tract: the initial stream of urine for the urethra; midstream urine for the bladder; and expressed prostatic secretion and post-prostatic massage urines for the prostate. However, a simplified method of evaluation has been proposed by the Chronic Prostatitis Collaborative Research Network Study Group (midstream urine culture plus post-prostatic massage culture, with good concordance between the two) [18]. Another proposed alternative is initial stream urine culture plus semen culture, which has the benefit of reducing the unnecessary discomfort of prostatic massage while potentially increasing sensitivity for identifying gram-negative and gram-positive organisms [19].

The Enterobacteriaceae, especially Escherichia coli, are the predominant pathogens in acute bacterial prostatitis whereas, in CBP, the spectrum of strains is wider, but remains dominated by E. coli. The significance of intracellular bacteria, such as C. trachomatis, is uncertain. In patients with immune deficiency, prostatitis may be caused by fastidious pathogens such as Mycobacterium tuberculosis, Candida spp. and rare pathogens, including Coccidioides immitis, Blastomyces dermatitidis and Histoplasma capsulatum. In cases of suspected prostate tuberculosis, urine should be investigated for Mycobacterium spp., using the polymerase chain reaction (PCR) technique.

Parenteral administration of high doses of a bactericidal antibiotic is usually required for acute bacterial prostatitis, which may include broad-spectrum penicillin, a third-generation cephalosporin or a fluoroquinolone combined with an aminoglycoside as initial therapy. After a successful initial treatment, patients can be transitioned to oral antibiotics (for example, fluoroquinolones), for a minimum duration of 3 to 4 weeks. However, one prospective study found a bacterial persistence rate of 33% at 3 months. Therefore, prolonged fluoroquinolone treatment for 6 weeks, followed by re-evaluation, has been recommended and should particularly be considered for patients with diabetes.

In CBP, antimicrobial therapy is a mainstay, but not all antibiotics are equal. It is mandatory to choose an antibiotic that diffuses into and becomes concentrated in the prostate, and also has a good tolerability profile. Fluoroquinolones have demonstrated the best penetration into the prostate and seminal fluid [14,20], with ciprofloxacin and levofloxacin being the most widely used quinolones in the treatment of CBP. It is recommended that fluoroquinolone treatment be given for at least 4 weeks [15]. However, to prevent the risk of recurrence, it is not unusual for a patient to require longer treatment of up to 2 to 3 months. In diabetic patients, treatment duration of 6 weeks appears to be a good compromise. The patient should then be reassessed, and antibiotics continued if cultures are still positive.

2.3. Bacterial orchitis and epididymitis

Symptoms of epididymitis are dominated by pain and swelling, which is often unilateral and relatively acute in onset. In some cases, the testes are also involved in the inflammatory process (epididymo-orchitis).

Orchitis and epididymitis are classified as either acute or chronic processes according to the onset and clinical course. Chronic disease with duration develops in 15% of acute epididymitis cases. In cases of testicular involvement, chronic inflammation may result in testicular atrophy and destruction of spermatogenesis [21].

Microbiological results from puncture of the epididymis and from urethral swabs, as well as from urine samples, have shown excellent correlation. Thus, before starting antimicrobial therapy, a urethral swab and urine culture should first be obtained for microbiological investigations.

The presence of intracellular gram-negative diplococci on a smear confirms infection with N. gonorrhoeae. In cases where isolated white blood cells (WBCs) have been present on a urethral smear, C. trachomatis has been isolated in approximately two-thirds of cases.

According to World Health Organization (WHO) criteria, ejaculate analysis, including leucocytes, can indicate persistent inflammatory activity. The most frequent abnormality on semen analysis is leukospermia, defined as a level >10⁵ WBC/mL. In many cases, transiently decreased sperm counts, motility and vitality are also found. Azospermia due to complete obstruction of both epididymides is a rare complication.

Antimicrobials are often prescribed on an empirical basis, considering that, in young sexually active men, C. trachomatis is usually the causal pathogen and that, in older men with benign prostatic hyperplasia (BPH) or other miceturition disturbances,
these uropathogens are also often involved. Fluoroquinolones, preferably those with activity against *C. trachomatis* (such as ofloxacin and levofloxacin), should be the drugs of first choice because of their broad antibacterial spectra and their favourable penetration into tissues of the urogenital tract. However, if *C. trachomatis* is indeed detected, then treatment could also be continued with doxycycline 200 mg/day for at least 2 weeks.

In any case, if uropathogens are found, a thorough search for micrutition disturbances should be carried out to prevent relapse.

### 2.4. Semen analysis

In a normal state, the male reproductive system harbours no bacterial flora except in the external genitalia and outermost third of the urethra, which is physiologically colonized by a flora complex usually composed of *Staphylococcus* spp., viridans streptococci, *Acinetobacter* spp., Enterobacteriaceae, *Corynebacterium* spp., *Mycobacterium smegmatis*, and species of *Peptostreptococcus*, *Bacteroides*, *Fusobacterium*, *Mycoplasma* and *Candida*. This makes it mandatory that semen analysis be performed after thorough cleansing of the meatus, glans, foreskin and hands. Various factors have been proposed to modulate flora composition, notably age, personal hygiene, history of genital infections, invasive surgery, sexual activity and sexual practices [22].

Semen collection for sperm analysis should always take place in a laboratory after a period of abstinence for 3 to 5 days, but not for semen culture. Nowadays, semen culture not only identifies the usual cultivable bacteria, but also, due to molecular biology, non-cultivable microorganisms (viruses, anaerobic bacteria), too. After pathogen-counting, a susceptibility treatment test is usually performed.

A semen culture is considered positive if there is the presence (even at a low count) of: obligate pathogens such as *N. gonorrhoeae*, *C. trachomatis*, *Staphylococcus aureus*, species of *Pseudomonas*, *Proteus*, *Haemophilus*, *Peptococcus* and *Klebsiella*, *Corynebacterium seminalae*, *Trichomonas vaginalis*, *E. coli*, *Mycoplasma* spp. (*hominis, genitalium* and *Ureaplasma* spp.); a bacterial count > 10,000 CFU (colony-forming units)/mL with optional pathogens such as *Streptococcus agalactiae*, *Corynebacterium* spp., *Eikenella* spp. and anaerobic bacteria (*Bacteroides* spp., *Prevotella* spp., *Gardnerella vaginalis* and *Actinomyces*); and a bacterial count > 100,000 CFU/mL with a suggestive clinical context for other bacteria [23].

Management of a positive semen culture must take into account the sperm parameters. If all are normal and there is an absence of symptoms, then a new semen culture should be performed and followed by treatment. If at least one sperm parameter is abnormal, then antibiotic treatment for 15 days is indicated; a control culture is advocated 8 days after the end of treatment to confirm the disappearance of infection [23].

However, whether male accessory genital organ infection can alter sperm parameters is still a matter of debate, even though the literature suggests it can negatively interfere with sperm quality in many ways. Several organisms, such as *Proteus*, are capable of adhering to the sperm head, while others such as *Chlamydia* and *Ureaplasma* spp. are able to cross the plasma membrane.

The inflammatory response may also have a negative impact on sperm function, as many inflammatory mediators, including reactive oxygen species and cytokines [24,25], have a detrimental effect on reproductive cells [26,27].

According to the WHO manual for standardized investigation and diagnosis of infertile couples [22], two types of situations should therefore be distinguished: leukospermia plus a positive sperm culture favour an infectious context, whereas leukospermia with a negative sperm culture point to an inflammatory context. In the former case, antibiotic treatment for 15 days is recommended [23]. In the latter case, it is recommended to prescribe non-steroidal anti-inflammatory drug (NSAID) treatment plus antioxidants for 2 months, and then perform semen analysis and semen culture as a control.

### 2.5. Balanitis

An inflammation of the glans penis, this more often occurs in uncircumcised individuals. Poor hygiene, exposure to sexual transmitted diseases, diabetes and immune deficiency are known risk factors for balanitis. Its treatment consists of topical antibiotics, antifungals and steroids. When topical therapy fails, biopsy of discrete lesions is recommended.

### 3. Diabetes and female urinary tract infections

Management of UTIs in diabetic women is clearly defined in urological as well as infectiological recommendations. Whatever the clinical presentation, importance of symptoms or severity of infection, UTI in diabetic women is considered a complicated infection, covering infections associated with anatomical abnormality of the urinary tract and the presence of underlying diseases favouring infections and/or antibiotic treatment failure. Other causes of complicated UTIs are: the presence of an indwelling catheter; obstructive uropathy; vesicoureteral reflex; renal failure/transplantation; and immunodeficiency. These are usually divided into two categories, based on whether the condition can be corrected or not [28,29]. Significant bacteria as a complication of UTI is defined by a bacterial count > 100,000 CFU/mL in a midstream urine sample. Empirical antibiotic therapy requires knowledge of the spectrum of potential pathogens, resistance level, renal function and urological anatomy. There is no place for one-day or short-term treatment.

By order of preference, the recommended treatments are: amoxicillin, 7 days; pivmecillinam, 7 days; nitrofurantoin, 7 days; and then, in alphabetical order, amoxicillin/clavulanic acid, cefixime or fluoroquinolones for 7 days (Table 2).

Fluoroquinolones have been widely used over the past decade and are now the fourth choice because of their ecological impact. Fosfomycin–trometamol is proposed as a last resort because the literature is limited for its indication, and there is uncertainty as to the best method of administration (as a single dose or three doses spaced over 48-h intervals).
Table 2
Female genitourinary infections and recommended treatment: a summary.

<table>
<thead>
<tr>
<th>Type of infection and main diagnosis</th>
<th>Recommended treatment</th>
<th>Dosage and duration of recommended treatment</th>
<th>Alternative treatment if necessary</th>
<th>Recommended reassessment time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female urinary tract infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td>Fosfomycin–trimetamol</td>
<td>1 day</td>
<td>Cephalosporin (group 1/2) or TMP-SMX or Fluoroquinolone for 3 days</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>Nitrofurantoin</td>
<td>5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporadic and uncomplicated in women</td>
<td>Pivmecillinam</td>
<td>3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection in women</td>
<td>Amoxicillin, pivmecillin, amitrofurantoin or amoxicillin-clavulanic acid or cefixime or fluoroquinolones</td>
<td>7– days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Female genital tract infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute vaginal candidiasis</td>
<td>Oral: Flucytosine 17%</td>
<td>200 mg daily, 3 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: clinical and microscopic examination of vaginal fluid</td>
<td>Local: Flucytosine 17% or Itraconazole 200 mg/day, 3 days</td>
<td>only if treatment fails</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Non-albicans acute vaginal candidiasis</td>
<td>Oral: Flucytosine 17%</td>
<td>600 mg/day, 14 days, once daily, 14 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: clinical history, yeast culture</td>
<td>Boric acid</td>
<td>600 mg/day, 14 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Recurrent vaginal candidiasis</td>
<td>Oral: Flucytosine 17%</td>
<td>600 mg/day, 14 days, once daily, 14 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: clinical history, yeast culture</td>
<td>Boric acid</td>
<td>600 mg/day, 14 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clotrimazole or Econazole</td>
<td>200 mg/day, 1–14 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Acute vaginal candidiasis in diabetic women</td>
<td>Oral: Flucytosine 17%</td>
<td>600 mg/day, 14 days, once daily, 14 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: clinical and microscopic examination of vaginal fluid ± yeast culture</td>
<td>Boric acid</td>
<td>600 mg/day, 14 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clotrimazole or Econazole</td>
<td>200 mg/day, 1–14 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Acute bacterial vaginosis</td>
<td>Oral: Metronidazole Secnidazole</td>
<td>1 g/day, 7 days, 2 g, single dose</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: clinical and Gram strain score of vaginal smear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bacterial vaginosis</td>
<td>Oral: Metronidazole</td>
<td>1 g/day, 10–14 days, ± local administration of probiotics</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: clinical and Gram strain score of vaginal smear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>Oral: Metronidazole</td>
<td>2 g, single dose</td>
<td>Only if treatment fails</td>
<td>Rescreening at 3 months after initial infection</td>
</tr>
<tr>
<td>Diagnosis: NAAT or culture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerobic vaginosis</td>
<td>Local: Clindamycin</td>
<td>100 mg/day, 6 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: clinical and wet-mount microscopy; culture not mandatory</td>
<td>Kihamycin</td>
<td>100 mg/day, 6 days</td>
<td>Only if treatment fails</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** TMP-SMX: trimethoprim-sulphamethoxazole (co-trimoxazole); BLI: beta-lactamase inhibitor.
4. Diabetes and female genital tract infections

Women with T2D are prone to developing lower genital tract infections [1,2]. Indeed, when Hirji et al. [4] evaluated the incidence of vaginal infections in diabetic patients and healthy controls, patients with diabetes displayed an increased risk of developing vaginal infection compared with non-diabetics with a relative risk of 1.81 [1.64–2.00], particularly in the younger age group. Poorly controlled disease and a history of vaginal infection were independent risk factors for developing infection during the study period. Of the observed cases, 87.5% were recorded as vaginitis/candidiasis, 8.6% as vulvitis, 2.2% as bacterial vaginosis and 1.7% as related to a sexually transmitted disease. Thus, the following recommendations refer to management of the main clinical entities — vaginal candidiasis, bacterial vaginosis, \textit{T. vaginalis} and aerobic vaginitis — and the recommended treatments are summarized in Table 2.

4.1. Vaginal candidiasis

This is a frequent cause of vaginal symptoms in women, and \textit{Candida albicans} is the most common pathogenic agent found. The infection mainly affects premenopausal women (up to 20% of them) due to the presence of a 17β-oestradiol-binding protein. Thus, vaginal candidiasis less frequently affects postmenopausal women and premenarche girls. Host predisposing risk factors include diabetes, obesity, oral contraceptive use (depending on oestrogen dosage), sexual activity and genetic factors [30,31].

Vaginal candidiasis is the leading cause of vaginal infection in patients with diabetes [32]. It is well known that yeasts thrive in a sugar-rich environment, and several mechanisms may facilitate \textit{Candida} vaginal colonization in the setting of hyperglycaemia, including inhibition of neutrophil-mediated killing, and promotion of vaginal adhesion and virulence of \textit{Candida} spp. When species-specific prevalence rates and the risk of candidiasis were assessed in T2D patients, these women had a higher risk of vaginal candidiasis than the control group, with a relative risk of 2.45 [33]. Surprisingly, \textit{Candida glabrata} was the predominant species (39%) in the diabetic subgroup, followed by \textit{C. albicans} (26%) and \textit{Candida tropicalis} (17%). In contrast, \textit{C. albicans} was predominant in the controls (43.5%).

Due to the influence of oestrogens, clinical presentation may vary according to the patient’s hormone status: premenopausal women primarily suffer from vaginal candidiasis that can secondarily extend to the vulvar area, while postmenopausal patients are usually diagnosed with perineal disease. Clinical symptoms typically appear prior to menstruation, as this period is associated with increased glucose levels in the vagina through the release and degradation of glycogen. Itching is the major symptom. Patients may also complain of vaginal redness, soreness, burning, dyspareunia and dysuria. The vaginal discharge varies from being fluid to clumpy. The diagnosis is made by a combination of medical history, clinical symptoms and yeast detection through microscopic examination of vaginal fluid [34]. Yeast culture may be used in complex or recurring cases [35].

Asymptomatic vaginal contamination does not require treatment in immune-competent and non-pregnant women without a history of recurrent vaginal candidiasis. Treatment of acute vaginal candidiasis is based on local administration of imidazoles (co-trimoxazole, econazole, miconazole) or polyenes (nystatin, amphotericin B) [35,36]. Noteworthy, vaginal amphotericin B is no longer available in France while local nystatin is only available in association with anti-bacterial agents. Treatment duration depends on dosages and the preparation, and ranges from 1 to 7 days. Additional antifungal skin creams can be applied whenever vaginal candidiasis extends to the vulvar region ( clotrimazole twice daily for 7 days). Oral treatment using fluconazole (150 mg as a single dose) or itraconazole (200 mg/day for 3 days) is another possibility. The choice between the two routes of administration should be made according to patients’ personal preferences [37]. The observed success rate is 85% of cases at 2 weeks and 75% at 6 weeks. Treatment of asymptomatic sexual partners is not of benefit for patients [38].

Standard treatments for \textit{C. albicans} are minimally effective for \textit{C. glabrata}. Several therapeutic protocols have been described: vaginal suppositories of boric acid (600 mg/day, 14 days) or amphotericin B (50 mg daily, 14 days) [39]; vaginal application of 17% flucytosine (once daily, 14 days); and oral fluconazole (800 mg/day, 14–21 days).

Recurrent vaginal candidiasis, defined as at least four symptomatic episodes per year, remains a challenging clinical situation. Vaginal cultures should systematically be performed to confirm the diagnosis and identify any unusual infective species [36]. The therapeutic approach includes the initial treatment and maintenance therapy. The available induction treatments comprise oral fluconazole (150 mg every 3 days, three doses) [40], vaginal boric acid (600 mg/day, 14 days) [41] or vaginal clotrimazole (500 mg/day, 10–14 days), all with similar efficacy. Maintenance therapy is usually given for 6 months. Various protocols have been reported: oral fluconazole (150 mg, once a week) [40]; oral itraconazole (200–400 mg, once a month); vaginal clotrimazole (500 mg, once a month); and vaginal boric acid (300 mg/day for 5 days from the first day of the menstrual cycle every month). Data regarding the efficacy of probiotics for the management of recurrent vaginal candidiasis are controversial [42]. Thus, to date, probiotic therapy is not recommended for this indication [43].

Standard treatments for acute vaginal candidiasis may not be effective in those with T2D: Goswami et al. [44] observed a 32.9% efficacy rate for single dose fluconazole therapy in diabetic patients vs. 52.7% in the control group. Thus, the first-line therapeutic regimens for diabetic patients should differ from those used in the non-diabetic population, particularly in women with uncontrolled diabetes. The 2010 US guidelines recommend more prolonged (7 to 14 days) conventional antifungal treatment [36], while the 2013 Canadian guidelines propose vaginal boric acid (600 mg/day, 14 days) as an alternative regimen.

4.2. Bacterial vaginosis

This complex, polymicrobial disorder is characterized by an overgrowth of strictly anaerobic or facultative anaerobic bacteria plus a reduction in peroxide-producing lactobacilli. Its incidence
rate ranges from 5% to 50% [45]. Bacterial vaginosis is initiated by *G. vaginalis*, which has the appropriate virulence factors to adhere to host epithelium, create a biofilm community and compete with lactobacilli for dominance. Its genetic diversity can lead to virulent and avirulent strains. In addition, symbiotic relationships with normally dormant vaginal anaerobes result in their further proliferation, which contributes to symptoms of bacterial vaginosis [46]. Common symptoms include an increased vaginal discharge that is homogeneous and white or grey in colour, with a “fishy” odour. In up to 50% of cases, no symptoms are observed.

Two methods are routinely used to make the diagnosis. First, there is the presence of at least three of the following Amsel criteria: (1) a thin, white, homogeneous discharge; (2) clue cells on microscopy; (3) pH of vaginal fluid >4.5; and (4) a positive KOH test. Then, the Gram stain (Nugent) score for a vaginal smear involves microscopic quantification of bacterial morphotypes based on a score range of 0 to 10, with a Gram stain score ≥7 considered indicative of bacterial vaginosis. It is noteworthy, however, that the identification of *G. vaginalis* in a vaginal smear does not ensure the presence of bacterial vaginosis.

The infection has been identified as an independent risk factor for sexually transmitted disease, human immunodeficiency virus (HIV) infection, pelvic inflammatory disease and pregnancy complications (such as preterm delivery, miscarriage, premature rupture of membranes and chorioamnionitis) [47].

Treatment relies on oral antibiotics: metronidazole (1 g/day, 7 days) or secnidazole (2 g, single dose). However, the long-term cure rate is low: it recurs in up to 40% of patients within 3 months of starting antibiotic therapy, and in up to 50% after 6 months [48]. Recurrent bacterial vaginosis is usually treated with prolonged metronidazole therapy after confirmation of the diagnosis [49]. However, this poses the problem of repeated exposure to antibiotics and the emergence of drug-resistant strains, and suggests the need for alternative therapeutic approaches [50]. Thus, several trials have assessed the efficacy of probiotics [51]. While the preferred route of administration was intravaginal, some authors delivered lactobacilli orally [51]. Of these studies, those combining antibiotics and probiotics have shown the most encouraging results [52]. However, substantial heterogeneity in the products used, trial methodologies and outcome measures have failed to provide sufficient evidence either for or against recommending probiotics as a treatment for bacterial vaginosis [51]. While T2D is commonly considered a risk factor for bacterial vaginosis, therapeutic regimens in diabetic patients do not differ from those for the general population. Nevertheless, probiotics may be beneficial for preventing recurrences [36]. Treatment of sexual partners is not associated with a reduced risk of recurrence and therefore should not be recommended.

4.3. *Trichomonas vaginalis*

Infection with *T. vaginalis* is the most common curable sexually transmitted disease worldwide, with around 7.4 million new infections diagnosed annually in the US [36]. The most common symptom is a malodorous vaginal discharge, which is typically yellow-green in colour, itchy and frothy. Women also report dyspareunia, dysuria, lower abdominal pain and/or vulvovaginal irritation. Nevertheless, >50% of patients are asymptomatic [36]. Diagnosis of *T. vaginalis* can be achieved by saline microscopy examination, culture or NAATs [53]. Although more expensive, the lattermost tests provide the best sensitivity and specificity rates [54]. *T. vaginalis* infection is a risk factor for HIV transmission, upper genital tract infections and adverse perinatal outcomes [53].

Recommended regimens include oral metronidazole (2 g, single dose, or 1 g/day, 7 days) and oral tinidazole (2 g, single dose) [36]. Cure rates range from 82% to 95% for metronidazole and from 86% to 100% for tinidazole [55]. Sexual partners should be treated using similar regimens. Because of a high rate of reinfection, rescreening for *T. vaginalis* at 3 months after the initial infection may be considered for sexually active women, although the benefit of this precaution has not been fully assessed. Metronidazole-resistant *T. vaginalis* occurs in 2.5% to 5% of cases, although increasing the metronidazole dose (1 g/day, 7 days) or switching to tinidazole usually overcomes such resistance. No specific regimens have been proposed for the treatment of *T. vaginalis* in diabetic patients [36].

4.4. Aerobic vaginitis

This recently defined clinical entity refers to the isolation of aerobes in women with symptoms of vaginitis. Its prevalence varies from 5% to 10% among non-pregnant women [56]. Converging data suggest that aerobic vaginitis results from an imbalance in vaginal flora: patients display lower levels of peroxide-producing lactobacilli and higher levels of aerobic bacteria [56]. Aerobic pathogens mostly comprise *Streptococcus* spp. (up to 58.7%), *Staphylococcus* spp. (up to 41.7%), *S. aureus* (up to 37.4%), *E. coli* (up to 23%) and *Klebsiella* spp. (up to 8.1%) [56]. Patients’ complaints include increased leukorrhoea, vaginal dyspareunia, intermittent vulvar and vaginal pruritus, and burning sensations. The typical vaginal discharge is homogeneous and purulent, yellowish or yellow-green in colour and negative on KOH tests. Vaginal inflammation is commonly observed, and is associated with ecchymosis-type bleeding and severe forms of ulceration.

Diagnosis is based on a combination of clinical features and wet-mount microscopy, including (1) abnormal yellowish leukorrhoea, (2) elevated vaginal pH (>5), (3) a foul, rotten smell (but negative KOH test), and (4) the presence of numerous leucocytes with a granular appearance [57]. Aerobic culture is not mandatory for diagnosis, as healthy women may also have a positive vaginal culture with low levels of aerobic bacteria. However, culture may be useful when clinical and microscopy examinations are ambiguous, as a massive growth of aerobes and low concentrations of lactobacilli will help to confirm the diagnosis and provide an antibacterial spectrum for antibiotic selection [57].

In fact, antibiotics are the cornerstone of aerobic vaginitis treatment. Kanamycin and clindamycin vaginal suppositories (1 per day, 6 days) appear to provide the best curative effect [57], and vaginal and oral probiotics may prevent relapses through
restoration of vaginal flora [58]. While aerobic vaginitis is associated with poorer outcomes in the setting of pregnancy, its implications in undiagnosed non-pregnant women remain unknown. In fact, no relevant data comparing outcomes in treated vs. untreated women are available. Thus, to date, no definitive conclusions can be drawn regarding the optimal management of such patients.

5. Conclusion

The care management of genitourinary infections in men with diabetes remains mainly empirical due to the lack of clear guidelines. On the other hand, UTIs in diabetic women are considered complicated infections, but recommended treatments are clearly defined. In general, there is no place for one-day or short-term treatments. Also, as women with T2D are more prone to developing lower genital tract infections, several clinical entities and recommended strategies have been proposed which sometimes require more prolonged treatment than in non-diabetic patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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