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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.

Keywords: Diabetes; Genital infections; SGLT2 inhibitors; Review; Urinary infections

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.

Abbreviations: UTI, urinary tract infection; CFU, colony-forming unit.

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Table 1
Male genitourinary infections: a summary.

Type of infection and main diagnosis	Recommended treatment	Dosage and duration of treatment	Alternative treatment if necessary
Urethritis Gonorrhoeal urethritis and non-gonococcal urethritis (*Chlamydia trachomatis*)	Ceftriaxone plus Azithromycin	Ceftriaxone 1 g single dose intramuscularly or intravenously plus Azithromycin 1.5 g orally	Cefixime 400 mg single dose orally or Azithromycin 1.0–1.5 g single dose orally
Acute prostatitis Predominantly Enterobacteriaceae, especially *Escherichia coli*	Broad-spectrum penicillin or Fluoroquinolone or Third-generation cephalosporin plus Aminoglycoside Transition to oral antibiotics (fluoroquinolones)	Fluoroquinolone prolonged for 6 weeks	Fluoroquinolones
Chronic prostatitis Spectrum of strains wider than for acute prostatitis, but dominated by *E. coli*	Fluoroquinolone	At least 4 weeks up to 3 months in some cases After reassessment, continue antibiotics if cultures positive	Ciprofloxacin or Levofloxacin
Bacterial orchitis and epididymis *Neisseria gonorrhoeae*; if WBCs found on urethral smear, *C. trachomatis* present in around two-thirds of cases	Empirical prescription: Fluoroquinolone	At least 2 weeks	If *C. trachomatis* detected: Doxycycline 200 mg/day after fluoroquinolone for at least 2 more weeks
Leucospermia ± semen infections	Antibiotic treatment according to semen culture results	Antibiotics for 2 weeks or anti-inflammatories for 2 months	For leucospermia plus negative semen culture: NSAID for 2 months plus antioxidants

WBCs: white blood cells; NSAID: non-steroidal anti-inflammatory drug.

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 gonorrhoeal 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