9.5 Urethritis 1606

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ESSENTIALS Urethritis is defined as detectable urethral inflammation in the pres- ence of symptoms or an observable urethral discharge. It is con- ventionally classified into gonococcal urethritis (caused by Neisseria gonorrhoeae) and nongonococcal urethritis (caused by Chlamydia trachomatis, Mycoplasma genitalium, and other causes, but with no known pathogen detected in over 30% of cases). Diagnosis is by urethral smear and microbiological investigations. Treatment with appropriate antibiotics should be given only to those with proven urethritis, and the diagnosis and its implications should be dis- cussed with the patient. Partner notification is essential, not only to prevent re-infection but also to prevent onward transmission from partner(s) and the development of complications if left untreated. Introduction Urethritis, as defined in clinical practice, is detectable urethral inflammation in the presence of symptoms (discharge, dysuria, and/or penile irritation) or an observable urethral discharge (acute urethritis). Detectable urethral inflammation in the ab- sence of symptoms or signs may not be uncommon in high-risk individuals (>1 sexual partner in the previous three months) and may resolve spontaneously. The detection of sexually transmitted organisms is much more common in men with acute urethritis who are clinically symptomatic. Our understanding of this con- dition is further complicated by the fact that some men with a discharge on examination do not report a urethral discharge (i.e. without an examination they would be classified as clinically asymptomatic). Historically urethritis was divided into gonococcal (GU) and nongonococcal (NGU) because they could be differentiated by microscopic examination of a urethral smear. Neisseria gonor- rhoeae could be confirmed by culture and specific treatment for gonorrhoea was effective in GU but not NGU. It was unclear why placebo treatments resulted in resolution of symptoms in 30% of symptomatic patients without GU and why some men had symp- toms in the absence of detectable inflammation, which could have a significant psychological morbidity. It was only in the 1970s that definitive diagnostic criteria for nongonococcal urethritis (NGU) were agreed, Chlamydia trachomatis identified as an important pathogen, and effective treatment regimens identified. Since then, Mycoplasma gentialium has also been identified as an important cause and the search is on to identify other causes. Aetiology of acute urethritis Urethritis is defined as either GU or NGU. This section will deal with acute (clinically symptomatic) urethritis (Table 9.5.1). GU is caused by Neisseria gonorrhoeae. The proportion of ureth- ritis cases attributable to gonorrhoea will depend on the popula- tion under investigation (e.g. geographical location and ethnicity) and the background asymptomatic carriage in high risk groups such as men who have sex with men. Chlamydia trachomatis is identified in 30–40% of cases. It is de- tected more often in younger men. Mycoplasma genitalium is identified in 10–25% of men. There is evidence of increasing macrolide antimicrobial resistance world- wide since 2009, probably as a result of azithromycin use to treat chlamydia and NGU. Quinolone

resistance is also on the increase. Ureaplasma urealyticum probably accounts for c.5% of cases. U. parvum is not associated with urethritis. Only recently have studies differentiated between U. urealyticum and U. parvum using nucleic acid amplification tests (NAAT), both of which are detected by culture. Nevertheless, asymptomatic carriage of U. urealyticum also occurs in men with urethritis, so even detection by NAAT does not indicate causality (see chapter on Mycoplasmas). Trichomonas vaginalis is an uncommon cause of urethritis in Western Europe. In countries or populations, such as the Afro- Caribbean community in the United Kingdom, where trichomonas is more common its importance as a cause of urethritis probably increases. Herpes virus and adenovirus account for less than 5% of cases. Bacterial urinary tract infection can occasionally present atypically as NGU. In over 30% of cases, none of these infections are identified. This has been termed idiopathic urethritis. N. meningitidis, Haemophilus sp., Candida sp., urethral stricture, and foreign bodies have all been 9.5 Urethritis Patrick Horner

9.5 Urethritis 1607 reported in a few cases. There is increasing evidence that bacterial vaginosis-associated bacteria, such as anaerobic peptococci or Leptotrichia/Sneathia spp. may potentially cause NGU in some men. It has also been postulated that a persistent immune response fol- lowing resolution of infection may account for some cases. Clinically asymptomatic urethritis often resolves spontaneously if left untreated, suggesting that in some men it may be a transient phenomenon. Although sexually transmitted infections (STIs) are isolated much less frequently from men with clinically asymptomatic ur- ethritis compared to those with symptoms or signs, the detection of STIs is more common than from men with no urethritis. Epidemiology Clinically symptomatic urethritis typically only occurs in men who are sexually active. It is associated with multiple sexual part- ners or recent change in sexual partner and unprotected sexual intercourse. Asymptomatic urethritis is also associated with high- risk behaviour. Although urethritis is commoner in younger men, it can also occur in older men (>35 years), which is consistent with the 2010 NATSAL survey indicating that more than 10% of men aged 35– 64 years had a new sexual partner in the previous year. Urethral infection with gonorrhoea usually results in symp- toms within 2–8 days, which is in general shorter than for micro- organisms that cause NGU (7–21 days). Pathology/Pathogenesis Urethritis is an inflammatory response to an infection which predominantly consists of polymorphonuclear leucocytes, al- though lymphocytes and macrophages are also present. This inflammatory response is, in general, greatest in men with gon- orrhoea, chlamydia, and M. genitalium. The greater the inflam- matory response, the greater the likelihood of symptoms, which probably explains the association of symptoms and/or signs with an STI in men with urethritis. Inflammation can persist even after eradication of the infection. In urethritis with a viral aeti- ology, mononuclear leucocytes predominate. Whether there are noninfective causes of urethritis following sexual intercourse is unknown. Clinical features The predominant symptoms are discharge and/or dysuria and/or penile/urethral irritation. Patients with gonorrhoea have a greater likelihood of a mucopurulent or purulent discharge than men without gonorrhoea (Figs. 9.5.1a and 9.5.1b). In men with ureth- ritis both a urethral discharge and/or dysuria are associated with detection of chlamydia and M. genitalium, but not in men solely with penile irritation. Men with symptoms of dysuria and/or penile irritation, with no observable discharge, and who do not have urethritis on micros- copy are not at increased risk of an STI. Differential diagnosis The differential diagnosis of urethritis is physiological urethral dis- charge, urinary tract infection, and acute pelvic pain of unknown aetiology. Clinical investigations Only clinically symptomatic patients should be examined for the presence of urethritis, and they are best managed in departments with access to microscopy to detect urethritis. Men should be examined for presence of a urethral discharge and

to check for other pathology such as ulceration (Figs. 9.5.1a and 9.5.1b). Ideally, examination and tests should be delayed for at least one hour after patients last voided urine. Urethral smear A urethral smear should be taken and used to prepare a Gram- stained slide for microscopic examination. More than four poly- morphonuclear cells per high power field (×1000) (pmns/hpf) in five or more fields is diagnostic of urethritis. The presence of intra- cellular Gram-negative diplococci has a more than 95% predictive value for N. gonorrhoeae. Low grade inflammation (5–15 pmns/ hpf) can be missed, particularly if the person taking the smear and/ or the microscopist is inexperienced. The patient should be reassured if their urethral smear is nega- tive. If their symptoms persist and microbiological tests are nega- tive, they should be advised to re-attend for an early morning urethral smear (EMS) having held their urine overnight (>8 hours) If microscopy is not possible, the following can be considered supportive of a diagnosis of urethritis, although their positive pre- dictive values are poor: (1) the presence of a mucopurulent/puru- lent urethral discharge (Figs. 9.5.1a and 9.5.1b); (2) a positive (>1+) leucocyte esterase test on a first voided urine (FVU) specimen; (3) the presence of urinary threads in the FVU specimen (Fig. 9.5.2). Microbiological investigations The following microbiological investigations should be under-taken: (1) urethral culture for N. gonorrhoeae; (2) NAAT of a FVU specimen for chlamydia and gonorrhoea; (3) FVU NAAT test for Table 9.5.1 Infections known to cause urethritis Causes of acute, clinically symptomatic urethritis Prevalence N. gonorrhoeae <1–30% C. trachomatis 25–40% M. genitalium 10–25% U. urealyticum (causal in <50%) 5–20% T. vaginalis <1–20% Adenoviruses, herpes simplex virus, urinary tract infection <5% None of these infections detected 30–40%

Section 9 Sexually transmitted diseases 1608 M. genitalium, which is highly likely to improve clinical outcomes. Ideally, if positive, these tests should also include macrolide and quinolone antimicrobial resistance genotyping; (4) dipstick urin- alysis of a mid-stream urine specimen if a urinary tract infection (UTI) is suspected. Treatment If urethritis is not identified, the UK and European guidelines recommend reassurance and awaiting results of microbiological investigations. An EMS is then indicated if symptoms persist, as discussed previously. Gonorrhoea Ceftriaxone intramuscularly as a single dose, with azithromycin (see Chapter 8.6.6). Nongonococcal urethritis The standard treatment is doxycycline 100 mg twice daily for seven days, which is recommended by the 2016 European treat- ment guideline. Although less effective against M. genitalium than azithromycin 1 g, it is not associated with the development of macrolide resistance. Azithromycin 1 g is no longer the recom- mended first-line treatment. If the patient is allergic to doxycycline, then azithromycin 500 mg as a single dose followed by 250 mg daily for four days is preferred. Discussion with the patient The diagnosis and its implications should be discussed with the patient. A patient information leaflet is available at: https://www. bashhguidelines.org/media/1040/ngu_pil_digital_2015.pdf Patients should be advised to abstain from sexual intercourse (even with a condom) for at least seven days or until symptoms have resolved, whichever is the longer. Partner notification is essential, not only to prevent re-infection but also to prevent onward transmission from partner(s) and the development of complications if left untreated (see Chapters 8.6.6 and 8.6.45). All sexual partners within the previous four weeks should be advised to be tested for chlamydia. Currently it is considered good practice to treat partners epidemiologically with doxycycline 100 mg twice daily for seven days before the results of tests are avail- able. Guidance may change when point-of-care NAAT testing for gonorrhoea, chlamydia, and M. genitalium becomes routinely avail- able, with treatment recommended only for those who are NAAT- positive, given the concerns about antimicrobial stewardship. Prognosis/outcome Ten to twenty per cent (10–20%) of patients with NGU will have recurrent or

persistent symptoms following initial treatment. For those with persistent symptoms, management is best undertaken in a specialist setting or in consultation with a specialist. Re-infection or persistent infection are the most likely causes, but symptoms (a) (b) Fig. 9.5.1 (a) Purulent gonococcal discharge. (b) Meatal inflammation in association with a mucopurulent discharge. A urethral discharge is sometimes only visible after urethral massage. Courtesy of Dr Colm O'Mahony. Fig. 9.5.2 Urinary threads in a first voided urine specimen. Courtesy of Mr Peter Greenhouse.

9.5 Urethritis 1609 can persist in the absence of inflammation and may resolve with reassurance. Further treatment should only be offered to men with confirmed urethritis on microscopy. The recommended second-line therapy is azithromycin 500 mg as a single dose, followed by 250 mg daily for four days, plus metronidazole 400 mg twice daily for five days. The optimal extended azithromycin regimen is not known and readers should refer to the European (IUSTI) or UK (BASHH) NGU guideline for up-to-date guidance. If macrolide-resistant M. genitalium is detected, treatment should be with moxifloxacin 400 mg once daily for 7–14 days, which should be used with caution because of rare but serious adverse hepatic reactions. Special circumstances/complications Men with urethritis may develop epididymo-orchitis or sexually acquired reactive arthritis, although these are uncommon compli- cations. Despite effective antimicrobial therapy, the symptoms may become chronic in some men, developing into chronic pelvic pain syndrome (CPPS). The aetiology of this condition is complex, with increased pelvic floor muscle tone probably playing an important role. A biopsychosocial pharmacotherapeutic approach for man- aging such patients has been demonstrated to be effective. Areas of uncertainty, controversy, and future developments With recent developments in bacterial genomics technology, re- search is beginning to focus on the male urethral microbiome with the prospect of other micro-organisms which can cause urethritis being elucidated. It is very likely that NAAT point-of-care testing for STIs will improve the management of men with symptoms of urethritis, enabling administration of infection specific treatment of index cases and their partner(s), resulting in better outcomes including possibly reducing costs and a reduction in use of antimicrobials. This will require evaluation through randomized controlled trials. Studies of the effect of the psyche on pelvic floor muscle tone and its role in the development and persistence of urogenital symptoms may lead to interventions that can help patients with distressing chronic pelvic pain. FURTHER READING BASHH (2014). UK Guidelines on the Management of Non-gonococcal Urethritis. https://www.bashh.org/guidelines Crofts M, et al. (2014). How to manage the chronic pelvic pain syn- drome in men presenting to sexual health services. Sex Transm Infect, 90, 370–3. Csonka GW (1965). Non-gonococcal urethritis. Br J Vener Dis, 41, 1–8. IUSTI (2012, 2016). European Guidelines on the Management of a) Gonorrhoea and b) Non-gonococcal Urethritis. https://www.iusti. org/regions/europe/euroguidelines.htm Moi H, Blee K, Horner PJ (2015). Management of non-gonococcal urethritis. BMC Infect Dis, 15, 294. Swartz SL, Kraus SJ (1979). Persistent urethral leukocytosis and asymptomatic chlamydial urethritis. J Infect Dis, 140, 614–7.

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