

Chlamydia and Nonspecific Urethritis

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C*hlamydia trachomatis* is the most common bacterial sexually transmitted micro-organism in the developed world, causing genital and ocular disease. Serovars A to C cause trachoma; serovars D to K primarily affect the genital tract. Non-gonococcal urethritis (NGU) or nonspecific urethritis is inflammation of the urethra. It is characterized by discharge and/or dysuria, but may be asymptomatic.

CHLAMYDIA TRACHOMATIS

Epidemiology

Chlamydia trachomatis genital infection is common. It is estimated that 3 to 5% of sexually active young women are infected, and up to 10% in selected groups. The prevalence in men is unknown but appears to be lower. Infection in the community is sustained by unrecognized, and thus untreated, symptomless infection, and appears to be increasing, particularly in the young. Worldwide, it is estimated that there are at least 89 million cases of *C trachomatis* infection each

year. In the USA, there are an estimated 4 to 5 million cases per year.

Chlamydial infection is associated with age under 25 years, a new sexual partner or more than one sexual partner in the recent past, lack of barrier contraception, use of the oral contraceptive pill, and termination of pregnancy.

Pathology and Pathogenesis

C trachomatis is an intracellular pathogen that provokes an inflammatory response. The pathogenesis of the chronic inflammatory sequelae of chlamydial infection is believed to be immunologically mediated. How this occurs is the subject of considerable research.

Infection is sexually acquired through penetrative sexual intercourse (including oral sex). There is some evidence that it can be acquired non-sexually, but this is rare. Most infected women are asymptomatic for months or even years, but 10 to 40% develop pelvic inflammatory disease (PID). The incubation period for this is unknown. Occasionally, perihepatitis also occurs. The risk of subsequent ectopic pregnancy

and infertility increases with the number of episodes of PID (sixfold after one episode, 17-fold after two episodes). Babies born through a *Chlamydia*-infected cervix may develop chlamydial conjunctivitis (30 to 50%) or chlamydial pneumonia.

Men usually develop urethritis within 1 month of acquiring infection, but up to 50% of men are asymptomatic. Occasionally, epididymo-orchitis develops. The incubation period for this is unknown.

Both men and women may develop sexually acquired reactive arthritis following infection (more common in men).

Diagnosis

About 80% of women with *Chlamydia* are asymptomatic. Any symptoms are usually nonspecific, and include increased vaginal discharge and irritation. Chlamydial infection can also cause post-coital or intermenstrual bleeding. Examination may reveal mucopurulent cervicitis with or without contact bleeding. (Figure 1) When PID is present, patients may complain of lower abdominal pain and may exhibit

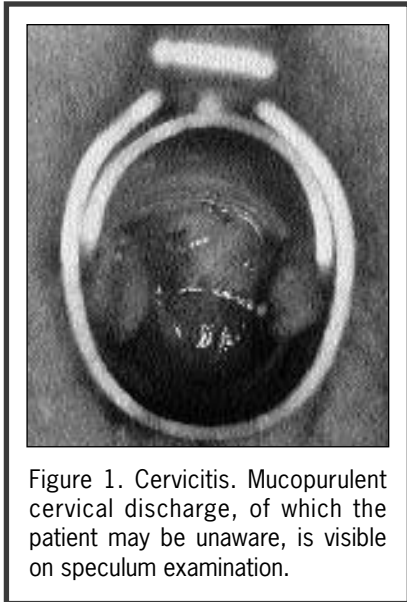


Figure 1. Cervicitis. Mucopurulent cervical discharge, of which the patient may be unaware, is visible on speculum examination.

cervical excitation (cervical motion tenderness) with uterine and adnexal tenderness on internal examination, but more commonly have symptomless tubal infection.

Some infected men have urethritis with urethral discharge (Figure 2) and/or dysuria, but the severity is variable and the symptoms may be so mild that they are unnoticed by the patient. Epididymo-orchitis is usually unilateral, but must be differentiated from torsion of the testicle, which is a surgical emergency.

Investigations

Diagnosis of *Chlamydia* continues to be a rapidly developing field. Several methods are currently used to detect infection, all of which have high specificity and variable sensitivity. They include culture, direct fluorescence antibody testing,

enzyme immunoassay (EIA) and nucleic acid amplification techniques such as ligase chain reaction and polymerase chain reaction analysis. Culture is now seldom used except for medicolegal purposes. EIAs are the most widely used tests, but have a wide range of sensitivities; only those with sensitivities of more than 85% should be used. Nucleic acid amplification techniques are more sensitive and specific but are considerably more expensive, and results of studies in the UK are awaited before they can be advocated as cost-effective.

In men, a first-void urine specimen should be used. Patients should hold their urine for at least 1 hour before the test, and preferably longer; otherwise, sensitivity is reduced. In women, a cervical swab combined with a urethral swab is the best specimen for EIA. EIA of a first-void urine specimen is not recommended in women. For nucleic acid amplification techniques, non-invasive sampling with both vulvovaginal swabs and first-voided urine specimens can be used. Endocervical swab samples must contain cellular material; the swab should be inserted inside the cervical os and rotated firmly against the endocervix. EIA should not be used for detecting *C trachomatis* in the rectum or pharynx.

Management

Ideally, patients should be referred to a department of genitourinary

medicine (GUM) for treatment, counselling and partner notification.

Drug Treatment

Doxycycline 100 mg bd for 7 days, or azithromycin 1 g po single dose are recommended. Both are highly efficacious in clinical practice. Azithromycin may be particularly useful in patients who might not complete a course of treatment. In pregnancy and in women who are breast-feeding, erythromycin 500 mg bd for 14 days, or amoxicillin 500 mg tds, are recommended. However, amoxicillin has been shown to induce latency *in vitro*, and there is therefore debate about its reliability. Both erythromycin and amoxicillin are less than 95% effective, and a test of cure 3 weeks after completing therapy is recommended.

Counselling

The following points should be discussed with the patient, and clear written information about them provided (this is best undertaken in a GUM department).

- What is *Chlamydia* and how is it transmitted?
- *Chlamydia* is often asymptomatic, particularly in women, and though tests are accurate, no test is absolutely so.
- What are the complications of untreated *Chlamydia*?
- The side effects of treatment and the importance of compliance should be discussed, and the patient

should be advised what to do if a dose is missed.

- Interactions between antibiotics and the oral contraceptive pill should be discussed.
- Patients should understand the importance of evaluation and treatment of their sex partner.
- Patients should be advised to abstain from sexual intercourse until they have completed therapy and their partner has been treated.
- Advice on safer sexual practices should be given.

Partner Notification

It is unknown how long *Chlamydia* can be carried asymptotically; an arbitrary cut-off time of 6 months or until the last previous sexual partner (whichever is longer)

is used in women and asymptomatic men. This time is 4 weeks in symptomatic male index patients. Common sense must be used in assessing which partners may be at risk.

Those at risk should be informed and invited to attend for evaluation and epidemiological treatment, even when tests are negative. This process may be patient-led, or provider-led if the patient is unwilling. It must be handled sensitively, and the confidentiality of the index patient must be maintained.

Follow-up

Follow-up is recommended at about 2 weeks to ensure that medication has been taken correctly and that the appropriate partners have been treated. This can be undertaken in person or by telephone.

NON-GONOCOCCAL URETHRITIS

Epidemiology

There are about 60,000 cases of NGU each year in the UK. It is most common in 20- to 24-year-olds, and is associated with a recent change in sexual partner and failure to use barrier contraception. It can also occur after unprotected fellatio. NGU can occur within a stable relationship, but this is unlikely in symptomatic disease.

Aetiology

C trachomatis is the most common cause of NGU (30 to 50%). *Urea-*

plasma urealyticum and *Mycoplasma genitalium* probably cause urethritis, each accounting for 10 to 20% of cases. These cannot be tested for in clinical practice. *Trichomonas vaginalis* is an uncommon cause of urethritis in the UK, but may account for up to 20% of cases in the developing world. *Neisseria meningitidis*, herpes simplex virus, *Candida* spp, bacterial urinary tract infection (UTI), urethral stricture and foreign bodies probably cause only a small proportion (<10%). In 20 to 30% of men with NGU, no organism is detected.

Pathology

Epididymo-orchitis or sexually acquired reactive arthritis develops in 1 to 3% of infected men. The latter is more common in chlamydial urethritis. Following initial treatment, 10 to 30% of men continue to have symptomatic disease (chronic NGU).

Diagnosis

Men usually complain of urethral discharge with or without dysuria. They may experience only penile tip irritation. Up to 30% are asymptomatic, but about one-half of these have an observable urethral discharge; this group has been termed 'genitally unaware'.

Examination often reveals urethral discharge (Figure 2), which may be present only on urethral massage (expression from base to tip of the penis). Inflammation of the

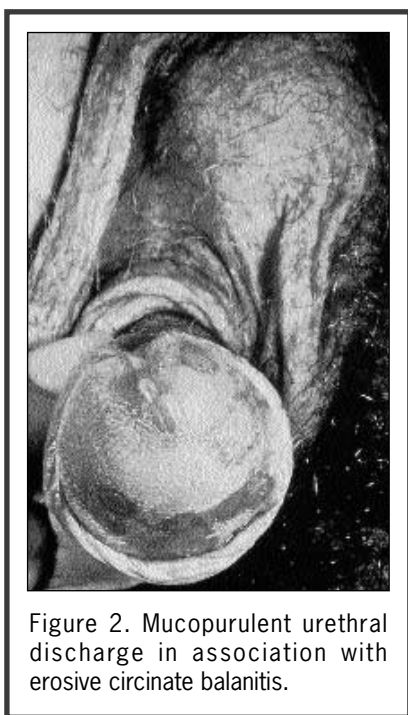


Figure 2. Mucopurulent urethral discharge in association with erosive circinate balanitis.

glans and prepuce may also be present. It is unknown whether this is a nonspecific cause of distal urethritis, a sign of NGU, or both. Circinate balanitis (Figure 2) is associated with sexually acquired reactive arthritis, but may occur independent of this.

Investigations

It is recommended that the diagnosis of urethritis should be confirmed by demonstrating neutrophils in the anterior urethra. This can be achieved by means of:

- a Gram-stained urethral smear containing ≥ 5 neutrophils/high-power ($\times 1000$) microscopic field (averaged over five fields with the greatest concentration of neutrophils);
- a Gram-stained preparation from a first-void urine specimen, containing ≥ 10 neutrophils/high-power ($\times 1000$) microscopic field (averaged over five fields with the greatest concentration of neutrophils).

In the UK, this test can currently be undertaken only in a GUM department with appropriate diagnostic facilities, to which all patients should be referred. If this is not possible, a mucopurulent or purulent urethral discharge can be considered presumptive evidence.

A urethral swab should be taken for gonococcal culture and a first-void urine specimen sent for chlamydial diagnosis (see above). Urinalysis of a mid-stream urine

(MSU) specimen using a dipstick that can detect leucocyte esterase and nitrites, and testing for blood, protein and glucose, should also be undertaken. In positive cases, an MSU specimen should be sent for microscopy and culture.

Differential Diagnosis

The symptoms of NGU overlap with those of UTI, emphasizing the importance of obtaining a sexual history from the patient. Patients with NGU do not usually report symptoms of cystitis (urinary frequency and urgency).

Management

The antibiotic regimens recommended for *C trachomatis* infection should be used in NGU. Patients should also be counselled as above.

Partner Notification

Partner notification is similar to that used for *C trachomatis* infection (see above). All at-risk sexual partners should be assessed and offered epidemiological treatment. The cut-off period is 4 weeks for symptomatic men and up to 6 months for asymptomatic men. Details of all contacts should be obtained at the first visit. Consent should be obtained to contact the patient or his partners if tests for *C trachomatis* or *N gonorrhoeae* are positive. This ensures that, if

the index patient does not reattend, he can be contacted and/or provider referral can be initiated for sexual contacts. When *C trachomatis* or *N gonorrhoeae* are detected, it is particularly important to ensure that all sexual partners who are potentially at risk have been notified. Female contacts of men with chlamydial urethritis should be treated regardless of the results of *Chlamydia* isolation.

Recurrent NGU

Ten to 30% of patients suffer symptomatic disease following treatment, though this is milder than at first presentation. The reasons for this are largely unknown. Patients should be referred to a GUM department for further management.

Follow-up

Patients should be followed-up at 2 weeks, by telephone or in person. Notification of partners, avoidance of intercourse and completion of treatment should be checked. A test of cure for *C trachomatis* is not required, but a repeat test for urethritis is advocated if the patient is symptomatic or a discharge is found on examination.

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