2015 UK national guideline for the management of infection with *Chlamydia trachomatis*

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Abstract

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of *Chlamydia trachomatis* genital infection. It covers the management of the initial presentation, as well the prevention of transmission and future infection. The guideline is aimed at individuals aged 16 years and older presenting to healthcare professionals working in departments offering Level 3 care in sexually transmitted infections management within the UK. However, the principles of the recommendations should be adopted across all levels, using local care pathways where appropriate.

Keywords

Sexually transmitted infection, Chlamydia, *Chlamydia trachomatis*, lymphogranuloma venereum, LGV, bacterial STIs, treatment, diagnosis, guideline

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New in the 2015 guidelines

- Use of nucleic acid amplification tests (NAATs) and point of care testing;
- Advice on repeat chlamydia testing;
- Discussion of adequacy of single-dose azithromycin treatment;
- Treatment of individuals co-infected with chlamydia and gonorrhoea;
- Treatment of rectal chlamydia;
- Vertical transmission and management of the neonate.

Introduction and methodology

Scope and purpose

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of *Chlamydia trachomatis* genital infection. It covers the management of the initial presentation, as well the prevention of transmission and future infection.

The guideline is aimed at individuals aged 16 years and older (see specific guideline for under 16 year olds) presenting to healthcare professionals working in departments offering Level 3 care in sexually transmitted infections (STIs) management within the UK.

However, the principles of the recommendations should be adopted across all levels, using local care pathways where appropriate.

Search strategy

This document was produced in accordance with the guidance set out in the CEG's document 'Framework for guideline development and assessment' at http://www.bashh.org/guidelines

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The following reference sources were used to provide a comprehensive basis for the guideline:

1. Medline, Pubmed and NeLH Guidelines Database searches up to 1 April 2015

The search strategy comprised the following terms in the title or abstract:

Chlamydia trachomatis
Management of *Chlamydia trachomatis*
Management of neonatal chlamydia infection
Natural history of *Chlamydia trachomatis*
Pelvic inflammatory disease
Chlamydia screening
Chlamydia treatment
Chlamydia partner notification
Chlamydia sequelae
Chlamydia repeat testing
Chlamydia treatment failure
Extra genital chlamydia infection

2. 2006 UK National Guideline on Management of Genital Tract Infection with *Chlamydia trachomatis*
3. 2012 BASHH statement on partner notification (PN) for sexually transmissible infections
4. The Scottish Intercollegiate Guidelines Network (SIGN)
5. 2015 CDC Sexually Transmitted Infections Guidelines
6. Cochrane Collaboration Databases (www.cochrane.org)
7. 2009 NICE Guidelines on management of uncomplicated genital chlamydia
8. UK National Chlamydia Screening Programme
9. 2013 UK National Guideline on the management of lymphogranuloma venereum (LGV)

Methods

Article titles and abstracts were reviewed and if relevant the full text article obtained. Priority was given to randomised controlled trial and systematic review evidence, and recommendations made and graded on the basis of best available evidence (Appendix 1).

Piloting and consultation, including public and patient involvement

The initial draft of the guideline, including the patient information leaflet (PIL), was piloted for validation by the CEG and a number of BASHH pilot sites. A standardised feedback form was completed by each pilot site for the PIL. The final draft guideline was then reviewed by the CEG using the AGREE instrument before posting it on the BASHH website for external peer review for a two-month period. Concurrently, it was reviewed by the BASHH Public and Patient Panel. Comments received were collated by the CEG editor and sent to the guideline chair for review and action. The final guideline was approved by the CEG, and a review date agreed before publication on the BASHH website.

Aetiology

Genital chlamydial infection is caused by the obligate intracellular bacterium *C. trachomatis*. Serotypes D–K cause urogenital infection, while serovars L1-L3 cause LGV.

Chlamydia is the most commonly reported curable bacterial STI in the UK. In 2013, 208,755 cases of infection were reported to Public Health England (PHE – formerly Health Protection Agency, England), with approximately 70% of these in sexually active young adults aged less than 25 years.[1] The highest prevalence rates are in 15–24-year olds and are estimated at 1.5–4.3% in the most recent National Survey of Sexual Attitudes and Lifestyles[2] and 5–10% in other studies.[3–6]

Risk factors for infection include age under 25 years, a new sexual partner or more than one sexual partner in the past year and lack of consistent condom use.[2,3,7–12]

Chlamydia infection has a high frequency of transmission, with concordance rates of up to 75% of partners being reported.[13,14]

The natural history of chlamydia infection is poorly understood. Infection is primarily through penetrative sexual intercourse, although the organism can be detected in the conjunctiva and nasopharynx without concomitant genital infection.[15,16]

If untreated, infection may persist or resolve spontaneously.[17–25] Studies evaluating the natural history of untreated genital *C. trachomatis* infection have shown that clearance increases with the duration of untreated infection, with up to 50% of infections spontaneously resolving approximately 12 months from initial diagnosis.[22–25] The exact mechanism of spontaneous clearance of *C. trachomatis* is not fully understood. Both host immune responses and biological properties of the organism itself have been shown to play a role.[22,23,26]

Chlamydia infection can cause significant short- and long-term morbidity. Complications of infection include pelvic inflammatory disease (PID), tubal infertility and ectopic pregnancy. A study by Aghaizu et al.[27] estimates the cost of treating a single episode of PID to be of the

order of £163, which in London alone, with 7000 cases per year, would equate to more than £1 m/year. Screening programmes have been introduced in some countries aimed at decreasing overall chlamydia prevalence and associated morbidity. In England, a National Chlamydia Screening Programme (NCSP) for sexually active women and men under 25 years of age has been in operation since April 2003.[28]

Clinical features

The majority of individuals with chlamydial infection are asymptomatic.[24] However, symptoms and signs include the following.

Women. Symptoms:

- Increased vaginal discharge;
- Post-coital and intermenstrual bleeding;
- Dysuria;
- Lower abdominal pain;
- Deep dyspareunia.

  Signs:

- Mucopurulent cervicitis with or without contact bleeding;
- Pelvic tenderness;
- Cervical motion tenderness;

Men. Symptoms (may be so mild as to be unnoticed):

- Urethral discharge;
- Dysuria;

  Signs:

- Urethral discharge.

Extra-genital infections

Rectal infections

Rectal infection is usually asymptomatic, but anal discharge and anorectal discomfort may occur.

Rates of rectal infection in men who have sex with men (MSM) have been estimated at between 3% and 10.5%.[29] Some studies of heterosexual women report high rates (up to 77.3%) of concurrent urogenital and anorectal infection,[30–32] other studies, however, report lower rates[33,34] with isolated rectal infections in some instances.[30,32] Not all women with rectal chlamydia report anal sex.[30–34] Further studies

with larger numbers of patients are needed to ascertain the utility of targeted versus routine rectal sampling in women.

Pharyngeal infections

Rates of chlamydia carriage in the throat in MSM range from 0.5 to 2.3%[35]; however, there is a paucity of good data on rates of pharyngeal infection in women.

Pharyngeal infection, as in the rectum, is usually asymptomatic.

Conjunctival infections

Chlamydial conjunctivitis in adults is usually sexually acquired. The usual presentation is of unilateral chronic, low-grade irritation; however, the condition may be bilateral.

Complications

Women

- PID, endometritis, salpingitis;
- Tubal infertility;
- Ectopic pregnancy;
- Sexually acquired reactive arthritis (SARA) (<1%);
- Perihepatitis.

In the literature, the estimated risk of developing PID after genital *C. trachomatis* infection varies considerably, and is estimated to be from less than 1% to up to 30%.[36–39] These differences in estimate are largely determined by the type of the test used (culture, enzyme immunoassay [EIA] or NAAT) and populations tested (symptomatic vs. asymptomatic, low risk vs. high risk). A recent analysis of all prospective studies of women with treated and untreated PID by Price et al.[40] estimated that up to 16% of women with untreated infection would be expected to develop clinical PID. One reason for the discrepancy in PID rates between earlier and more recent studies may be the enhanced sensitivity of NAATs, which results in more infections being diagnosed at an early stage before complications develop.

Symptomatic PID is associated with significant reproductive and gynaecologic morbidity, including infertility, ectopic pregnancy and chronic pelvic pain.[41,42]

The risk of developing tubal infertility after PID is estimated to range from 1 to 20%.[42] Prolonged exposure to *C. trachomatis*, either by persistent infection, or by frequent re-infection is considered a major contributing factor for tubal tissue damage,[43,44] and the importance of early diagnosis and treatment in reducing the risk of

subsequent infertility cannot be overemphasized.[45] In young people, reinfection rates of 10–30% have been found.[46]

Men

- SARA;
- Epididymo-orchitis.

Epididymo-orchitis has been described following infection with *C. trachomatis*,[47–49] and recent studies describe a possible association with male infertility[50–54]; however, the evidence for this is not conclusive.

LGV (see also BASHH LGV guideline – www.bashh.org)

Caused by the L1, L2 and L3 serotypes of *C. trachomatis*, LGV was rare in Western Europe and the USA for many years, but outbreaks of infection have occurred amongst MSM since 2003. Most cases have occurred in HIV-positive MSM.[55–59] Most patients present with proctitis,[60,61] however, asymptomatic infection may occur[62] (please see BASHH LGV guideline). A recent multi-centre study from PHE showed that 26% of patients with LGV were asymptomatic and these asymptomatic patients were more likely to be HIV infected than those with asymptomatic non-LGV chlamydial infection.[63]

Symptoms

- Tenesmus;
- Anorectal discharge (often bloody) and discomfort;
- Diarrhoea or altered bowel habit.

Diagnosis

NAAT. The current standard of care for all cases, including medico-legal cases and extra-genital infections, is NAAT.[64–67]

Although no test is 100% sensitive or specific, NAATs are known to be more sensitive and specific than EIAs.[68] Screening using EIA is no longer acceptable (Level IIa, Grade B).

There has been considerable debate as to whether a single reactive NAAT requires further confirmation, either by re-testing using a second NAAT with a different target/platform or simply repeating the test using the same NAAT platform. Many authorities no longer recommend testing with a second platform (except for medico-legal cases) as the positive predictive value of a single positive result is high in the context of a high prevalence population (Level IV, Grade C).[66,67,69–71]

It is desirable for an inhibition control to be present in the NAAT as substances may be present in biological fluids which can inhibit the test.[72] Failure to include an inhibitory control with each specimen could lead to false-negative results. However, this is not available with all commercial NAATs platforms (Table 1). Modern nucleic acid extraction techniques are likely to be able to effectively remove the majority of inhibitors.[73] It is important that users are aware of whether the method provided by their laboratory has this function and know how to interpret invalid results due to the presence of inhibitors (Level IV, Grade C).

nvCT. In 2006, a variant of *C. trachomatis* was reported in Sweden (new variant *C. trachomatis* – nvCT) with a 377 bp deletion in the cryptic plasmid.[74–76] Some commercial NAATs used this region of the cryptic plasmid as the amplification target[76] resulting in false-negative results. This new strain of chlamydia circulated mainly in Scandinavian countries and was likely selected in the population due to a failure in diagnosis.[77] There has so far, not been significant evidence for this organism in the UK and all major commercial platforms that use this region of the plasmid as target have re-designed their assays to mitigate against failure to detect this strain (Table 1).

Window period. The BASHH Bacterial Special Interest Group recommend that patients undergo testing for chlamydia when they first present, and that if there is concern about a sexual exposure within the last two weeks, that they return for a repeat NAAT test two weeks after the exposure (Level IV, Grade C).

Sites to be sampled

Vulvo-vaginal swabs (VVS). A vulvo-vaginal sample is the specimen of choice in women (Level IIa, Grade B).[78–81] This is collected by inserting a dry swab about 2–3 inches into the vagina and gently rotating for 10 to 30 s.

VVS has a sensitivity of 96–98% and can be either taken by the patient or a healthcare worker (HCW). Several studies indicate that VVS sensitivities are higher than those of cervical swabs,[82–85] as they pick up organisms in other parts of the genital tract. Self-taken VVS are more acceptable to women than urine or cervical specimens.[86,87] In addition, a dry VVS can be sent by post by the patient back to the laboratory for testing without significant loss of sensitivity.[88]

Endocervical swabs. These have been shown to be less sensitive than VVS (see above), and require a speculum examination performed by an HCW.

Table 1. Comparison of the characteristics of four commonly used automated NAAT platforms for the detection of *Chlamydia trachomatis* nucleic acid in clinical specimens.

	Abbott	BD	GenProbe	Roche
Name of test	Real-time CT/NG	BD Probe Tec	Aptima Combo AC2	Cobas c4800
Amplification method	Real-time PCR	Strand Displacement Amplification (SDA)	Transcription Mediated Amplification (TMA)	Real-time PCR
Chlamydia trachomatis **targets**	Cryptic plasmid (dual targets)	Cryptic plasmid	23S rRNA	Cryptic plasmid and ompA gene (dual targets)
nvCT detection	Yes	Yes	Yes	Yes
Plasmid free *Chlamydia trachomatis* **detection**	No	No	Yes	Yes
Confirmation test using an alternative target	No	No	Yes (16S rRNA)	No
Internal control	Internal control (from extraction to amplification)	Extraction control only, no amplification control	None	Internal control (from extraction to amplification)
Validation for extra-genital site testing[96,99,100]	No data	Rectal (sensitivity 63%); oropharyngeal (sensitivity 67%)	Rectal (sensitivity 93%); oropharyngeal (sensitivity 100%)	NA[a]

[a]An older version of Roche Cobas PCR was evaluated, sensitivity for rectal *Chlamydia trachomatis*: 91.4% to 95.8%.

An endocervical swab is taken and as the sample must contain cervical columnar cells, the swab should be inserted into the cervical os and firmly rotated against the endocervix. Inadequate specimens reduce the sensitivity of NAATs.[78,80]

First-catch urine

Variable sensitivities have been reported using first-catch urine (FCU) specimens in women.[80,84,85] The lower sensitivity is attributed to the presence of fewer organisms in the female urethra compared to other parts of the female genital tract. As self-taken vulvo-vaginal swabs (VVS) have a high acceptance rate and generally perform well, these should be preferred over FCU (Level IIa, Grade B).

FCU in men is reported to be as,[89,90] or more[91] sensitive than urethral sampling (Level IIa, Grade B). Urine samples are easy to collect, do not cause discomfort and thus are preferable to urethral swabs.

To collect FCU, patients should be instructed to hold their urine for at least 1 h before being tested. The first 20 ml of the urinary stream should be captured as the earliest portion of the FCU contains the highest organism load.[92]

Urethral swabs. Urethral swabs, if taken, should be inserted 2–4 cm inside the urethra and rotated once before removal. Studies of self-taken penile-meatal swabs have yielded good results[93,94] but may be less acceptable to patients compared to urine.[94]

Extra-genital sampling

Rectal swabs. NAATs are the assays of choice for both genital and extra-genital samples, though the sensitivities are variable (Table 1) (Level IIa, Grade B).[66,67,95,96]

Rectal swabs can be obtained via proctoscopy or taken 'blind' by the patient or a HCW.[67] In order to minimise testing costs, some centres are also piloting combination samples by pooling urine, rectal swab and oro-pharyngeal swabs together into a single sample. Validation of such an approach is required as the pooling may reduce sensitivity and in the event of a reactive result, the precise site of infection would be unknown.

As a result of high rates of LGV infection in MSM (and particularly HIV-positive MSM),[55–59,62] PHE recommends that LGV testing should be performed in individuals with proctitis and on HIV-positive MSM (with or without symptoms) with *C. trachomatis* at any site (Level III, Grade B).[63] Samples should be sent to the Public Health England Sexually Transmitted Bacterial Reference Unit (STBRU) or to a local laboratory if a properly validated test is available.

Women with proctitis should be tested for LGV and managed in the same way as men (Level IV, Grade C).

Acceptability of self-taken extra-genital samples. Several studies have favourably evaluated the acceptability of self-taken rectal and pharyngeal swabs.[67,97–99]

Recommendations

1. Testing for genital and extra-genital chlamydia should be performed using NAATs (Level IIa, Grade B).
2. VVS are the specimens of choice for women (Level IIa, Grade B).
3. FCU is the sample of choice to identify urethral chlamydia in men (Level IIa, Grade B).
4. LGV testing should be performed in individuals with proctitis (Level III, Grade B).
5. HIV-positive MSM with *C. trachomatis* at any site should be routinely tested for LGV regardless of symptoms (Level III, Grade B).
6. Individual services may choose to conduct LGV testing according to the characteristics of their own case mix and resources (Level IV, Grade C).
7. Women with symptoms of proctitis should be managed in the same way as men (Level IV, Grade C).

Medico-legal cases

For medico-legal cases, a NAAT should be taken from all the sites where penetration has occurred. Due to the low sensitivity of culture (60–80%) and its lack of availability in many centres, this technique is no longer recommended (Level III, Grade B).

In medico-legal cases, for best practice, a reactive NAAT result should be confirmed using a different target to ensure reproducibility.

Point-of-care testing (POCT)

The majority of chlamydia tests available in clinical practice are laboratory-based with a significant lag time between testing and diagnosis.

Previous generation EIA-based point-of-care testing (POCTs) have lacked sensitivity[100]; however, enhanced sensitivity POCTs have been developed with sensitivities up to 82–84% compared to NAAT.[101,102]

A new generation of POCTs using NAAT is being developed, which are likely to be cost-effective compared to laboratory-based NAATs. These are suitable for genital samples and considerably reduce the time from testing to diagnosis.[103] When testing extra-genital specimens and as confirmatory tests using residual specimens from other commercial platforms, these tests require more validation, however, preliminary work is promising.[104]

Management

General advice

Ideally, treatment should be effective (microbiological cure rate >95%), easy to take (not more than twice daily), with a low side-effect profile and cause minimal interference with daily lifestyle (Level Ia, Grade A).

Uncomplicated genital infection with *C. trachomatis* is not an indication for removal of an IUD or IUS (Level Ia, Grade B).

Patients should be advised to avoid sexual intercourse (including oral sex) until they and their partner(s) have completed treatment (or wait seven days if treated with azithromycin) (Level IV, Grade C).

Patients should be given detailed information on the natural history of chlamydia infection, as well as its transmission, treatment and complications, and directed to clear, accurate written or web-based patient information (Level IV, Grade C).

PILs for STIs can be found on the guidelines page of the BASHH website and are produced and updated when new guidance is published or new information becomes available.

Further investigation

All patients diagnosed with *C. trachomatis* should be encouraged to have screening for other STIs, including HIV, and where indicated, hepatitis B screening and vaccination (Level IV, Grade C).

If the patient is within the window periods for HIV and syphilis, these should be repeated at an appropriate time interval. All contacts of *C. trachomatis* should be offered the same screening tests (Level IV, Grade C).

Treatment of uncomplicated genital, rectal and pharyngeal infection (see appropriate guidelines for management of complications) and epidemiological treatment

Single dose (1 g) azithromycin and seven days of doxycycline have been found to be equally efficacious for the treatment of genital chlamydial infection with cure rates of 97% and 98%, respectively.[105] In more recent years however, reports of azithromycin treatment failures[106,107] (up to 8%) have questioned the effectiveness of this treatment.[108–110]

A meta-analysis of randomised controlled trials comparing doxycycline with azithromycin published

in 2014 found a small (3%) but statistically significant increased benefit of doxycycline over azithromycin for urogenital chlamydia and a benefit of doxycycline over azithromycin of 7% in men with symptomatic urethral chlamydia. The quality of studies varied, and there were few double-blind, placebo-controlled trials.[111]

On the strength of currently available evidence, there are insufficient data to recommend the use of doxycycline over azithromycin for the treatment of urogenital chlamydial infection.

Azithromycin has also been found to be less effective than doxycycline in some studies of rectal chlamydial infection.[112,113]

This has resulted in doxycycline being used in preference to azithromycin for the treatment of rectal chlamydia in the UK over the last few years, but it is important to note that no randomised controlled trials have been performed for the treatment of rectal chlamydia infection.

A 2015 meta-analysis of eight observational studies by Kong et al.[114] showed a 19.9% difference in efficacy in favour of doxycycline over azithromycin for treatment of rectal chlamydia. The authors noted the poor quality of the available evidence; however, the size of the difference between the two drugs in this meta-analysis is cause for concern. In view of these concerns, doxycycline is recommended as the preferred treatment for rectal chlamydia.

There are no randomised controlled trials comparing the efficacy of doxycycline with azithromycin for the treatment of pharyngeal infection.

It is vital that randomised controlled trials, including follow-up studies of treated patients with genital and extra-genital infection, are performed to address this important question.

Recommended regimens

Uncomplicated urogenital infection (Level Ia, Grade A) and pharyngeal infection (Level IV, Grade C):

- Doxycycline 100 mg bd for seven days (contraindicated in pregnancy)
  or
- Azithromycin 1 g orally in a single dose.

Alternative regimens (if either of the above treatments is contraindicated):

- Erythromycin 500 mg bd for 10–14 days (Level IV, Grade C)
  or
- Ofloxacin 200 mg bd or 400 mg od for seven days (Level Ib, Grade A)

Rectal infection (non-LGV) (Level III, Grade C)

Preferred treatment

- Doxycycline 100 mg bd for seven days

Alternative treatment

- Azithromycin 1 g orally in a single dose (see section on Test of Cure [TOC] below).

Other antimicrobials

There is less information from published studies on antimicrobials other than doxycycline and azithromycin.

Ofloxacin (Level Ib, Grade A)

- Ofloxacin has similar efficacy to doxycycline[115] but carries a risk of *C. difficile* infection and tendon rupture. It is also considerably more expensive than doxycycline.

Erythromycin (Level IV, Grade C)

- Erythromycin is less efficacious than either azithromycin or doxycycline.[116]
- When taken four times daily, 20–25% of individuals may experience side-effects sufficient to cause discontinuation of treatment.[117]
- There are only limited data on erythromycin 500 mg twice a day, with efficacy reported at between 73 and 95%. A 10–14 day-course appears to be more efficacious than a seven-day course of 500 mg twice a day, with a cure rate >95%.[117]

HIV-positive individuals

HIV-positive individuals with genital and pharyngeal chlamydial infection should be managed in the same way as HIV-negative individuals. (Level IV, Grade C).

Due to the high prevalence of LGV in this population, HIV-positive individuals with rectal chlamydia who do not have a test for LGV should be treated with three weeks of doxycycline or should have a TOC (Level IV, Grade C).

Pregnancy and breast feeding

Doxycycline and ofloxacin are contraindicated in pregnancy.

Recommended regimens (Level Ia, Grade A)

- Azithromycin 1 g as a single dose
  or
- Erythromycin 500 mg four times daily for seven days
  or
- Erythromycin 500 mg twice daily for 14 days
  or
- Amoxicillin 500 mg three times a day for seven days.

Clinical experience and published studies suggest that azithromycin is safe and efficacious in pregnancy,[117–120] and the World Health Organization (WHO) recommends its use in pregnancy although the British National Formulary (BNF) states that manufacturers advise use only if adequate alternatives not available.

Erythromycin has a significant side-effect profile and is less than 95% effective. A randomised non-blinded study comparing azithromycin with erythromycin in pregnant women showed similar efficacy; however, azithromycin was much better tolerated and 19% of women in the erythromycin arm discontinued treatment compared with 2% in the azithromycin arm.[121]

Amoxycillin had a similar cure rate to erythromycin in a meta-analysis and a much better side-effect profile.[120] However, penicillin *in vitro* has been shown to induce latency and re-emergence of infection at a later date is a theoretical concern of some experts.

It is recommended that women treated for chlamydia in pregnancy undergo a TOC (which should be performed no earlier than three weeks after completing treatment) (Level IV, Grade C).

Treatment of chlamydia and gonorrhoea co-infection

BASHH recommends treatment for uncomplicated *Neisseria gonorrhoeae* infection with ceftriaxone 500 mg given intramuscularly with 1 g of azithromycin.[122] The azithromycin is given as an adjunct treatment to protect the ceftriaxone in order to delay the development of resistance and not to treat co-existing chlamydia, although it will also do this. It should be noted, however, that because *N. gonorrhoeae* exhibits significant tetracycline resistance,[123] doxycycline should not be used in place of azithromycin.

Individuals with gonorrhoea who require doxycycline for treatment of rectal chlamydia or LGV should be treated with all three drugs (Level IV, Grade C).

Reactions to treatment and cautions

Azithromycin, erythromycin, doxycycline, ofloxacin and amoxicillin may all cause gastro-intestinal upset including nausea, vomiting, abdominal discomfort and diarrhoea. These side-effects are more common with erythromycin than with azithromycin. With all macrolides, hepatotoxicity (including cholestatic jaundice) and rash may occur but are infrequent.

Azithromycin may be associated with prolongation of the QT interval and should be used with caution or avoided in individuals with abnormalities of cardiac rhythm.

Doxycycline may cause dysphagia and oesophageal irritation. Patients should be advised to swallow capsules whole with plenty of fluid during meals while sitting or standing and should be advised to avoid sunlamps and direct sunshine.

Amoxicillin should not be administered to penicillin-allergic individuals.

Recommendations

- Doxycycline and azithromycin are recommended as equal treatments for uncomplicated genital and pharyngeal infections (Level 1 a, Grade B).
- Doxycycline is the preferred treatment for rectal infection (Level III, Grade B).
- Women with proctitis should be managed in the same way as men (Level IV, Grade C).
- Doxycycline and ofloxacin should not be used in pregnancy (Level IV, Grade C).
- Individuals co-infected with gonorrhoea and rectal chlamydia should be treated with ceftriaxone, azithromycin and doxycycline (Level IV, Grade C).
- HIV-positive individuals with genital and pharyngeal chlamydial infection should be managed in the same way as HIV-negative individuals. (Level IV, Grade C).
- HIV-positive individuals with rectal chlamydia who do not have a test for LGV should be treated with three weeks of doxycycline or should have a TOC (Level IV, Grade C).

Test of Cure (TOC)

TOC is not routinely recommended for uncomplicated genital chlamydia infection, because residual, non-viable chlamydial DNA may be detected by NAAT for 3–5 weeks following treatment.[124,125]

TOC is recommended in pregnancy, where poor compliance is suspected and where symptoms persist (Level IV, Grade C).

It should be noted that asymptomatic LGV infections have been identified in both HIV-positive and -negative MSM,[62,126–129] and such individuals who test positive for rectal chlamydia who are not also tested for LGV risk not being treated for this.

Asymptomatic HIV-negative MSM with rectal chlamydia (unless an LGV test has been performed and is negative) should therefore be retested after treatment with single-dose azithromycin or seven days of doxycycline to ensure that LGV infection is not missed. Alternatively, consideration should be given to a three-week course of doxycycline to cover LGV if a test is not performed (Level IV, Grade C).

There are few data on the optimum time to perform a TOC; however, for the reasons discussed above, this should be deferred for at least three weeks after treatment is completed.[116,124,125,130]

Re-infection and repeat testing

The recent studies showing higher treatment failure rates with azithromycin compared to doxycycline have raised concerns about antibiotic resistance. There have been no published cases of isolates with genetic resistance to azithromycin *in vivo*,[131–133] however, these concerns underline the need for further work in this area. TOC should be differentiated from testing for re-infection. Re-infection is common[134,135] and usually occurs within two to five months of the previous infection.[136] In practice, it may be difficult to distinguish between treatment failure and rapid re-infection.

Following an extensive review of the evidence and a professional and public consultation, in August 2013, the National Chlamydia Screening Programme (NCSP) in England issued a recommendation that young people under the age of 25 who test positive for chlamydia should be offered a repeat test around three months after treatment of the initial infection.[28] This guidance is based on evidence that young adults who test positive for chlamydia are 2–6 times more likely to have a subsequent positive test, and that repeated chlamydia infection is associated with an increased risk of complications such as PID and tubal infertility.[45] Several other countries recommend repeat testing in individuals with a positive test at intervals ranging from 3 to 12 months.[130,137–139]

A positive result following treatment may be due to poor adherence to treatment, re-infection from an untreated or new partner, inadequacy of treatment or a false-positive result.

Mathematical modelling has shown that re-infections are likely to be important in sustaining a chlamydia epidemic.[136] Because individuals who test positive for chlamydia are at higher risk of a repeat infection, repeat testing allows rapid diagnosis and treatment thereby reducing the risk of onward transmission and long-term complications. Modelling studies in the USA have shown that repeat infection rates peak at 2–5 months after the initial infection[140] which provides the rationale for recommendations to re-test 3–6 months after treatment (Level III, Grade B).[28,130,137–139]

Data regarding the utility of repeat testing in over 25-year olds are limited, as the majority of published studies are in 16–25-year olds. Studies that have included subjects over 25 years of age found a significantly greater incidence in younger subjects than in older individuals.[134–135,140] There is therefore, at present, insufficient evidence for extending the recommendation for repeat testing to adults over the age of 25 years.

The introduction of repeat testing for all individuals with a positive chlamydia diagnosis is likely to result in a reduction in the prevalence of chlamydial infection which would have significant public health benefits. However, careful consideration of the costs of this and the impact on service delivery are warranted. Effective partner notification, education and treatment remain paramount.

The STBRU at PHE offers a *C. trachomatis* culture reference service which is available for clinicians to refer specimens from patients who have failed treatment and are at low risk of having been re-infected.[141]

Recommendations

- TOC is not routinely recommended following completion of treatment but should be performed in pregnancy, where LGV (in the absence of a definite negative result) or poor compliance is suspected, where symptoms persist, and in rectal infection when single-dose azithromycin or one week of doxycycline are used as these are inadequate to treat LGV. Alternatively, consideration should be given to treating for three weeks with doxycycline (Level IV, Grade C).
- TOC should be performed no earlier than three weeks after completion of treatment (Level III, Grade B).
- Repeat testing should be performed 3–6 months after treatment in under 25-years olds diagnosed with chlamydia (Level III, Grade B)
- There is insufficient evidence to recommend routine repeat testing in individuals over the age of 25; however, this should be considered in those considered to be at high risk of re-infection (Level IV, Grade C).

Vertical transmission and management of the neonate

Neonatal chlamydia infection is a significant cause of neonatal morbidity. Its most common manifestations are ophthalmia neonatorum and pneumonia. Transmission to the neonate is by direct contact with the infected maternal genital tract, and infection may involve the eyes, oropharynx, urogenital tract or rectum.[142] Infection may be asymptomatic. Conjunctivitis generally develops 5–12 days after

birth and pneumonia between the ages of one and three months. Neonatal chlamydial infection is much less common nowadays because of increased screening and treatment of pregnant women. However, chlamydial infection should be considered in all infants who develop conjunctivitis within 30 days of birth.[130] In view of the fact that infection may occur at multiple sites, oral therapy is recommended.

Diagnosis of neonatal chlamydia infection

The diagnosis is most frequently made on clinical grounds, as the results of tests are not routinely immediately available.

Although NAAT testing is not validated, its widespread use in the diagnosis of rectal and pharyngeal infection in adults suggests that it should be effective in the diagnosis of neonatal infections. In conjunctivitis, specimens should be obtained from the everted eyelid using a dacron-tipped swab or the swab specified by the manufacturer's test kit, and should contain conjunctival cells and not exudate alone. Specimens should also be tested for *N. gonorrhoeae*. For pneumonia, specimens should be collected from the nasopharynx. NAATs for *Chlamydophila pneumoniae* (formerly known as *C. pneumoniae*) do not detect *C. trachomatis*.

Treatment of the infected neonate

Treatment is with oral erythromycin (topical treatment is inadequate and unnecessary if oral treatment is given) 50 mg/kg/day in four divided doses for 14 days.[130] There are limited data on the use of other macrolides, although one study suggested that azithromycin 20 mg/kg/day orally, one dose daily for three days, might be effective.[130,143]

Mothers of infants with chlamydial infection should be tested, treated and offered PN if this has not already been done.

Follow-up

Compliance with therapy. In general, compliance with therapy is improved if there is a positive therapeutic relationship between the patient and the HCW.[144]

This can probably be improved if the following are applied (Level IV, Grade C):

Discussion with patient and provision of clear written information on:

- What *C. trachomatis* is and how it is transmitted?
  – It is sexually transmitted.
  – If asymptomatic, there is evidence that it could have persisted for months or years.

- The diagnosis of *C. trachomatis*, particularly:
  – It is often asymptomatic in both men and women.
  – While tests are extremely accurate, no test is absolutely so.
- The complications of untreated *C. trachomatis*.
- Side-effects and importance of complying fully with treatment and what to do if a dose is missed.
- The importance of sexual partner(s) being evaluated and treated.
- The importance of abstention from sexual intercourse until they and their partner(s) have completed therapy (and waited seven days if treated with azithromycin).
- Advice on safer sexual practices, including advice on correct, consistent condom use.

Reducing the risk of retesting chlamydia positive after treatment

A repeat positive test following treatment may result from suboptimal initial treatment, re-infection or re-testing too early.

NAATs may remain positive for at least three weeks post-treatment. This does not necessarily mean active infection as it may represent the presence of non-viable organisms.

Identification and treatment of partners are essential to reduce the risk of re-infection. With training and support, PN in primary care can be effective without having to refer to health advisors in genito-urinary medicine clinics.[145] HCWs providing PN should have documented competencies appropriate to the care given.[146] These competencies should correspond to the content and methods described in the Society of Sexual Health Advisers (SSHA) Competency Framework for Sexual Health Advisers.[147,148]

Recommendations

- Ensure that there has been no further potential exposure since treatment. If still within window period (two weeks), patient and partner(s) should be offered epidemiological treatment (with no further unprotected sex until treatment complete) (Level IV, Grade C).
- Advise (and document that advice has been given) no genital, oral or anal sex even with condom, until both index patient and partner(s) have been treated. If partner(s) chooses to test before treatment, advise no sex until partner is known to have tested negative. Level IV, Grade C).

- After treatment with azithromycin, patients should abstain from sexual activity for one week; after doxycycline, patients may resume sexual activity at the end of the seven-day course. (Level IV, Grade C).

Contact tracing and treatment

Management of sexual partners. Services should have appropriately trained staff in PN skills to improve outcomes (Level Ib, Grade A).

- All patients identified with *C. trachomatis* should have PN discussed at the time of diagnosis by a trained healthcare professional.
- The method of PN for each partner/contact identified should be documented, as should PN outcomes.
- All sexual partners should be offered, and encouraged to take up, full STI screening, including HIV testing and if indicated, hepatitis B screening ± vaccination (Level IV, Grade C).

Look-back period

HCWs should refer to the BASHH statement on PN.[146]

There are limited data regarding how far back to go when trying to identify sexual partners potentially at risk of infection. Any sexual partners in the look back periods below should be notified, if possible, that they have potentially been in contact with *C. trachomatis.*

- Male index cases with urethral symptoms: all contacts since, and in the four weeks prior to, the onset of symptoms (Level IV, Grade C).
- All other index cases (i.e. all females, asymptomatic males and males with symptoms at other sites, including rectal, throat and eye): all contacts in the six months prior to presentation (Level IV, Grade C).

Risk reduction

Index cases should have one-to-one structured discussions on the basis of behaviour change theories to address factors that can help reduce risk taking and improve self-efficacy and motivation.[148] In most cases, this can be a brief intervention discussing condom use and re-infection at the time of chlamydia treatment. Some index cases may require more in-depth risk reduction work and referral to a HCW trained in PN for motivational interviewing (Level Ib, Grade A).

Follow-up and resolution of PN

Follow-up is important for the following reasons:

- It enables resolution of PN.
- It provides an opportunity to reinforce health education.
- It provides a means of ascertaining adherence to treatment and appropriate abstinence from sexual activity.

Follow-up may be by attendance to clinic or by telephone. There is evidence to suggest that follow-up by telephone may be as good as a clinic visit in achieving PN outcomes,[148] a view endorsed in the BASHH PN statement.[146]

PN resolution (the outcome of an agreed contact action) for each contact should be documented within four weeks of the date of the first PN discussion (Level IV, Grade C). Documentation about outcomes may include the attendance of a contact at a service for the management of the infection, testing for the relevant infection, the result of testing and appropriate treatment of a contact. A record should be made of whether this is based on index case report, or verified by a HCW.

Auditable outcome measures

- The percentage of cases offered a recommended treatment according to the type of chlamydial infection (performance standard 97%).
- The percentage of LGV tests performed on *C. trachomatis* reactive rectal specimens, both for MSM with proctitis, as well as for MSM with HIV infection (with or without symptoms) (performance standard 97%).
- Individuals provided with written information about their diagnosis and management (performance standard 97%).
- PN performed and documented according to BASHH Statement on PN for sexually transmissible infections (see www.bashh.org/guidelines) (performance standard 97%).

Declaration of Conflicting Interests

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Appendix 1

Levels of evidence and grading of recommendations

Level of evidence

Ia Meta-analysis of randomised controlled trials
Ib At least one randomised controlled trial
IIa At least one well designed controlled study without randomisation
IIb At least one other type of well-designed quasi-experimental study
III Well designed non-experimental descriptive studies
IV Expert committee reports or opinions of respected authorities

Grading of recommendation

A Evidence at level Ia or Ib
B Evidence at level IIa, IIb or III
C Evidence at level IV