European Dermatology Forum

Guideline on the Management of Chlamydia trachomatis Infections

Developed by the Guideline Subcommittee “Chlamydia trachomatis” of the
European Dermatology Forum

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GUIDELINE

2015 European guideline on the management of *Chlamydia trachomatis* infections

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Summary: *Chlamydia trachomatis* infections, which most frequently are asymptomatic, are major public health concerns globally. Compared to the outdated 2010 European *C. trachomatis* guideline, the present 2015 European *C. trachomatis* guideline provides up-to-date guidance regarding broader indications for testing and treatment of *C. trachomatis* infections; clearer recommendation of using NAATs only for diagnosis; advice on (repeated) *C. trachomatis* testing; recommendation of increased testing to reduce the incidence of pelvic inflammatory disease and prevent exposure to infection; and recommendations to identify, verify and report *C. trachomatis* variants.

Improvement of access to testing, test performance, diagnostics, antimicrobial treatment and follow-up of *C. trachomatis* patients are crucial to control its spread. For detailed background, evidence base and discussions, see the background review for the present 2015 European guideline on the management of *Chlamydia trachomatis* infections (Lanjouw E, et al. Int J STD AIDS. 2015).

Keywords: *Chlamydia trachomatis*, chlamydial infection, European guideline, management, diagnosis, treatment, antibiotic, systematic review, meta-analysis

AETIOLOGY, TRANSMISSION AND EPIDEMIOLOGY

Chlamydia trachomatis is an obligate intracellular bacterium that infects over 100 million people each year worldwide by sexual transmission. The majority of persons with anogenital *C. trachomatis* infection are not aware of their infection because it is frequently asymptomatic. Urogenital chlamydial infection can lead to serious adverse outcomes in women, e.g., pelvic inflammatory disease (PID) that can result in tubal factor infertility, ectopic pregnancy and chronic pelvic pain.[1] Urogenital chlamydial infections do not result in any sustained immunity.

Since the 1990's, an increase of urogenital *C. trachomatis* infections has been reported from several countries, e.g., the USA, Canada, United Kingdom (UK) and the Scandinavian countries.[2-4] The prevalence estimates in nationally representative samples of sexually experienced 18–26 year olds in Europe have been relatively similar in women and men (estimated ranging between 3-5.3% and 2.4-7.3%, respectively) and statistically consistent with those in other high income countries.[3-6] The incidence of diagnosed *C. trachomatis* cases reported to the European Centre for Disease Prevention and Control (ECDC) from 26 European Union (EU) and European Economic Area (EEA) countries in 2013 was 182 per 100 000 population (384 555 cases). Nevertheless, there was substantial variation across the EU/EEA countries in the incidence of reported *C. trachomatis* cases, with rates ranging from below 1 to more than 600 cases per 100 000 population.[4] Comparison between countries is considerably challenged by differences in the surveillance systems, the diagnostic methods used, the access to and amount of testing and screening (general screening programme or opportunistic testing) for

chlamydial infection, and the proportion of underreporting.[3] Young age (usually below 25 years of age) and behavioural risk factors such as prior *C. trachomatis* infection, lack of consistent condom use and new or multiple partners per year are the main risk factors for acquisition of *C. trachomatis* infection.[7]

Transmission of *C. trachomatis* usually takes place by direct mucosal contact between two individuals during sexual intercourse or at birth through an infected cervical canal. It is difficult to estimate the risk of sexual transmission. One transmission dynamic mathematical modeling study provided estimates,[8] based on data from a cross-sectional heterosexual partnership study in clinical attendees.[9] The model estimated a median transmission probability of around 10% for a single act of vaginal coitus and around 55% over the course of a partnership in a population that has two partnerships in a six month period. Partners of people with *C. trachomatis* infection are very likely to be infected themselves,[9] so contact notification and subsequent treatment are very important.

C. trachomatis belongs to the genus Chlamydia (phylum Chlamydiae, order Chlamydiales, family Chlamydiaceae) together with *Chlamydia muridarum* and *Chlamydia suis*. Other chlamydiae infecting humans, *Chlamydophila pneumoniae* and *Chlamydophila psittaci*, are currently classified in a separate genus.[10] However, this subdivision of the family into the two genera Chlamydia and Chlamydophila has been discussed controversially during the past decade. Recently, in the light of recent genomic data and in the context of the unique biological properties of these microorganisms it was proposed to classify all the 11 currently recognized Chlamydiaceae species in a single Chlamydia genus.[11] Three *C. trachomatis* biovars comprising all 15 classical serovars and several additional serovars and genovars are recognized within the *C. trachomatis* species: the trachoma biovar (serovars A–C), the urogenital biovar (serovars D–K) and the LGV biovar (serovars L1–L3). This guideline only covers the urogenital and LGV biovars of *C. trachomatis*.

CLINICAL FEATURES, COMPLICATIONS AND SEQUELAE

Molano et al. described a *C. trachomatis* clearance (from the point of detection of the infection) in 54% of untreated asymptomatic women at 1 year of follow-up, 82% at 2 years, and 94% at 4 years.[12] In another study examining untreated asymptomatic women, the

clearance rate was similar (44.7%) during the first year.[13] The long duration of undetected and untreated infection in women can result in that the bacteria cross the cervix and uterus, ascend into the upper genital tract, adhere, and ultimately result in associated complications and sequelae such as PID, ectopic pregnancy, and tubal factor infertility. Appropriate testing of symptomatic and asymptomatic sexually active individuals is necessary to identify and treat the *C. trachomatis* infections.

Urogenital infections

Symptoms and signs in women:[1]

- 70-95% asymptomatic
- Mucopurulent cervicitis with or without contact bleeding
- Cervical friability
- Cervical oedema
- Endocervical ulcers
- Urethritis
- Dysuria
- Vaginal discharge
- Postcoital bleeding and intermenstrual bleeding
- Poorly differentiated abdominal pain or lower abdominal pain

Symptoms and signs suggestive of pelvic inflammatory disease (PID):[14-16]

- Lower abdominal tenderness and pain – usually bilateral
- Cervical motion tenderness on bimanual vaginal examination
- Adnexal tenderness on bimanual vaginal examination
- Deep dyspareunia – particularly of recent onset
- Abnormal bleeding – intermenstrual bleeding, post coital bleeding and menorrhagia can occur secondary to associated cervicitis and endometritis
- Abnormal vaginal or cervical discharge – as a result of associated cervicitis, endometritis or bacterial vaginosis
- Fever (>38°C) – in moderate to severe PID

Complications in women (see also below):

- PID (endometritis, salpingitis, parametritis, oophoritis, tuboovarian abscess and/or pelvic peritonitis)
- Chronic pelvic pain
- Tubal infertility
- Ectopic pregnancy
- Sexually acquired reactive arthritis (SARA) (<1%)
- Fitz-Hugh-Curtis syndrome (PID and perihepatitis)

Symptoms and signs in men (may be so mild that they are not noticed):[1,17]

- Usually more than 50% (25-100%) asymptomatic
- Urethritis
- Dysuria
- Urethral discharge
- Epididymitis
- Testicular pain

Complications in men (see also below):

- SARA (<1%)
- Epididymitis, epididymo-orchitis

Rectal and pharyngeal infections

C. trachomatis infections of the rectum are typically asymptomatic, however, the infections may cause anal discharge and anorectal discomfort and also progress to proctocolitis.[18,19] The rates of rectal chlamydial infection in men who have sex with men (MSM) have been reported to be between 3% and 10.5% in some settings.[20,21] An 8.4% prevalence of anorectal *C. trachomatis* in women has been reported and almost all (94.5%) of these women also had urogenital *C. trachomatis*.[22,23] Pharyngeal chlamydial infections are also usually asymptomatic, but symptoms of a mild sore throat can occur.[24]

The rates of *C. trachomatis* detection in the pharynx in MSM can range from 0.5% to 2.3%.[21,25,26]

Ocular infections

Ocular infections can result in conjunctivitis in neonates and adults,[1,12,27-30] and can lead to chronic conjunctivitis and persist for several months if left untreated.

Neonatal infections

Infants born to mothers through an infected birth canal may become colonized and develop conjunctivitis and/or pneumonia.[29] The vertical transmission risk for a newborn is 50-75%.[30]

Lymphogranuloma venereum (LGV)

LGV is an invasive ulcerative disease caused by the serovars L1, L2, or L3 of *C. trachomatis*.[31] Since 2003, LGV outbreaks have been verified amongst MSM, particularly HIV positive, in several European countries.[32-35] Most patients have presented with proctitis[1,36] or tenesmus, anorectal discharge (often bloody) and discomfort, diarrhoea or altered bowel habits. Due to similarities between LGV and inflammatory bowel disease (IBD), LGV should be considered as a differential diagnosis in patients with proctitis or IBD-related symptoms, especially among HIV-positive men.[37,38]

It has been shown that approximately 25% of LGV infections can be asymptomatic and form an easily missed undetected reservoir.[39] For additional and updated information, see the latest version of the "European Guideline on the Management of Lymphogranuloma Venereum"[40] (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

Complications and sequelae

Women

In older observational treatment studies, up to 30% of women with untreated urogenital *C. trachomatis* infections developed PID.[41,42] The reported incidence of PID has fallen in several countries over the last decades,[2,43-46] and the risk of complications has been reported to be lower than previously estimated.[47-51] Regardless of symptom intensity, the

consequences of PID are severe. Of those with symptomatic PID, about 20% are subsequently infertile; 18-42% will experience debilitating, chronic pelvic pain; and 1-9% will have a life-threatening tubal pregnancy.[52-56] For additional information regarding management of PID, see the latest version of the "European guideline for the management of pelvic inflammatory disease"[57] (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

Men

Complications (e.g., epididymitis, epididymo-orchitis) affect a minority of infected men and rarely result in reproductive health sequelae.[58] There is no strong evidence base that *C. trachomatis* causes infertility in men. However, *C. trachomatis* has been indirectly associated with male sub-fertility or infertility as a result of a direct effect on sperm production, maturation, motility and viability.[59-61]

Sexually acquired reactive arthritis (SARA)

SARA is a possible consequence of *C. trachomatis* infection (30-40/100 000 infections).[62,63] SARA is a multisystem disease, which predominantly occurs in human leukocyte antigen B27 positive young males, and includes a combination of urethritis, conjunctivitis and arthritis. The fact that the causative agents are found in the synovial membrane or synovial fluid is indicative of infectious rather than reactive arthritis.[64] For additional and updated information regarding the management of SARA, see the latest version of the "European guideline for the management of sexually acquired reactive arthritis"[65] (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

INDICATIONS FOR LABORATORY TESTING [Level of evidence IV; Grade C recommendation]

- Risk factor(s) for *C. trachomatis* infection and/or other STI (age <25 years, new sexual contact in the last year, more than one partner in the last year);
- Symptoms or signs of urethritis in men;
- Cervical or vaginal discharge with risk factor for STI;
- Acute epididymo-orchitis in a male aged <40 years or with risk factors for STI;

- Acute pelvic pain and/or symptoms or signs of PID;
- Proctitis/proctocolitis according to risk:
- Purulent conjunctivitis in a neonate or adult;
- Atypical neonatal pneumonia;
- Persons diagnosed with other STI;
- Sexual contact of persons with an STI or PID;
- Termination of pregnancy;
- Any intrauterine interventions or manipulations.

LABORATORY DIAGNOSTICS

Recommended diagnostic assays:

- Nucleic acid amplification tests (NAATs), identifying *C. trachomatis* specific nucleic acid (DNA or RNA) in clinical specimens, are recommended to be used for diagnostics, due to their superior sensitivity, specificity, and speed [I; A].[66-77]

Only if *C. trachomatis* NAATs are not available or affordable, isolation of *C. trachomatis* in cell culture or identification of *C. trachomatis* by direct fluorescence assays (DFA) can be used for diagnosis of acute *C. trachomatis* infection.

Evidence on the minimum period necessary before testing can be recommended is lacking, although clinical experience suggests that positive NAAT results may be observed within 1–3 days of *C. trachomatis* exposure. Patients should be tested when they first present, however, if there is concern about a sexual exposure within the last two weeks they should have a repeat NAAT test two weeks after the exposure [IV; C].

For adequate performance characteristics of all NAATs and other diagnostic methods, it is crucial to follow precisely the recommendations from the manufacturer concerning collection, transportation, and storage of samples, as well as performance of the specific assay, including internal controls (positive, negative and, if required in NAATs, inhibition controls) and participation in an appropriate national and/or international external quality assessment (EQA) scheme [I; A]. Re-evaluation of random samples by an independent laboratory with an independent test will help reduce false positive and false negative results. Furthermore, all diagnostic laboratories should have a quality assurance system

and strive towards accreditation.

Nucleic acid amplification test (NAAT)

Validated and quality assured NAATs are recommended due to their superior sensitivity, specificity, and speed of diagnosis of both symptomatic and asymptomatic chlamydial infections compared to all other diagnostic techniques [I; A].[66-77] Due to the high specificity of the NAATs and risk of losing low positive results in repeated testing, confirmatory testing of positive specimens is not recommended.[75.78]

Given the rigorous evaluation required before approval of a diagnostic test by the United States of America Food and Drug Administration (FDA), FDA-approved *C. trachomatis* NAATs are primarily recommended for diagnosis. However, internationally there are many additional commercially available or laboratory-developed *C. trachomatis* NAATs in use.[79-81] If non-FDA approved NAATs are used, regional (e.g. EU) and/or other national validation and regulatory processes should provide safeguards on the quality and performance of the diagnostic NAAT. If validated and approved NAATs cannot be used, it is strongly recommended that the effectiveness of the proposed NAAT for the local settings is validated and quality-assured before use against at least one internationally approved NAAT and subsequently used with appropriate positive, negative, and inhibition controls; participation in appropriate external quality assessment system is strongly recommended as well. Furthermore, laboratories should use NAATs capable of detecting all known *C. trachomatis* variants, e.g. the Swedish new variant (nvCT),[82-84] and to further investigate any unexplained significant increases or declines in the local incidence or positivity rate [I; A].

Point of care tests (POCT)

Rapid point of care tests (POCT) provide a quick and easy test result, and diagnosis and subsequent treatment can be provided at the same visit at clinic or even in remote settings. However, compared to NAATs the sensitivity of the current, mostly immunochromatographic, tests is clearly insufficient.[85-89] POCT with increased sensitivity have been developed, and newer POC NAATs are under development.[86,89-93] Currently available rapid POCT cannot be recommended in Europe, unless other more sensitive

tests are unavailable and results are interpreted with caution.

Specimens

Urogenital specimens

- The recommended first choice specimens for diagnosis of urogenital chlamydial infections with NAATs are first-void urine for men (up to 20 ml sampled >1 h after previous micturition) and (health-care worker- or self-collected) vulvo-vaginal swabs for women [I; A].[66,68,70,94-107]

Women can also send dry vulvo-vaginal swabs by mail to the laboratory without significant loss of sensitivity.[108] If clinical examination is performed, a cervical specimen can be sampled. However, according to recent data NAATs on a (self-collected) vulvo-vaginal specimen is at least as sensitive. Due to suboptimal sensitivity, first-void urine for women should only be used if other specimens are not available [II; B].[66,74,95,96]

The use of Pap-smears is not recommended for screening, case finding or other diagnostic purposes, even though several methods to optimize detection in Pap-smears have been published.[109,110] Penile skin swabs can not currently be recommended.[111]

Pharyngeal, rectal and conjunctival specimens

No manufacturer of *C. trachomatis* NAATs has licensed extra-genital specimens for diagnosis. However, NAATs are the preferred test for all these specimens and some NAATs have been adequately validated for these specimens [IIa; B].[112-117] Nevertheless, the sensitivity and specificity can be lower compared to urogenital specimens.[114,118-121] Confirmation of the positive results with an independent assay may be appropriate [II].[114,118,119] Collecting pharyngeal and rectal specimens should always be considered in MSM, and in heterosexuals according to risk.[117]

With the increase (or persisting presence) of rectal LGV infections, especially in MSM,[34,122,123] it is recommended to identify LGV patients by testing all MSM who report receptive anal sex in the previous 6 months for anorectal *C. trachomatis* infection with a NAAT.[124] Furthermore, positive rectal specimens from MSM are recommended to be genotyped for LGV, irrespective of the presence of anorectal symptoms [II; B]. For

additional and updated information, see the latest versions of the “European Guideline on the Management of Lymphogranuloma Venereum”[40] and the “European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens”[124] (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

Semen specimens

There is a good correlation between first-void urine positivity and semen positivity,[125-127] first-void urine is easier to obtain, and it is exceedingly difficult to exclude that the *C. trachomatis* detected in semen is not only from the urethra. Accordingly, testing of semen specimens is not recommended [II; B].

Serology

Serology is not recommended for screening or diagnosis of acute uncomplicated anogenital *C. trachomatis* infections. In many patients, only invasive *C. trachomatis* infections will lead to detectable levels of antibodies and antibody levels might also remain positive for years as well as differ between persons. However, when NAATs are not available detection of specific antibodies to *C. trachomatis* may support the diagnosis of invasive disease, such as LGV involving the lymph nodes and neonatal pneumonia (*C. trachomatis* specific IgM) [I; A].[29,128-133] Serology might also have limited value in the diagnosis of ascending infections[134-136] and for infertility work-up.[137] Specificity has been greatly enhanced by using peptide-based assays, which can be useful in detecting infections in the past, for instance as testing assays in infertility work-up.

INCREASED TESTING (IN STI AND SEXUAL HEALTH CLINICS) AND REPEAT TESTING

- Annual *C. trachomatis* testing in STI or sexual health clinics is recommended for all sexually active young females and males (<25 years of age), and should be considered for MSM [2a, B].
- Repeated testing in 3-6 months should ideally be offered to young females and males (<25 years of age) who test positive for *C. trachomatis* [III; C].[78,138-144]

Clinical guidelines in many countries recommend annual *C. trachomatis* screening for all sexually active young (<25 years of age) women[78,138,145] and extend to young men in some countries.[146,147] However, mathematical modeling studies have suggested that to achieve population level impact on *C. trachomatis* transmission, screening programmes need to achieve very high testing coverage and also high rates of partner notification, including treatment, and repeated testing for reinfection after treatment.[148-151] The main rationale for current *C. trachomatis* screening or opportunistic testing is, however, that early detection and treatment will prevent or interrupt reproductive tract morbidity, particularly in women. The reduction in the incidence of PID in randomised clinical trials (RCTs) comparing women receiving chlamydia screening interventions with control groups[50,152-154] suggests that there must be an interval after endocervical infection during which screening can prevent or limit clinical PID.

Mathematical modelling studies in the USA have shown that repeat infection rates peak at 2-5 months after the initial infection,[155] supporting the US CDC recommendation that any person diagnosed as having *C. trachomatis* infection should be retested within 3-12 months of treatment [III; C].[78,139,141,142,156] The English National Chlamydia Screening Programme (NCSP) guidelines recommend retesting annually or on change of sexual partner for all sexually active <25 years old and, in 2013, began to include recommendations of retesting around 3 months after a positive test.[157-159]

MANAGEMENT OF PATIENTS

Information, explanation and advice for the patient

- Patients with positive *C. trachomatis* test should be advised to abstain from sexual contact for seven days after they and their partners have completed treatment and their symptoms have resolved [IV; C];
- Patients with positive *C. trachomatis* test (and their sexual contacts) should be given information about their infection, including details about transmission, prevention and complications. It is recommended that both verbal and written information be provided [IV; C];
- Information for patients is available on the IUSTI Europe website for guidelines (http://www.iusti.org/regions/Europe/euroguidelines.htm);

- Patients with positive *C. trachomatis* test should be considered for and encouraged testing for other STIs, including gonorrhoea, syphilis and HIV [IV; C].

Indications for therapy [IV; C]

- Identification of *C. trachomatis* or *C. trachomatis* specific nucleic acid (DNA or RNA) in a clinical specimen;
- On epidemiological grounds, if a recent sexual contact has confirmed chlamydial infection (ideally NAAT specimen should also be sampled for testing);
- On epidemiological grounds, mother of neonate with confirmed chlamydial infection (ideally NAAT specimen should also be sampled for testing);
- On epidemiological grounds, treatment can be considered following sexual assault (ideally NAAT specimen should also be sampled for testing);
- On demonstration of a purulent urethral discharge in men or mucopurulent cervicitis in women when diagnostic tests are not available and after specimen collection for laboratory testing. In this circumstance, dependent on local gonorrhoea incidence combined treatment for chlamydial infection and gonorrhoea should be considered.

Therapy

There is still no evidence of any stable, homotypic genetic and phenotypic resistance to any therapeutic antimicrobial in clinical *C. trachomatis* strains that affects the treatment in humans.[160-164] Nevertheless, in recent years concerns have been raised over clinical failures in *C. trachomatis* infected patients treated particularly with azithromycin 1 g single oral dose.[165-168] Some of these treatment failures can be explained by reinfection, poor compliance or tolerance of treatment, or detection of nucleic acid from non-viable *C. trachomatis* due to test-of-cure (TOC) performed too early.[168,169] However, the reasons for the remaining treatment failures remain unclear,[170] though a suboptimal duration of exposure to azithromycin after the 1 g single dose and a low-level absorption of azithromycin in some patients may be involved.[161] Some earlier work suggested that a prolonged course of azithromycin is likely to be sufficiently bactericidal to *C. trachomatis*[171] and in respiratory tract infections azithromycin 1.5 g administered over 3

to 5 days has been reported to achieve therapeutic levels in target tissues for up to 10 days.[172,173] It has also been suggested that use of azithromycin 1 g stat increases the risk of inducing macrolide antimicrobial resistance in *Mycoplasma genitalium*.[174-177] Accordingly, when a concomitant *M. genitalium* infection has been verified or can be suspected, treatment with azithromycin 500 mg day 1, followed by azithromycin 250 mg once a day for 4 days[174-178] should be considered [III; C]. Recently, it was shown that this five days azithromycin treatment regimen can effectively eradicate also *C. trachomatis*, that is, the eradication rate for *C. trachomatis* was 98.8% (79 of 80 patients infected with both *M. genitalium* and *C. trachomatis*).[178] Nevertheless, appropriate RCTs using the five days azithromycin regimen to examine the eradication frequency of both *M. genitalium* and *C. trachomatis* are crucial, and when using this regimen TOC for both bacteria should be considered.

Recommended treatment for uncomplicated urogenital *C. trachomatis* infections

First-line [Ia; A]:[179]

- Doxycycline 100 mg twice a day for 7 days (oral; contraindicated in pregnancy)
  Or
- Azithromycin 1 g stat (oral)

Second-line [II; B] (TOC should be subsequently performed):[180-184]

- Erythromycin 500 mg twice a day for 7 days (oral)
  Or
- Levofloxacin 500 mg once a day for 7 days (oral; contraindicated in pregnancy)
  Or
- Ofloxacin 200 mg twice a day for 7 days (oral; contraindicated in pregnancy)

Third-line [II; B] (TOC should be subsequently performed):[185-187]

- Josamycin 500 mg three times or 1000 mg twice a day for 7 days (oral)

A meta-analysis of 23 RCTs comparing azithromycin 1 g stat and doxycycline 100 mg twice daily for seven days for urogenital chlamydial infections showed a statistical

superiority in favour of doxycycline.[179] However, the difference in efficacy was small at 1.5%-2.6% (approximately 97% versus 95% efficacy). This difference is not clinically significant and both azithromycin and doxycycline can be recommended as first-line regimens [Ia; A]. When a concomitant *M. genitalium* infection has been verified or is suspected, treatment with azithromycin 500 mg day 1, followed by azithromycin 250 mg once a day for 4 days,[174,175,177,178] should be considered [III; C].

HIV positive patients should be treated in the same way as HIV negative ones [IV; C].

Recommended treatment for uncomplicated *C. trachomatis* non-LGV rectal and pharyngeal infections

- Doxycycline 100 mg twice a day for 7 days (oral) [I; A] (preferred if rectal infection)

Or alternatively:

- Azithromycin 1 g stat (oral) [IIa; A] (if rectal infection, a TOC should be subsequently performed)

For rectal infections, four non-randomised clinical studies have been published which showed higher efficacy rates for doxycycline (98.8-100%) than for azithromycin (74-87%) at this anatomical site.[188-191] Conversely, another study (also non-randomised) showed azithromycin to be 94% effective; a similar rate to that for urogenital infections.[192] However, all these five studies had important limitations. Because of the low quality of the data supporting the superiority of doxycycline over azithromycin for treating rectal infections both regimens continue to be recommended as first-line. However, pending further studies and ideally double-blinded, placebo controlled RCTs, if rectal chlamydia is treated with azithromycin then a TOC should be performed [IIa, A].

Recommended treatment for uncomplicated LGV infections

For detailed and updated information regarding the management of LGV, including adjunctive therapy, see the latest versions of the “European Guideline on the Management of Lymphogranuloma Venereum”[40] and the “European Guideline on the

management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens"[124] (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

Recommended treatment for uncomplicated urogenital *C. trachomatis* infection in pregnancy and during breast feeding *(TOC should be subsequently performed)*

First-line [I; A]:[78,141,193-196]

- Azithromycin 1 g stat (oral)

Second line:[194]

- Amoxicillin 500 mg 3 times a day for 7 days (oral)

  Or

- Erythromycin 500 mg 4 times a day for 7 days (oral)

Third line:[184]

- Josamycin 500 mg three times or 1000 mg twice a day for 7 days (oral)

Azithromycin has been considered safe and effective according to clinical experience and in some studies,[194,196] and azithromycin is also recommended by the WHO in pregnancy.

Pelvic inflammatory disease (PID)

For detailed and updated information, see the latest version of the "European guideline for the management of pelvic inflammatory disease"[57] (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

***C. trachomatis* conjunctivitis**

C. trachomatis infection should be included in the differential diagnosis in sexually active individuals presenting with acute or chronic follicular conjunctivitis.[141,197,198] *C. trachomatis* conjunctivitis should prompt for testing for genital *C. trachomatis* infection and other STIs such as HIV, gonorrhoea, and syphilis.

- Azithromycin 1 g stat (oral)[199] [IIa; A]

Or alternatively:

- Doxycycline 100 mg twice a day for 7 days (oral) [I; A]

CONTACT NOTIFICATION AND MANAGEMENT OF SEXUAL CONTACT(S)

- Contact notification should be performed and documented by appropriately trained professionals at the time of diagnosis to improve outcome [Ib; A];
- Sexual contacts should be contacted and offered (and encouraged) testing together with treatment and, if infected, counseling (as index patient) for chlamydial infection and other STIs [IV; C];[78,160,200-203]
- All sexual contacts within the preceding 6 months of onset of symptoms or diagnosis should ideally be evaluated, tested and treated [IV; C];[78,138,160,202,204]
- If sexual contact(s) does not attend for evaluation and testing, epidemiological treatment should ideally be offered [IV; C].[78,160,202]

Where no regulatory barriers exist, expedited partner therapy or patient-delivered partner therapy can be an efficient way to treat partners and reduce the infection rates.[204-211] However, patient delivered therapy should only be implemented as part of a larger system of contact notification strategies.

For further information, see the latest version of the “European guidelines for the management of partners of persons with sexually transmitted infection”[202] (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

FOLLOW-UP AND TEST-OF-CURE (TOC)

- A TOC is not recommended to be routinely performed in patients treated with recommended first-line regimens but should be performed in pregnancy, in complicated infections, if symptoms persist, if second-line regimens have been used, and if non-compliance to therapy or re-exposure of infection is suspected [IV; C]. It should also be considered in extra-genital infections,[188] particularly when azithromycin 1 g stat has been administered for treatment of rectal infections.

When indicated, TOC using NAATs should be performed 4 weeks after completion of therapy [III; B];[78,140,160,188,213,214]

- Repeated testing, to detect reinfection, in 3-6 months should ideally be offered to young females and males (<25 years of age) who test positive for *C. trachomatis* [III; C].[78,138-144,146,215]

Repeated testing for TOC of asymptomatic MSM with rectal chlamydia after treatment for uncomplicated chlamydial infection (azithromycin 1 g single oral dose or doxycycline 100 mg, 7 days) should be considered to ensure that any LGV infection is not missed.

For further information, see the latest version of the "European guidelines for the management of partners of persons with sexually transmitted infection"[202] and the "European Guideline on the Management of Lymphogranuloma Venereum"[40] (http://www.iusti.org/regions/europe/euroguidelines.htm#Current).

NOTIFICATION OF *C. TRACHOMATIS* CASES

C. trachomatis infections should be notified to local, regional and national authorities as mandated by statute. The ECDC is responsible for the EU/EEA-wide surveillance of communicable diseases including *C. trachomatis* infections.

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Composition of the IUSTI European STI Guidelines Editorial Board

The composition of the current IUSTI European STI Guidelines Editorial Board can be found at: http://www.iusti.org/regions/Europe/pdf/2014/Editorial_Board2014.pdf

Contributing organisations

A list of contributing organisations can be found at:
www.iusti.org/regions/Europe/euroguidelines.htm

Search strategy

This guideline represents an updated and substantially revised version of the "2010 European guideline for the management of *Chlamydia trachomatis* infections".[139] The present guideline was produced according to the protocol for production and revision of European STI guidelines, which has been written and approved by the IUSTI European STI Guidelines Editorial Board, and an evidence-based approach.

Evidence was provided by a thorough and systemic review of the literature in the databases Embase.com, Medline (OvidSP), PubMed (articles supplied by publishers not yet indexed in Medline), Web-of-science, Scopus, Cinahl, Cochrane DARE, and Google Scholar. Searches were performed on 18th of March 2014 and on 28th of November 2014, and the following broad search terms were used: *Chlamydia trachomatis*, systematic review, meta-analysis, guideline, protocol. After deduplication, 3041 articles published from 1992 to 2014 were screened on title/abstract, which resulted in 824 references considered for inclusion when the guideline was written. Relevant STI guidelines produced by the US Centers for Disease Control and Prevention (www.cdc.gov/std/treatment/2015/) and the British Association for Sexual Health and HIV (www.bashh.org) were also reviewed.

Levels of evidence and grading of recommendations

Tables of levels of evidence and grading of recommendations that were used in the present guideline can be found at:

http://www.iusti.org/regions/Europe/pdf/2013/Levels_of_Evidence.pdf

Qualifying statement

Decisions to follow these recommendations must be based on professional clinical judgement, consideration of individual patient circumstances and available resources. All possible care has been undertaken to ensure publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing clinician to ensure the accuracy and appropriateness of the medication they prescribe.

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Conflicts of interests

The Work Under Consideration for Publication					
		Magnus Unemo	**Keith Radcliffe**	**Esmee Lanjouw**	**Henry de Vries**
1	Grant	No	No	No	No
2	Consulting fee or honorarium	No	No	No	No
3	Support for travel to meetings for the study or other purposes	No	No	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	No	No
5	Payment for writing or reviewing the manuscript	No	No	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	No	No	No

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	No	No	No	No
2	Consultancy	No	No	No	Willpharma, GSK
3	Employment	No	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	No	No	No	No
6	Payment for lectures including service on speakers bureaus	No	No	No	Willpharma
7	Payment for manuscript preparation	No	No	No	No
8	Patents (planned, pending or issued)	No	No	No	No
9	Royalties	No	No	No	No
10	Payment for development of educational presentations	No	No	No	No
11	Stock/stock options	No	No	No	No
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	No	No	No
13	Other (err on the side of full disclosure)	No	No	No	No

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No	No	No

Conflicts of interests

The Work Under Consideration for Publication					
		Angelika Stary	**Name**	**Name**	**Name**
1	Grant	No			
2	Consulting fee or honorarium	No			
3	Support for travel to meetings for the study or other purposes	No			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No			
5	Payment for writing or reviewing the manuscript	No			
6	Provision of writing assistance, medicines, equipment, or administrative support	No			
7	Other	No			

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	No			
2	Consultancy	No			
3	Employment	No			
4	Expert testimony	No			
5	Grants/grants pending	No			
6	Payment for lectures including service on speakers bureaus	No			
7	Payment for manuscript preparation	No			
8	Patents (planned, pending or issued)	No			
9	Royalties	No			
10	Payment for development of educational presentations	No			
11	Stock/stock options	No			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No			
13	Other (err on the side of full disclosure)	No			

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No			

Conflicts of interests

The Work Under Consideration for Publication					
		Magnus Unemo	**Sander Ouburg**	**Name**	**Name**
1	Grant	no	No		
2	Consulting fee or honorarium	no	No		
3	Support for travel to meetings for the study or other purposes	no	No		
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no	No		
5	Payment for writing or reviewing the manuscript	no	No		
6	Provision of writing assistance, medicines, equipment, or administrative support	no	No		
7	Other	no	No		

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Relevant financial activities outside the submitted work					
1	Board membership	no	No		
2	Consultancy	No	No		
3	Employment	No	No		
4	Expert testimony	No	No		
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9	Royalties	No	No		
10	Payment for development of educational presentations	No	No		
11	Stock/stock options	No	No		
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	No		
13	Other (err on the side of full	no	No		

	disclosure)				

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No