Complete Summary

GUIDELINE TITLE

2002 national guideline for the management of Chlamydia trachomatis genital tract infection.

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of Chlamydia trachomatis genital tract infection. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [42 references]

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SCOPE

DISEASE/CONDITION(S)

Chlamydia trachomatis genital tract infection

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Obstetrics and Gynecology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To present a national guideline for the management of Chlamydia trachomatis genital tract infection

TARGET POPULATION

Men and women in the United Kingdom with Chlamydia trachomatis genital tract infection

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Cell culture
2. Direct fluorescent antibody (DFA)
3. Enzyme immunoassays (EIA)
4. Nucleic acid amplification techniques (NAAT)

Treatment/Management

1. Doxycycline or azithromycin
2. Erythromycin, deteclo, ofloxacin or tetracycline
3. Patient education
4. Partner notification

MAJOR OUTCOMES CONSIDERED

- Diagnostic test performance measures such as sensitivity and specificity
- Treatment: microbiological cure rate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developers performed Medline searches for the years 1970 to present using keywords "Chlamydia trachomatis" in association with "polymerase chain reaction" or "PCR" or "ligase chain reaction" or "lcr" or "lcx" and "immunoenzyme techniques" or "enzyme linked immunosorbent assay." "Chlamydia trachomatis" combined with the following keywords "detection," "diagnosis," "treatment." The guideline developers also searched the Cochrane Library using the keyword "Chlamydia trachomatis."

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence:

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The revision process commenced with authors being invited to modify and update their 1999 guidelines. These revised versions were posted on the website for a 3 month period and comments invited. The Clinical Effectiveness Group and the authors concerned considered all suggestions and agreed on any modifications to be made.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations:

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial versions of the guidelines were sent to the following for review:

- Clinical Effectiveness Group (CEG) members

- Chairs of UK Regional GU Medicine Audit Committees who had responded to an invitation to comment on the guidelines
- Chair of the Genitourinary Nurses Association (GUNA)
- President of the Society of Health Advisers in Sexually Transmitted Diseases (SHASTD)
- Clinical Effectiveness Committee of the Faculty of Family Planning and Reproductive Health Care (FFP)

Comments were relayed to the authors and attempts made to reach a consensus on points of contention with ultimate editorial control resting with the Clinical Effectiveness Group. Finally, all of the guidelines were ratified by the councils of the two parent societies.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (I-IV) and grades of recommendation (A-C) are defined at the end of the "Major Recommendations" field.

Diagnostic Recommendations

- Ideal diagnostic test sensitivity is >90% with specificity >99%. The tests that most closely approach this are the nucleic acid amplification techniques (NAATs). These perform better or at least as well as any of the other tests.
- Only the better performing enzyme immunoassays (EIAs) should be used, with sensitivities >80% and where sensitivity comparisons against the nucleic acid amplification techniques have been carried out.
- With enzyme immunoassays, the technique of confirmation in the negative grey zone, either by direct fluorescent antibody or nucleic acid amplification techniques, should be introduced. (Dean, Ferrero, & McCarthy, 1998; Tong, Donnelly, & Hood, 1997) This improves sensitivity by 5% to 30%.
- Quality control to validate the sensitivity and specificity of the assay used by individual laboratories should be undertaken, in view of the reported wide range in the sensitivity of all tests. Both interlaboratory and intralaboratory control samples should be carried out, using both strong positives and negative and weakly reactive specimens.

Specimen of Choice

<u>Men</u>

Antigen detection techniques - enzyme immunoassay and direct immunofluorescence

- First voided urine sample is as good as, if not better than, a urethral swab. (Caul et al., 1989; Hay et al., 1991) The former is preferred because some patients find urethral swabbing painful and tolerate it poorly and thus there is the potential for obtaining an inadequate quality specimen. Patients should hold their urine at least 1 hour before being tested and preferably longer, as otherwise sensitivity is reduced (the optimum duration is not known).

- Enzyme immunoassay should not be used for detecting Chlamydia trachomatis in the rectum or pharynx.

Nucleic acid amplification techniques

- First voided urine sample is the preferred specimen (Chernesky et al., 1994) (see above).

Women

Antigen detection techniques - enzyme immunoassay and direct immunofluorescence

- Cervical swab is the best specimen.
- 10% to 20% additional positives will be detected by assaying an urethral specimen as well.(Hay et al., 1994; Paavonen, 1979) This can be combined with the cervical specimen for analysis. Urethral swabbing suffers from the same disadvantages as in men.
- Urine specimens perform significantly less well with enzyme immunoassays than cervical specimens and are not recommended.
- Enzyme immunoassay should not be used for detecting Chlamydia trachomatis in the rectum or pharynx.

Nucleic acid amplification techniques

- Cervical swabs consistently have sensitivities >80% (Black, 1997; Ridgway et al., 1996)
- Urine has reported sensitivities of 44% to 94% (Jensen, Thorsen, & Moller, 1997; Andrews et al., 1997; Black, 1997; Ridgway et al., 1996; Horner et al., 1998; Lee et al., 1995; Rabenau et al., 1997)
- Vulvo-vaginal swabs have a sensitivity >85%

Menstrual cycle and testing

- Preliminary data suggest that testing for Chlamydia trachomatis may detect more cases when undertaken in the latter part of the menstrual cycle (Horner et al., 1998; Taylor-Robinson et al., 1998; Crowley et al., 1997). This is further supported by the findings from a community based study conducted in Denmark (Moller et al., 1999).

Quality of Specimens

- The sample must contain cellular material. Swabs should be inserted inside the cervical os and firmly rotated against the endocervix.
- Inadequate specimens reduce the sensitivity of all diagnostic tests. (Welsh, Quinn, & Gaydos et al., 1997)
- Urethral swab in men should be inserted 1 to 4 cm inside and rotated once before removal.
- There is no consensus on how to take a urethral swab in women.
- Direct immunofluorescence is the only method that gives information concerning the quality of the sample.

Management

Further investigations: assessment for other sexually transmitted infections (STIs)

All patients in whom Chlamydia trachomatis is detected should be assessed for the presence of other sexually transmitted infections (Grade of Recommendation C).

Treatment

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 (Grade of Recommendation C).

Treatment of Uncomplicated Infection (see appropriate guidelines for treatment of complications)

Recommended regimens (Grade of Recommendation A):

- Doxycycline 100 mg twice a day for 7 days

or

- Azithromycin 1 gm orally in a single dose.

Alternative regimens (Grade of Recommendation A):

- Erythromycin 500 mg 4 times a day for 7 days

or

- Erythromycin 500 mg 2 times a day for 14 days

or

- Deteclo 300 mg 2 times a day for 7 days

or

- Ofloxacin 200 mg 2 times a day or 400 mg once a day for 7 days

or

- Tetracycline 500 mg 4 times a day for 7 days

Doxycycline and azithromycin (Level of Evidence Ia)

- These have been shown to have equal efficacy in clinical studies. (Weber & Johnson, 1995; Moore, McQuay & Muir Gray, 1996; Hillis et al., 1998)
- Azithromycin is considerably more expensive than doxycycline.
- Azithromycin may be particularly useful in patients with erratic healthcare seeking behaviour. (Handsfield & Stamm, 1998)

Ofloxacin (Level of Evidence Ib)

- It is unknown whether 200 mg twice a day is superior to 400 mg once a day. There is no evidence to suggest that compliance with a once a day regimen is better than twice daily regimens. (Drug and Therapeutics Bulletin, 1991) Whether missing a dose with 400 mg daily results in a less efficacious regimen than missing a dose with 200 mg twice daily is unknown.
- Ofloxacin has similar efficacy to doxycycline and a better side effect profile but is considerably more expensive, so is not recommended as first line treatment.

Erythromycin (Level of Evidence Ib)

- Erythromycin is less efficacious than either azithromycin or doxycycline.
- When taken four times a day, 20% to 25% may experience side effects sufficient to cause the patient to discontinue treatment. (Linneman, Heaton & Ritchey, 1987)
- There are only limited data on erythromycin 500 mg twice a day, with efficacy reported to be between 73% to 95%. (Linneman, Heaton & Ritchey, 1987; Stenberg & Mardh, 1993; Ross, Crean & McMillan, 1996) A 2 week course appears to be more efficacious than a 1 week course of 500 mg twice a day, with a cure rate $\geq$95% in a small study. (Linneman, Heaton & Ritchey, 1987; Stenberg & Mardh, 1993)

Other tetracyclines (Level of Evidence Ib)

- Deteclo is probably as efficacious as doxycycline (Munday et al., 1995). However, photosensitivity occurs more frequently and there are not as many data on efficacy if compliance is poor.
- Tetracycline 500 mg is effective when taken four times a day for 7 days. Compliance with such a regimen is likely to be poor, particularly in less motivated patients, and whether such a regimen would then be efficacious is unknown.
- Oxytetracycline 250 mg four times a day has also been shown to be effective, although the published evidence is limited. (Ross, Crean & McMillan, 1996)

Compliance with therapy

In general, compliance with therapy is improved if there is a positive therapeutic relationship between the patient and the doctor. (Sanson-Fisher, Bowman & Armstrong, 1992) This can probably be improved if the following are applied (C):

Discuss with patient and provide clear written information on:

- What chlamydia is and how it is transmitted:

    - it is a sexually transmitted infection
    - if asymptomatic there is evidence that it could persist for months or even years
    - it can be isolated from the throat and eye without detectable infection in the lower genital tract. (Stenberg & Mardh, 1993; Postema, Remeijer & van der Meijden, 1996) It can therefore not always be assumed to be sexually acquired (Midulla et al., 1987)
- The diagnosis of chlamydia, particularly:
    - it is often asymptomatic especially in women
    - whilst tests are accurate, no test is absolutely so
- The complications of untreated chlamydia
- Side effects and importance of complying fully with treatment and what to do if a dose is missed
- Interaction between antibiotics and oral contraceptive pill
- The importance of their sexual partner(s) being evaluated and treated
- Advice to abstain from sexual intercourse until they have completed therapy and their partner has been treated
- Advice on safer sexual practices.

Pregnancy and Breast Feeding

- Doxycycline and ofloxacin are contraindicated in pregnancy.
- The safety of azithromycin in pregnancy and lactating mothers has not yet been fully assessed, although available data indicate that it is effective.
- Erythromycin has a significant side effect profile and is less than 95% effective. There are no trials of erythromycin 500 mg twice a day for 14 days, which would be better tolerated than four times a day.
- Amoxycillin had a similar cure rate to erythromycin in a meta-analysis and had a much better side effect profile. (Brocklehurst & Rooney, 1998) However, amoxycillin in vitro has been shown to induce latency: there is therefore debate as to whether it is reliable.

Regimens (Level of Evidence Ia, Grade of Recommendation A)

- Erythromycin 500 mg four times a day for 7 days

or

- Erythromycin 500 mg twice a day for 14 days

or

- Amoxycillin 500 mg three times a day for 7 days.

Patients should have a test of cure 3 weeks after completing therapy.

Management of Sexual Partners

- All patients identified with Chlamydia trachomatis infection should be referred to a department of Genitourinary Medicine to discuss partner notification with a trained health advisor, where possible at initial diagnosis. This appears to

be acceptable to patients diagnosed outside Genitourinary Medicine departments as evidenced by the findings from the chlamydia pilot screening study in Portsmouth. (Tobin, Harindra & Tucker, 2000) The Chlamydia Screening Study (ClaSS) project will evaluate whether this is more cost effective than partner notification undertaken in general practice.

- The method of partner notification agreed for each partner/contact identified should be documented.
- At subsequent follow up, partner notification outcomes should be ascertained and documented.

Look back period

Only limited evaluation has taken place of the incubation period following exposure to the development of symptoms. In the United Kingdom (FitzGerald et al., 1998) an arbitrary cut off of 4 weeks is used to identify those sexual partner(s) potentially at risk if the index male patient is symptomatic. As it is not known how long a patient can carry chlamydia asymptomatically, an arbitrary cut off of 6 months or until the last previous sexual partner (whichever is the longer time period), is used in women and asymptomatic men. Common sense needs to be used in assessing which sexual partner(s) may have been at risk in these situations.

Those at risk should be informed and invited to attend for evaluation and epidemiological treatment even if tests are negative. This may be patient led or provider led if the patient is unwilling to undertake it.

Follow up

This is an important part of the management of chlamydial infection. However, some patients may not return, emphasising the importance of the initial consultation. Follow up has a number of objectives including:

- following up partner notification
- reinforcing health education
- providing reassurance
- assessment of treatment efficacy/exclusion of re-infection

Patients do not need to be retested for Chlamydia trachomatis after completing treatment with doxycycline or azithromycin unless symptoms persist or re-infection is suspected, as both are highly efficacious (Grade of Recommendation C). A test of cure should be considered 3 weeks after the end of treatment with erythromycin. A test of cure earlier will miss late failures and may detect non-viable organisms.

Definitions:

Levels of Evidence:

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- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

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C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is graded and identified for select recommendations (see "Major Recommendations").

The majority of studies on the efficacy of antibiotic therapy have suffered from flaws in design. Studies have often been small, and the duration of follow up has usually been short. In many studies no details were given on treatment of the sexual partner(s), and often no distinction made between persistence or re-infection in the study population at follow up. In addition, the majority of studies have only used culture to detect Chlamydia trachomatis. Doxycycline and azithromycin have been the most rigorously investigated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis, treatment and management of patients with Chlamydia trachomatis genital tract infection.

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Chlamydial diagnostics continues to be such a rapidly developing field that it is inappropriate to be proscriptive or prescriptive about methodology. There are also problems in interpreting many published trials because they use inappropriate reference standards: either culture, which is now known to be insensitive, or discrepant analysis, which overestimates both sensitivity and specificity. The Chlamydia Screening Study (ClaSS) project will also investigate which specimen and which test is the most cost-effective method for diagnosing Chlamydia trachomatis.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The Clinical Effectiveness Group reminds the reader that guidelines in themselves are of no use unless they are implemented systematically. The following auditable outcome measures are provided:

- Compliance with clinical standards of care
- Partner notification
- Patient's knowledge of chlamydia and how to reduce the risk of acquiring it

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of Chlamydia trachomatis genital tract infection. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [42 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2002)

GUIDELINE DEVELOPER(S)

British Association of Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

Not stated

GUIDELINE COMMITTEE

Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: Dr Patrick J Horner; Dr E Owen Caul

Clinical Effectiveness Group (CEG) Members: Keith Radcliffe (Chairman); Imtyaz Ahmed-Jushuf; Jan Welch; Mark FitzGerald; Janet Wilson

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Conflict of interest: P. Horner – none. Dr. Owen Caul – Adviser to Dako UK on microbiological R&D.

GUIDELINE STATUS

This is the current release of the guideline. This guideline updates a previously released version.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available in HTML format from the Association for Genitourinary Medicine (AGUM) Web site. Also available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- UK national guidelines on sexually transmitted infections and closely related conditions. Introduction. Sex Transm Infect 1999 Aug;75(Suppl 1):S2-3.

Electronic copies: Available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

The following is also available:

- Revised UK national guidelines on sexually transmitted infections and closely related conditions 2002. Sex Transm Infect 2002;78:81-2

Print copies: For further information, please contact the journal publisher, BMJ Publishing Group.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 15, 2000. The information was verified by the guideline developer on October 13, 2000. This summary was updated by ECRI on June 24, 2002.

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