GUIDELINE

2010 European guideline for the management of *Chlamydia trachomatis* infections

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Summary: This guideline aims to provide comprehensive information regarding the management of infections caused by *Chlamydia trachomatis* in European countries. The recommendations contain important information for physicians and laboratory staff working with sexually transmitted infections (STIs) and/or STI-related issues. Individual European countries may be required to make minor national adjustments to this guideline as some of the tests or specific local data may not be accessible, or because of specific laws.

Keywords: *Chlamydia trachomatis*, urogenital infections, guidelines, diagnostics, treatment, follow up

SUMMARY OF RECOMMENDATIONS

Recommendation list is given in Table 1.

AETIOLOGY AND TRANSMISSION

Chlamydia trachomatis is an obligate intracellular bacterium that infects over 90 million people each year by sexual transmission. It is the most common bacterial sexually transmitted infection worldwide, especially among young adults. *C. trachomatis* belongs to the genus *Chlamydia* together with *Chlamydia muridarum* and *Chlamydia suis*. Other chlamydiae infecting human beings, *Chlamydophila pneumoniae* and *Chlamydophila psittaci*, have been classified in a separate genus.[1] Three biovars comprising all 15 classical serovars and several additional serovars and genotypes are recognized within *C. trachomatis*: the trachoma biovar (serovars A–C), the urogenital biovar (serovars D–K) and the lymphogranuloma venereum (LGV) biovar (serovars L1–L3). This guideline only covers urogenital infections caused by the urogenital and the LGV biovar of *C. trachomatis*.

Usually transmission takes place by direct mucosal contact between two individuals during sexual contact or at birth. Occasionally, other ways of transmission (fomites, enemas, sex toys) may play a role, as has been suggested in the LGV proctitis epidemic. The rate of transmission between sexual partners may be as high as 75%.[2] Thus, partner notification and subsequent treatment are very important.

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CLINICAL FEATURES

Clinical features in women[3,4]

- Up to 90% asymptomatic
- Urethritis
- Dysuria
- Vaginal discharge
- Postcoital bleeding
- Cervicitis
- Contact bleeding
- Mucopurulent cervical discharge
- Cervical friability
- Cervical oedema
- Endocervical ulcers
- Mid-cycle spotting
- Poorly differentiated abdominal pain or lower abdominal pain
- Pelvic inflammatory disease (PID)
- Proctitis.

Clinical features in men[5,6]

- More than 50% asymptomatic
- Burning with micturition
- 'Penile tip irritation'
- Watery, viscous excretion ('morning milker')
- Urethral discharge
- Proctitis.

Neonatal infections

Infants born to mothers through an infected birth canal may become colonized and may develop conjunctivitis and or pneumonia.[7]

Table 1   List of recommendations

Grade	Recommendation
A	Only NAATs detecting all known genotypes and variants should be employed for the diagnosis of *Chlamydia trachomatis* infections
B	Laboratories should participate in (expert) networks for timely communication about genetic variants, less common serovars and uncommon clinical presentations
A	For males first-void urine and for females a (self-collected) vaginal swab are the recommended specimens for *C. trachomatis* testing
B	Further testing for LGV of *C. trachomatis* positive rectal specimens from MSM should be considered
B	Testing of semen specimens is not recommended
B	Pooling of urine specimens is not recommended
B	Confirmatory testing of *C. trachomatis*-positive samples is not recommended
A	Antibody testing to *C. trachomatis* is only recommended for the diagnosis of invasive disease, such as LGV and neonatal pneumonia, when NAAT is not possible or not reliable
A	Laboratories should participate in quality assurance programs, either by their own choice or by national requirements
A	First-choice treatment of uncomplicated urogenital chlamydial infections is a single dose of 1 g azithromycin
B	Alternative treatments are a course of doxycycline, 100 mg two times daily for seven days, or josamycin, 1000 mg twice daily for seven days
C	When infection with *Mycoplasma genitalium* is confirmed or suspected, patients should be treated with a short course of azithromycin: 500 mg on day 1, followed by 250 mg on days 2–5
A	First-choice treatment in pregnancy is a single dose of 1 g azithromycin. Alternative treatment is a course of amoxicillin, 500 mg four times daily for seven days. Erythromycin is not recommended
B	In high-prevalence populations pregnant women should be screened for *C. trachomatis* infection and, if positive, receive appropriate treatment
B	First-choice treatment of rectal non-LGV chlamydial infections is a course of doxycycline, 100 mg twice daily for seven days
B	First-choice treatment of rectal LGV infection is a course of doxycycline, 100 mg twice daily for 21 days
A	Patients tested positive for *C. trachomatis* should be offered screening for at least hepatitis B, gonorrhoea, syphilis and HIV

NAATs, nucleic acid amplification techniques; MSM, men who have sex with men; LGV, lymphogranuloma venereum

Complications and sequelae[8–10]

- PID
- Endometritis
- Salpingitis
- Ectopic pregnancy
- Tubal factor infertility
- Sexually acquired reactive arthritis (SARA).

Approximately 10% of women with *C. trachomatis* infection will develop PID if left untreated. While PID caused by *Neisseria gonorrhoeae* infection may be accompanied by more acute symptoms, PID caused by *C. trachomatis* infection is associated with a higher rate of subsequent infertility (level III).[11] Early and appropriate therapy has the potential of significantly reducing the long-term complications of PID.[12] Other complications of *C. trachomatis* infection consist of SARA or perihepatitis (Fitz-Hugh-Curtis syndrome), chronic pelvic pain (women), anorectal discharge and adult conjunctivitis. *C. trachomatis* has also been associated with male infertility (level III)[13–15] and epididymitis (level III).[16–19]

Lymphogranuloma venereum

- Caused by the L1–L3 serovars of *C. trachomatis*;
- Rarely reported in developed countries before 2004;

- Since 2003, outbreaks reported in The Netherlands and other developed countries in men who have sex with men (MSM);[20–22]
- The main site of infection: the rectum;
- Symptoms:
  - Tenesmus
  - Constipation
  - Anorectal pain
  - Mucopurulent discharge
  - Bleeding *per rectum*
  - Diarrhoea
  - Abdominal pain.

Proctitis has been known for many years in MSM. LGV was implicated as a causative agent as early as 1976.[23] Since the symptoms of LGV proctitis resemble those of Crohn's disease, many patients have been mistakenly treated for Crohn's disease.[24,25] In order to manage this epidemic among MSM, the need for standardized criteria and procedures as well as guidelines became obvious.[26,27]

DIAGNOSIS OF CHLAMYDIAL INFECTIONS

Diagnostic assays

- Nucleic acid amplification techniques (NAATs)
- Cell culture
- Enzyme immunoassays (EIA)
- Direct fluorescence assays.

Since many studies have shown the superiority of NAATs over other techniques, only NAATs can be recommended (level I, grade A).[28]

Assessing performance of NAATs

In evaluating the performance of highly sensitive NAATs, a perfect gold standard has not been defined and discrepant analysis has been used to reassess the supposedly false-positive reactions of the NAATs. Discrepant analysis might introduce a bias towards a higher sensitivity than can be accounted for.[29] Since many studies have been reported, including studies using highly sensitive NAATs only, it is not likely that this bias will lead to ill-advised guidelines (level I).[30]

Sampling error, biological variation, local differences and prevalence of *C. trachomatis* infections in populations sampled are more important determinants of performance evaluations (level IV).

Choice of NAAT

Different manufacturers have developed their own amplification technology platforms. Although sensitivity and specificity do vary slightly, other factors like cost, hands-on time, combined testing for other agents and degree of automation play an important role in choosing a specific NAAT.[31] The latest versions of the NAATs of major manufacturers are all adequate (level II). However, the chosen NAAT should be able to detect the Swedish variant.

Diagnostic challenges

- Emergence of LGV among MSM
- Emergence of the Swedish *C. trachomatis* variant.

Detecting LGV

LGV proctitis has always been described in textbooks, but due to a very low prevalence is not always considered in the differential diagnosis of proctitis. All NAATs will detect LGV as *C. trachomatis*-positive, but without designating the result as LGV-positive. Genotyping to identify LGV strains should be conducted according to local guidelines. Where LGV is suspected clinically, e.g. symptomatic proctitis in MSM, then genotyping is recommended, if available (level II, grade B).[32]

Detecting variants

Possible variants:

- Plasmid-free strains
- Plasmid mutant strains.

Most commercially available NAATs only detect one target, either the cryptic plasmid, the major outer membrane protein gene (MOMP) or ribosomal RNA. Thus, NAATs are prone to erroneous results in cases of genetic alterations. The plasmid occurs in an average copy number of 4.0 plasmids per chromosome[33] and is highly conserved.[34] Therefore, the plasmid is an attractive target for NAATs. However, NAATs based only on plasmid sequences will not detect plasmid-free *C. trachomatis* variants. It is not clear if this constitutes a real problem since only a few reports exist on the occurrence of plasmid-free strains. Although all genes located on the plasmid are transcribed during infection,[35] three groups reported the isolation of a strain lacking the plasmid.[36–38] Matsumoto *et al.* indeed showed that plasmid-free strains can be isolated from clinical specimens using special cloning techniques and that these strains may survive.[39] Thus, the plasmid is not essential for survival. One group studied a series of 40 specimens from high-risk patients with various nucleic acid assays and concluded that nine specimens contained no plasmid sequences.[40] Further analysis comparing these specimens with *C. trachomatis* type strains showed they were genetically similar.[41] However, confirmation of these results has not been reported (level III).

An unexpected 25% decrease in the prevalence of *C. trachomatis* infections triggered Ripa and Nilsson to study the cause. They reported a new variant of *C. trachomatis* with a 377-base pair deletion in the plasmid exactly at the target sequence of several commercial NAATs.[42,43] Later it became clear that laboratories relying on these NAATs missed between 20% and 65% of *C. trachomatis* infections.[44] A real-time polymerase chain reaction assay for detection of the Swedish variant has been developed[45] and subsequent analysis showed that this strain has to date only rarely been encountered outside of the Scandinavian countries. Laboratories need to choose a NAAT capable of detecting the Swedish variant (level I, grade A).

It is recommended that laboratories participate in quality assurance programs, including monitoring systems, to detect genetic variants and uncommon clinical presentations (level II, grade B).

Expert networks

Both the experience with LGV and with the Swedish variant show the added value of expert networks like the *European Surveillance of Sexually Transmitted Infections* for quickly assessing new findings and for notifying professionals in Europe

and the rest of the world.[21,46] It is recommended that laboratories participate in (expert) networks for timely communication about genetic variants and uncommon clinical presentations (level II, grade B).

Choice of specimen

Until recently different types of specimens were recommended for screening programs and clinical settings. This is no longer the case.

Type of specimen of first choice

- Men: first-void urine
- Women: (self-collected) vaginal swab.

The sensitivity of testing male first-void urine is 85–95%.[30,47] The concordance of different NAATs is highest for symptomatic men. Also, the acceptability by men of first-void urine specimens is generally good.[48] First-void urine should be used to diagnose genital chlamydial infections in men (level I, grade A).

For females, the sensitivity of testing first-void urine is slightly lower than that for males: 80–90%.[30] Vaginal swabs can be either clinically collected or self-collected. Self-collected vaginal swabs provide an acceptable alternative.[49–56] Also, self-collected vaginal swabs are well accepted by women.[57] The difference in sensitivities between tests on specimens from various sites is likely to be the result of the difference in bacterial load in these specimens.[58] Self-collected vaginal swabs should be used to diagnose chlamydial infections in women (level I, grade A).

Pap-smears provide an attractive type of specimen for epidemiological purposes using already available specimens. Although several procedures have been described to optimize the performance of detection of *C. trachomatis* in Pap-smears,[59] they cannot be recommended for specific screening programmes, nor for diagnostic purposes (level II).

C. trachomatis infections also occur during pregnancy. Infection is associated with premature labour, preterm birth and neonatal conjunctivitis and pneumonitis.[60,61] The positive effect of treatment on pregnancy outcome suggests screening and treatment of all pregnant women.[62] Preferably all pregnant women, but at least pregnant women from high prevalence populations (e.g. >5%), should be screened for *C. trachomatis* infection and, if positive, receive appropriate treatment (level II, grade B).

Other types of specimen

Pharyngeal and conjunctival specimens
Due to the low bacterial load NAATs are the test of choice for adult and infant pharyngeal specimens if indicated.[63] Although the bacterial load in neonatal conjunctivitis is probably higher, NAATs still show a higher sensitivity compared to non-amplification assays. NAATs have now been adequately validated for these specimens (level II).[64–67]

Rectal specimens
Isolation in cell culture and EIA are not suited for rectal specimens, due to toxicity of the specimens and extensive cross-reactions, respectively.

The specificity of current commercial NAATs seems adequate, although laboratories employing these assays should recognize that specificity is less than 95% and confirmation by another assay might be appropriate (level II).[66–68] In MSM, positive rectal specimens should be genotyped for LGV according to local guidelines. If available, it is recommended in MSM with symptomatic proctitis (level II, grade B).[69]

Semen specimens

Up to 10% of semen specimens might contain inhibitors for NAATs. However, a good correlation exists between first-void urine positivity and semen positivity.[70–72]

Therefore, testing of semen specimens is not recommended (level II, grade B).

Pooling of urine specimens

To reduce the workload and/or cost, laboratories might want to pool urine specimens. Depending on the prevalence, calculations can be made on cost and benefits. However, female urine might contain inhibitors[73,74] that could cause false-negative results in other specimens from the pool. In addition, most NAATs are neither FDA cleared nor CE marked for using pooled specimens. Therefore, in the era of automated high-throughput equipment and considering the need for unambiguous identification and tracking of specimens, as well as the need for reduction of human errors, pooling of urine cannot be recommended (level II, grade B).[75]

Sampling error

First portions of urine have a higher bacterial load than second and third portions. Thus, first-void urine should be used.[76] Voiding interval seems not to affect diagnostic performance.[77] Early-morning urine seems not to be more sensitive than urine at the time of visit.[78] Thus, male urines can be collected at the time of the visit (level II).

Hormonal levels

Hormonal levels have been suggested to influence *C. trachomatis* detection by NAATs.

Factors involved are:

- Bacterial load (increase or decrease)
- Presence of inhibitors (increase or decrease).

Bacterial load seems to increase with time after the last menstrual bleeding, while the presence of inhibitors in urine seems to be maximal three weeks after the last menstrual bleeding.[73,79] Thus, the optimal period for taking vaginal swabs would be four weeks after the last menstrual bleeding (level III).

Inhibition

In some studies differences between NAATs have been observed,[80] but this has not been confirmed in other studies. Urine from pregnant women might contain inhibitors, as well as urine taken in the third week after menstrual bleeding.[73,74] It is likely that hormones play a role in this inhibition. Various solutions (e.g. freezing, boiling or diluting the specimens) have been suggested to deal with inhibition, but none of these are generally applicable or generally accepted.

Another concern (competitive inhibition) is raised by the use of duplex or multiplex assays detecting more than one target. If one of the targets is present in excess, other targets may be reported as falsely negative.[81,82] In these cases, the use of monoplex assays is needed to achieve the desired sensitivity (level II).

Confirmatory testing

Several strategies have been evaluated for confirmatory testing. One could use the same specimen, a second specimen taken at the same time or a new specimen. Also, one could repeat the original test or one could use a different test.

Using a second platform for confirmatory testing can only be implemented when the second platform is at least as sensitive as the initial platform.[83] After all, using a less sensitive test would reduce the overall sensitivity to the level of the least sensitive test.

For specimens with a high bacterial load, all types of confirmatory testing will be positive and, therefore, confirmatory testing is unnecessary and expensive. For specimens with a low bacterial load, as can be expected in low prevalence populations or in screening programs of asymptomatic individuals, confirmatory testing will confirm 80–90% depending on the initial test and the confirmatory procedure. More rigorous testing shows that the assumption that non-confirmed specimens are negative is wrong. Thus, confirmatory testing of specimens with a low bacterial load does not solve the issue of true positivity and is therefore not recommended (level II, grade B).[84] Proficiency testing and laboratory accreditation seem more appropriate ways to assure a high quality of laboratory results (level II).

Serology

In general, only invasive disease will lead to antibody levels useful for diagnostic purposes.

Chlamydial serology

- Only MOMP-derived synthetic peptide-based EIAs show no cross-reactions;
- Duration of antibody-positivity is not known;
- No value in the diagnosis of uncomplicated cervicitis and urethritis;[85]
- Limited value in the diagnosis of ascending infections;[86–88]
- Limited value for infertility workup;[89]
- LGV: high titres (IgG and/or IgA) can be diagnostic;[20,25,90,91]
- Neonatal pneumonia: IgM can be diagnostic.[7]

Especially when direct detection by NAAT is not possible or not reliable, antibody testing to *C. trachomatis* may be helpful in the diagnosis of invasive disease, such as LGV involving the lymph nodes and neonatal pneumonia (level I, grade A).

Quality assurance

As mentioned in the paragraph on confirmatory testing, quality assurance is important to guarantee correct test results of high quality. For blood products, a working group was convened dealing with NAAT validation and standardization, reference

standards, proficiency testing and external assessment of laboratory performance to assure quality of testing and safety of products across all laboratories.[92] In general for NAATs, procedures have been developed to assure quality.[93,94] Diagnostic procedures for *C. trachomatis* are not different from other diagnostic procedures. Performance problems can be detected that would remain undetected following manufacturer's instructions only.[95] Laboratories should participate in quality assurance programs, either by their own choice or by national requirements (level I, grade A).

THERAPY

Uncomplicated urogenital *C. trachomatis* infections

Although the natural course of infection has not been studied in great detail, it is assumed that many infections will clear spontaneously over time.[96] Some infections may proceed to a chronic persistent state.[97] Since sequelae might be severe, treatment is recommended. Resistance, although infrequently reported to date, may occur in *C. trachomatis* and is associated with treatment failure.[98,99] The incidence of resistance is unknown, but estimated very low. Thus, therapy is initiated empirically. A recent meta-analysis revealed that a single dose of azithromycin and a seven-day course of doxycycline are equally effective (level I, grade A).[100] The rate of compliance is of major concern and has been shown to be substantially higher in the case of single dose azithromycin, in both patients[101] and their partners[102,103] (level I). Alternatively, josamycin has been used with success in some countries (level II, grade B).[104]

First-choice treatment of uncomplicated urogenital infections consists of one of the following (level I, grade A):

- Single dose of 1 g azithromycin.

Alternative treatment (level II, grade B):

- Course of doxycycline, 100 mg two times daily for seven days;
- Course of josamycin, 1000 mg two times daily for seven days.

Please note that this recommendation is only valid in case of an infection with *C. trachomatis* as a single agent. In case of concurrent sexually transmitted infections (STIs), see below.

Therapy in pregnancy

C. trachomatis infections also occur during pregnancy. Infection is associated with premature labour, preterm birth and neonatal conjunctivitis and pneumonitis.[60,61] The choice of drugs for treatment is important because of their possible adverse effects on foetal development and pregnancy outcome. Recently, a meta-analysis comprising 587 pregnant women reported equivalent efficacy of azithromycin, erythromycin and amoxicillin. Side-effects were however, significantly less in the azithromycin group than in the erythromycin group. There were no differences in pregnancy outcome.[105] In some studies, erythromycin is less efficacious than azithromycin and amoxicillin.[106] In countries where the drug is available, josamycin seems safe and efficacious and might also be

considered.[107,108] First-choice treatment in pregnancy is a single dose of 1 g azithromycin. Alternative treatment is a course of amoxicillin, 500 mg four times daily for seven days. Erythromycin is not recommended (level I, grade A).

Rectal infection with LGV and non-LGV *C. trachomatis*

In some reports a higher failure rate of the standard single dose of azithromycin has been described in rectal chlamydial infections. The reason for this observation is not clear.[109] Usually a distinction between rectal non-LGV chlamydial infections and rectal LGV chlamydial infections is not made. Recently, evidence for treatment recommendations has been examined[110,111] and a new guideline for rectal LGV infection has been published.[27] Doxycycline (100 mg two times daily for 21 days) remains the treatment of choice (level III, grade B). First choice for treatment of rectal non-LGV chlamydial infections is a course of doxycycline, 100 mg two times daily for seven days (level III, grade B).[111]

Therapy failure

Limited data exist on alternative therapy in cases of therapy failure. A repeated course or a longer course (10–14 days) with doxycycline or a macrolide has been suggested, but evidence is lacking (level IV). Resistance has been shown rarely,[98,99] but therapy failure might also be caused by the persistence of chlamydial strains. Probably, the most common reason for therapy failure is re-infection from an untreated partner (level II).[112] An interesting suggestion is the combined use of rifampicin and a macrolide.[113–116] Further studies are needed.

CONCURRENT STIs

Men and women with a diagnosis of *C. trachomatis* infection should be offered a complete work-up for other STIs. *C. trachomatis* infection is a risk factor for the acquisition or transmission of HIV and other STIs. Patients should be offered screening for at least hepatitis B, gonorrhoea, syphilis and HIV (level I, grade A).[117,118] *Mycoplasma genitalium* is a sexually transmitted pathogen causing clinical disease similar to *C. trachomatis*, including PID.[119,120] An association with long-term sequelae has not been established yet. If facilities are available, patients may be offered screening for *M. genitalium* as well. This is particularly important in patients with persistent or recurrent disease (level II).[120] Recently, data were presented indicating that a single dose of 1 g azithromycin may lead to macrolide resistance in *M. genitalium*.[121,122] When infection with *M. genitalium* is confirmed, patients should not be treated with a single dose of 1 g azithromycin, but with a short course of azithromycin: 500 mg on day 1 followed by 250 mg on days 2–5 (level III, grade C).[123]

COMPLICATIONS

PID remains one of the most important sequelae of STIs, resulting in severe morbidity and acting as the economic justification for STI screening programmes. Early and appropriate therapy has the potential to significantly reduce the long-term

complications of PID, and evidence-based guidelines provide advice on the management of pelvic infection including the use of appropriate antimicrobial regimens.[12]

Several pathogens that may play a role in the aetiology of PID should be covered by empiric therapy: *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and anaerobes.[12,124]

PARTNER NOTIFICATION

There is a wide difference in the practice of partner notification between countries.[125] Besides scientific aspects, legal and privacy aspects are important and these differ from country to country. Also, no data are available to recommend a specific duration for the look-back period. Human studies on the duration of genital *C. trachomatis* infections have shown that chlamydia clearance increases over time, with approximately half of the infections spontaneously resolving one year after initial chlamydia testing.[126] However, practical restrictions will usually limit a look-back period to approximately two months. Overall, 50–80% of partners may be reached. The higher rates were associated with various enhancements to basic referral instructions, especially if patients were offered additional counselling or medications for their partners.[127,128] Expedited partner therapy or patient-delivered partner therapy might be an efficient way to treat partners,[129] but is not always permitted by law.[130] Major concerns are the unsupervised administration of prescription drugs, lack of monitoring of therapeutic effect, side effects and allergies, the lack of opportunity to test for *C. trachomatis* or other STIs as well as the lack of onward partner notification and safe sex education. In the UK, one-third of surveyed health professionals is strongly opposed to this.[131,132] It is, however, well accepted by patients and partners.[132,133] Given the wide differences between countries, no definitive recommendation can be given.

FOLLOW UP

NAATs cannot discriminate between live and dead microorganisms. Up until four weeks after the start of the therapy a test result may still be positive, based on remnants of microorganisms that have not been cleared by the host. Therefore, a test of cure is not recommended. Since a previous *C. trachomatis* infection is a risk factor for future STIs, a control visit after three months can be considered (level II).[75,117]

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APPENDIX A

The last version of the IUSTI guideline for chlamydial infection was published in 2001.[134] Since then, the Guidelines Editorial Board has decided to introduce evidence-based guidelines for all STIs, including chlamydial infections. Here we present the revised version of the guideline, produced according to the protocol approved by the IUSTI STI Guidelines Editorial Board and an evidence-based approach. This guideline is intended to be used by any clinician having to deal with one or more aspects of *C. trachomatis* infections.

Search strategy

The guideline for management of *C. trachomatis* infections was written after a literature search in the Medline, Embase and Cochrane databases for English-language articles published between January 1999 and December 2008. For this purpose a well-established algorithm developed by the Dutch Institute for Healthcare Improvement (CBO) was used.[135] This algorithm guarantees the inclusion of most if not all major publications on this topic. The resulting database of publications was extended with searches on specific topics and existing guidelines.[12,27,75,117,134] The level of evidence was assigned according to Table B1 and the grading of recommendations according to Table B2.

APPENDIX B

Table B1   Levels of evidence

Level	Description
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed study without randomization
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, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Table B2   Grading of recommendations

Grading	Evidence level	Description
A	Evidence levels Ia, Ib	Requires at least one randomized control 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 randomized 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 the absence of directly applicable studies of good quality