Chlamydial Infections

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CHLAMYDIAL INFECTIONS

(For Lymphogranuloma venereum, see *Genital Ulcer Disease* and *Lymphogranuloma Venereum* chapters)

Etiology

- Caused by *Chlamydia trachomatis* serovars D to K.

Epidemiology

- Reported rate in Canada and elsewhere has been increasing since 1997.[1]
- According to preliminary data, over 65,000 cases were reported in Canada in 2006 (202 per 100,000 population).[2]
- Sexually active youth and young adults are disproportionately represented in the case reports for Chlamydia. The reported rate in 2004 was highest in youth/young adults 15 to 24 years of age, accounting for approximately 2/3 of the national reported cases.
- Chlamydia is underdiagnosed because the majority of infected individuals are asymptomatic.[3–8]
- Underscreening is a gap in high-risk males and females. Males, the forgotten reservoir, have infrequent health-maintenance visits.[9–11]
- The usual incubation period from time of exposure to onset of symptoms is 2 to 3 weeks, but can be as long as 6 weeks.
- In the absence of treatment, infection persists for many months.
- Individuals infected with *Neisseria gonorrhoeae* are often co-infected with *C. trachomatis*.[12,13]
- Risk factors:
  - Sexual contact with a chlamydia-infected person.
  - A new sexual partner or more than two sexual partners in the past year.
  - Previous sexually transmitted infections (STIs).
  - Vulnerable populations (e.g., injection drug users, incarcerated individuals, sex trade workers, street youth etc.) (see *Specific Populations* section).

Prevention

Infection and its sequelae can be prevented by:

- Consistent practice of safer sex (see *Primary Care and Sexually Transmitted Infections* chapter).
- Identifying barriers to prevention practices and the means to overcome them.
- Increased acceptance of testing by using a non-invasive urine-based nucleic acid amplification test (NAAT).
- Screening of at-risk groups (as per risk factors listed above):
  - Sexually active females under 25 years of age.
  - Infected men under the age of 25 are a hidden reservoir for infections and re-infections of their partners. There is an evidence gap to determine whether routine screening of asymptomatic young males decreases the incidence of anogenital Chlamydia infection in women.[14,15] While waiting for such data, it is prudent to screen all sexually active males under the age of 25 for *Chlamydia trachomatis*.[7,8,10,16–24]

  - Pregnant women. All pregnant women should be screened at the first prenatal visit. For those who are positive or who are at high risk for reinfection, rescreening at third trimester is indicated.[25–31]
- Repeat screening of individuals with chlamydia infection after 6 months.[26,32-35]
- To prevent reinfection, partners need to be assessed, tested, treated, and counselled.
- Patients and contacts should abstain from unprotected intercourse until treatment of both partners is complete (i.e., after completion of a multiple-dose treatment or for 7 days after single-dose therapy).

Manifestations

Table 1. Symptoms and signs[36]

Females	Males	Neonates and Infants
• Most often asymptomatic • Cervicitis • Vaginal discharge • Dysuria • Lower abdominal pain • Abnormal vaginal bleeding • Dyspareunia • Conjunctivitis • Proctitis (commonly asymptomatic)	• Often asymptomatic • Urethral discharge • Urethritis • Urethral itch • Dysuria • Testicular pain • Conjunctivitis • Proctitis (commonly asymptomatic)	• Conjunctivitis in neonates • Pneumonia in infants <6 months of age

Table 2. Major sequelae

Females	Males
• Pelvic inflammatory disease • Ectopic pregnancy • Infertility • Chronic pelvic pain • Reiter syndrome	• Epididymo-orchitis • Reiter syndrome

Diagnosis

Laboratory diagnosis

(See *Laboratory Diagnosis of Sexually Transmitted Infections* chapter.)

- Results are highly dependent on the type of test available; specimen collection and transport; and laboratory expertise. Consult with your local laboratory regarding available tests and their test performance.
- NAATs (e.g., polymerase chain reaction [PCR], transcription-mediated amplification [TMA]) are more sensitive and specific than culture, enzyme immunoassay (EIA) and direct fluorescent antibody assay (DFA). For non–medico-legal purposes, NAATs should be used whenever possible for urine, urethral or cervical specimens. Blood and mucus interfere with NAAT performance and can result in false-negative results, therefore culture is recommended in such situations.
- Although some NAATs have not been approved in Canada for use with vaginal or rectal specimens, recent data show that NAATs for *C. trachomatis, N. gonorrhoeae* and *Trichomonas vaginalis* may identify as many or more infected women using vaginal swabs than cervical swabs, urethral swabs or urine.[37] Check with your laboratory to see if this is an option.* (see *Specimen collection* in this chapter).
- There are promising data on the use of rectal and oral swabs for *C. trachomatis* and *N. gonorrhoeae* tested by NAATs and current clinical trials are underway through the U.S. National Institutes of Health.** (see *Specimen collection* in this chapter).
- **Currently, only culture is recommended for throat specimens.**
- Due to its non-invasive nature a urine-based NAAT is ideal for screening asymptomatic females when a pelvic examination is not warranted for other reasons. However, a physical examination remains essential, and more invasive specimens may be needed for diagnostic purposes in symptomatic individuals.
- Post exposure NAAT testing can be taken at the time of presentation without waiting for 48 hours; this is based on expert opinion, which assumes that NAATs are able to detect inoculum (DNA or RNA).
- Both chlamydia and gonorrhea can be detected from a single specimen by some NAATs.
- Culture is the preferred method for medico-legal purposes, but NAATs may be suitable, provided that positive results are confirmed. Confirmation of positive results can be done with a NAAT using a different set of primers or by DNA sequencing techniques.
- *C. trachomatis* IgM serology is useful for diagnosing *C. trachomatis* pneumonia in infants less than 3 months of age.
- Serology is not useful for the diagnosis of acute genital chlamydial infections.

Specimen collection

Potential specimen sites:

- Cervix in pubertal or older females for NAAT.
  - If the cervix has been surgically removed:
  - urine or urethral swab for NAAT

  or
  - vaginal swab for culture or NAAT* (see *Laboratory Diagnosis* section in this chapter).

  or
  - rectal swab for culture or NAAT** (see *Laboratory Diagnosis* section in this chapter.)
- Urethral swab in males for NAAT (preferably not have voided for at least 2 hours, but this does not preclude testing).
- Urine NAAT, vaginal/rectal swab for culture in prepubertal girls.
- Urine NAAT for females and males of any age.
  - Any time of day.
  - Initial 10 to 20 mL of the urine stream (not mid-stream).
  - Preferably not having voided for at least 2 hours, but this does not preclude testing.
- Endometrial or fimbrial biopsy specimens for NAAT in women undergoing laparoscopy for investigation of pelvic inflammatory disease.
- Conjunctival swab for culture, EIA, DFA.
- Nasopharyngeal aspirate for culture in infants <6 months of age.
- Oropharyngeal and rectal specimens as required.
- For information on specimen transport, see *Laboratory Diagnosis of Sexually Transmitted Infections* chapter.

Management

- Evaluation should be appropriate for the presenting symptoms, signs and sexual history.
- Treatment for chlamydia is indicated for the following:
  - A positive chlamydia test.
  - Diagnosis of a syndrome compatible with a chlamydial infection, without waiting for the test results of *C. trachomatis*.
  - Diagnosis of chlamydial infection in a sexual partner.
  - Empirical co-treatment when a diagnosis of *N. gonorrhoeae* is made without waiting for test results of *C. trachomatis* due to the significant probability of co-infection (20–42%)[12,13] and the possibility of false-negative results, especially with non-NAAT methods.

Treatment

- Efficacy and use-effectiveness studies evaluating single-dose azithromycin and a 7-day course of doxycycline have demonstrated similarly high cure rates; azithromycin is much more expensive.[38–47]
- Ofloxacin has an efficacy similar to doxycycline and azithromycin, but it is more expensive and needs to be taken as a multiple-dose course.[48–56]
- Erythromycin is associated with significantly higher gastrointestinal side effects than other regimens.[56–60]
- Drug resistance is rare but may become an emerging issue.[61,62]
- In the absence of a contraindication, the following treatment options are recommended.

Adults (non-pregnant and non-lactating): urethral, endocervical, rectal, conjunctival infection

(For pelvic inflammatory disease, see *Pelvic Inflammatory Disease* chapter; for epididymitis, see *Epididymitis* chapter.)

Table 3. Adults (non-pregnant and non-lactating): urethral, endocervical, rectal, conjunctival infection

Preferred	Alternative
• **Doxycycline** 100 mg PO bid for 7 days *[A-I]* OR • **Azithromycin** 1 g PO in a single dose if poor compliance is expected* *[A-I]*	• **Ofloxacin** 300 mg PO bid for 7 days *[B-II]* OR • **Erythromycin** 2 g/day PO in divided doses for 7 days† *[B-II]* OR • **Erythromycin** 1g/day PO in divided doses for 14 days† *[B-I]*

*If vomiting occurs more than 1 hour post-administration, a repeat dose is not required.

† Erythromycin dosages refer to erythromycin base. Equivalent dosages of other formulations may be substituted **(with the exception of the estolate formulation, which is contraindicated in pregnancy)**. If erythromycin has been used for treatment, test of cure should be performed 3-4 weeks after completion of therapy.

Children

- Topical therapy alone for conjunctivitis is NOT adequate and is unnecessary when systemic treatment is used.
- **The use of erythromycin in infants under 6 weeks of age has been associated with infantile hypertrophic pyloric stenosis (IHPS).[63-66] The risk of IHPS with other macrolides (e.g., azithromycin, clarithromycin) is unknown. The risks and benefits of using erythromycin in such infants should be explained to parents. When erythromycin is used in such infants, it is important to monitor for signs and symptoms of IHPS. IHPS following erythromycin use should be reported to the Canadian Adverse Drug Reaction Monitoring Program at 1-866-234-2345.**
- The need to treat infants less than 6 weeks of age for *C. trachomatis* can be avoided by screening pregnant women and treating before delivery.

- **Doxycycline is contraindicated in children under 9 years of age.**
- Quinolones have been associated with articular damage in young animals. Such joint changes have not been clearly attributable to quinolone use in children. Its safety in children has not been established. **Quinolones should not be used in prepubertal patients. Experience in pubertal patients under 18 years of age is limited.**

Table 4. Children

First week of life	>1 week to 1 month	>1 month to <9 years	9–18 years
Infants ≤ 2000 g • **Erythromycin** 20 mg/kg/day PO in divided doses for at least 14 days*† *[B-II]* **Infants >2000 g** • **Erythromycin** 30 mg/kg/day PO in divided doses for at least 14 days*† *[B-II]*	• **Erythromycin** 40 mg/kg/day PO in divided doses for at least 14 days*† *[B-II]*	• **Azithromycin** 12–15 mg/kg (max. 1 g) PO in a single dose *[B-II]* **Alternatives** • **Erythromycin** 40 mg/kg/day PO in divided doses (max. 500 mg qid for 7 days or 250 mg qid for 14 days)*† *[B-II]* OR • **Sulfamethoxazole** 75 mg/kg/day PO in divided doses (max. 1 g bid) for 10 days† *[B-II]*	**Preferred** • **Doxycycline** 5 mg/kg/day PO in divided doses (max. 100 mg bid) for 7 days *[A-I]* OR • **Azithromycin** 12–15 mg/kg (max. 1 g) PO in a single dose if poor compliance is expected *[A-I]* **Alternatives** • **Erythromycin** 40 mg/kg/day PO in divided doses (max. 500 mg qid for 7 days or 250 mg qid for 14 days)*† *[B-I]* OR • **Sulfamethoxazole** 75 mg/kg/day PO in divided doses (max. 1 g bid) for 10 days† *[B-II]*

* Erythromycin dosages refer to the use of erythromycin base. Equivalent dosages of other formulations may be substituted (**with the exception of the estolate formulation, which is contraindicated in pregnancy**).

† If erythromycin or sulfamethoxazole has been used for treatment, repeat testing after completion of therapy is advisable.

Notes:

- Neonates born to infected mothers need to be tested for *C. trachomatis.* Neonates should be treated if their test results are positive. They should be closely monitored for signs of chlamydial infection (e.g., conjunctivitis, pneumonitis). Prophylaxis is not recommended unless follow-up cannot be guaranteed.
- Test of cure should be performed 3-4 weeks after the completion of treatment in all prepubertal children.

Pregnant women and nursing mothers: urethral, endocervical, rectal infection

- Clinical trials comparing amoxicillin, erythromycin and azithromycin have demonstrated similar microbiological and clinical cure, but maternal gastrointestinal side effects are more common with erythromycin.[67–75]
- To date, there are limited data collected on azithromycin in pregnancy, but it is considered to be safe in this context by many experts.[68–70,72–74]
- **Doxycycline and quinolones are contraindicated in pregnancy and in lactating women.**
- Clindamycin requires dosing three to four times a day for 10-14 days and does not offer any advantage. In addition, it is even more expensive than azithromycin and is thus not being listed as an option.
- Data on neonatal outcomes are limited.

Table 5. Pregnant women and nursing mothers: urethral, endocervical, rectal infection

- **Amoxicillin** 500 mg PO tid for 7 days* *[A-I]*

OR

- **Erythromycin** 2 g/day PO in divided doses for 7 days*† *[B-I]*

OR

- **Erythromycin** 1g/day PO in divided doses for 14 days*† *[B-I]*

OR

- **Azithromycin** 1 g PO in a single dose, if poor compliance is expected‡ *[B-I]*

* If erythromycin or amoxicillin has been used for treatment in nursing mothers, test of cure should be performed 3-4 weeks after the completion of treatment.

† Erythromycin dosage refers to the use of erythromycin base. Equivalent dosages of other formulations may be substituted **(with the exception of the estolate formulation being contraindicated in pregnancy).** Gastrointestinal side effects are more severe with erythromycin than amoxicillin.

‡ If vomiting occurs more than 1 hour post-administration, a repeat dose is not required.

Note: Test of cure should be performed 3-4 weeks after the completion of treatment in all pregnant women.

Consideration for Other STIs

- See *Primary Care and Sexually Transmitted Infections* chapter.
- Obtain specimen(s) for the diagnosis of *N. gonorrhoeae*.
- Obtain a blood sample for serologic testing for syphilis (see *Syphilis* chapter).
- HIV testing and counselling are recommended (see *Human Immunodeficiency Virus Infections* chapter).
- Immunization against hepatitis B is recommended in non-immune non-immunized individuals (see *Hepatitis B Virus Infections* chapter).
- Discuss HPV vaccine with women as per the recommendations outlined in the Canada Communicable Disease Report, Volume 33 ACS-2, (2007) *National Advisory Committee on Immunization* (NACI) *statement on Human papillomavirus vaccine*.

Reporting and Partner Notification

- *C. trachomatis* infections are reportable by laboratories and physicians to local public health authorities in all provinces and territories.
- All partners who have had sexual contact with the index case within 60 days prior symptom onset or date of diagnosis (if asymptomatic) should be tested and empirically treated regardless of clinical findings and without waiting for test results. If there was no partner during this period, then the last partner should be tested and treated.
- Parents of infected neonates (i.e., mother and her sexual partner[s]) should be located, clinically evaluated and treated.
- Local public health authorities are available to assist with partner notification and help with appropriate referral for clinical evaluation, testing, treatment and health education. If resources for local public health authority support are limited, priority for partner notification should be directed toward youth/young adults <25 years of age.

Follow-up

- Test of cure for *C. trachomatis* is not routinely indicated if a recommended treatment is taken AND symptoms and signs disappear AND there is no re-exposure to an untreated partner except:
  - Where compliance is suboptimal.
  - If an alternative treatment regimen has been used.
  - In all prepubertal children.
  - In all pregnant women.
- Test of cure using a NAAT, if needed, should be performed at 3-4 weeks after the completion of effective treatment to avoid false-positive results due to the presence of non-viable organisms.
- Repeat testing in all individuals with *C. trachomatis* infection is recommended 6 months post-treatment, as reinfection risk is high.
- In patients with apparent treatment failure, possibilities include the following:
  - Failure to take medication correctly or to finish course of therapy.
  - Re-exposure to an untreated partner.
  - Infection acquired from a new partner.
  - A false-positive result.
  - Rarely, resistance is an issue.
- In patients with persistent symptoms, infection with other pathogens and a non-infective etiology should also be considered.

Special Considerations

Children

- **It is essential** that neonates born to infected mothers be tested for *C. trachomatis*. Neonates should be treated if test results are positive. They should be closely monitored for signs of chlamydial infection (e.g., conjunctivitis, pneumonitis). Prophylaxis is not recommended unless follow-up cannot be guaranteed.
- **Sexual abuse needs to be considered when genital, rectal or pharyngeal chlamydial infection is diagnosed in any prepubertal child, although perinatally acquired *C. trachomatis* can persist in an infant for up to 3 years. Consultation with a colleague experienced in such cases should be sought. Siblings and other children possibly at risk should also be evaluated.**
- **Sexual abuse of children must be reported to the local child protection agency (See *Sexual Abuse in Peripubertal and Prepubertal Children* chapter).**
- **All persons named as suspects in child sexual abuse cases should be located and clinically evaluated; prophylactic treatment may or may not be offered and the decision to treat or not should be based on history, clinical findings and test results (See *Sexual abuse in Peripubertal and Prepubertal Children* chapter).**
- Follow-up cultures for "test of cure" are indicated approximately 3-4 weeks after completion of therapy in prepubertal children.