

# Canadian Guidelines on Sexually Transmitted Infections

## *Gonococcal Infections* Chapter

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**This document is intended to provide information to public health and clinical professionals and does not supersede any provincial/territorial legislative, regulatory, policy and practice requirements or professional guidelines that govern the practice of health professionals in their respective jurisdictions, whose recommendations may differ due to local epidemiology or context.**

# GONOCOCCAL INFECTIONS

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## Etiology

- Caused by *Neisseria gonorrhoeae*.

## Epidemiology

- Since 1997, there has been a gradual but steady increase in reported cases of gonococcal infection. Most affected are males 20–24 years of age and females 15–19 years of age. Infection rates are increasing more rapidly among females than among males.<sup>(1)</sup>
- A network of people with high-transmission activities may play a key role in current prevalence levels and in sustaining infections within a community.
- For the most up-to-date Canadian surveillance data on gonorrhea, please refer to the Public Health Agency of Canada's website <http://www.phac-aspc.gc.ca/sti-its-surv-epi/index-eng.php>.

## Antimicrobial resistance

- A national enhanced surveillance protocol has been developed to integrate epidemiologic and treatment failure data into existing laboratory-based monitoring of antimicrobial resistant *N. gonorrhoeae*. This surveillance is important to rapidly identify changes in antimicrobial susceptibility and assess risk factors associated with the development of resistance. This information enables early identification and prevention of the spread of drug-resistant gonorrhea and assists in identifying appropriate treatment regimens.<sup>(2,3)</sup>
- **Local public health should be promptly notified of cefixime, ceftriaxone or azithromycin treatment failures.** Prompt notification will allow provincial and territorial (P/T) STI prevention and control programs to quickly identify emerging patterns of antimicrobial resistance within their jurisdictions. This will enable P/Ts to collaborate with the Public Health Agency of Canada to issue timely electronic alerts through the Canadian Network for Public Health Intelligence (CNPHI).
- The growing shift towards the use of nucleic acid amplification testing (NAAT) rather than culture has resulted in fewer samples being submitted for susceptibility testing, making it difficult to get an accurate picture of drug resistance. The number of Canadian isolates found to be resistant to penicillin and/or tetracyclines is high.<sup>(4)</sup> **These antimicrobial agents should not be used for the treatment of gonorrhea.**
- Quinolone resistance has been steadily increasing in Canada.<sup>(4)</sup> In certain regions of the country, quinolone resistance is significantly higher than the national rate.
- **Quinolones are not recommended for the treatment of *N. gonorrhoeae* in Canada** unless resistance rates are known to be under 5%.<sup>(5-7)</sup> (Refer to the *Treatment* section of this chapter for recommendations on the use of quinolones in Canada).
- Shifts in minimal inhibitory concentrations (MICs) for third-generation oral and injectable cephalosporins have been increasing in Canada and globally, particularly among men who have sex with men (MSM).<sup>(4,5,8-27)</sup>

- The reported rates of antimicrobial resistance in Canada are calculated from samples that have been submitted by individual provinces and territories to the National Microbiology Laboratory (NML). Isolates are submitted to NML when the provincial laboratories identify resistance to at least one antibiotic or if the provincial laboratories do not perform antimicrobial susceptibility testing. The total number of isolates cultured in all provinces is used as the denominator to calculate resistance proportion.<sup>(4)</sup>
- Please refer to your local and P/T public health officials for specific information about antimicrobial resistance patterns in your region.

## Individuals at Risk

- Individuals who have had sexual contact with a person with a confirmed or suspected gonococcal infection.
- Individuals who have had unprotected sex with a resident of an area with high gonorrhea burden and/or high risk of antimicrobial resistance.
- Individuals with a history of previous gonococcal infection; a Canadian passive surveillance study reported re-infection to be at least 2% per year.<sup>(28)</sup>
- Individuals with a history of other STIs, including HIV.
- Sex workers and their sexual partners.
- Sexually active youth < 25 years of age.
- Street-involved youth and other homeless populations.
- Men who have unprotected sex with men.
- Individuals who have had sex with multiple partners.

## Special considerations

- HIV transmission and acquisition is enhanced in people with gonococcal infections.<sup>(29,30)</sup>

## Prevention and Control

- Case finding and partner notification are critical in controlling infection.
- At the time of diagnosis, reviewing and providing education on prevention practices should include discussion of:
  - The risk of re-infection,
  - The need for the index case and his/her contact(s) to abstain from unprotected sex until at least 3 days after completion of treatment and the case/contact(s) are asymptomatic (i.e., signs and symptoms have resolved),
  - Strategies for effective prevention practices (refer to the *Primary Care and Sexually Transmitted Infections* chapter), and
  - Prevention of reproductive sequelae.
- Individuals with concerns about STIs and/or pregnancy prevention should be provided with information to encourage consistent safe sexual practices.

## Manifestations, Symptoms and Major Sequelae

- Usual incubation period is 2–7 days.
- Infection is often asymptomatic in females and symptomatic in males. In both males and females, rectal and pharyngeal infections are more likely to be asymptomatic.<sup>(31)</sup>



**Table 1. Manifestations** <sup>(31-38)</sup>

Neonates and infants	Children	Youth and adults		
		Females	Males	Females and males
<ul style="list-style-type: none"> <li>• Ophthalmia neonatorum</li> <li>• Conjunctivitis</li> <li>• Sepsis</li> <li>• Disseminated gonococcal infection*</li> </ul>	<ul style="list-style-type: none"> <li>• Urethritis</li> <li>• Vaginitis</li> <li>• Conjunctivitis</li> <li>• Pharyngeal infection</li> <li>• Proctitis</li> <li>• Disseminated gonococcal infection*</li> </ul>	<ul style="list-style-type: none"> <li>• Cervicitis</li> <li>• Pelvic inflammatory disease</li> <li>• Urethritis</li> <li>• Perihepatitis</li> <li>• Bartholinitis</li> </ul>	<ul style="list-style-type: none"> <li>• Urethritis</li> <li>• Epididymitis</li> </ul>	<ul style="list-style-type: none"> <li>• Pharyngeal infection</li> <li>• Conjunctivitis</li> <li>• Proctitis</li> <li>• Disseminated gonococcal infection*</li> </ul>

\*e.g., arthritis, dermatitis, endocarditis, meningitis.

**Table 2. Symptoms** <sup>(39-41)</sup>

Females	Males
<ul style="list-style-type: none"> <li>• Vaginal discharge</li> <li>• Dysuria</li> <li>• Abnormal vaginal bleeding</li> <li>• Lower abdominal pain</li> <li>• Deep dyspareunia</li> <li>• Rectal pain and discharge with proctitis*</li> </ul>	<ul style="list-style-type: none"> <li>• Urethral discharge</li> <li>• Dysuria</li> <li>• Urethral itch</li> <li>• Testicular pain and/or swelling or symptoms of epididymitis</li> <li>• Rectal pain and discharge with proctitis*</li> </ul>

\*Refer to the Sexually Transmitted Intestinal and Enteric Infections chapter.

**Table 3. Major sequelae** <sup>(31,36,38)</sup>

Females	Males
<ul style="list-style-type: none"> <li>• Pelvic inflammatory disease</li> <li>• Infertility</li> <li>• Ectopic pregnancy</li> <li>• Chronic pelvic pain</li> <li>• Reactive arthritis (oculo-urethro-synovial syndrome)</li> <li>• Disseminated gonococcal infection*</li> </ul>	<ul style="list-style-type: none"> <li>• Epididymo-orchitis</li> <li>• Reactive arthritis (oculo-urethro-synovial syndrome)</li> <li>• Infertility (rare)</li> <li>• Disseminated gonococcal infection *</li> </ul>

\*e.g., arthritis, dermatitis, endocarditis, meningitis.

## Laboratory Testing/Diagnosis and Specimen Collection/Transport

### Nucleic acid amplification tests (NAATs)

- Due to the higher sensitivity and specificity of the most recently approved commercial NAATs, they can increase the number of cases diagnosed.<sup>(42,43)</sup> However, culture is strongly recommended because it allows for testing of antimicrobial susceptibility.<sup>(44)</sup>
- NAATs may be the only available testing method in some jurisdictions.
- Where a NAAT is used, sentinel surveillance mechanisms using culture are important to ensure continued monitoring for antimicrobial resistance.<sup>(13)</sup>
- NAAT may be done at the time of presentation **without individuals having to wait 48 hours post-exposure**; this is based on expert opinion, which assumes that NAAT is able to detect small amounts of DNA or RNA.
- Validated NAATs can be used to detect rectal and oropharyngeal infections. Although no products are currently licensed in Canada; individual laboratories may offer NAATs after in-house laboratory validation, including confirmation of positives with culture or a second NAAT.<sup>(42)</sup>
- If a NAAT is used as a test of cure (refer to indications for test of cure in the *Follow-up* section of this chapter), specimen collection should be **delayed for 2–3 weeks after completion of treatment**.<sup>(45,46)</sup>

### Culture

- As well as providing clinicians with important case management information, cultures are critical for improved public health monitoring of antimicrobial resistance patterns and trends.<sup>(13,47-51)</sup>
- Depending on the clinical situation, consideration should be given for collection of samples using both culture and NAAT, especially in symptomatic patients.
- Cultures obtained less than 48 hours after exposure may give false negative results.
- All suspected treatment failures should be investigated using culture, allowing for antimicrobial susceptibility testing.
- Culture is strongly recommended in the following situations:
  - To determine antimicrobial sensitivities prior to treatment, when possible,
  - As a **test of cure** for suspected treatment failure or in situations where there is an increased probability of treatment failure (refer to the *Follow-up* section of this chapter),
  - For symptomatic MSM,
  - In the case of sexual abuse/sexual assault (rectal, pharyngeal, vaginal),\*
  - To evaluate pelvic inflammatory disease (PID), and
  - If the infection was acquired in countries or areas with high rates of antimicrobial resistance.

**\*Note:** When a NAAT is used to screen victims of sexual abuse or sexual assault for medico-legal purposes, two different primer pairs should be used in the laboratory<sup>(42,52)</sup> (refer to the *Laboratory Diagnosis of Sexually Transmitted Infections* chapter).

### Specimen collection

- Due to high rates of concomitant infection, specimens should be taken for the diagnosis of both gonococcal and chlamydial infections<sup>(53)</sup> (refer to the *Laboratory Diagnosis of Sexually Transmitted Infections* chapter).
- For information on routine specimen sites, tests and clinical considerations, refer to *Table 4* below. For further information on specimen collection, refer to the *Laboratory Diagnosis of Sexually Transmitted Infections* chapter.

### Specimen transport

- Successful culture of specimens requires proper collection and transportation of appropriate specimens or immediate inoculation of medium.<sup>(54,55)</sup> Consult with your laboratory for specific instructions on enhancing pathogen survival.
- NAAT is appropriate when transport and storage conditions are not conducive to maintaining the viability of *N. gonorrhoeae*.<sup>(54)</sup>
- For further information on specimen collection and transport, refer to the *Laboratory Diagnosis of Sexually Transmitted Infections* chapter.

**Table 4. Recommended routine specimen sites and tests**

Specimen sites/tests*	Situations where specimen is appropriate†	Considerations
<b>Urethral Gram stain</b> <ul style="list-style-type: none"> <li>• For Gram-negative intracellular diplococci</li> </ul>	<ul style="list-style-type: none"> <li>• Postpubertal males</li> <li>•</li> </ul>	<ul style="list-style-type: none"> <li>• Recommended for symptomatic patients only.</li> <li>• Generally diagnostic of gonorrhea.</li> </ul>
<b>Urethral Culture or NAAT</b> <ul style="list-style-type: none"> <li>• For laboratory detection of <i>N. gonorrhoeae</i></li> </ul>	<ul style="list-style-type: none"> <li>• Optimal for all postpubertal males</li> <li>• Optimal for females with urethral syndrome (i.e., dysuria/pyuria) (cervical swab or urine recommended for other women)</li> </ul>	
<b>Endocervical Gram stain</b> <ul style="list-style-type: none"> <li>• For Gram-negative intracellular diplococci</li> </ul>	<ul style="list-style-type: none"> <li>• Postpubertal females</li> </ul>	<ul style="list-style-type: none"> <li>• Sensitivity lower than in male urethral specimens and not routinely recommended.</li> </ul>

Specimen sites/tests*	Situations where specimen is appropriate†	Considerations
<p><b>Endocervical or vaginal Culture or NAAT</b></p> <ul style="list-style-type: none"> <li>For laboratory detection of <i>N. gonorrhoeae</i></li> </ul>	<ul style="list-style-type: none"> <li>Optimal for postpubertal females</li> </ul>	<ul style="list-style-type: none"> <li>Vaginal swabs for NAAT are as accurate as cervical swabs.</li> <li>Self-obtained vaginal swabs can also be used when a pelvic examination is not warranted or refused by the individual, or the setting inappropriate (non-conventional settings). A physical examination is preferable, and more invasive specimens may be needed for diagnostic purposes in some situations.</li> <li>If the cervix has been surgically removed, urine NAAT, or vaginal swabs for culture or NAAT should be collected.</li> <li>Urethral specimens can also be collected if a woman is menstruating at the time of the exam.</li> </ul>
<p><b>Urine NAAT</b></p> <ul style="list-style-type: none"> <li>First catch 10–20 mL (can be sampled any time of the day)</li> </ul>	<ul style="list-style-type: none"> <li>Males or females where a urethral swab or pelvic examination is not practical<sup>(56)</sup></li> </ul>	<ul style="list-style-type: none"> <li>In females, first catch urine may have reduced performance when compared to NAAT for cervical swabs.</li> </ul>
<p><b>Oropharyngeal Culture or validated NAAT</b></p> <ul style="list-style-type: none"> <li>For laboratory detection of <i>N. gonorrhoeae</i></li> </ul>	<ul style="list-style-type: none"> <li>Females with a history of performing oral sex</li> <li>Males with a history of performing oral sex who are at high risk of exposure (e.g., MSM, multiple sexual partners, or sex with a partner who is at high risk of infection)</li> </ul>	<ul style="list-style-type: none"> <li>Culture is preferred; validated NAAT may be used if culture is not available.</li> </ul>
<p><b>Rectal Culture or validated NAAT</b></p> <ul style="list-style-type: none"> <li>For laboratory detection of <i>N. gonorrhoeae</i></li> </ul>	<ul style="list-style-type: none"> <li>All females with anogenital symptoms, as colonization can occur without anal penetration<sup>(57)</sup></li> <li>Females with a history of receptive anal intercourse, whether or not condoms were used</li> <li>MSM who practice receptive anal intercourse, whether or not condoms were used</li> </ul>	

\*Refer to the *NAAT tests and the Culture* sections above *Table 4* for specific guidance on the use of these testing methods.

†For guidance on specimen collection in prepubertal males and females refer to the *Sexual Abuse in Peripubertal and Prepubertal Children* and the *Laboratory Diagnosis of Sexually Transmitted Infections* chapters.

## Management

- Appropriate samples (as listed above) should be obtained prior to treatment.
- Management choices should be based on the site of infection and on laboratory test results (*Table 5*) unless presumptive treatment is to be provided for syndromic management (i.e., mucopurulent cervicitis [MPC], non-gonococcal urethritis [NGU], PID or epididymitis) (*Table 6*) or if the patient is being treated as a contact. When making treatment decisions, relevant history, physical examination and epidemiologic factors should be considered.
- All confirmed cases need to be treated and suspected cases should be considered for treatment.
- For treatment of PID, refer to the *Pelvic Inflammatory Disease* chapter.
- For treatment of epididymitis/epididymo-orchitis, refer to the *Epididymitis* chapter.

### **Consideration for other STIs**

- Obtain a specimen to test for chlamydial infection (refer to the *Chlamydial Infections* chapter).
- Obtain a blood sample for serologic testing for syphilis.
- HIV counselling and testing are recommended.
- Immunization is recommended for:
  - hepatitis B for all individuals being evaluated or treated for an STI, if not already immune, and
  - hepatitis A for high-risk individuals (e.g., MSM, injection drug users) if not already immune. (For a complete list of individuals at increased risk of hepatitis A, refer to the *Canadian Immunization Guide, Part 4, Active Vaccines*, available at <http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-hepa-eng.php>).
- Discuss human papillomavirus (HPV) vaccine with male and female patients as per the recommendations outlined in the National Advisory Committee on Immunization (NACI) *Update on Human Papillomavirus (HPV) Vaccines*, available at <http://www.phac-aspc.gc.ca/naci-ccni/>; and the *Canadian Immunization Guide, Part 4, Active Vaccines, Human Papillomavirus Vaccine*, available at <http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-hpv-vph-eng.php>.

### **Considerations in children (refer to the *Sexual Abuse in Peripubertal and Prepubertal Children* chapter)**

- Sexual abuse should be considered when genital, rectal or pharyngeal gonorrhoea is diagnosed in any child after the neonatal period.<sup>(37,58)</sup>
  - Consultation with an experienced colleague should be sought.
- Every province and territory has legislation that requires the reporting of suspected or confirmed sexual abuse of children.
- Siblings and other children who may be at risk should also be evaluated.<sup>(37)</sup>
- All individuals named as contacts in suspected sexual abuse cases should be located and clinically evaluated; prophylactic treatment may or may not be offered and the decision to treat should be based on history, clinical findings and test results.
- Local public health authorities should be notified; they may be able to provide guidance on evaluating suspected source cases.

**Table 5. Recommended patient management: test results available**

<p><b>Positive Gram stain</b></p>	<ul style="list-style-type: none"> <li>• If Gram-negative intracellular diplococci are observed, treatment for both gonococcal and chlamydial infection should be provided.<sup>(32,53,54,59)</sup></li> <li>• The presence of extracellular Gram-negative diplococci is an equivocal finding and confirmation by culture/NAAT should be performed. If the individual is at high risk of infection and follow-up is not assured, treatment should be provided for gonococcal infection while waiting for laboratory test results.<sup>(59,60)</sup></li> <li>• The presence of polymorphonuclear leukocytes without diplococci does not indicate or exclude gonococcal infection but suggests non-gonococcal urethritis (refer to the <i>Urethritis</i> chapter).<sup>(59,60)</sup></li> </ul>
<p><b>Positive culture or NAAT</b></p>	<ul style="list-style-type: none"> <li>• Is diagnostic of gonorrhea; treatment for both gonococcal and chlamydial infection should be provided.<sup>(32,42,53)</sup></li> </ul>

**Table 6. Recommended patient management: test results pending**

<p><b>Urethral/cervical mucopurulent discharge</b></p>	<ul style="list-style-type: none"> <li>• Treatment should be provided for both gonococcal and chlamydial infection if partner is infected with gonorrhea or if follow-up is not assured.<sup>(32,53,59)</sup></li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Treatment should be provided for chlamydial infection, and consideration should be given for treating gonococcal infection, if local prevalence is high or sexual contact occurred in a region with high prevalence.<sup>(32,53,59)</sup></li> </ul>
<p><b>No urethral/cervical mucopurulent discharge</b></p>	<ul style="list-style-type: none"> <li>• Therapy should be deferred until smear/culture/NAAT results available.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Treatment should be provided for both gonococcal and chlamydial infection if the individual is at high risk of infection and follow-up is not assured or if partner is infected with gonorrhea.<sup>(32,53,59)</sup></li> </ul>

## Treatment

### **Medication-specific considerations and contraindications**

- Patients should optimally be treated with combination gonorrhea infection therapy in response to increasing antimicrobial resistance.<sup>(61)</sup>
  - This combination therapy also includes effective treatment for chlamydia due to high rates of concomitant infection.<sup>(7,32,53,59)</sup>
  - Combination therapy using medications with two different mechanisms of action is thought to improve treatment efficacy as well as to potentially delay the emergence of cephalosporin-resistant gonorrhea.
- Based on pharmacokinetic considerations, an effective treatment for gonorrhea should maintain serum levels at least **4 times the minimum inhibitory concentration (MIC) for a minimum of 20 hours** to effectively treat infection caused by an organism with reduced sensitivity to an antimicrobial agent.<sup>(15)</sup>
- Directly observed therapy with single-dose regimens is desirable.<sup>(32,62)</sup>
- Clinicians should base their treatment choices and tailor recommendations on local epidemiologic data where available.

## Cephalosporins

- Cefixime and ceftriaxone should not be given to patients who are allergic to cephalosporins.
- Cross-sensitivity between penicillin and second- or third-generation cephalosporins such as ceftriaxone, cefixime, cefoxitin and cefotaxime is low. However, patients with a history of immediate hypersensitivity reaction to penicillin (e.g., anaphylaxis, urticarial rash, bronchospasm) may be at increased risk of similar reactions with all cephalosporins. If cephalosporins are administered to patients hypersensitive to penicillin, a protocol (e.g., epinephrine, airway management, etc.) to respond to serious reactions should be in place.
- The recommended diluent for ceftriaxone is 1% lidocaine without epinephrine to a final concentration of 250–350 mg/mL<sup>(63)</sup> to reduce discomfort.
- The Expert Working Group for the Canadian Guidelines on Sexually Transmitted Infections reviewed the scientific literature to address safety, efficacy, reported treatment failures and rising MICs. Their review resulted in the following recommendations:
  - There is scientific evidence that cefixime 800 mg is safe and effective in treating gonococcal infections.<sup>(9,64-68)</sup> Pharmacodynamic studies have shown that 800 mg of cefixime compared to 400 mg, increases the period when the free drug concentration exceeds the MIC. Therefore, a dosage of 800 mg may be more effective than the previously recommended 400 mg at reducing the risk of gonococcal treatment failure in settings of reduced cephalosporin susceptibility.<sup>(9,15,27)</sup>
  - No data exists on the efficacy of cefixime 800 mg in pregnancy. However, based on safety and efficacy data for the use of cefixime 400 mg, a single dose of cefixime 800 mg may be considered for use in pregnant women.
  - The penetration of cefixime into the oropharynx is not ideal and cases of treatment failure with cefixime have been reported.
  - There are limited data on the effectiveness of cefixime 800 mg PO in treating a pharyngeal infection.
  - There are more efficacy data on the use of ceftriaxone than of cefixime for treating uncomplicated infection<sup>(67)</sup> and in situations where higher tissue penetration is necessary to achieve cure (such as pharyngeal infection<sup>(69-71)</sup> and complicated cases such as PID<sup>(72,73)</sup> and epididymitis/epididymo-orchitis<sup>(74)</sup>). Ceftriaxone 250 mg IM is now recommended for pharyngeal infection, PID and epididymitis/epididymo-orchitis.
  - Ceftriaxone is recommended as the preferred treatment for gonococcal infections in MSM (refer to *Table 8* in this chapter) due to recent cases of cefixime treatment failures reported primarily among MSM.

## Quinolones

- Due to the rapid increase in quinolone-resistant *N. gonorrhoeae*, quinolones such as ciprofloxacin, levofloxacin and ofloxacin are no longer recommended for treating gonococcal infections in Canada.<sup>(5,6,22,27)</sup>
- Quinolones should **ONLY be given as an alternative treatment IF**:
  - Antimicrobial susceptibility testing is available and quinolone susceptibility is demonstrated;**OR**
  - Local quinolone resistance is under 5% AND a test of cure can be performed.
- Quinolones should be avoided in prepubertal children.

## **Azithromycin**

- Azithromycin should not be used as monotherapy unless cephalosporins are contraindicated (e.g., history of anaphylactic reaction to penicillin or allergy to cephalosporin), as resistance has been reported.<sup>(75-78)</sup>
- The recommended dose of azithromycin 2 g for gonococcal infections is associated with a significant incidence of gastrointestinal adverse effects.
  - Taking azithromycin with food may minimize these effects.
  - Prophylactic antiemetics may be used, unless contraindicated.
  - If vomiting occurs within 1 hour post-administration, a repeat dose should be given.
- Azithromycin can cause potentially life-threatening arrhythmias, especially in individuals taking a multi-day course of the medication<sup>(79)</sup>, and who:
  - have prolonged QT interval,
  - have clinically significant bradycardia,
  - have arrhythmias,
  - have heart failure,
  - are taking antiarrhythmic agents and other medications known to prolong the QT interval,
  - have low serum potassium or magnesium,
  - are elderly.



**Table 7. Recommended treatment of uncomplicated anogenital and pharyngeal infection in adults and youth ≥ 9 years of age.\* (7,15,65-67,71,80-88)**

For MSM refer to table 8.

Anogenital infection (urethral, endocervical, vaginal, rectal)	
Preferred treatment*	<b>Ceftriaxone</b> 250 mg IM in a single dose [A-I] <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†</sup> [B-II] <b>OR</b> <b>Cefixime</b> 800 mg PO in a single dose <sup>†</sup> [A-I] <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†</sup> [B-II]
Alternate treatment	<b>Spectinomycin</b> 2 g IM in a single dose [A-I] (available only through SAP) <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†</sup> [B-II] <b>OR</b> <b>Azithromycin</b> 2 g PO in a single dose <sup>§</sup> [A-I]
Pharyngeal infection	
Preferred treatment*	<b>Ceftriaxone</b> 250 mg IM in a single dose [A-I] <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†</sup> [B-III]
Alternate treatment	<b>Cefixime</b> 800 mg PO in a single dose <sup>†</sup> [B-III] <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†</sup> [B-III] <b>OR</b> <b>Azithromycin</b> 2 g PO in a single dose <sup>§</sup> [A-I]

SAP=Health Canada's Special Access Program, available at <http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogués/index-eng.php>

\*General consensus of the Expert Working Group. For information on antimicrobial resistance and medication-specific considerations and contraindications, refer to the related section above *Table 7* in this chapter.

<sup>†</sup>**Alternate combination therapy:** Azithromycin 1 g PO is preferred over the alternative of doxycycline 100 mg PO bid x 7 days, due to significant rates of tetracycline-resistant gonorrhea and concerns regarding compliance with a 7-day treatment regimen. **Doxycycline is contraindicated in pregnant and breastfeeding women.**

<sup>‡</sup>There is scientific evidence that cefixime 800 mg is safe and effective in treating gonococcal infections.<sup>(9,64-68)</sup> Pharmacodynamic studies have shown that 800 mg of cefixime compared to 400 mg, increases the period when the free drug concentration exceeds the MIC. Therefore, a dosage of 800 mg may be more effective than the previously recommended 400 mg at reducing the risk of gonococcal treatment failure in settings of reduced cephalosporin susceptibility.<sup>(9,15,27)</sup>

<sup>§</sup>Azithromycin 2 g PO in a single dose should only be considered as an alternate treatment option if there is a history of severe allergy to cephalosporins. It is important to recognize the risk of treatment failure when using azithromycin monotherapy for the treatment of gonorrhea in settings of emerging azithromycin resistance. There are also significant gastrointestinal side effects associated with high dose azithromycin.

**Table 8. Recommended treatment of uncomplicated anogenital and pharyngeal infection in men who have sex with men (MSM)\* (15,65-67,71,80-84)**

<b>Anogenital infection (urethral, rectal)</b>	
<b>Preferred treatment*</b>	<b>Ceftriaxone</b> 250 mg IM in a single dose [A-I] <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†</sup> [B-II]
<b>Alternate treatment</b>	<b>Cefixime</b> 800 mg PO in a single dose <sup>‡</sup> [A-I] <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†</sup> [B-II] <b>OR</b> <b>Spectinomycin</b> 2 g IM in a single dose [A-I] (available only through SAP) <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†</sup> [B-II] <b>OR</b> <b>Azithromycin</b> 2 g PO in a single dose <sup>§</sup> [A-I]
<b>Pharyngeal infection</b>	
<b>Preferred treatment*</b>	<b>Ceftriaxone</b> 250 mg IM in a single dose [A-I] <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†</sup> [B-III]
<b>Alternate treatment</b>	<b>Cefixime</b> 800 mg PO in a single dose <sup>‡</sup> [B-III] <b>PLUS azithromycin</b> 1 g PO in a single dose <sup>†  </sup> [B-III]

SAP=Health Canada's Special Access Program, available at <http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogués/index-eng.php>

\*General consensus of the Expert Working Group. For information on antimicrobial resistance and medication-specific considerations and contraindications, refer to the related section above *Table 7* in this chapter.

<sup>†</sup>**Alternate combination therapy:** Azithromycin 1 g PO is preferred over the alternative of doxycycline 100 mg PO bid x 7 days, due to significant rates of tetracycline-resistant gonorrhea and concerns regarding compliance with a 7-day treatment regimen.

<sup>‡</sup>There is scientific evidence that cefixime 800 mg is safe and effective in treating gonococcal infections.<sup>(9,64-68)</sup> Pharmacodynamic studies have shown that 800 mg of cefixime compared to 400 mg, increases the period when the free drug concentration exceeds the MIC. Therefore, a dosage of 800 mg may be more effective than the previously recommended 400 mg at reducing the risk of gonococcal treatment failure in settings of reduced cephalosporin susceptibility.<sup>(9,15,27)</sup>

<sup>§</sup>For anogenital infection, azithromycin 2 g PO in a single dose should only be considered as an alternate treatment option if there is a history of severe allergy to cephalosporins. It is important to recognize the risk of treatment failure when using azithromycin monotherapy for the treatment of gonorrhea in settings of emerging azithromycin resistance. There are also significant gastrointestinal side effects associated with high dose azithromycin.

<sup>||</sup>For pharyngeal infection, in case of severe allergy to cephalosporins, azithromycin 2 g PO [A-I] may be considered as an alternate treatment option.

**Table 9. Recommended treatment of uncomplicated anogenital and pharyngeal infection in children < 9 years of age\*** (31,39,89)

Anogenital infection (urethral, vaginal, rectal)	
<b>Preferred treatment*</b>	<p><b>Ceftriaxone</b> 50 mg/kg IM up to 250 mg in a single dose [A-II]  <b>PLUS azithromycin</b> 20 mg/kg (maximum dose of 1 g) PO in a single dose [B-II]</p> <p><b>OR</b></p> <p><b>Cefixime</b> 8 mg/kg PO BID x 2 doses<sup>†</sup> (maximum 400 mg per dose) [B-III]  <b>PLUS azithromycin</b> 20 mg/kg (maximum dose of 1 g) PO in a single dose [B-II]</p>
<b>Alternate treatment</b>	<p><b>Spectinomycin</b> 40 mg/kg IM in a single dose (maximum dose of 2 g ) [A-II] (available only through SAP)  <b>PLUS azithromycin</b> 20 mg/kg (maximum dose of 1 g) PO in a single dose [B-II]</p>
Pharyngeal infection	
<b>Preferred treatment*</b>	<p><b>Ceftriaxone</b> 50 mg/kg IM up to 250 mg in a single dose [A-II]  <b>PLUS azithromycin</b> 20 mg/kg (maximum dose of 1 g) PO in a single dose [B-III]</p>
<b>Alternate treatment</b>	<p><b>Cefixime</b> 8 mg/kg PO BID x 2 doses<sup>†</sup> (maximum 400 mg per dose) [A-II]  <b>PLUS azithromycin</b> 20 mg/kg (maximum dose of 1 g) PO in a single dose [B-III]</p>
<p><b>Important notes related to neonates (birth to one month of age):</b></p> <ul style="list-style-type: none"> <li>• In neonates the recommended dosage for ceftriaxone is 25-50 mg/kg (maximum 125 mg).</li> <li>• <b>Routine combination therapy with a macrolide is not recommended</b> due to the association with pyloric stenosis. Testing should be done for chlamydia and if results are positive, treatment should be provided as per <i>table 4</i> in the <i>Chlamydial Infections</i> chapter.</li> </ul>	

SAP=Health Canada's Special Access Program, available at <http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php>

\*General consensus of the Expert Working Group. For information on antimicrobial resistance and medication-specific considerations and contraindications, refer to the related section above *Table 7* in this chapter.

<sup>†</sup>Whenever possible, oral therapies are recommended for children. Recommendations for the use of cefixime are based on data showing efficacy in the treatment of infections caused by organisms similar to *N. gonorrhoeae*. Because there is limited experience with the use of cefixime in children with gonococcal infections, antimicrobial susceptibility should be ascertained and a follow-up culture ensured. If follow-up cannot be ensured, ceftriaxone should be used in place of cefixime.

**Table 10. Recommended treatment of gonococcal ophthalmia and disseminated infections in adults and youth ≥ 9 years of age<sup>(31,39)</sup>**

Infection	Preferred initial therapy while awaiting consultation with an experienced colleague* †
Arthritis	Ceftriaxone 2 g IV/IM daily for 7 days <sup>†</sup> [A-II] PLUS azithromycin 1 g PO in a single dose x 1 dose <sup>‡</sup> [B-III]
Meningitis	Ceftriaxone 2 g IV/IM <sup>§</sup> daily for 10–14 days <sup>†</sup> [A-II] PLUS azithromycin 1 g PO in a single dose x 1 dose <sup>‡</sup> [B-III]
Endocarditis	Ceftriaxone 2 g IV/IM <sup>§</sup> daily for 28 days <sup>†</sup> [A-II] PLUS azithromycin 1 g PO in a single dose x 1 dose <sup>‡</sup> [B-III]
Ophthalmia	Ceftriaxone 2 g IV/IM in a single dose <sup>†</sup> [A-II] PLUS azithromycin 1 g PO in a single dose <sup>‡</sup> [B-III]
<b>Note: Hospitalization is indicated for meningitis and may also be indicated for other disseminated infections.</b>	

\*General consensus of the Expert Working Group. For information on antimicrobial resistance and medication-specific considerations and contraindications, refer to the related section above *Table 7* in this chapter.

<sup>†</sup>This is the usual duration of therapy but all cases should be discussed with an infectious diseases expert.

<sup>‡</sup>**Alternate combination therapy:** Azithromycin 1 g PO is preferred over the alternative of doxycycline 100 mg PO bid x 7 days, due to significant rates of tetracycline-resistant gonorrhoea and concerns regarding compliance with a 7-day treatment regimen. **Doxycycline is contraindicated in pregnant and breastfeeding women.**

<sup>§</sup>IM administration should only be considered if an IV line is not available.

**Table 11. Recommended treatment of gonococcal ophthalmia and disseminated infections in children > 1 month to < 9 years of age\* † (31,39)**

Infection	Preferred treatment*
Arthritis	<b>Ceftriaxone</b> 50 mg/kg IV/IM <sup>†</sup> daily for 7 days (maximum dose of 1 g/day) <sup>§</sup> [A-III] <b>PLUS azithromycin</b> 20 mg/kg (maximum dose of 1 g) PO in a single dose x 1 dose [B-III]
Meningitis	<b>Ceftriaxone</b> 50 mg/kg IV/IM <sup>†</sup> q12h for 10–14 days (maximum of 1 g/dose and 2 g/day) <sup>§</sup> [A-III] <b>PLUS azithromycin</b> 20 mg/kg (maximum dose of 1 g) PO in a single dose x 1 dose [B-III]
Endocarditis	<b>Ceftriaxone</b> 50 mg/kg IV/IM <sup>†</sup> q12h for 28 days (maximum of 1 g/dose and 2 g/day) <sup>§</sup> [A-III] <b>PLUS azithromycin</b> 20 mg/kg (maximum dose of 1 g) PO in a single dose x 1 dose [B-III]
Ophthalmia beyond the neonatal period	<b>Ceftriaxone</b> 50 mg/kg IV/IM in a single dose (maximum dose of 2 g) [A-III] <b>PLUS azithromycin</b> 20 mg/kg (maximum dose of 1 g) PO in a single dose <sup>§</sup> [B-III]
<b>Note: Hospitalization is indicated for disseminated infections and consultation with an expert in infectious diseases should be initiated as soon as possible.</b>	

\*General consensus of the Expert Working Group. For information on antimicrobial resistance and medication-specific considerations and contraindications, refer to the related section above *Table 7* in this chapter.

<sup>†</sup>For treatment recommendations for neonates (birth to one month old), refer to the *Recommended treatment of neonates* section in this chapter.

<sup>‡</sup>IM administration should only be considered if an IV line is not available.

<sup>§</sup>This is the usual duration of therapy but all cases should be discussed with an infectious diseases expert.

## Recommended treatment of neonates

- It is important that neonates born to infected untreated mothers be tested and that treatment be initiated without waiting for test results.
- Culture conjunctivae prior to administering antibiotics. If the infant is unwell in any way, also culture blood and cerebrospinal fluid to rule out disseminated infection.

**Table 12. Neonates born to women with untreated gonorrhoea\*** (31,39,89)

<b>Preferred treatment*</b>	<b>Ceftriaxone</b> 25-50 mg/kg IM in a single dose (maximum dose of 125 mg) [A-III]
<p>Important notes:</p> <ul style="list-style-type: none"> <li>• Prophylactic treatment for possible chlamydial co-infection is not recommended unless follow-up cannot be assured.</li> <li>• Testing should be done for chlamydia and if results are positive, treatment should be provided as per <i>table 4</i> in the <i>Chlamydial Infections</i> chapter.</li> </ul>	

\*General consensus of the Expert Working Group. For information on antimicrobial resistance and medication-specific considerations and contraindications, refer to the related section above *Table 7* in this chapter.

**Table 13. Ophthalmia neonatorum**(39,89)

<b>Preferred treatment*</b>	<b>Ceftriaxone</b> 25-50 mg/kg IM in a single dose (maximum dose of 125 mg) <sup>†</sup> [A-II]
<p>Important notes:</p> <ul style="list-style-type: none"> <li>• Irrigate eyes immediately with sterile normal saline and at least hourly as long as necessary to eliminate discharge.</li> <li>• Prophylactic treatment for possible chlamydial co-infection is not recommended unless follow-up cannot be assured. Testing should be done for chlamydia and if results are positive, treatment should be provided as per <i>table 4</i> in the <i>Chlamydial Infections</i> chapter.</li> <li>• <b>Hospitalization and consultation with an expert in infectious diseases should be initiated as soon as possible.</b></li> <li>• Appropriate infection prevention and control precautions are necessary for all cases.</li> </ul>	

\*General consensus of the Expert Working Group. For information on antimicrobial resistance and medication-specific considerations and contraindications, refer to the related section above *Table 7* in this chapter.

<sup>†</sup>Routine gonococcal combination therapy with a macrolide is not recommended due to the association with pyloric stenosis.

**Table 14. Neonates with disseminated gonococcal arthritis, meningitis or endocarditis**

<b>Preferred treatment*</b>	• <b>Cefotaxime</b> 50 mg/kg IV/IM <sup>†</sup> q6h for 10-14 days <sup>‡§</sup> [A-III]
<p>Important notes:</p> <ul style="list-style-type: none"> <li>• <b>Hospitalization and consultation with an expert in infectious diseases should be initiated as soon as possible.</b></li> <li>• <b>Prophylactic treatment for possible chlamydial co-infection is not recommended unless follow-up cannot be assured. Testing should be done for chlamydia and if results are positive, treatment should be provided as per <i>table 4</i> in the <i>Chlamydial Infections</i> chapter.</b></li> </ul>	

\*General consensus of the Expert Working Group. For information on antimicrobial resistance and medication-specific considerations and contraindications, refer to the related section above *Table 7* in this chapter.

<sup>†</sup>IM administration should only be considered if an IV line is not available.

<sup>‡</sup>This is the usual duration of therapy but all cases should be discussed with an infectious diseases expert.

<sup>§</sup>Routine gonococcal combination therapy with a macrolide is not recommended due to the association with pyloric stenosis.

## Reporting and Partner Notification

- Case finding and partner notification are critical strategies for maintaining control of gonococcal infections in Canada.
- Local public health authorities may assist with partner notification and with appropriate referral for clinical evaluation, testing, treatment and health education.
- Gonococcal infections are reportable in all provinces and territories; positive test results should be reported to local public health authorities.
- All partners who have had sexual contact with the index case within 60 days prior to symptom onset or date of specimen collection (if the index case is asymptomatic) should be notified, tested and empirically treated regardless of clinical findings and without waiting for test results.<sup>(32,62)</sup>
- The length of time for the trace-back period should be extended in the following circumstances:
  - To include additional time between the date of testing and date of treatment,
  - If the index case states that there were no partners during the recommended trace-back period, the most recent partner should be notified, and
  - If all partners traced (according to recommended trace-back period) test negative, the last partner prior to the trace-back period should be notified.
- When a neonate is confirmed to have gonorrhoea, the mother and her most recent sexual partner plus any other partners within 60 days of delivery should be located, clinically evaluated and empirically treated regardless of clinical findings and without waiting for test results.

## Follow-up

- Repeat screening for individuals with a gonococcal infection is recommended 6 months post-treatment.<sup>(28)</sup>
- Follow-up cultures for test of cure from all positive sites should be done **3–7 days** after the completion of therapy, particularly in the following situations:
  - All pharyngeal infections,<sup>(69)</sup>
  - Persistent symptoms or signs post-therapy,<sup>(32,62)</sup>
  - Case treated with a regimen other than ceftriaxone, where ceftriaxone is first line,
  - Quinolones were given for treatment in the absence of susceptibility testing,
  - Case is linked to another case with documented antimicrobial resistance to the treatment given,
  - Antimicrobial resistance to the administered therapy is documented,<sup>(32,62)</sup>
  - Case is linked to a treatment failure case that was treated with the same antibiotic,<sup>(32)</sup>
  - Treatment failure for gonorrhoea has occurred previously in the individual,
  - Compliance is uncertain,
  - There is re-exposure to an untreated partner,
  - Infection occurs during pregnancy,<sup>(86)</sup>
  - Disseminated gonococcal infection is diagnosed,
  - Case is a child,
  - Follow-up testing should also be considered for PID if *N. gonorrhoeae* was initially isolated, and
  - Women undergoing therapeutic abortion (TA) who have a positive test result for gonococcal infection, as they are at increased risk of developing pelvic inflammatory disease.
- If NAAT is the only choice for test of cure, tests should not be done for 2–3 weeks after treatment<sup>(45,46)</sup> to avoid false-positive results due to the presence of non-viable organisms.

## Treatment Failure<sup>(5)</sup>

### **Definition**

- Treatment failure is defined as absence of reported sexual contact during the post-treatment period **AND one of the following:**
  - The presence of intracellular Gram-negative diplococci on microscopy in specimens taken at least 72 hours after completion of treatment,**OR**
  - Positive *N. gonorrhoeae* on culture of specimens taken at least 72 hours after completion of treatment,**OR**
  - Positive NAAT of specimens taken at least 2–3 weeks after completion of treatment.

### **Recommended management of primary cephalosporin treatment failures**

- For cephalosporin combination therapy treatment failures (i.e., cefixime 800 mg PO or ceftriaxone 250 mg IM **plus** azithromycin 1 g PO), **local public health authorities should be promptly notified.** This will allow for the P/T STI programs to work with the Public Health Agency of Canada to post alerts related to treatment failures in Canada.
- It is strongly recommended that treatment be guided by antimicrobial susceptibility test results to determine the appropriate antimicrobial agent in consultation with an expert in infectious diseases and local public health authorities.
- **A test of cure by culture is strongly recommended and should be collected/obtained 3–7 days after completion of treatment.**



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