PARTICIPANTS IN THE GUIDELINE DEVELOPMENT PROCESS:

These guidelines are a result of Public Health Ontario’s (PHO) collaboration and consultation with several partner organizations and individuals. They include the Ontario Multi-drug-Resistant Neisseria gonorrhoeae Working Group, the Ministry of Health and Long-Term Care, Medical Officers of Health, the Provincial Infectious Disease Advisory Committee (PIDAC) on Communicable Diseases, PIDAC Sexually Transmitted Infections (STI) Working Group, Medical Directors of STI clinics, primary-care and specialist health care providers. Where recommendations differ from the Canadian Guidelines on Sexually Transmitted Infections (CGSTI), rationale for the Ontario recommendations is provided. The CGSTI are available from the following link: http://www.phac-aspc.gc.ca/ std-mts/sti-its/guide-lignesdir-eng.php

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## Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>BASHH</td>
<td>British Association for Sexual Health and HIV</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CGSTI</td>
<td>Canadian Guidelines on Sexually Transmitted Infections</td>
</tr>
<tr>
<td>iPHIS</td>
<td>Integrated Public Health Information System</td>
</tr>
<tr>
<td>IUSTI</td>
<td>International Union against Sexually Transmitted Infections</td>
</tr>
<tr>
<td>MSM</td>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration</td>
</tr>
<tr>
<td>NAAT</td>
<td>Nucleic acid amplification testing</td>
</tr>
<tr>
<td>PHAC</td>
<td>Public Health Agency of Canada</td>
</tr>
<tr>
<td>PHO</td>
<td>Public Health Ontario</td>
</tr>
<tr>
<td>PID</td>
<td>Pelvic inflammatory disease</td>
</tr>
<tr>
<td>PIDAC</td>
<td>Provincial Infectious Disease Advisory Committee</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually transmitted infections</td>
</tr>
</tbody>
</table>
Summary of Recommendations

Laboratory diagnosis

- All sexually active persons who have signs and symptoms of gonorrhea should be tested. Consideration should also be given to laboratory screening of asymptomatic persons who have risk factors for gonorrhea.

- Asymptomatic persons should be screened using urine NAAT for males and cervical or urine NAAT for females.

- Symptomatic persons should be tested using urethral culture or urine NAAT for males and cervical swab culture or cervical NAAT for females.

- Culture is also recommended in specific situations as per the CGSTI (see page 17 for full list).

Treatment of gonorrhea

- Recommended first-line therapy of individuals with confirmed or suspected uncomplicated urogenital, rectal or pharyngeal gonorrhea and their sex partners is ceftriaxone 250 mg intramuscularly plus azithromycin 1 g orally.

- Second-line therapeutic options are less effective than combination ceftriaxone and azithromycin in the treatment of gonorrhea. Second line therapies are only to be considered if first-line therapy is not possible, and must be followed by a test of cure.

Follow-up for gonorrhea cases and contacts

- A test of cure is recommended when first-line therapy is not used and in other specific situations (see page 28 for full list). The preferred testing method for test of cure is culture.

- Sexual partners of the case should be notified for the purposes of evaluation, testing and treatment. The sex partners are recommended to receive empiric treatment as per recommendations as soon as possible to reduce the risk of further transmission.
• Rescreening after six months, or when they next seek medical care within the next 12 months, is recommended for all who are diagnosed with gonorrhea.

• Health care professionals should report any suspected or confirmed gonorrhea clinical failures to their local public health unit.

• Once notified of a suspect or confirmed case of gonorrhea treatment failure, the local public health unit should work with the responsible health care practitioner to complete the PHO enhanced surveillance form for gonorrhea clinical failures and notify PHO of the suspected or confirmed case as soon as possible to discuss any further public health action that may be required.
Scope and purpose

Increasing resistance of Neisseria gonorrhoeae to the cephalosporins, the last available class of antibiotics recommended for the treatment of gonorrhea, has been described worldwide.\textsuperscript{1-4} Antibiotic resistance in \textit{N. gonorrhoeae} increases the risk of clinical failure and sequelae in an infected individual. Furthermore, inadequate treatment of antibiotic-resistant gonorrhea can lead to the selection of drug-resistant strains, increasing the risk of untreatable gonorrhea spreading more broadly in the population.

This document provides recommendations for Ontario health care providers to address the immediate threat of increasing cephalosporin resistance in \textit{N. gonorrhoeae}. These include:

1. Laboratory testing recommendations, including when to perform a Gram stain, bacterial culture or nucleic acid amplification testing (NAAT);

2. Treatment recommendations for uncomplicated urogenital, rectal and pharyngeal \textit{N. gonorrhoeae} infections;

3. Recommendations for follow-up of \textit{N. gonorrhoeae} infections, including public health reporting, testing and treatment of sexual contacts, indications for test of cure and follow-up testing.

The recommendations within this document are based on the shared clinical and public health goals to facilitate access to appropriate laboratory diagnosis, and timely and effective treatment and follow-up for cases and contacts. In addition, access to adequate antimicrobial susceptibility information will allow for optimal patient treatment and enhance public health monitoring of antimicrobial resistance patterns and clinical treatment failures.

These guidelines do not address other issues critical to reducing the burden of gonorrhea in Ontario. These include strategies for the primary prevention of gonorrhea, including counselling and risk reduction strategies, infections among specific populations (e.g., children) or co-infections. References for these topics include the Ontario Sexual Health and Sexually Transmitted Infections Prevention and Control Protocol,\textsuperscript{5} the Canadian Guidelines on Sexually Transmitted Infections,\textsuperscript{6} and the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines.\textsuperscript{7}
Grading of evidence

These guidelines are based on the current scientific evidence, epidemiology and antimicrobial susceptibility profiles of *N. gonorrhoeae* in Ontario, available laboratory testing methods in Ontario, and the Canadian Guidelines on Sexually Transmitted Infections. Whenever possible the strength of recommendation, and the quality of the evidence supporting each recommendation, was graded using the Infectious Diseases Society of America/U.S. Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines (Table 1).

Table 1. Grading system for ranking recommendations in clinical guidelines from the Infectious Diseases Society of America/U.S. Public Health Service.

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strength of recommendation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>Strongly in favour</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Moderately in favour</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
<td>Optional</td>
</tr>
<tr>
<td>D</td>
<td>D</td>
<td>Moderately against</td>
</tr>
<tr>
<td>E</td>
<td>E</td>
<td>Strongly against</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td>I</td>
<td>Evidence from ( \geq 1 ) properly randomized, controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>II</td>
<td>Evidence from ( \geq 1 ) well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from ( \geq 1 ) centre); from multiple time series studies; or from dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees</td>
</tr>
</tbody>
</table>
1. Background

1.1 Antimicrobial resistance in *N. gonorrhoeae*

Gonorrhea, caused by the Gram-negative bacteria *N. gonorrhoeae*, is the second most frequently reported bacterial STI in Ontario, behind chlamydia.\(^9\)

Historically, gonorrhea was treated with penicillin and the tetracyclines, until antimicrobial resistance to these antibiotics emerged in the 1980s.\(^10\) In the 1990s, fluoroquinolones such as ciprofloxacin were the treatment of choice for gonorrhea. However, due to the rapid emergence of resistance, ciprofloxacin has not been recommended for the empiric treatment of gonorrhea in Canada since 2008.\(^6\)

Currently, third-generation cephalosporins, ceftriaxone or cefixime (depending on particular guidelines), are recommended as first-line treatment for gonorrhea.\(^11-14\) All current treatment guidelines also recommend a second adjuvant agent in combination with the recommended cephalosporin treatment for the treatment of gonorrhea. Azithromycin is the recommended adjuvant in the Canadian, British and European guidelines,\(^11-13\) whereas the U.S. CDC recommends adjuvant azithromycin or doxycycline for the treatment of gonorrhea.\(^14\)

Multi-drug resistance in *N. gonorrhoeae* is rapidly evolving, threatening the effectiveness of all currently available single-dose antibiotics in common use, including the third-generation cephalosporins. Clinical failures associated with the use of cephalosporins have been identified worldwide. The potential for widespread multi-drug-resistant *N. gonorrhoeae* is a genuine concern and could lead to increased rates of pelvic inflammatory disease, urethritis, disseminated disease and neonatal ophthalmia. In Ontario by January 2013, there have been at least nine cases of clinical failure associated with the use of oral cefixime to treat gonorrhea.\(^15\) The number of documented clinical failures is most likely an underestimate as the ability to identify potential clinical failures is limited by the occurrence of asymptomatic infection as well as the lack of a routine test of cure.

The identification of antimicrobial resistance and potential clinical failures is further complicated by an increasing reliance on NAAT rather than culture. NAAT is a more sensitive test than culture for the diagnosis of gonorrhea\(^16\) and can be performed on urine samples, facilitating easier specimen collection. However, NAAT does not allow for antimicrobial susceptibility testing, failing to detect those that are at highest risk of treatment failure.

The threat of untreatable gonorrhea, evidence of clinical failures to cefixime in Ontario and worldwide, and the decreased use of culture for the diagnosis of gonorrhea in Ontario provide the rationale for the diagnosis and treatment guidelines presented in this document.
1.2 Clinical features

Transmission of *N. gonorrhoeae* most commonly occurs by direct contact from vaginal, anal or oral sex, but it can also be transmitted from mother to child during childbirth. The most frequent sites of infection include the urethra, endocervix, rectum and pharynx.

Common presentations of gonorrhea in men include acute urethral discomfort, urethral discharge and dysuria. Other symptoms may include urethral itch; testicular pain, redness, or swelling; or rectal pain and discharge (if proctitis is present).

Common presentations of gonorrhea in women include vaginal discharge, dysuria, abnormal vaginal bleeding, lower abdominal pain, pain and/or bleeding during intercourse; and/or rectal pain and discharge (if proctitis is present).

It should be noted that up to 50 per cent of urogenital infections in women and up to 10 per cent of urogenital infections in men are asymptomatic; rectal and pharyngeal infections are often asymptomatic.

If left untreated, gonorrhea can lead to a number of complications in both women (e.g., pelvic inflammatory disease (PID), infertility, ectopic pregnancy, chronic pelvic pain, Reiter syndrome or disseminated gonococcal infection) and men (epididymoorchitis, Reiter syndrome, infertility or disseminated gonococcal infection). Gonorrhea also increases the risk of HIV acquisition and transmission.

1.3 Epidemiology

The overall incidence of gonorrhea has increased over the past 10 years in Ontario (Figure 1). In 2011, 4,196 cases of gonorrhea were reported, with males accounting for the majority of cases (57.2 per cent). In 2011, the highest incidence rate for both males and females was in the 20-to-24-years age group (Figure 2). Males 25 years and over made up the highest proportion of total gonorrhea cases, at 38.3 per cent (1,603/4,189), followed by females under 25 years, at 28.1 per cent (1,177/4,189).

The majority of gonorrhea cases had defined risk factors for infection. In cases where age and sex were known, 73.5 per cent (3,079/4,189) reported at least one risk factor, the most common being “no condom use.” Of males reporting at least one risk factor, 40.9 per cent (748/1,827) also reported “sex with same sex.” Of those, 77.9 per cent (583/748) were age 25 and over. For a geographical breakdown of the incidence rate of gonorrhea in 2011 by health unit jurisdiction, please refer to figure 3.
Figure 1: Reported gonorrhea cases and rate by year and sex: Ontario, 2001–2011

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by PHO March 9, 2012.

Note: Does not include cases of unknown age/sex
Figure 2: Reported gonorrhea cases and rate by age and sex: Ontario, 2011

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by PHO March 9, 2012.

Note: Does not include cases of unknown age/sex
Figure 3: Reported rate of gonorrhea by health unit: Ontario, 2011

Source: Ontario Ministry of Health and Long-Term Care, integrated Public Health Information System (iPHIS) database, extracted by PHO March 9, 2012.

Note: Does not include cases of unknown age
2. Laboratory diagnosis

Key Messages

- The three laboratory methods available for the diagnosis of gonorrhea are microscopy, bacterial culture, and NAAT.

Laboratory Diagnosis Recommendations

- All sexually active persons who have signs and symptoms of gonorrhea should be tested. Consideration should also be given to laboratory screening of asymptomatic persons who have risk factors for gonorrhea.

- Asymptomatic persons should be screened using urine NAAT for males and cervical or urine NAAT for females.

- Symptomatic persons should be tested using urethral culture or urine NAAT for males and cervical swab culture or cervical NAAT for females.

- Culture is also recommended in specific situations as per the CGSTI (see page 17 for full list).

2.1 What laboratory test methods are available for the diagnosis of gonorrhea?

Microscopy

The identification of intracellular Gram-negative diploccci by microscopy has a relatively high sensitivity and specificity for the diagnosis of gonorrhea in men, with a sensitivity > 90 per cent in symptomatic men, a sensitivity of 50 to 75 per cent in asymptomatic men and a specificity of > 90 per cent for both symptomatic and asymptomatic men (Table 2). Microscopy for *N. gonorrhoeae* women is not recommended due to low sensitivity and specificity in this population.

The primary advantage of microscopy for the diagnosis of gonorrhea is the rapid turn-around time particularly when performed in the clinical setting. For improved sensitivity, it is recommended that all specimens tested by microscopy be supplemented by an additional specimen for culture or NAAT. If *N. gonorrhoeae* is identified by microscopy, culture is preferred in order to obtain antimicrobial susceptibility results.
Culture

Bacterial culture for *N. gonorrhoeae* has a test specificity of more than 99 per cent, the highest of the three testing methods, and is the only diagnostic method that enables susceptibility testing (Table 2). The sensitivity of culture for the detection of *N. gonorrhoeae* ranges from 50 to 92 per cent and is reduced with suboptimal transport times (i.e., exceeding 24 to 48 hours). Culture can be used for testing of all potentially infected anatomic sites, including urethral, cervical, pharyngeal, rectal, conjunctiva, joint fluid and blood.

Nucleic Acid Amplification Testing (NAAT)

NAAT for *N. gonorrhoeae* was introduced in the late 1990s and has become the predominant method of testing due to ease of collection of specimens and the ability to test for *C. trachomatis* and *N. gonorrhoeae* in the same sample. The sensitivity of NAAT for the detection of *N. gonorrhoeae* is higher than bacterial culture (Table 2). The high sensitivity of NAAT for *N. gonorrhoeae* is robust to suboptimal sample transport times and conditions, which can affect organism viability for culture. NAAT specificity (96.1 to 99.8 per cent) is slightly lower than bacterial culture leading to a slightly higher risk of false positive results.

Urine, cervical and urethral samples can be tested for *N. gonorrhoeae* using NAAT. Urine testing by NAAT has the advantage of being less invasive than cervical and urethral swabs for culture and NAAT. However, when testing women, urine NAAT for *N. gonorrhoeae* is less sensitive than cervical NAAT. The primary disadvantage of NAAT is that it cannot provide antimicrobial susceptibility results, which can currently only be performed on cultured isolates. NAAT for *N. gonorrhoeae* is also not licensed for pharyngeal or rectal sites. Lastly, NAAT is not ideal for test of cure as it can result in false positive results from samples that contain only DNA from dead bacteria, sometimes up to two weeks post-treatment. In contrast, culture-based testing for test of cure can be done as early as four days post-treatment as all living organisms should be eradicated with effective antimicrobial therapy by this time.

Most Ontario labs offer testing for *N. gonorrhoeae*. The PHO laboratories perform microscopy, culture and NAAT for the detection of *N. gonorrhoeae*. Similarly, most Ontario private and hospital laboratories also offer microscopy, NAAT and/or culture for the detection of *N. gonorrhoeae*, depending on the laboratory. Please contact your local laboratory to determine the testing methods available and ideal collection and transport media.
Table 2: Sensitivity, specificity and other characteristics of laboratory tests for *N. gonorrhoeae*

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Susceptibility testing</th>
<th>Specimen collection details (please contact your testing lab for specific requirements)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram stain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men: Symptomatic: &gt; 90%</td>
<td></td>
<td>Men: &gt; 90%</td>
<td>No</td>
<td>Most commonly performed from slide or Amies charcoal swab</td>
</tr>
<tr>
<td>Asymptomatic: 50-75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women: &lt; 50%</td>
<td></td>
<td>Women: &lt; 90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bacterial culture</strong></td>
<td>50 – 92%</td>
<td>&gt;99%</td>
<td>Yes</td>
<td>Most commonly performed from Amies charcoal swab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sensitivity decreases with long transport times and asymptomatic infection</td>
</tr>
<tr>
<td><strong>Nucleic acid amplification testing (NAAT)</strong></td>
<td>92 – 97.2%</td>
<td>96.1 – 99.8%</td>
<td>No</td>
<td>Proprietary collection kits specific to commercial assays or urine containers</td>
</tr>
</tbody>
</table>
2.2 Recommended populations who should be tested/screened for *N. gonorrhoeae*

All sexually active persons who have signs and/or symptoms of gonorrhea should be tested for *N. gonorrhoeae* (A-III). Since a high proportion of individuals with gonorrhea are at risk of co-infection with chlamydia, when testing for *N. gonorrhoeae* practitioners should concurrently test for chlamydia.

Consideration should also be given to laboratory screening of asymptomatic persons who have risk factors for gonorrhea and unprotected sexual exposure. The CGSTI do not recommend a particular testing interval for these persons. The risk factors for gonorrhea listed in the CGSTI are the following:6

- Sexually active youth <25 years of age with multiple partners
- Men who have sex with men
- Those who have had contact with a person with proven infection or a compatible syndrome
- Sex workers and their sexual partners
- Street-involved youth
- Previous gonorrhea and other STI infection
- Those who have had a sexual partner originating from an area with high endemicity (there is also a higher risk of resistance in this population)
- Travellers to an endemic country who have had sex with a resident of that area (there is also a higher risk of resistance in this population)

In Ontario, risk factors for gonorrhea of particular importance among those with unprotected sexual exposure include (A-II):

- Sexually active women under 25 years of age as they represent 65 per cent of infections in women in Ontario. Also, up to 50 per cent of urogenital infections in women are asymptomatic, and those infections may lead to complications such as pelvic inflammatory disease and infertility.
- Sexually active men who have sex with men (MSM), as they represent 41 per cent of all gonorrhea diagnoses in men.
2.3 Recommended methods for screening asymptomatic persons for *N. gonorrhoeae*

See Figure 4 for a testing algorithm for asymptomatic persons.

**Males:** For asymptomatic males, the preferred testing method is urine NAAT testing because of the higher sensitivity and non-invasiveness of NAAT testing (B-II). Please note that antimicrobial susceptibility testing cannot be performed on NAAT samples.

**Females:** For asymptomatic females, the preferred testing method is either cervical or urine NAAT (B-II). NAAT is more sensitive than culture, with cervical NAAT being more sensitive than urine NAAT. Please note that antimicrobial susceptibility testing cannot be performed on NAAT samples.

Rectal and pharyngeal sites: Culture is the only method currently available in Ontario for testing for *N. gonorrhoeae* from rectal and pharyngeal sites. Rectal and pharyngeal sample collection is recommended for MSM with unprotected exposure at these sites (B-II). There is insufficient evidence to date to support the routine screening of asymptomatic women and heterosexual men for *N. gonorrhoeae* at rectal and pharyngeal sites (C-III). Screening may be considered in individual circumstances based on clinical evaluation and local epidemiology.

**Figure 4: Testing algorithm for asymptomatic persons**
2.4 Recommended methods for testing symptomatic persons for *N. gonorrhoeae*

See Figure 5 for a testing algorithm for symptomatic persons.

**Males:** For symptomatic males with discharge consistent with gonorrhea (acute white urethral discharge), the preferred testing method is urethral culture in order to obtain antimicrobial susceptibility testing (**C-III**). If culture testing is not locally available or there is no acute urethral discharge, then urine NAAT testing is recommended (**C-III**).

**Females:** For symptomatic females, the preferred testing method is cervical culture or cervical NAAT (**B-III**). Cervical culture has the advantage of obtaining antimicrobial susceptibility. If a cervical specimen is unobtainable, urine NAAT is a second-line option (**C-III**).

**Rectal and pharyngeal sites:** Culture is the only method currently available in Ontario for testing for *N. gonorrhoeae* from rectal and pharyngeal sites (**C-III**).

**Figure 5: Testing algorithm for symptomatic persons**
While not examined in the published literature, symptomatic persons infected with *N. gonorrhoeae* are likely to have a larger bacterial load. In such cases, the sensitivity of culture is postulated to be closer to that of NAAT.

### 2.5 Additional considerations for using culture to diagnose gonorrhea

Note that as per the CGSTI, culture testing is also strongly recommended in the following situations:\(^6\)

- Sexual abuse of children (rectal, pharyngeal, vaginal)
- Sexual assault
- Presumed treatment failure
- Evaluation of pelvic inflammatory disease
- Infection acquired overseas or in areas with recognized antimicrobial resistance
3. Treatment of gonorrhea

Key Messages

- In a recent review of gonorrhea infections in Ontario, over 10 per cent of *N. gonorrhoeae* culture isolates had decreased susceptibility to cefixime. These isolates were more likely to be isolated from males compared to females (p<0.001) and more likely to be identified in Toronto.

- Over nine clinical failures of gonorrhea associated with the use of cefixime have been identified in Ontario. In a recent Ontario study, there was a 25-per-cent rate of clinical failure associated with isolates with reduced susceptibility to cefixime (defined as an MIC ≥ 0.12 μg/mL).

- Oral cefixime is no longer considered first line therapy for the treatment of gonorrhea in Ontario, even when in combination with azithromycin or doxycycline.

Summary of Recommendations

- Persons above nine years of age with confirmed or suspected uncomplicated urogenital gonorrhea and their sex partners should be treated with ceftriaxone 250 mg intramuscularly plus azithromycin 1 g orally.

- Second-line therapeutic options are less effective than combination ceftriaxone and azithromycin in the treatment of gonorrhea. These therapies are only to be considered if first-line therapy is not possible and must be followed by a test of cure.

3.1 Increasing antibiotic resistance to cephalosporins

The minimum inhibitory concentration (MIC) is used in laboratories to measure lowest possible concentration of antibiotics that is required to inhibit the growth of bacteria. Reduced susceptibility is identified when higher concentrations of antibiotic are needed to stop the growth of bacteria. Non-susceptibility to both cefixime and ceftriaxone is defined as > 0.25 μg/mL in North America. However, clinical failures described in Ontario and Europe have also occurred at lower MICs.

In a recent review of all *N. gonorrhoeae* cultures submitted to PHO, over 10 per cent of culture isolates (272/2,586) from July 10, 2010, to Oct, 24, 2012, had decreased susceptibility to cefixime. These isolates were more likely to be isolated from males...
compared to females (p<0.001). Isolates with decreased susceptibility to cefixime were identified in 17 health unit jurisdictions, and most were from cases in Toronto (69.5 per cent, 189/272).\textsuperscript{27} The isolates described above, with MICs ≥ 0.12 μg/mL, are of great concern because they indicate a trend toward greater resistance and increasing risk of treatment failure.

Canadian national surveillance efforts have confirmed the increase in cephalosporin resistance in \textit{N. gonorrhoeae} seen in Ontario. As part of the national antimicrobial surveillance program led by the Public Health Agency of Canada and the National Microbiology Laboratory, which tests all isolates with resistance to at least one antimicrobial, the modal cefixime MIC shifted from 0.016 μg/mL to 0.12 μg/mL from 2001 to 2010, representing a four-fold increase in the concentration of cefixime required to suppress growth of \textit{N. gonorrhoeae}.\textsuperscript{28} The shift toward higher MICs has also been seen in Ontario (Figure 6).

\textbf{Figure 6: Comparison of cefixime MICs for \textit{N. gonorrhoeae} isolates in 2005 and 2011 Ontario}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6}
\caption{Comparison of cefixime MICs for \textit{N. gonorrhoeae} isolates in 2005 and 2011 Ontario}
\end{figure}

\textit{Source:} unpublished data from the Canadian \textit{Neisseria gonorrhoeae} surveillance program, 2011. Courtesy of the National Microbiology Laboratory, Public Health Agency of Canada. \textit{MIC} = minimum inhibitory concentration
3.2 Clinical failures of gonorrhea associated with the cephalosporins

Clinical failures associated with reduced susceptibility to the oral cephalosporins were first identified in Japan in the early 2000s. Deguchi et al., using a regimen of two doses of 200 mg each of cefixime six hours apart, saw consistent therapeutic success (45/45 cases) in male patients treated for gonococcal urethritis with isolates that had MICs ≤0.06 μg/mL, but reported five failures in 11 patients infected with isolates that had MICs of 0.125 μg/mL. Since then, over 50 clinical failures have been reported in Japan, leading to changes in Japanese guidelines, which currently recommend ceftriaxone one gram intravenously as empiric therapy for gonorrhea.

Pharmacokinetic/pharmacodynamics data, using the recommended single 400 mg oral dose of cefixime, suggests that *N. gonorrhoeae* with a MIC of ≥ 0.12 μg/mL may fail cefixime therapy, as this single dose does not result in sustained serum concentrations above the MIC for 20 hours. Consistent with this data, clinical failures associated with the use of cefixime have also been identified in North America and Europe. Prior to 2013, the only published North American case of clinical failure associated with the cephalosporins in North America in 2001 had been imported from a Japanese sexual partner. More recently, five clinical failures associated with the use of cefixime were identified in Europe, all involving urethral sites of infection. Four of these were locally acquired.

A historical cohort study of 133 *N. gonorrhoeae* infections in a single clinic in Toronto, Ont., identified nine clinical failures associated with the use of cefixime over a single year, representing 6.77 per cent of all individuals who returned for test of cure. The rate of clinical failure was 25 per cent (7/28, 95 per cent CI, 12.4–43.6) among those who had isolates with a cefixime MIC of ≥0.12 μg/mL. These clinical failures occurred primarily among men who have sex with men, but one heterosexual man and one woman also failed cefixime therapy in this series.

Pharyngeal infections present a more challenging treatment dilemma, and several cases of clinical failure with the use of both cefixime and ceftriaxone have been described. In one study, two of 16 cases of pharyngeal infections treated with cefixime had a positive test of cure, as did two of 17 of those treated with ceftriaxone. Similarly in a review of 178 cases of pharyngeal gonorrhea from 1995 to 2007, nine per cent of these infections had a positive test of cure. The cephalosporin MICs were not provided in either of these studies, but case reports suggest that treatment failure associated with pharyngeal infections occur even among highly susceptible strains.
3.3 International comparison of gonorrhea treatment recommendations

The World Health Organization recommends the discontinuation of empiric use of an antibiotic once five per cent of locally acquired isolates of *N. gonorrhoeae* demonstrate resistance.\(^{39}\) To address the issue of increasing cephalosporin resistance, CGSTI, the CDC and the British Association for Sexual Health and HIV (BASHH) have all recently revised their treatment recommendations.\(^ {11-13,40}\)

Combination therapy with cephalosporins plus azithromycin (or doxycycline) is the preferred regimen in all guidelines.\(^ {11,13,40}\) Treatment of gonorrhea with two antimicrobials is recommended on the theoretical basis that this may offer synergistic therapy, potentially improving treatment efficacy and delaying the emergence and spread of resistance in *N. gonorrhoeae*. These recommendations are supported by two small studies. One study supported the inadequacy of cephalosporins as monotherapy for pharyngeal gonorrhea infections and demonstrated the trend toward increased effectiveness when administered in combination with azithromycin.\(^ {35}\) A second study suggested a synergistic effect of cephalosporins and azithromycin using an *in vitro* model.\(^ {41}\)

Guidelines from the CDC, BASHH and the European chapter of the International Union against Sexually Transmitted Infections (IUSTI) all recommend intramuscular ceftriaxone as the first-line cephalosporin agent for all infections to be given in combination with azithromycin.\(^ {11,12,40}\) The U.K. and European guidelines increased their recommended dosages for ceftriaxone to 500 mg IM, and oral cefixime is no longer recommended as front-line therapy. Similarly in the U.S., the CDC recommends ceftriaxone 250 mg IM plus azithromycin 1 g orally as the only first line therapy. In Canada, the CGSTI do recommend this combination therapy but have also retained the use of cefixime at a higher dose of 800 mg as a potential first-line cephalosporin agent in non-pharyngeal infections in the non-MSM population.
3.4 Indications for treatment of gonorrhea

Indications for treatment:

- Identification of Gram-negative intracellular diplococci by microscopy in male urethral samples
- Confirmed culture or NAAT specimen for *N. gonorrhoeae*
- Epidemiological link to a gonorrhea case
- Based on clinical assessment and/or risk behaviours following testing but before results are available
- Following sexual assault
- Mother of neonate with confirmed gonorrhea

3.5 Recommended treatment for gonorrhea

See Figure 8 for a testing algorithm for treatment.

PHO recommends a treatment approach similar to the CDC, BASHH and IUSTI aimed to effectively treat gonorrhea given current trends of antimicrobial resistance and progression of antimicrobial resistance in Ontario. These recommendations are based on Ontario surveillance data of gonorrhea, pharmacokinetic/pharmacodynamics modelling studies, and clinical efficacy data including the historical cohort study in Ontario that demonstrated a high rate of clinical failures. Given the propensity of *N. gonorrhoeae* to develop antimicrobial resistance, the current treatment recommendations may be revised with larger doses or different antimicrobials in the near future.

**First-line treatment** for persons above nine years of age (including pregnant women and nursing mothers) with confirmed or suspected uncomplicated urogenital gonorrhea (cervix, vagina, pharynx or rectum) and their sex partners is

**Ceftriaxone 250 mg intramuscularly plus azithromycin 1 g orally (B-II).**

Treatment of clinical failures if first-line therapy was used should include a higher dose of ceftriaxone and azithromycin (1 g ceftriaxone IM + 2 g azithromycin) and a test of cure using culture at four or greater days post-treatment. If first-line treatment is not used initially, suggest using first-line treatment.
**Second-line therapy** options are less effective than the combination of ceftriaxone and azithromycin in the treatment of gonorrhea. These therapies are only to be considered if first-line therapy is not possible and must be followed by a test of cure. Second-line therapies include:

- Cefixime 400 mg orally plus azithromycin 1 g orally \((C-III)\)
- Spectinomycin 2 g intramuscularly plus azithromycin 1 g orally \((C-III)\)
- Azithromycin 2 g orally * \((C-II)\)

For information regarding preparation, dosage, administration, storage and contraindications please refer to the product monograph for the drug you are administering.

* Higher doses of azithromycin are associated with significant incidence of gastrointestinal adverse effects.
Ciprofloxacin is no longer recommended as empiric therapy for gonorrhea in Ontario. Ciprofloxacin is only recommended if treatment is guided by a culture isolate of *N. gonorrhoeae* demonstrating susceptibility to this drug. Similarly, doxycycline is not recommended as a treatment option for gonorrhea due to high rates of tetracycline-resistant *N. gonorrhoeae*. In the event of confirmed or suspected co-infection with chlamydia, where azithromycin was not administered, doxycycline 100 mg oral dose twice daily for seven days should be given to treat chlamydia.
3.6 Treatment of individuals with a history of penicillin or cephalosporin allergy

Beta–lactams which include penicillins and cephalosporins (such as cefixime and ceftriaxone) are generally very safe, and only a small number of patients that are told that they have a penicillin allergy will have any reaction if they take one of these drugs. The estimated rate of severe reactions to the administration of a cephalosporin to an individual with a history of a penicillin allergy are between 0.0001 and 0.1%.\textsuperscript{52,43}

Patients with a history of a severe reaction to penicillin, or any allergic reaction to the cephalosporins should be prescribed a non-cephalosporin based regimen for any suspected or confirmed gonorrhea infection and referred to a drug allergy clinic if available. Therapies to consider in this context include spectinomycin 2 g intramuscularly plus azithromycin 1 g orally, or azithromycin 2 g orally (Figure 8), both of which require a test of cure.
4. Follow-up for gonorrhea cases and contacts

Key Messages

- Gonorrhea is a reportable disease in Ontario. The medical officer of health of the health unit in which the case is from is notified by the laboratory of any positive laboratory findings in respect to reportable diseases. Health care professionals should report to their local medical officer of health any suspected or confirmed \textit{N. gonorrhoeae} treatment failures.

- Test of cure, contact tracing and repeat testing of individuals with gonorrhea are reviewed.

Summary of Recommendations

- A test of cure is recommended when first-line therapy is not used and in other specific situations (see page 28 for full list). The preferred testing method for test of cure is culture.

- Sexual partners of the case should be notified for the purposes of evaluation, testing, and treatment. The sex partners are recommended to receive empiric treatment as per the treatment recommendations as soon as possible to reduce the risk of further transmission.

- Rescreening after six months, or when they next seek medical care within the next 12 months, is recommended for all who are diagnosed with gonorrhea.

- Health care professionals should report to the medical officer of health any suspected or confirmed gonorrhea clinical failures.

- Once notified of a suspect or confirmed case of gonorrhea treatment failure, the local health unit should work with the responsible health care practitioner to complete the PHO enhanced surveillance form for gonorrhea clinical failures and notify PHO of the suspected or confirmed case as soon as possible to discuss any further public health action that may be required.
4.1 Reporting and notification

PHAC notes that case finding and partner notification are critical to maintaining control of gonococcal infections; as a result, such infections are reportable across the country. Local boards of health are often able to assist with partner notification and referrals for evaluation, testing, treatment and education. Gonorrhea is a reportable disease in Ontario. Pursuant to Section 29 (1) of the Health Protection and Promotion Act (1990), the operator of a laboratory is required to notify the medical officer of health of the health unit in which the person from whom the specimen was taken resides. Each case of a positive laboratory finding in respect of a reportable disease, must be reported as soon as possible after the making of the finding. Physicians and identified health care professionals are also required under Section 25 (1) of the Health Protection and Promotion Act (1990) to report to the medical officer of health of the health unit in which the professional services are provided any patients (outside of receiving hospital care) that they believe have a reportable disease.

4.2 Recommended testing and treatment of sex partners

All partners who have had sexual contact with the index case within 60 days prior to symptom onset or date of specimen collection should be notified for the purposes of evaluation, testing and treatment (B-III). If the index case had no partners during the 60-day trace-back period, the last partner should be notified.

It is recommended that sexual partners of cases should be evaluated, counselled, tested and treated. Regardless of the test results, the sex partners are recommended to receive empiric treatment as per the treatment recommendations as soon as possible to reduce the risk of further transmission. For sex partners of cases, the preferred testing method is as per Figures 4 and 5 (algorithms for testing symptomatic and asymptomatic persons).
4.3 Recommendations for test of cure for gonorrhea

Test of cure is recommended in the following circumstances (B-III):

- First-line treatment is not used
- Pharyngeal and rectal infection
- Pregnancy
- Suspected or confirmed gonorrhea clinical treatment failure or sexual contact of a suspected or confirmed clinical failure
- Infection with *N. gonorrhoeae* with reduced susceptibility to the cephalosporins (defined as an ceftriaxone or cefixime minimum inhibitory concentration of ≥ 0.12 μg/mL based on culture results) or sexual contact of person infected with *N. gonorrhoeae* isolate with reduced susceptibility to the cephalosporins.
- Treatment failure has occurred previously
- Compliance is uncertain
- There is a re-exposure to an untreated partner
- There is concern over a false-positive non-culture test result
- PID or disseminated gonococcal infection is diagnosed
- Children ≤ 12 years of age.

For test of cure, regardless of presence or absence of symptoms, the preferred testing method is culture. Test of cure using culture should be performed after four days post-treatment. If culture is not locally available, NAAT testing is a second-line option, but should be performed at earliest two weeks post-treatment. The time period for NAAT test of cure is less than that recommended in the CGSTI due to the need to identify a treatment failure as early as possible.
4.4 Reporting of clinical failures

Gonorrhea treatment failures are defined as treated individuals with confirmed gonorrhea and a positive test of cure (NAAT or culture) in the absence of risk of reinfection (i.e., patient denies potential sexual re-exposure).

Health care professionals should report all cases of gonorrhea to their local public health unit, including any suspected or confirmed gonorrhea treatment failures.

Once a local health unit has been notified of a suspect or confirmed case of gonorrhea treatment failure, it should work with the responsible health care practitioner to complete the PHO enhanced surveillance form for gonorrhea clinical failures. The local health unit should notify PHO of the suspected or confirmed clinical failure as soon as possible to discuss any further clinical and public health action that may be required.

4.5 Recommended repeat testing/rescreening for persons diagnosed with gonorrhea

The CGSTI recommend rescreening for all who are diagnosed with gonorrhea six months after initial diagnosis as they are at high risk for a reinfection as evidenced from Ontario data. If rescreening within six months is not possible, cases should be rescreened when they next seek medical care within the next 12 months. From January 1, 2006, to July 31, 2012, 13 per cent of gonorrhea cases reported in Ontario were repeat infections. Of the repeat infections, 33 per cent occurred between one and six months post-infection, with 55 per cent of repeat infections occurring between one month and less than one year of the initial infection. Males accounted for 61.8 per cent of repeat infections, and of males with repeat infection who reported risk factors 51.8 per cent identified sex with same sex (MSM).
Summary

The Guidelines for Testing and Treatment of Gonorrhea in Ontario, 2013 was completed to address the immediate threat of increasing cephalosporin resistance in *N. gonorrhoeae* in Ontario. Particularly concerning, is that over 10 percent of culture isolates submitted to Public Health Ontario from July 10, 2010 to October 24, 2012 had decreased susceptibility to cefixime. Isolates of *N. gonorrhoeae* with reduced susceptibility to cefixime were identified in 17 health units across Ontario. By January 2013, there were at least nine cases of clinical failure associated with the use of oral cefixime to treat gonorrhea in Ontario. This document is guided by the best available evidence to assist health care practitioners in clinical decision making to ensure appropriate laboratory testing for gonorrhea, timely and effective treatment, and follow-up for cases. A key recommendation is that oral cephalosporins are no longer recommended as first line therapy for the treatment of gonorrhea in Ontario, similar to recent recommendations in the US and Europe. Intramuscular ceftriaxone 250 mg and azithromycin 1 g orally combination therapy is recommended for all cases of suspected or confirmed gonorrhea in Ontario. This guidance document will be reviewed in 2015 or sooner if new evidence mandates an earlier revision.
Appendices

Appendix A: Testing Instructions by Site of Specimen
(See Table 2 for specimen collection details)

Collection of Specimens:°

**CERVIX**

1. Insert a speculum to view the cervix
2. Remove overlying vaginal secretions and cervical exudate.
3. Insert a sterile swab one to two centimetres into the endocervical canal, rotate 180 degrees and withdraw for collection of columnar epithelial cells for diagnosis of *C. trachomatis* and *N. gonorrhoeae*.

**NOTE:** The choice of swab should be based on the type of testing being done; consult with the laboratory providing the service.

**NOTE:** Obtain a specimen for *N. gonorrhoeae* before taking a specimen for *C. trachomatis*.

**NOTE:** If a culture is to be performed for *N. gonorrhoeae*, directly inoculate the culture tube or plate, or place the swab in the transport medium. Alternatively, place the swab in a nucleic acid amplification transport tube.

**Consideration:** In women who have had a hysterectomy, collect first void urine or vaginal swab for NAAT.

**PHARYNX**

1. Swab the posterior pharynx and the tonsillar crypts.
2. Use the swab to directly inoculate the appropriate culture medium or place it in a transport medium.

**NOTE:** Specify that the swab should be tested for *N. gonorrhoeae* on the requisition form.
**RECTUM**

1. For blind swabbing, insert two to three centimetres into the anal canal.

2. Press laterally to avoid fecal material and, in the case of *C. trachomatis* or *N. gonorrhoeae*, to obtain columnar epithelial cells.

**NOTE:** If there is visible fecal contamination, discard the swab and obtain another specimen.

**NOTE:** With unlubricated anoscope using only tap water, fecal contamination can be avoided and specimens can be collected under direct visualization.

**Consideration:** Specimens may be obtained blindly or through an anoscope. The latter is preferred for symptomatic patients.

**URETHRA**

1. Warn the patient that specimen collection may be painful, that the next urination may be painful and that increasing fluid intake may help to decrease urine concentration and therefore discomfort.

**NOTE:** Ideally, the patient should not have voided for at least two hours, as voiding reduces the amount of exudate and may decrease the ability to detect organisms.

2. Use a thin, dry swab with a flexible wire shaft. Moistening the swab with water before insertion may help reduce discomfort.

3. Introduce the swab slowly (three to four centimetres in males), rotate slowly and withdraw gently.

4. The swab can be used to prepare a smear by slowly unrolling the secretions onto a slide; then, directly inoculate the appropriate culture medium or place the swab in a transport medium.

**NOTE:** If a NAAT is used, follow the manufacturer’s instructions.

**Consideration:** “Milking” the penis three or four times from the base to the glans enhances the ability to detect otherwise unapparent urethral discharge.
**URINE (FIRST VOID)**

1. Provide the patient with a sterile leak-proof container.

**NOTE:** The patient should not have voided for at least two hours, but having done so does not preclude testing.

2. Ask the patient to collect only the first 10 to 20 millilitres of urine into the container and to cap it tightly.

**Consideration:** Commercial NAATs for *C. trachomatis* and *N. gonorrhoeae* are approved for urine testing and are recommended for detecting these organisms in asymptomatic men or women, women without a cervix or those who wish to avoid pelvic examination. A first-void urine may be collected at any time and may also be termed a first-catch urine.
References


