Gonococcal Infections

Revised: July 2013

TABLE OF CONTENTS

Acknowledgments

Lead authors

Barbara Romanowski, MD, FRCPC

Joan Robinson, MD, FRCPC

Tom Wong, MD, MPH, FRCPC

Expert working group members

Joshua Bergman, RN, BScN, MPH, Clinical Instructor, Alberta Health Services, Edmonton STI Clinic;

Max Chernesky, PhD, Professor Emeritus, McMaster University, St Joseph's Healthcare, Hamilton;

William A. Fisher, PhD, Distinguished Professor, Departments of Psychology and Obstetrics and Gynaecology, University of Western Ontario;

Annie-Claude Labbé, MD, FRCPC, Associate Professor, Department of Microbiology Infectious Diseases and Immunology, Faculty of Medicine, Université de Montréal; Department of Infectious Diseases and Medical Microbiology, Hôpital Maisonneuve-Rosemont;

Tim T.Y. Lau, PharmD, FCSHP, Pharmacotherapeutic Specialist, Infectious Diseases & Antimicrobial Stewardship, Pharmaceutical Sciences, Vancouver General Hospital; Clinical Associate Professor, Faculty of Pharmaceutical Sciences, University of British Columbia;

Ed Lee, MDCM, Medical Director, Hassle Free Clinic, Toronto;

Richard Lester, MD, FRCPC, Medical Head, Division of STI/HIV Control, BC Centre for Disease Control. Clinical Assistant Professor in the Division of Infectious Diseases, Department of Medicine, University of British Columbia;

Irene Martin, BSc, Head, Streptococcus and STI Unit, Bacteriology and Enterics Division, National Microbiology Laboratory, Public Health Agency of Canada;

Gina Ogilvie, MD, DrPH, Medical Director, Clinical Prevention Services, BCCDC; Associate Professor, Family Practice, Obstetrics & Gynecology, School of Population & Public Health, University of British Columbia;

Sam Ratnam, PhD, Surveillance and Reference Services Advisor, National Microbiology Laboratory, Public Health Agency of Canada;

Ron Read, MD, PhD, FRCPC, Associate Professor, Medicine, Microbiology and Infectious Diseases, University of Calgary; Consultant in Infectious Diseases, Provincial Medical Director, STI (South), STI Program, Alberta Health Services;

Joan Robinson, MD, FRCPC, Pediatric Infectious Diseases Physician, University of Alberta and Stollery Children`s Hospital;

Barbara Romanowski, MD, FRCPC, Clinical Professor of Medicine, Division of Infectious Diseases, Faculty of Medicine and Dentistry, University of Alberta;

Ameeta Singh, BMBS, MSc, FRCPC, Clinical Professor, Division of Infectious Diseases, Department of Medicine, University of Alberta; Medical Director, Alberta Health Services-STI Clinic, Provincial Medical Director, STI (North), Alberta Health Services;

Marc Steben, MD, CCFP, FCFP, Medical advisor, Sexually Transmitted Infections Unit, Institut national de santé publique du Québec; Medical director, Clinique A;

Mark H. Yudin, MD, MSc, FRCSC, Associate Professor, University of Toronto, Department of Obstetrics, Gynecology, and Reproductive Infectious Diseases, St. Michael's Hospital;

Tom Wong, MD, MPH, FRCPC, Director, Professional Guidelines and Public Health Practice, Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada.

External reviewers

Health professionals with specialized expertise volunteered their time as external reviewers for this guideline chapter. The Agency and the Expert working group would like to thank those individuals for their valuable time and input.

Centre for Communicable Diseases and Infection Control contributors

Writing/editorial support:

Catherine Dickson, MD, MSc

Margaret Gale-Rowe, MD, MPH, DABPM

Cathy Latham-Carmanico, RN, BScN

Christine Weir, RN, MSc, CIC

Project management and support:

Manon Fiset

Simon Foley, BA (hons)

Research support:

Dana Paquette, PhD

Lisa Marie Pritchard, BSc, MSc

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.

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.[1]
- 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.[2,3]
- **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.[4] **These antimicrobial agents should not be used for the treatment of gonorrhea.**
- Quinolone resistance has been steadily increasing in Canada.[4] 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%.[5-7] (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). [4,5,8-27]
- 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.[4]

- 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.[28]
- 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.[29,30]

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.[31]

Table 1. Manifestations [31-38]

Neonates and infants	Children	Youth and adults		
		Females	Males	Females and males
• Ophthalmia neonatorum • Conjunctivitis • Sepsis • Disseminated gonococcal infection*	• Urethritis • Vaginitis • Conjunctivitis • Pharyngeal infection • Proctitis • Disseminated gonococcal infection*	• Cervicitis • Pelvic inflammatory disease • Urethritis • Perihepatitis • Bartholinitis	• Urethritis • Epididymitis	• Pharyngeal infection • Conjunctivitis • Proctitis • Disseminated gonococcal infection*

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

Table 2. Symptoms [39-41]

Females	Males
• Vaginal discharge • Dysuria • Abnormal vaginal bleeding • Lower abdominal pain • Deep dyspareunia • Rectal pain and discharge with proctitis*	• Urethral discharge • Dysuria • Urethral itch • Testicular pain and/or swelling or symptoms of epididymitis • Rectal pain and discharge with proctitis*

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

Table 3. Major sequelae [31,36,38]

Females	Males
• Pelvic inflammatory disease • Infertility • Ectopic pregnancy • Chronic pelvic pain • Reactive arthritis (oculo-urethro-synovial syndrome) • Disseminated gonococcal infection*	• Epididymo-orchitis • Reactive arthritis (oculo-urethro-synovial syndrome) • Infertility (rare) • Disseminated gonococcal infection *

*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.[42,43] However, culture is strongly recommended because it allows for testing of antimicrobial susceptibility.[44]
- 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.[13]
- 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.[42]
- 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.**[45,46]

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.[13,47-51]
- 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[42,52] (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[53] (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.[54,55] 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*.[54]
- 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
Urethral **Gram stain** • For Gram-negative intracellular diplococci	• Postpubertal males	• Recommended for symptomatic patients only. • Generally diagnostic of gonorrhea.

Specimen sites/tests*	Situations where specimen is appropriate†	Considerations
Urethral **Culture or NAAT** • For laboratory detection of *N. gonorrhoeae*	• Optimal for all postpubertal males • Optimal for females with urethral syndrome (i.e., dysuria/pyuria) (cervical swab or urine recommended for other women)	
Endocervical **Gram stain** • For Gram-negative intracellular diplococci	• Postpubertal females	• Sensitivity lower than in male urethral specimens and not routinely recommended.
Endocervical or vaginal **Culture or NAAT** • For laboratory detection of *N. gonorrhoeae*	• Optimal for postpubertal females	• Vaginal swabs for NAAT are as accurate as cervical swabs. • 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. • If the cervix has been surgically removed, urine NAAT, or vaginal swabs for culture or NAAT should be collected. • Urethral specimens can also be collected if a woman is menstruating at the time of the exam.

Specimen sites/tests*	Situations where specimen is appropriate†	Considerations
Urine NAAT • First catch 10–20 mL (can be sampled any time of the day)	• Males or females where a urethral swab or pelvic examination is not practical[56]	• In females, first catch urine may have reduced performance when compared to NAAT for cervical swabs.
Oropharyngeal **Culture or validated NAAT** • For laboratory detection of *N. gonorrhoeae*	• Females with a history of performing oral sex • 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)	• Culture is preferred; validated NAAT may be used if culture is not available.
Rectal **Culture or validated NAAT** • For laboratory detection of *N. gonorrhoeae*	• All females with anogenital symptoms, as colonization can occur without anal penetration[57] • Females with a history of receptive anal intercourse, whether or not condoms were used • MSM who practice receptive anal intercourse, whether or not condoms were used	

*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 gonorrhea is diagnosed in any child after the neonatal period.[37,58]
  - 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.[37]
- 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

Positive Gram stain	• If Gram-negative intracellular diplococci are observed, treatment for both gonococcal and chlamydial infection should be provided.[32,53,54,59] • 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.[59,60] • The presence of polymorphonuclear leukocytes without diplococci does not indicate or exclude gonococcal infection but suggests non-gonococcal urethritis (refer to the *Urethritis* chapter). [59,60]
Positive culture or NAAT	• Is diagnostic of gonorrhea; treatment for both gonococcal and chlamydial infection should be provided.[32,42,53]

Table 6. Recommended patient management: test results pending

Urethral/cervical mucopurulent discharge	• Treatment should be provided for both gonococcal and chlamydial infection if partner is infected with gonorrhea or if follow-up is not assured.[32,53,59] **OR** • 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.[32,53,59]
No urethral/cervical mucopurulent discharge	• Therapy should be deferred until smear/culture/NAAT results available. **OR** • 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.[32,53,59]

Treatment

Medication-specific considerations and contraindications

- Patients should optimally be treated with combination gonorrhea infection therapy in response to increasing antimicrobial resistance.[61]
  - This combination therapy also includes effective treatment for chlamydia due to high rates of concomitant infection.[7,32,53,59]

  - 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.[15]
- Directly observed therapy with single-dose regimens is desirable.[32,62]
- 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[63] 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.[9,64-68] 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.[9,15,27]
  - 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[67] and in situations where higher tissue penetration is necessary to achieve cure (such as pharyngeal infection[69-71] and complicated cases such as PID[72,73] and epididymitis/epididymo-orchitis[74]. Ceftriaxone 250 mg IM is now recommended for pharyngeal infection, PID and epididymitis/epidiymo-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.[5,6,22,27]
- 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.[75-78]
- 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[79], and who:
  - have prolonged QT interval,
  - have clinically significant bradycardia,
  - have arrythmias,
  - 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*	**Ceftriaxone** 250 mg IM in a single dose *[A-I]* **PLUS azithromycin** 1 g PO in a single dose† *[B-II]* **OR** **Cefixime** 800 mg PO in a single dose‡ *[A-I]* **PLUS azithromycin** 1 g PO in a single dose† *[B-II]*
Alternate treatment	**Spectinomycin** 2 g IM in a single dose *[A-I]* (available only through SAP) **PLUS azithromycin** 1 g PO in a single dose† *[B-II]* **OR** **Azithromycin** 2 g PO in a single dose§ *[A-I]*
Pharyngeal infection	
Preferred treatment*	**Ceftriaxone** 250 mg IM in a single dose *[A-I]* **PLUS azithromycin** 1 g PO in a single dose† *[B-III]*
Alternate treatment	**Cefixime** 800 mg PO in a single dose‡ *[B-III]* **PLUS azithromycin** 1 g PO in a single dose† *[B-III]* **OR** **Azithromycin** 2 g PO in a single dose§ *[A-I]*

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.

†**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**.

‡There is scientific evidence that cefixime 800 mg is safe and effective in treating gonococcal infections.[9,64-68] 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.[9,15,27]

§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]*

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

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.

†**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.

‡There is scientific evidence that cefixime 800 mg is safe and effective in treating gonococcal infections.[9,64-68] 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.[9,15,27]

§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.

‖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)	
Preferred treatment*	**Ceftriaxone** 50 mg/kg IM up to 250 mg in a single dose *[A-II]* **PLUS azithromycin** 20 mg/kg (maximum dose of 1 g) PO in a single dose *[B-II]* **OR** **Cefixime** 8 mg/kg PO BID x 2 doses† (maximum 400 mg per dose) *[B-III]* **PLUS azithromycin** 20 mg/kg (maximum dose of 1 g) PO in a single dose *[B-II]*
Alternate treatment	**Spectinomycin** 40 mg/kg IM in a single dose (maximum dose of 2 g) *[A-II]* (available only through SAP) **PLUS azithromycin** 20 mg/kg (maximum dose of 1 g) PO in a single dose *[B-II]*
Pharyngeal infection	
Preferred treatment*	**Ceftriaxone** 50 mg/kg IM up to 250 mg in a single dose‡ *[A-II]* **PLUS azithromycin** 20 mg/kg (maximum dose of 1 g) PO in a single dose *[B-III]*
Alternate treatment	**Cefixime** 8 mg/kg PO BID x 2 doses† (maximum 400 mg per dose) *[A-II]* **PLUS azithromycin** 20 mg/kg (maximum dose of 1 g) PO in a single dose *[B-III]*

Important notes related to neonates (birth to one month of age):

- In neonates the recommended dosage for ceftriaxone is 25-50 mg/kg (maximum 125 mg).
- **Routine combination therapy with a macrolide is not recommended** due to the association with pyloric stenosis. Testing should be done for chlamydia and if results are positive, treatment should be provided as per *table 4* in the *Chlamydial Infections* chapter.

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.

†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[31,39]

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

*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.

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

‡**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.**

§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	**Ceftriaxone** 50 mg/kg IV/IM‡ daily for 7 days (maximum dose of 1 g/day)§ *[A-III]* **PLUS azithromycin** 20 mg/kg (maximum dose of 1 g) PO in a single dose x 1 dose *[B-III]*
Meningitis	**Ceftriaxone** 50 mg/kg IV/IM‡ q12h for 10–14 days (maximum of 1 g/dose and 2 g/day)§ *[A-III]* **PLUS azithromycin** 20 mg/kg (maximum dose of 1 g) PO in a single dose x 1 dose *[B-III]*
Endocarditis	**Ceftriaxone** 50 mg/kg IV/IM‡ q12h for 28 days (maximum of 1 g/dose and 2 g/day)§ *[A-III]* **PLUS azithromycin** 20 mg/kg (maximum dose of 1 g) PO in a single dose x 1 dose *[B-III]*

Infection	Preferred treatment*
Ophthalmia beyond the neonatal period	**Ceftriaxone** 50 mg/kg IV/IM in a single dose (maximum dose of 2 g) *[A-III]* **PLUS azithromycin** 20 mg/kg (maximum dose of 1 g) PO in a single dose[§] *[B-III]*
Note: Hospitalization is indicated for disseminated infections and consultation with an expert in infectious diseases should be initiated as soon as possible.	

*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.

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

[‡]IM administration should only be considered if an IV line is not available.

[§]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 gonorrhea** [(31,39,89)]

Preferred treatment*	**Ceftriaxone** 25-50 mg/kg IM in a single dose (maximum dose of 125 mg) *[A-III]*
Important notes: • 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 *table 4* in the *Chlamydial Infections* chapter.	

*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]

Preferred treatment*	**Ceftriaxone** 25-50 mg/kg IM in a single dose (maximum dose of 125 mg)† *[A-II]*

Important notes:

- Irrigate eyes immediately with sterile normal saline and at least hourly as long as necessary to eliminate discharge.
- 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 *table 4* in the *Chlamydial Infections* chapter.
- **Hospitalization and consultation with an expert in infectious diseases should be initiated as soon as possible.**
- Appropriate infection prevention and control precautions are necessary for all cases.

*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.

†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

Preferred treatment*	**Cefotaxime** 50 mg/kg IV/IM† q6h for 10-14 days‡ § *[A-III]*

Important notes:

- **Hospitalization and consultation with an expert in infectious diseases should be initiated as soon as possible.**
- 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 *table 4* in the *Chlamydial Infections* chapter.

*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.

†IM administration should only be considered if an IV line is not available.

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

§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.[32,62]
- 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 gonorrhea, 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.[28]
- 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,[69]
  - Persistent symptoms or signs post-therapy,[32,62]
  - 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,[32,62]
  - Case is linked to a treatment failure case that was treated with the same antibiotic,[32]
  - Treatment failure for gonorrhea has occurred previously in the individual,
  - Compliance is uncertain,
  - There is re-exposure to an untreated partner,
  - Infection occurs during pregnancy,[86]
  - 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[45,46] to avoid false-positive results due to the presence of non-viable organisms.

Treatment Failure[5]

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.**

References

(1) Hepatitis C and STI Surveillance and Epidemiology Section, Community Acquired Infections Division, Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada. **Reported cases and rates of gonorrhea by province/territory and sex, 1980 to 2009**. 2011; Available at: http://www.phac-aspc.gc.ca/std-mts/sti-its_tab/gonorrhea_pts-eng.php#a2. Accessed 10/19, 2011.

(2) Tapsall JW, Limnios EA, Shultz TR. Continuing evolution of the pattern of quinolone resistance in Neisseria gonorrhoeae isolated in Sydney, Australia. Sex Transm Dis 1998 Sep;25(8):415-417.

(3) Ng LK, Sawatzky P, Martin IE, Booth S. Characterization of ciprofloxacin resistance in Neisseria gonorrhoeae isolates in Canada. Sex Transm Dis 2002 Dec;29(12):780-788.

(4) Martin I, Jayaraman G, Wong T, Liu G, Gilmour M, on Behalf of the Canadian Public Health Laboratory Network. Trends in Antimicrobial Resistance in Neisseria gonorrhoeae Isolated in Canada: 2000-2009. Sex Transm Dis 2011 Oct;38(10):892-898.

(5) World Health Organization, Department of Reproductive Health and Research. Global action plan to control the spread and impact of antimicrobial resistance in Neisseria gonorrhoeae. 2012; Available at: http://www.who.int/reproductivehealth/publications/rtis/9789241503501/en/index.html, 2013.

(6) Tapsall J, WHO Collaborating Center for STD and HIV. Antimicrobial resistance in Neisseria gonorrhoeae. 2001; Available at: http://www.who.int/emc, 2013.

(7) Tapsall JW. What management is there for gonorrhea in the postquinolone era? Sex Transm Dis 2006 Jan;33(1):8-10.

(8) Hottes TS, Lester RT, Hoang LM, McKay R, Imperial M, Gilbert M, et al. Cephalosporin and azithromycin susceptibility in Neisseria gonorrhoeae isolates by site of infection, British Columbia, 2006 to 2011. Sex Transm Dis 2013 Jan;40(1):46-51.

(9) Allen VG, Mitterni L, Seah C, Rebbapragada A, Martin IE, Lee C, et al. Neisseria gonorrhoeae treatment failure and susceptibility to cefixime in Toronto, Canada. JAMA 2013 Jan 9;309(2):163-170.

(10) Ota KV, Ng LK, Melano RG, Martin IE, Brown EM, Richardson SE, et al. Identification of sexual networks through molecular typing of quinolone-resistant Neisseria gonorrhoeae in Ontario, Canada. Sex Transm Dis 2011 Sep;38(9):811-814.

(11) Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. N Engl J Med 2012 Feb 9;366(6):485-487.

(12) Bala M, Sood S. Cephalosporin Resistance in Neisseria gonorrhoeae. J Glob Infect Dis 2010 Sep;2(3):284-290.

(13) Centers for Disease Control and Prevention (CDC). Cephalosporin susceptibility among Neisseria gonorrhoeae isolates--United States, 2000-2010. MMWR Morb Mortal Wkly Rep 2011 Jul 8;60(26):873-877.

(14) Chisholm SA, Alexander S, Desouza-Thomas L, Maclure-Webster E, Anderson J, Nichols T, et al. Emergence of a Neisseria gonorrhoeae clone showing decreased susceptibility to cefixime in England and Wales. J Antimicrob Chemother 2011 November;66(11):2509-2512.

(15) Chisholm SA, Mouton JW, Lewis DA, Nichols T, Ison CA, Livermore DM. Cephalosporin MIC creep among gonococci: time for a pharmacodynamic rethink? J Antimicrob Chemother 2010 Oct;65(10):2141-2148.

(16) de Vries HJ, van der Helm JJ, Schim van der Loeff MF, van Dam AP. Multidrug-resistant Neisseria gonorrhoeae with reduced cefotaxime susceptibility is increasingly common in men who have sex with men, Amsterdam, the Netherlands. Euro Surveill 2009 Sep 17;14(37):19330.

(17) Deguchi T, Nakane K, Yasuda M, Maeda S. Emergence and spread of drug resistant Neisseria gonorrhoeae. J Urol 2010 Sep;184(3):851-8; quiz 1235.

(18) Forsyth S, Penney P, Rooney G. Cefixime-resistant Neisseria gonorrhoeae in the UK: a time to reflect on practice and recommendations. Int J STD AIDS 2011 May;22(5):296-297.

(19) Ison CA, Hussey J, Sankar KN, Evans J, Alexander S. Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. Euro Surveill 2011 Apr 7;16(14):19833.

(20) Ohnishi M, Saika T, Hoshina S, Iwasaku K, Nakayama S, Watanabe H, et al. Ceftriaxone-resistant Neisseria gonorrhoeae, Japan. Emerg Infect Dis 2011 Jan;17(1):148-149.

(21) Tapsall J. Multidrug-resistant Neisseria gonorrhoeae. CMAJ 2009 Feb 3;180(3):268-269.

(22) Tapsall J. Antibiotic resistance in Neisseria gonorrhoeae is diminishing available treatment options for gonorrhea: some possible remedies. Expert Rev Anti Infect Ther 2006 Aug;4(4):619-628.

(23) Tapsall JW. Neisseria gonorrhoeae and emerging resistance to extended spectrum cephalosporins. Curr Opin Infect Dis 2009 Feb;22(1):87-91.

(24) Unemo M, Golparian D, Hestner A. Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, Sweden, July 2010. Euro Surveill 2011 Feb 10;16(6):19792.

(25) Unemo M, Golparian D, Syversen G, Vestrheim DF, Moi H. Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010. Euro Surveill 2010 Nov 25;15(47):19721.

(26) Golparian D, Hellmark B, Fredlund H, Unemo M. Emergence, spread and characteristics of Neisseria gonorrhoeae isolates with in vitro decreased susceptibility and resistance to extended-spectrum cephalosporins in Sweden. Sex Transm Infect 2010 Nov;86(6):454-460.

(27) Martin I, Sawatzky P, Allen V, Hoang L, Lefebvre B, Mina N, et al. Emergence and characterization of Neisseria gonorrhoeae isolates with decreased susceptibilities to ceftriaxone and cefixime in Canada: 2001-2010. Sex Transm Dis 2012 Apr;39(4):316-323.

(28) De P, Singh AE, Wong T, Kaida A. Predictors of gonorrhea reinfection in a cohort of sexually transmitted disease patients in Alberta, Canada, 1991-2003. Sex Transm Dis 2007 Jan;34(1):30-36.

(29) Laga M, Manoka A, Kivuvu M, Malele B, Tuliza M, Nzila N, et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. AIDS 1993 Jan;7(1):95-102.

(30) Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis. Sex Transm Dis 2008 Nov;35(11):946-959.

(31) Committee on Infectious Diseases, American Academy of Pediatrics. Gonococcal Infections. In: Pickering L, editor. Red book: 2012 report of the committee on infectious diseases. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012. p. 336-344.

(32) Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010 Aug 4;59(RR-12):1-110.

(33) Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis 2005 Jul 1;41(1):67-74.

(34) Kodner C. Sexually transmitted infections in men. Prim Care 2003 Mar;30(1):173-191.

(35) Chacko MR, Wiemann CM, Smith PB. Chlamydia and gonorrhea screening in asymptomatic young women. J Pediatr Adolesc Gynecol 2004 Jun;17(3):169-178.

(36) Banikarim C, Chacko MR. Pelvic inflammatory disease in adolescents. Semin Pediatr Infect Dis 2005 Jul;16(3):175-180.

(37) American Academy of Pediatrics. Committee on Child Abuse and Neglect. American Academy of Pediatrics. Committee on Child Abuse and Neglect. Gonorrhea in prepubertal children. Pediatrics 1998 Jan;101(1 Pt 1):134-135.

(38) Burgis JT, Nawaz H,3rd. Disseminated gonococcal infection in pregnancy presenting as meningitis and dermatitis. Obstet Gynecol 2006 Sep;108(3 Pt 2):798-801.

(39) Sung L, MacDonald NE. Gonorrhea: a pediatric perspective. Pediatr Rev 1998 Jan;19(1):13-16.

(40) Korenromp EL, Sudaryo MK, de Vlas SJ, Gray RH, Sewankambo NK, Serwadda D, et al. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? Int J STD AIDS 2002 Feb;13(2):91-101.

(41) Mehta SD, Rothman RE, Kelen GD, Quinn TC, Zenilman JM. Clinical aspects of diagnosis of gonorrhea and Chlamydia infection in an acute care setting. Clin Infect Dis 2001 Feb 15;32(4):655-659.

(42) Association of Public Health Laboratories. Laboratory diagnostic testing for Chlamydia trachomatis and Neisseria gonorrhoeae. Expert consultation meeting summary report, January 13-15, 2009. 2009; Available at: http://www.aphl.org/aphlprograms/infectious/std/Documents/CTGCLabGuidelinesMeetingReport.pdf, 2013.

(43) Kapala J, Biers K, Cox M, Kamionka M, Sumner J, Toor R, et al. Aptima Combo 2 testing detected additional cases of Neisseria gonorrhoeae infection in men and women in community settings. J Clin Microbiol 2011 May;49(5):1970-1971.

(44) Johnson RE, Newhall WJ, Papp JR, Knapp JS, Black CM, Gift TL, et al. Screening tests to detect Chlamydia trachomatis and Neisseria gonorrhoeae infections--2002. MMWR Recomm Rep 2002 Oct 18;51(RR-15):1-38; quiz CE1-4.

(45) Bachmann LH, Desmond RA, Stephens J, Hughes A, Hook EW,3rd. Duration of persistence of gonococcal DNA detected by ligase chain reaction in men and women following recommended therapy for uncomplicated gonorrhea. J Clin Microbiol 2002 Oct;40(10):3596-3601.

(46) Hjelmevoll SO, Olsen ME, Sollid JU, Haaheim H, Melby KK, Moi H, et al. Appropriate time for test-of-cure when diagnosing gonorrhoea with a nucleic acid amplification test. Acta Derm Venereol 2012 May;92(3):316-319.

(47) Dillon JA. Sustainable Antimicrobial Surveillance Programs Essential for Controlling Neisseria gonorrhoeae Superbug. Sex Transm Dis 2011 Oct;38(10):899-901.

(48) Kirkcaldy RD, Ballard RC, Dowell D. Gonococcal resistance: are cephalosporins next? Curr Infect Dis Rep 2011 Apr;13(2):196-204.

(49) Macdonald NE, Stanbrook MB, Flegel K, Hebert PC, Rosenfield D. Gonorrhea: what goes around comes around. CMAJ 2011 Oct 4;183(15):1567.

(50) Tapsall JW, Ndowa F, Lewis DA, Unemo M. Meeting the public health challenge of multidrug- and extensively drug-resistant Neisseria gonorrhoeae. Expert Rev Anti Infect Ther 2009 Sep;7(7):821-834.

(51) Unemo M, Shipitsyna E, Domeika M, Eastern European Sexual and Reproductive Health (EE SRH) Network Antimicrobial Resistance Group. Recommended antimicrobial treatment of uncomplicated gonorrhoea in 2009 in 11 East European countries: implementation of a Neisseria gonorrhoeae antimicrobial susceptibility programme in this region is crucial. Sex Transm Infect 2010 Nov;86(6):442-444.

(52) Black CM, Dreibe EM, Howard LA, Fajman NN. Multicenter study of nucleic acid amplification tests for detection of*Chlamydia trachomatis* and*Neisseria gonorrheae* in children being evaluated for sexual abuse. Pediatr Infect Dis J 2009;7:608-613.

(53) Lyss SB, Kamb ML, Peterman TA, Moran JS, Newman DR, Bolan G, et al. Chlamydia trachomatis among patients infected with and treated for Neisseria gonorrhoeae in sexually transmitted disease clinics in the United States. Ann Intern Med 2003 Aug 5;139(3):178-185.

(54) Ng LK, Martin IE. The laboratory diagnosis of Neisseria gonorrhoeae. Med Microbiol 2005;16:15–25.

(55) Ison C, Lewis D. Gonorrhea. In: Morse S, Ballard R, Holmes K, Moreland A, editors. Atlas of sexually transmitted diseases and AIDS. 4th ed. Netherlands: Elsevier; 2010. p. 24-39.

(56) Davies PO, Low N, Ison CA. The role of effective diagnosis for the control of gonorrhoea in high prevalence populations. Int J STD AIDS 1998 Aug;9(8):435-443.

(57) McCormack WM, Stumacher RJ, Johnson K, Donner A. Clinical spectrum of gonococcal infection in women. Lancet 1977 Jun 4;301(8023):1182-1185.

(58) Hammerschlag MR, Guillen CD. Medical and legal implications of testing for sexually transmitted infections in children. Clin Microbiol Rev 2010 Jul;23(3):493-506.

(59) World Health Organization. Guidelines for the managment of sexually transmitted infections. 2003; Available at: http://www.who.int/hiv/pub/sti/pub6/en/, 2013.

(60) Ng LK, Martin IE. The laboratory diagnosis of Neisseria gonorrhoeae. Can J Infect Dis Med Microbiol 2005 Jan;16(1):15-25.

(61) Centers for Disease Control (CDC). Cephalosporin-resistant Neisseria gonorrhoeae public health response plan. 2012; Available at: http://www.cdc.gov/std/treatment/Ceph-R-ResponsePlanJuly30-2012.pdf, 2013.

(62) Centers for Disease Control and Prevention (CDC). Update to CDC's*Sexually Transmitted Diseases Treatment Guidelines, 2010*: Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections. Morbidity and Mortality Weekly Report (MMWR) 2012 August 10;61(31);590-594.

(63) Repchinsky CE. Compendium of pharmaceuticals and specialties: the Canadian drug reference for health professionals. Ottawa, ON: Canadian Pharmacists Association; 2009.

(64) Bai ZG, Bao XJ, Cheng WD, Yang KH, Li YP. Efficacy and safety of ceftriaxone for uncomplicated gonorrhoea: a meta-analysis of randomized controlled trials. Int J STD AIDS 2012 Feb;23(2):126-132.

(65) Dunnett DM, Moyer MA. Cefixime in the treatment of uncomplicated gonorrhea. Sex Transm Dis 1992 Mar-Apr;19(2):92-93.

(66) Portilla I, Lutz B, Montalvo M, Mogabgab WJ. Oral cefixime versus intramuscular ceftriaxone in patients with uncomplicated gonococcal infections. Sex Transm Dis 1992 Mar-Apr;19(2):94-98.

(67) Handsfield HH, McCormack WM, Hook EW,3rd, Douglas JM,Jr, Covino JM, Verdon MS, et al. A comparison of single-dose cefixime with ceftriaxone as treatment for uncomplicated gonorrhea. The Gonorrhea Treatment Study Group. N Engl J Med 1991 Nov 7;325(19):1337-1341.

(68) Megran D, Lefebvre K, Willetts V, Bowie W. Single-dose oral cefixime versus amoxicillin plus probenicid for the treatment of uncomplicated gonorrhea in men. Antimicrobial Agents and Chemotherapy 1990.

(69) Ota KV, Fisman DN, Tamari IE, Smieja M, Ng LK, Jones KE, et al. Incidence and treatment outcomes of pharyngeal Neisseria gonorrhoeae and Chlamydia trachomatis infections in men who have sex with men: a 13-year retrospective cohort study. Clin Infect Dis 2009 May 1;48(9):1237-1243.

(70) Tapsall J, Read P, Carmody C, Bourne C, Ray S, Limnios A, et al. Two cases of failed ceftriaxone treatment in pharyngeal gonorrhoea verified by molecular microbiological methods. J Med Microbiol 2009 May;58(Pt 5):683-687.

(71) Barbee LA, Kerani RP, Dombrowski JC, Soge OO, Golden MR. A retrospective comparative study of 2-drug oral and intramuscular cephalosporin treatment regimens for pharyngeal gonorrhea. Clin Infect Dis 2013 Jun;56(11):1539-1545.

(72) Piyadigamage A, Wilson J. Improvement in the clinical cure rate of outpatient management of pelvic inflammatory disease following a change in therapy. Sex Transm Infect 2005 Jun;81(3):233-235.

(73) Haggerty CL, Ness RB. Newest approaches to treatment of pelvic inflammatory disease: a review of recent randomized clinical trials. Clin Infect Dis 2007 Apr 1;44(7):953-960.

(74) Geny F, Costa P, Bressolle F, Galtier M. Ceftriaxone pharmacokinetics in elderly subjects and penetration into epididymis. Biopharm Drug Dispos 1993 Mar;14(2):161-169.

(75) Young H, Moyes A, McMillan A. Azithromycin and erythromycin resistant Neisseria gonorrhoeae following treatment with azithromycin. Int J STD AIDS 1997 May;8(5):299-302.

(76) Habib AR, Fernando R. Efficacy of azithromycin 1g single dose in the management of uncomplicated gonorrhoea. Int J STD AIDS 2004 Apr;15(4):240-242.

(77) Yuan LF, Yin YP, Dai XQ, Pearline RV, Xiang Z, Unemo M, et al. Resistance to azithromycin of Neisseria gonorrhoeae isolates from 2 cities in China. Sex Transm Dis 2011 Aug;38(8):764-768.

(78) Katz AR, Komeya AY, Soge OO, Kiaha MI, Lee MV, Wasserman GM, et al. Neisseria gonorrhoeae with high-level resistance to azithromycin: case report of the first isolate identified in the United States. Clin Infect Dis 2012 Mar;54(6):841-843.

(79) Mosholder AD, Mathew J, Alexander JJ, Smith H, Nambiar S. Cardiovascular risks with azithromycin and other antibacterial drugs. N Engl J Med 2013 May 2;368(18):1665-1668.

(80) Handsfield HH, Dalu ZA, Martin DH, Douglas JM,Jr, McCarty JM, Schlossberg D. Multicenter trial of single-dose azithromycin vs. ceftriaxone in the treatment of uncomplicated gonorrhea. Azithromycin Gonorrhea Study Group. Sex Transm Dis 1994 Mar-Apr;21(2):107-111.

(81) Bignell C, Garley J. Azithromycin in the treatment of infection with Neisseria gonorrhoeae. Sex Transm Infect 2010 Nov;86(6):422-426.

(82) Dan M, Poch F, Amitai Z, Gefen D, Shohat T. Pharyngeal Gonorrhea in female sex workers: Response to a single 2-g dose of azithromycin. Sex Transm Dis 2006 Aug;33(8):512-515.

(83) Gil-Setas A, Navascues-Ortega A, Beristain X. Spectinomycin in the treatment of gonorrhoea. Euro Surveill 2010 May 13;15(19):pii/19568; author reply pii/19569.

(84) Kojima M, Masuda K, Yada Y, Hayase Y, Muratani T, Matsumoto T. Single-dose treatment of male patients with gonococcal urethritis using 2g spectinomycin: microbiological and clinical evaluations. Int J Antimicrob Agents 2008 Jul;32(1):50-54.

(85) Ramus RM, Sheffield JS, Mayfield JA, Wendel GD,Jr. A randomized trial that compared oral cefixime and intramuscular ceftriaxone for the treatment of gonorrhea in pregnancy. Am J Obstet Gynecol 2001 Sep;185(3):629-632.

(86) Donders GG. Treatment of sexually transmitted bacterial diseases in pregnant women. Drugs 2000 Mar;59(3):477-485.

(87) Brocklehurst P. Update on the Treatment of Sexually Transmitted Infections in Pregnancy. International Journal STD AIDS 1999;10(9):571-572-578.

(88) Cavenee MR, Farris JR, Spalding TR, Barnes DL, Castaneda YS, Wendel GD,Jr. Treatment of gonorrhea in pregnancy. Obstet Gynecol 1993 Jan;81(1):33-38.

(89) Comkornruecha M. Gonococcal infections. Pediatr Rev 2013 May;34(5):228-234.