GONOCOCCAL INFECTIONS

This chapter from the Canadian Guidelines on Sexually Transmitted Infections 2006 Edition has undergone revisions and has been updated as of October 2007. The chart below summarizes the most significant changes made to the chapter and cross-references the corresponding page numbers in the current hard copy version of the guidelines.

Section	Page	Current Wording/Problem	Update/Clarification
Numerous		Due to the rapid rise of Quinolone resistance in Canada, there have been significant changes made to the entire chapter.	Changes are too numerous to list, please print the entire chapter and discard/disregard previous version.

GONOCOCCAL INFECTIONS

Etiology

- Caused by *Neisseria gonorrhoeae.*

Epidemiology

- Preliminary data show that reported gonorrhea incidence between 1997 and 2006 has more than doubled. There were 4,477 reported cases of gonorrhea in 1997 and preliminary data show 10,808 reported cases of gonorrhea in 2006. The rate per 100,000 population for 1997 was 14.9 and the preliminary rate for 2006 is 33.1. Most affected are males 20-24 years of age and females 15-19 years .[1]
- There has been a gradual but steady increase in gonococcal infections since 1997. It appears that a network of people with high-transmission activities play a key role in current prevalence levels. Case finding and partner notification are critical strategies for controlling this infection.
- Continued monitoring for antimicrobial resistance is important to prevent the spread of drug-resistant gonorrhea and to ensure high cure rates for this treatable infection.[2,3]
- The proportion of penicillin-resistant organisms is >1% in most areas of Canada and may reach 15% or higher in certain urban and rural areas.[4] Also, numbers of isolates resistant to tetracyclines or a combination of penicillin and tetracyclines are still high, and these antimicrobial agents should *not* be considered in the treatment of gonorrhea.
  - Quinolone resistance in Canada has been steadily increasing, from 1% of the tested isolates in the late 1990s to a rate of 15.7% in 2005.[4-6] This rate reflects samples which have been submitted by individual provinces and territories to the National Microbiology Laboratory (NML). The current rate reported by the NML may not truly reflect the national picture as the submission of samples from individual provinces and territories is voluntary and not standardized across the country. The shift from culture to Nucleic Acid Amplification Test (NAAT) has also created difficulty in providing an accurate picture for resistance as the availability of samples for resistance testing is becoming increasingly limited.
  - Quinolone resistance in certain regions of Canada is significantly higher than the national rate. Please check with your local public health officials to learn about quinolone resistance in your area. Quinolones are not recommended for the treatment of *N. gonorrhoeae* in Canada due to resistance rates being > 3-5%. (See "Treatment" section for recommendations on the use of quinolones in Canada).
- HIV transmission is enhanced in people with concomitant gonococcal infections.[7]
- People at risk:
  - Those who have had contact with a person with proven infection or a compatible syndrome.
  - Those who have had unprotected sex with a 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 unprotected sex with a resident of that area (there is also a higher risk of resistance in this population).
  - Sex workers and their sexual partners.
  - Sexually active youth <25 years of age with multiple partners.
  - Street-involved youth.

- Men who have unprotected sex with men.
- Previous gonorrhea and other STI infection.
- In a Canadian passive surveillance study, re-infection was reported to be at least 2% per year.[8]

Prevention

- Patients presenting with concerns about sexually transmitted infections (STIs) and/or prevention of pregnancy should be provided with instructions and encouragement about the consistent practice of safer-sex.
- At the time of diagnosis, review and monitor prevention practices.
- Identify barriers to prevention practices and the means to overcome them. (See *Primary Care and Sexually Transmitted Infections* chapter).
- Provide counselling for the prevention of reproductive sequelae.
- Patients and contacts should abstain from unprotected intercourse until treatment of both partners is complete (i.e., after completion of a multiple-dose treatment or for 7 days after single-dose therapy).

Manifestations

Table 1. Manifestations

Neonates and infants	Children	Youth and adults		
		Females	Males	Females and males
• Ophthalmia • Neonatal amniotic fluid infection • 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: arthritis, dermatitis, endocarditis, meningitis

Table 2. Symptoms of gonococcal infection [9–11]

Neonates	Females	Males
• Conjunctivitis • Sepsis	• Vaginal discharge • Dysuria • Abnormal vaginal bleeding • Lower abdominal pain • Rectal pain and discharge if proctitis (see *Sexually Transmitted Intestinal and Enteric Infections* chapter) • Deep dyspareunia	• Urethral discharge • Dysuria • Urethral itch • Testicular pain, swelling or symptoms of epididymitis • Rectal pain and discharge if proctitis (see *Sexually Transmitted Intestinal and Enteric Infections* chapter)

Notes:
- Usual incubation period, 2-7 days.
- Some patients are asymptomatic or have symptoms not recognized to be due to *N. gonorrhoeae.*
- Contacts are also likely to be asymptomatic.
- Long-term carriage occurs.

Table 3. Major sequelae

Females	Males
• Pelvic inflammatory disease • Infertility • Ectopic pregnancy • Chronic pelvic pain • Reiter syndrome • Disseminated gonococcal infection	• Epididymo-orchitis • Reiter syndrome • Infertility (rare) • Disseminated gonococcal infection

Diagnosis[12]

Laboratory diagnosis

- Cultures obtained less than 48 hours after exposure may be negative.
- Post exposure NAAT testing can be taken at the time of presentation without waiting for 48 hours; this is based on expert opinion, which assumes that NAATs are able to detect inoculum (DNA or RNA).
- If possible, culture is the recommended method, because it allows for antimicrobial susceptibility testing. It is recognized that nucleic acid amplification tests (NAATs) are the only available method in some jurisdictions. NAATs may be most useful when patients resist pelvic examination or urethral swabbing.[13] In these situations, urine NAATs should be used.
- Culture is especially important in the following cases:
  - Sexual abuse of children (rectal, pharyngeal, vaginal).†
  - Sexual assault.†
  - Presumed treatment failure.

  - Evaluation of pelvic inflammatory disease (PID).
  - Infection acquired overseas or in areas with recognized antimicrobial resistance.
- Antimicrobial susceptibility testing for all isolates is suggested and is *required* for all isolates from positive (test of cure) follow-up cultures and presumed treatment failures.
- Non-culture tests are an ideal method when transport and storage conditions are not conducive to maintaining the viability of *N. gonorrhoeae*[14] (see *Laboratory Diagnosis of Sexually Transmitted Infections* chapter).
- NAATs may be considered, but sentinel resistance surveillance measures should be taken to ensure continued surveillance for antimicrobial resistance. If NAAT is used for a test of cure (see indications for test of cure in the Follow-up section), specimen collection should be delayed for 3 weeks post completion of treatment.[15]

Notes:

† When NAAT is used, two different primers should be used in the laboratory (see *Laboratory Diagnosis of Sexually Transmitted Infections* chapter).

Specimen collection[12,14]

Routine specimen sites

- Urethra in young and adult males, with/without meatal discharge (see *Table 4 in this chapter and Laboratory Diagnosis of Sexually Transmitted Infections chapter*).
  - For prepubertal boys, see *Laboratory Diagnosis of Sexually Transmitted Infections* and *Sexual Abuse in Peripubertal and Prepubertal Children* chapters.
- Cervix in young and adult females (see *Table 4 in this chapter and Laboratory Diagnosis of Sexually Transmitted Infections* chapter).
- Rectum in all females because colonization can occur without anal intercourse [16] and in men who have sex with men who practice receptive anal intercourse (see *Table 4 in this chapter and Laboratory Diagnosis of Sexually Transmitted Infections* chapter).
- Vagina in prepubertal girls (see *Laboratory Diagnosis of Sexually Transmitted Infections* and *Sexual Abuse in Peripubertal and Prepubertal Children* chapters).
- Pharynx in those with a history of performing oral sex (see *Table 4 in this chapter and Laboratory Diagnosis of Sexually Transmitted Infections* chapter).
- Urine (first 10-20 mL) for NAAT if culture is not available, patient is resistant to pelvic examination or urethral swabbing, or problems exist with storage and transport of specimen.

Other specimen sites (see Table 4 below)

- If the cervix has been surgically removed, urine and vaginal swabs are convenient specimens; specimens can also be collected from the rectum and urethra.
- Self-obtained vaginal swabs may be suitable for women when a pelvic examination is not warranted or refused by the patient. However, a physical examination remains essential, and more invasive specimens may be needed for diagnostic purposes in some situations.
- Women undergoing laparoscopy for investigation of PID should have intra-abdominal specimens taken (i.e., fallopian tube, cul de sac fluid etc.).
- Urethra in women with urethral syndrome.
- Blood and synovial fluid (in blood culture tube/bottle) in disseminated disease. Synovial fluid should also be examined by Gram stain.
- Epididymal aspirate in men with epididymitis may be considered.

- Conjunctiva for ocular infection.

Note:

For further information on specimen transport, see Laboratory Diagnosis of Sexually Transmitted Infections chapter.

Table 4. Specimen collection

Site/specimen	Test	Comments
Urethra (intraurethral) (young and adult males)	Gram stain (for Gram negative intracellular diplococci) (symptomatic men only)	Generally diagnostic of gonorrhea
	Culture	Confirmation and antimicrobial susceptibility testing
	Non-culture test (NAAT)	In cases where culture not practical (does not provide antibiotic susceptibility)
Endocervix/urethra (young and adult females)	Gram stain (for Gram negative intracellular diplococci)	Sensitivity lower than in male urethral specimens and not routinely recommended
	Culture	Confirmation and antimicrobial susceptibility testing
	Non-culture test (NAAT)	In cases where culture not practical (does not provide antibiotic susceptibility)
Vagina	Culture	Confirmation and antimicrobial susceptibility testing
	Non-culture test (NAAT)	In cases where culture not practical (does not provide antibiotic susceptibility)

NAAT=nucleic acid amplification test

Notes:

- Specimens should be taken for the diagnosis of both gonococcal and chlamydial infections (see *Laboratory Diagnosis of Sexually Transmitted Infections* chapter).
- All suspected treatment failures should be investigated with a culture to ensure the availability of antimicrobial susceptibility data.

Table 4. Specimen collection(continued)

Site/specimen	Test	Comments
Pharynx/conjunctiva/ rectum	• Culture (Gram stain and non-culture tests not suitable for these sites) • NAAT is not approved in Canada for oropharyngeal or rectal use. For conjunctiva, pharynx and rectum refer to package insert for specific test.	Confirmation and antimicrobial susceptibility testing
Urine (males and females)	Non-culture test (NAAT)	Should not be used in cases of treatment failure when antimicrobial susceptibility data are critical
Disseminated infection	• Genital testing • Blood culture • Gram stain and culture of skin lesion • Synovial fluid if arthritis	

NAAT=nucleic acid amplification test

Notes:

- Specimens should be taken for the diagnosis of both gonococcal and chlamydial infections (see *Laboratory Diagnosis of Sexually Transmitted Infections* chapter).
- All suspected treatment failures should be investigated with a culture to ensure the availability of antimicrobial susceptibility data.

Transport

- Contact the laboratory for specific instructions regarding the preferred method of specimen transport to ensure pathogen survival for purposes of culture.
- Transport of gonococcal specimens for culture should be at ambient temperature, *not* 4^{o}C as recommended for other organisms.

Management

- Management choices should be based on the site of infection and laboratory results unless presumptive treatment is to be provided for syndromic management (i.e. MPC, NGU, PID or epididymitis) or if being treated as a contact. In the latter scenarios, relevant history, physical examination and epidemiologic factors should be considered when making treatment decisions.
- A diagnosis of gonorrhea should be confirmed by the identification of *N. gonorrhoeae* by culture, or if culture is not available, by NAATs. All confirmed or suspected cases *must* be treated.

Table 5. Management: test results available

Gram stain	• Treat for gonococcal and chlamydial infection if Gram-negative intracellular diplococci observed • The presence of Gram-negative diplococci outside polymorphonuclear leukocytes (PMNs) is an equivocal finding that needs to be confirmed by culture • The presence of PMNs without diplococci does not indicate or exclude gonococcal infection
Culture test	• Treat all positives
NAATs	• A positive initial NAAT test confirmed by a second set of primers or by DNA sequencing is diagnostic of gonorrhea, and the patient should be treated

NAAT=nucleic acid amplification test
PMN=polymorphonuclear leukocyte

Table 6. Management: test results unavailable

Urethral/cervical mucopurulent discharge observed	• Treat for *N. gonorrhoeae* and *C. trachomatis* if partner is infected with gonorrhea or if follow-up is not assured. OR • Treat for *C. trachomatis* and consider treating for *N. gonorrhoeae* if local prevalence is high or sexual contact occurred in a region with high prevalence.
No urethral/cervical mucopurulent discharge	• Defer therapy until smear/culture/NAAT results available OR • Treat for *N. gonorrhoeae* and *C. trachomatis* if patient is at high risk for infection and follow-up is not assured or if partner is infected with gonorrhea.

NAAT=nucleic acid amplification test

Treatment

- Due to the rapid increase in quinolone resistant *Neisseria gonorrhoeae,* quinolones such as ciprofloxacin and ofloxacin are no longer preferred drugs for the treatment of gonococcal infections in Canada.
- Quinolones may be considered as an **alternative treatment option ONLY IF** :
    - antimicrobial susceptibility testing is available and quinolone susceptibility is demonstrated;

    OR
    - where antimicrobial testing is not available, a test of cure is essential.

- All patients treated for gonorrhea should also be treated for chlamydial infection, unless a chlamydia test result is available and negative.
- Directly observed therapy with single-dose regimens is desirable if poor compliance is expected.
- For PID, see *Pelvic Inflammatory Disease* chapter.
- For epididymitis, see *Epididymitis* chapter.

Youth 9 years of age or older and adults

Table 7: Urethral, endocervical, rectal, pharyngeal infection (except in pregnant women and nursing mothers)[17–24]

Preferred	Alternatives
• Cefixime 400 mg PO in a single dose[† ¥] *[A-I]*	• Ceftriaxone 125 mg IM in a single dose[† ‖ ¥] *[A-I]* OR • Azithromycin 2 g PO in a single dose[¶] *[A-I]* OR • Spectinomycin 2 g IM in a single dose[#] (available only through Special Access Program [SAP]) *[A-I]* *OR* • Ciprofloxacin 500 mg PO in a single dose* *[A-I]* OR • Ofloxacin 400 mg PO in a single dose* *[A-I]*
All regimens should be followed by empiric treatment for chlamydial and non-gonococcal infections (see *Chlamydial Infections* and *Urethritis* chapters)	

* Quinolones may be considered as an **alternative treatment option ONLY IF** :
- antimicrobial susceptibility testing is available and quinolone susceptibility is demonstrated;

OR
- where antimicrobial testing is not available, a test of cure is essential.

†Cefixime and ceftriaxone should not be given to persons with a cephalosporin allergy or a history of immediate and/or anaphylactic reactions to penicillins.

¥ Cefixime is preferred over ceftriaxone as a factor of cost and ease of administration. In the province of Quebec ceftriaxone is the only choice for pharyngeal gonorrhoea.

‖The preferred diluent for ceftriaxone is 1% lidocaine without epinephrine (0.9 mL/250 mg, 0.45 mL/125 mg) to reduce discomfort.

¶Associated with a significant incidence of gastrointestinal adverse effects. Taking medication with food may minimize adverse effects. Prophylactic anti-emetics may be needed.

#Not effective for pharyngeal infection. Test of cure is recommended.

Table 8. Urethral, endocervical, rectal or pharyngeal infection in pregnant women and nursing mothers[25–27]

Preferred	Alternatives
• Cefixime 400 mg PO in a single dose* *[A-I]*	• Ceftriaxone 125 mg IM in a single dose *¥† *[A-I]* OR • Spectinomycin 2 g IM in a single dose‡ (available only through SAP) *[A-I]*
All regimens should be followed by empiric treatment for chlamydial and non-gonococcal infections (see *Chlamydial Infections* and *Urethritis* chapters)	

SAP=Special Access Program
*Cefixime and ceftriaxone should not be given to persons with a cephalosporin allergy or a history of immediate and/or anaphylactic reactions to penicillins.
¥ Cefixime is preferred over ceftriaxone as a factor of cost and ease of administration. In the province of Quebec ceftriaxone is the only choice for pharyngeal gonorrhoea.
†The preferred diluent for ceftriaxone is 1% lidocaine without epinephrine (0.9 mL/250 mg, 0.45 mL/125 mg) to reduce discomfort.
‡Not effective for pharyngeal infection. Test of cure is recommended.

Table 9. Gonococcal ophthalmia/disseminated infection in youth 9 years of age or older and adults (arthritis, meningitis)

Preferred initial therapy
Ceftriaxone 2 g/day IV/IM AND doxycycline 100 mg PO bid x 7 days OR azithromycin 1 gm PO in a single dose while awaiting consultation* *[A-II]*
• Consultation with a colleague experienced in this area is essential • **Hospitalization** is necessary for meningitis and may be necessary for other disseminated infections

*The preferred diluent for **IM** ceftriaxone is 1% lidocaine without epinephrine (0.9 mL/250 mg, 0.45 mL/125 mg) to reduce discomfort.

Children under 9 years of age[9,28]

Table 10. Urethral, vaginal, rectal, pharyngeal infection

Preferred	Alternatives
• Cefixime 8 mg/kg PO in a single dose (maximum 400 mg)*† *[A-II]*	• Ceftriaxone 125 mg IM in a single dose†‡ *[A-II]* OR • Spectinomycin 40 mg/kg IM (maximum 2 g) in a single dose (available only through SAP)¥ *[A-II]*
• **All regimens should be followed by treatment for chlamydial infection. See *Chlamydial Infections* chapter for treatment recommendations for children under 9 years of age.**	

SAP = Special Access Program
*Oral therapies are preferred in 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, use ceftriaxone 125 mg IM in place of cefixime.
†Cefixime and ceftriaxone should not be given to persons with a cephalosporin allergy or a history of immediate and/or anaphylactic reactions to penicillins.
‡The preferred diluent for ceftriaxone is 1% lidocaine without epinephrine (0.9 mL/250 mg, 0.45 mL/125 mg) to reduce discomfort.
¥Not effective for pharyngeal infection. Test of cure is recommended.

Table 11. Disseminated infection in children under 9 years of age

Infection	Preferred treatment
Arthritis	Ceftriaxone 50 mg/kg IV/IM in a single daily dose for 7 days* *[A-III]*
Meningitis, endocarditis	Ceftriaxone 25 mg/kg IV/IM every 12 hours for 10–14 days for meningitis, 28 days for endocarditis **[A-III]*
Gonococcal ophthalmia beyond neonatal period	Ceftriaxone 50 mg/kg IV/IM in a single dose (maximum 1 g)* *[A-III]*
Hospitalization and consultation with a colleague experienced in this area is essential	

***The preferred diluent for IM ceftriaxone is 1% lidocaine without epinephrine (0.9 mL/250 mg, 0.45 mL/125 mg) to reduce discomfort.

Neonatal infection

Ophthalmia neonatorum

- Hospitalize and institute appropriate infection-control precautions until 24 hours of effective therapy completed.
- Culture eye discharge, blood (cerebrospinal fluid only if evidence of systemic disease).
- Irrigate eyes immediately with sterile normal saline and at least hourly as long as necessary to eliminate discharge.
- Start ceftriaxone 100 mg/kg IV or IM single-dose therapy *[A-II]*.
- Consult with a colleague experienced in this area as soon as possible

Table 12. Neonates born to women infected with gonorrhea

Recommended therapy (include therapy for chlamydia for 14 days unless the mother's tests are negative)
Ceftriaxone 125 mg IM in a single dose AND erythromycin in the following dosage schedule*† *[A-III]:* • If ≤7 days old and ≤2000 g: erythromycin 20 mg/kg/day PO in divided doses† *[A-III]* • If ≤7 days old and >2000 g: erythromycin 30 mg/kg/day PO in divided doses† *[A-III]* • If >7 days of age: erythromycin 40 mg/kg/day PO in divided doses† *[A-III]*

*The preferred diluent for ceftriaxone is 1% lidocaine without epinephrine (0.9 mL/250 mg, 0.45 mL/125 mg) to reduce discomfort.
†Erythromycin dosages refer to erythromycin base. Equivalent dosages of other formulations may be substituted. The use of erythromycin in infants under 6 weeks of age has been associated with infantile hypertrophic pyloric stenosis (IHPS).[29–32] The risk of IHPS with other macrolides (e.g., azithromycin) is unknown. The risks and benefits of using erythromycin in such infants should be explained to parents. When erythromycin is used, it is important to monitor for symptoms and signs of IHPS. IHPS following erythromycin use should be reported to the Canadian Adverse Drug Reaction Monitoring Program at 1-866-234-2345 or online @ http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index_e.html

Consideration for Other STIs

- See *Primary Care and Sexually Transmitted Infections* chapter.
- Obtain a specimen for the diagnosis of chlamydial infection.
- Obtain a blood sample for serologic testing of syphilis (see *Syphilis* chapter).
- HIV counselling and testing are recommended (see *Human Immunodeficiency Virus* Infections chapter).
- Immunization against hepatitis B is recommended, if not already immune (see *Hepatitis B Virus Infections* chapter).
- Discuss HPV vaccine with women as per the recommendations outlined in the Canada Communicable Disease Report, Volume 33 ACS-2, (2007) *National Advisory Committee on Immunization (NACI) statement on Human papillomavirus vaccine.*

Reporting and Partner Notification

- With the changing epidemiology of *N. gonorrhoeae*, case finding and partner notification are critical strategies for maintaining control of gonococcal infections in Canada.
- Gonococcal infections are reportable in all provinces and territories.
- Positive culture and non-culture tests are reportable to the local public health authorities.
- All partners who have had sexual contact with the index case within at least 60 days prior to symptom onset or date of diagnosis (if asymptomatic); parents of infected neonates (i.e., mother and her sexual partner)should be located, clinically evaluated and empirically treated regardless of clinical findings and without waiting for test results.
- Since co-infections are common, persons treated for gonococcal infections should also be treated for *C. Trachomatis,* unless concurrent test results for chlamydia are available and negative.
- Local public health authorities are available to assist with partner notification and with appropriate referral for clinical evaluation, testing, treatment and health education.

Follow-up

- Repeat screening of individuals with gonorrhea after 6 months is recommended.
- Follow-up testing by culture *is essential* if any of the following exist:
  - Quinolones were administered for treatment and there was no previous antimicrobial testing done.
  - Treatment failure has occurred previously.
  - Antimicrobial resistance to therapy is documented.
  - Compliance is uncertain.
  - There is re-exposure to an untreated partner.
  - There is concern over a false-positive non-culture test result.
  - Infection occurs during pregnancy.
  - PID or disseminated gonococcal infection is diagnosed.
  - Patient is a child.

Notes:

- Follow-up cultures for test of cure are indicated approximately 4-5 days after the completion of therapy. These should include reculturing of all positive sites.
- NAAT is not recommended for test of cure. However, if this is the only choice, tests should not be done for 3 weeks after treatment to avoid false-positive results due to the presence of non-viable organisms.

Special Considerations

Children

- Neonates born to infected mothers *must* be tested and treated.
- Sexual abuse needs to be considered when genital, rectal or pharyngeal gonorrhea is diagnosed in any child after the neonatal period. Consultation with a colleague experienced in such cases should be sought. Siblings and other children possibly at risk should also be evaluated.
- All persons named as suspects in child sexual abuse cases should be located and clinically evaluated; prophylactic treatment may or may not be offered and the decision to treat or not should be based on history, clinical findings and test results. (See *Sexual Abuse in Peripubertal and Prepubertal Children*).
- Sexual abuse of children must be reported to the local child protection agency.
- Local public health authorities may be helpful in evaluating the source of infection and spread to others. See *Sexual Abuse in Peripubertal and Prepubertal Children* chapter.

Notes:

- Follow-up cultures for test of cure are indicated approximately 4-5 days after the completion of therapy. These should include reculturing of all positive sites.
- NAAT is not recommended for test of cure. However if this is the only choice, tests should not be done for 3 weeks after treatment to avoid false-positive results due to the presence of non-viable organisms.

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