

Guidelines for the management of suspected and confirmed bacterial meningitis in Canadian children older than one month of age

Nicole Le Saux; Canadian Paediatric Society
Infectious Diseases and Immunization Committee
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Abstract

The incidence of bacterial meningitis in infants and children has decreased since the routine use of conjugated vaccines targeting *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and *Neisseria meningitidis*. However, this infection continues to be associated with considerable mortality and morbidity if not treated effectively with empirical antimicrobial therapy. Diagnosis still rests on clinical signs and symptoms, and cerebrospinal fluid analysis. This position statement outlines the rationale for current recommended empirical therapy using a third-generation cephalosporin and vancomycin for suspected bacterial meningitis. It also provides new recommendations for the use of adjuvant corticosteroids in this setting. Once antibiotic susceptibilities of the pathogen are known, antimicrobials should be reviewed and modified accordingly. Recommendations for treatment duration as well as audiologic testing are included. The present statement replaces a previous Canadian Paediatric Society position statement on bacterial meningitis published in 2007 and revised in 2008.

Key Words: Ampicillin; Antimicrobial resistance; Cephalosporin; Corticosteroids; PCV13; Vancomycin

The purpose of the present statement is to review the current epidemiology of bacterial meningitis in children beyond the neonatal period and provide guidelines for the empirical management of suspected bacterial meningitis in Canadian children. It does not address meningitis associated with cerebrospinal fluid (CSF) shunts or meningitis caused by organisms that are uncommon beyond one month of age such as *Escherichia coli* and other Gram-negative bacteria. Referral to other resources and, preferably, consultation with an infectious diseases specialist are recommended in such cases. Viral meningoencephalitis caused by herpes simplex or other viral pathogens is also beyond the scope of the present statement;

however, this diagnosis should be considered in the proper clinical contexts.

Current epidemiology

The epidemiology of meningitis in Canada has been influenced dramatically by universal immunization programs delivering conjugate vaccines for *Haemophilus influenzae* type b (Hib), *Neisseria meningitidis* and *Streptococcus pneumoniae*.^{[1][2]} The epidemiology of meningitis in the United States, where universal immunization programming is similar to Canadian schedules, is also evolving (see Figure 1 at www.nejm.org/doi/full/10.1056/NEJMoa1005384).^[3] However, the epidemiology of bacterial meningitis is very different in other parts of the world, where access to vaccines for these three main pathogens is lower or nonexistent, and/or immunization uptake is low.^{[4][5]}

In Canada, the Hib vaccine has been provided in public programs in all provinces and territories since 1998. Hib meningitis is now very rare and primarily occurs in unimmunized or partially immunized children, or in individuals who are immune-incompetent or immunosuppressed. It is worth noting that disease due to other serogroups (ie, non-b) has been increasing in all parts of Canada but particularly in Northern populations.^{[6][8]}

Publicly funded infant immunization programs with heptavalent conjugate vaccines against *S pneumoniae* (PCV7), which contained the capsular serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, were offered in all provinces and territories by 2005. The incidence of pneumococcal meningitis in the United States and in Canada has decreased significantly in all age groups following the introduction of PCV7.^{[9][13]} In Canada, the number of meningitis cases caused by *S pneumoniae* reported to Immunization Monitoring Program ACTIVE (IMPACT) hospitals decreased from 75 to 20 cases annually between 2000 and 2007, and there was an 87.5% decrease in cases of invasive pneumococcal disease (which includes meningitis and isolation of pneumococcus from other sterile sites). However, the phenomenon of serotype replacement,

with increases in the relative and absolute incidence of 19A, 15B, 6A and other serotypes not present in PCV7, did occur here and elsewhere.^{[3][10][14][15]}

A 13-valent pneumococcal conjugate vaccine (PCV13) has now replaced the PCV7 vaccine. The PCV13 vaccine includes the seven serotypes in the PCV7 vaccine and an additional six serotypes (1, 3, 5, 6A, 7F and 19A). In 2010, a significant proportion of invasive pneumococcal isolates from children <2 years of age were serotypes included in PCV13 and not in PCV7. As of 2011, all Canadian immunization programs had completed the conversion to PCV13. One recent study, using isolates collected from sterile clinical sites since 2010, determined that the PCV13 serotypes in Canada declined from 66% (224 of 339) to 41% (101 of 244; $P < 0.001$) in children <5 years of age, and from 54% (1262 of 2360) to 43% (1006 of 2353; $P < 0.001$) in children ≥ 5 years of age. Serotypes 19A, 7F, 3 and 22F were the most common serotypes in 2012, with 19A decreasing from 19% (521 of 2727) to 14% (364 of 2620; $P < 0.001$).^[11]

The incidence of meningococcal disease in children and adults has decreased significantly since the introduction of routine meningococcal serogroup C immunization programs.^{[16][17]} The impact of the introduction of the quadrivalent conjugated A, C, Y and W meningococcal vaccine for adolescents is not yet known because these programs only started several years ago, and this vaccine is not part of publicly funded programs in all provinces and territories. A vaccine that targets serogroup B (Bexsero, Novartis Canada) is now licensed in Canada, although it is not currently included in publicly funded programs.^{[18][19]}

Meningitis caused by group B streptococcus (GBS; also referred to as *Streptococcus agalactiae*) is less common beyond one month of life than in neonates. Although *Listeria monocytogenes* is an uncommon cause of meningitis beyond the neonatal period, it should be considered if specific host risk factors, such as immunosuppression, are present or if brain stem infection is the initial presentation.

Antimicrobial susceptibility of the major pathogens

Given the requirement for adequate drug levels in the central nervous system, *S pneumoniae* breakpoints for susceptibility have been specifically designed for interpretation in the context of meningitis. The current breakpoints for susceptibility for *S pneumoniae*, when isolated from CSF, are as follows: penicillin susceptible if minimal inhibitory concentration (MIC) ≤ 0.06 $\mu\text{g/mL}$ penicillin, and penicillin resistant if MIC ≥ 0.12 $\mu\text{g/mL}$.^[20]

Using the current criteria for antimicrobial susceptibility, of the 2049 isolates available from cases of paediatric invasive pneumococcal disease (meningitis and nonmeningitis cases) in Canada from 2000 to 2007, 81 meningitis isolates were

penicillin resistant, leaving 96.1% penicillin susceptible.^[3] Of the 2047 isolates in which cefotaxime or ceftriaxone resistance was determined, 34 isolates were resistant, leaving 98.3% susceptible to third-generation cephalosporins. The Canadian Ward Surveillance study (CANWARD) collected isolates of *S pneumoniae* from both adults and children between 2007 and 2009 and reported that of 800 isolates, 80.8% were susceptible to penicillin and 98.1% were susceptible to ceftriaxone based on meningitis susceptibility criteria.^[21] Both Canadian surveillance programs indicated that while penicillin resistance is not common, it is present in a small proportion of invasive isolates of *S pneumoniae*. The number of ceftriaxone-resistant isolates among serotypes that were represented in PCV7 remained constant over the full eight study years, ranging from two to seven per year. Most cases occurred in children <5 years of age.^[3] In both studies, serotype 19A, a strain typically associated with greater penicillin resistance, was predominately found in children <2 years of age.^[3] However, the 19A strain and others that are penicillin resistant are, proportionally, better represented in the current PCV13 vaccine compared with the former PCV7 vaccine (87.5% versus 62.5%).^[21]

In the past several years, many countries, notably Belgium, Australia and several countries in Latin America, have reported increasing prevalence (ranging from 30% to 80%) of *N meningitidis* with reduced susceptibility to penicillin.^{[22][24]} In the United States, ciprofloxacin-resistant *N meningitidis* has also emerged.^[25] A report from Ontario indicated that the percentage of strains with reduced susceptibility to penicillin between 2000 and 2006 was 21.7%.^[26] Surveillance data of 408 Canadian isolates of *N meningitidis* analyzed at the National Microbiology Laboratory from 1996 to 2010 showed 18.6% with reduced susceptibility to penicillin, although no endemic isolates were resistant to ciprofloxacin (personal communication, Raymond Tsang, National Microbiology Laboratory [Winnipeg, Manitoba]).

While Hib is now an uncommon cause of meningitis in children, it should still be considered in a child who is not fully immunized or unimmunized, or who is new to Canada. Increasingly, Hib and other typeable strains of *H influenzae* have shown increasing beta-lactamase production ranging from 4% to 42%, making these isolates resistant to ampicillin.^[5] Because of this trend, ceftriaxone or cefotaxime should be used as empirical therapy, pending susceptibility testing.

Penicillin is currently the drug of choice for infection caused by group B streptococcus. However, empirical coverage with cefotaxime or ceftriaxone in infants would be reasonable until culture results are available.

Diagnosis

Infants with meningitis often present with nonspecific findings of fever, poor feeding, lethargy (or decreased interaction

with caregivers), vomiting and irritability. They sometimes have a rash. Inconsolable crying, prolonged or worsening irritability or progressive lethargy are also important clinical features that may indicate a central nervous system (CNS) focus such as meningitis. Nuchal rigidity is uncommon in infants; older children are more likely to have more specific symptoms related to meningitis, such as headache, nuchal pain or rigidity, and impaired consciousness as well as other nonspecific symptoms.^[27] Patients should undergo a full examination, including respiratory status and detailed neurological examinations to detect focal neurological signs, posturing, cranial nerve abnormalities and assessment of level of consciousness.

A lumbar puncture (LP) for CSF analysis (cell count, glucose and protein levels, microbiological culture and molecular detection of bacterial DNA [if clinical suspicion is high and bacterial cultures are negative] and viral studies where appropriate, as well as consideration for specific testing for tuberculosis in high-risk children) is indispensable for the definitive diagnosis of meningitis. An LP should always be attempted unless there are contraindications. Molecular diagnostics may still be useful even if antimicrobials have been administered, and available options should be discussed with a microbiologist. Contraindications to LP include coagulopathy, cutaneous lesions at the proposed puncture site, signs of herniation or an unstable clinical status such as shock. If there is papilledema, the presence of focal neurological signs, decreased level of consciousness or coma, an LP should be deferred until imaging (a contrast-enhanced computed tomography and/or magnetic resonance imaging of the head) is performed and the risk of potential herniation is ruled out. Although there are no specific studies involving children, herniation following an LP in meningitis is rare in the absence of focal CNS lesions.^{[28][29]}

Because timely empirical antimicrobial therapy is critical to treatment, antimicrobial administration should not be delayed when imaging studies are not immediately available or an LP cannot be performed. Blood cultures should be obtained before starting antimicrobial therapy, with minimum total blood volumes drawn as per the weights specified below to improve yield, using one or two samples:

- 2 mL for a child weighing 1.5 kg to <4 kg;
- 4 mL for a child weighing 4 kg to <8 kg;
- 6 mL for a child weighing 8 kg to <14 kg;
- 10 mL for a child weighing 14 kg to <19 kg;
- 16 mL for a child weighing 19 kg to <26 kg; and
- 20 mL for a child weighing >26 kg

Other investigations, such as urine culture, pharyngeal culture or chest radiograph, should be performed as clinically indicated.

Managing suspected meningitis

Because the prognosis of meningitis depends on treating infection before clinically severe disease ensues, the timely administration of empirical antimicrobial therapy (Table 1) is critical. Antimicrobials should be administered as soon as possible when meningitis is suspected or confirmed. Also, the careful, ongoing assessment and appropriate management of hemodynamic stability is required. An LP should be performed to support the diagnosis, but if an LP is not possible, antimicrobials should be given empirically irrespective of the delay in obtaining an LP. The patient should be transferred to a facility where an LP can be performed. One study involving adults showed that a delay in starting antimicrobial treatment was one of three independent variables associated with poor prognosis. The other two factors were the severity of clinical state at presentation and the isolation of nonpenicillin-susceptible *S pneumoniae*.^{[30][31]} Other factors to consider in the choice of antimicrobials are the child's age, and underlying diseases or risk factors such as immunodeficiency. For example, if there is an underlying immunodeficiency, then *Listeria* is a possible risk and ampicillin should be added to the empirical regimen. Management should also include monitoring for early complications associated with acute meningitis (eg, syndrome of inappropriate antidiuretic hormone secretion and increased intracranial pressure). The bacterial organisms most likely to cause community-acquired meningitis in healthy, immunized children >1 month of age are *S pneumoniae* and *N meningitidis*, but *E coli* and GBS should also be considered in infants up to three months of age. As mentioned previously, Hib is still occasionally observed in incompletely immunized patients, but other encapsulated *H influenzae* cases are being diagnosed with increasing frequency. In Canada, where penicillin-resistant *S pneumoniae* is known to occur, empirical therapy using a third-generation cephalosporin (ceftriaxone or cefotaxime) is recommended. In areas where there have not been cephalosporin-resistant *S pneumoniae* cases, this single drug may be adequate as empirical therapy. However, pending culture results, most experts recommend adding vancomycin to the third-generation cephalosporin to protect against the possibility of a cephalosporin-resistant *S pneumoniae*, which has emerged in some parts of Canada.^{[3][21]} Third-generation cephalosporins will also be adequate empirical coverage for *N meningitidis* and *H influenzae*, because both organisms remain susceptible to these agents. If there are contraindications to empirical third-generation cephalosporin use, other alternatives (such as meropenem) may be used empirically and the early advice of an infectious disease expert should be requested.

The close contacts of any patient diagnosed with meningococcal disease or Hib should be treated with rifampin or another suitable alternative according to local public health guidelines.

TABLE 1 Recommended antimicrobials for suspected and proven bacterial meningitis in children >1 month of age

	Recommended therapy	
Empirical treatment (pending blood and cerebrospinal fluid cultures)		
	Ceftriaxone OR cefotaxime AND vancomycin ADD ampicillin to cover <i>Listeria</i> if patients are at risk because they are immunocompromised	
Blood and CSF cultures negative or not performed, but a diagnosis of bacterial meningitis is supported by clinical course and laboratory investigations (including cases detected using molecular methods)		
	Ceftriaxone OR cefotaxime, without vancomycin* *Vancomycin could be continued if there is local epidemiological evidence of third-generation cephalosporin resistance of <i>Streptococcus pneumoniae</i>	
Specific bacteria	Recommended treatment	Alternative therapy
<i>S pneumoniae</i> (culture positive)		
Penicillin susceptible (MIC ≤0.06 µg/mL)	Penicillin G or ampicillin	Cefotaxime, ceftriaxone
Penicillin resistant (MIC ≥0.12 µg/mL) AND ceftriaxone or cefotaxime susceptible (MIC ≤0.5 µg/mL)	Ceftriaxone or cefotaxime	Meropenem
Penicillin resistant (MIC ≥0.12 µg/mL) AND ceftriaxone or cefotaxime intermediate or fully resistant (MIC ≥1.0 µg/mL)	Ceftriaxone or cefotaxime AND vancomycin* *Consult an infectious disease expert	Meropenem
<i>Neisseria meningitidis</i>		
Penicillin susceptible (MIC <0.12 µg/mL)	Penicillin G or ampicillin	Ceftriaxone or cefotaxime
Penicillin resistant (MIC ≥0.12 µg/mL)	Ceftriaxone or cefotaxime	
<i>Haemophilus influenzae</i>		
Ampicillin susceptible	Ampicillin	
Ampicillin resistant	Ceftriaxone or cefotaxime	
<i>Streptococcus agalactiae</i> (Group B streptococci [GBS])	Penicillin G or ampicillin; ADD gentamicin for the first 5 to 7 days or until cerebrospinal fluid sterility confirmed	
Other organisms	Consult an infectious disease expert	
<i>MIC Minimum inhibitory concentration</i>		

Steroids as adjuvant therapy

The role of steroids in the management of acute bacterial meningitis in children is controversial, except in the case of Hib meningitis, for which there is evidence that steroids de-

crease hearing loss in children if they are administered just before or with the initial antimicrobial therapy.^[32]

One recent Dutch study involving adults only compared individuals who had received dexamethasone in the period from

2006 to 2009 with a group between 1998 and 2002 who did not. Both short- and long-term mortality and hearing loss were lower in the group given dexamethasone.^[33] Another review by an Italian group advocates for the use of dexamethasone in children with Hib meningitis but acknowledges that the data supporting its use in meningitis caused by *S pneumoniae* is less certain.^[34] A few trials have been performed in children with pneumococcal meningitis. A review of these studies indicates that the different patient ages and the considerable heterogeneity of clinical severity at presentation are probably the major risk factors for sequelae, making any conclusion regarding the beneficial effects of steroids problematic.^{[35][36]} On balance, however, later studies in adults and in children do appear to indicate a potential outcomes benefit of a short course of steroids when they are administered just before or with initial empirical antimicrobial therapy.

If there are no contraindications to steroid use for a particular infant or child, when a meningitis of bacterial etiology is

suspected (especially if the CSF Gram stain indicates Gram-positive diplococci or Gram-negative coccobacilli), some experts recommend starting intravenous steroids: dexamethasone at a dose of 0.6 mg/kg/day in four divided doses administered every 6 h immediately before, concomitant with, or within 30 min after the first dose of antimicrobials. If *S pneumoniae* or Hib is cultured or identified by molecular testing, steroids should be continued for a total duration of two days. If another etiology is identified within 48 h, steroids should be discontinued – there has been no benefit identified in continuing steroids for other causes. In some cases, there is a rebound of fever after steroids are discontinued, but if all other parameters indicate improvement and the clinical diagnosis continues to support bacterial meningitis alone, fever is not an indication for additional testing.

At present, there is insufficient information available to recommend other types of adjuvant therapy.

TABLE 2
Recommended doses for antimicrobials used to treat suspected or confirmed bacterial meningitis

Antimicrobial	Dose	Route
Ceftriaxone	100 mg/kg/day in 2 divided doses administered every 12 h (some experts recommend a loading dose of 100 mg/kg followed 12 h later by another dose, then 100 mg/kg/day in 2 divided doses administered every 12 h) Maximum dose 4 g/day	Intravenous (intramuscular route can be used if intravenous route is not immediately available)
Cefotaxime	300 mg/kg/day in 4 divided doses administered every 6 h Maximum dose 8 g/day to 12 g/day	Intravenous
Vancomycin	60 mg/kg/day in 4 divided doses administered every 6 h To achieve trough concentrations of 10 mg/L to 15 mg/L	Intravenous
Penicillin G	300,000–400,000 units/kg/day in divided doses administered every 4 h to 6 h Maximum dose 24 million units/day	Intravenous
Ampicillin	300 mg/kg/day in divided doses administered every 4 h to 6 h Maximum dose 12 g/day	Intravenous
Meropenem	120 mg/kg/day in divided doses administered every 6 h to 8 h Maximum dose 6 g/day	Intravenous

Therapy modifications after laboratory cultures or molecular diagnosis become available

When cultures and antimicrobial susceptibility data are available, therapy should be adjusted accordingly. As mentioned previously, a *S pneumoniae* isolate is considered to be susceptible to penicillin when the MIC is ≤ 0.06 $\mu\text{g/mL}$. However, an isolate is considered to be susceptible to cefotaxime or ceftriaxone if the MIC is ≤ 0.5 $\mu\text{g/mL}$, intermediate if the MIC is 1.0 $\mu\text{g/mL}$, and resistant if the MIC is ≥ 2.0 $\mu\text{g/mL}$.^[20] Van-

comycin is active against cefotaxime- or ceftriaxone-resistant strains. Treatment should be modified according to Table 1, depending on the results of the CSF culture and sensitivity. See Table 2 for dosage recommendations for antimicrobial agents. Other investigations

Generally, repeat CSF sampling is not required in the context of common pathogens, unless a child does not clinically improve with initial therapy. For meningitis due to GBS, some experts recommend documentation of CSF sterilization at 24

h to 48 h after initiation of therapy.^[37] Although not discussed in this statement, repeat CSF culture at 24 h to 48 h is recommended for meningitis caused by Gram-negative enteric pathogens (eg, *E coli*). CNS imaging is recommended when there is failure of sterilization of CSF, or if neurological symptoms or other specific complications develop during the course of treatment.

Duration of treatment

Treatment should always be with intravenous antimicrobials to achieve high CSF levels. The recommended length of treatment varies with the pathogen and the clinical course of infection. Recommended length of therapy for uncomplicated meningitis due to *S pneumoniae* is 10 to 14 days; due to Hib, seven to 10 days; and due to *N meningitidis*, five to seven days. Recommended therapy for GBS meningitis is 14 to 21 days and may depend on whether cerebritis is present. Routine formal audiology assessment before discharge or within one month of discharge is recommended for all children with a diagnosis of bacterial meningitis.

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