Therapy of suspected bacterial meningitis in Canadian children six weeks of age and older

Infectious Diseases and Immunization Committee, Canadian Paediatric Society (CPS)

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The present statement reviews recent developments in the epidemiology and makes recommendations for the treatment of suspected bacterial meningitis in Canadian children six weeks of age and older and replaces the 2001 Canadian Paediatric Society statement on this subject (1). Earlier recommendations for mono antibiotic therapy for empirical treatment of suspected bacterial meningitis in children have changed (2,3). The current recommended empirical treatment of bacterial meningitis in infants six weeks of age and older are for a combination of vancomycin and a third-generation cephalosporin. This combination of antibiotics is effective against the three major pathogens that cause meningitis in this age group: *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis*. However, the epidemiology of bacterial meningitis in Canada and the United States continues to change. Thus paediatricians should report cases of bacterial meningitis to public health authorities to assist in ongoing surveillance and the management of contacts within the community. The levels of evidence used in this statement are taken from the Canadian Task Force on Preventive Health.

CURRENT EPIDEMIOLOGY AND SUSCEPTIBILITY OF CAUSATIVE ORGANISMS

Cases of meningitis caused by Hib have declined steadily in Canada and the United States since 1988 after the introduction of Hib conjugate vaccines for use in children 18 months of age (4). There was a further decline in cases after the vaccines were approved in 1991/92 for use during infancy (4). In 1985 (during the prevaccine era), 485 cases of invasive Hib cases were reported in Canada, while only 2 to 5 cases were reported each year from 2001 to 2006 in the 12 Canadian paediatric tertiary care centres that participate in the Immunization Monitoring Program, Active (IMPACT) surveillance network (5-7). Thus, since 2000, bacterial meningitis in Canada has been mostly caused by *S pneumoniae* and *N meningitidis*, with few cases caused by Hib in children one month of age and older.

According to guidelines of the United States-based National Committee for Clinical Laboratory Standards, strains of *S pneumoniae* that have minimum inhibitory concentrations (MICs) to penicillin of 0.06 µg/ml or less are considered to be susceptible; strains with a MIC of 0.1 to 1 µg/ml are considered to have intermediate- level resistance and strains with a MIC of 2 µg/ml or more are considered to be resistant (8). Strains of *S pneumoniae* with intermediate-level resistance and strains that are resistant are usually

considered to have 'reduced susceptibility' to penicillin (8). The rates of resistance of *S pneumoniae* to penicillin and other antibiotics increased in the United States and Canada from 1990 to 2003. In the United States, up to 40% of isolates of pneumococcus from sterile body sites in some geographic areas are now penicillin-resistant, with up to one-half of the resistant isolates having high-level resistance (9). In Canada, the 12 paediatric centres participating in the IMPACT surveillance system have monitored penicillin-resistance of *S pneumoniae* strains isolated from sterile sites since 1991. The rate of penicillin-resistance among these strains gradually increased over time: 2.5% in 1991, 4% in 1992/93, 7% in 1994 -1996, 11.6% in 1997 and 13% in 1998. In the most recently reported period (1998 - 2003), penicillin non-susceptibility rate has been stable at 16%. The rate of resistance to cefotaxime/ceftriaxone was 5% and limited to penicillin-resistant isolates (10). Serotypes found in the conjugate pneumococcal vaccine (PCV7) accounted for 89% of penicillin-resistant isolates.

MIC of an organism to penicillin and third-generation cephalosporins and other data such as tissue penetration should be used by clinicians to guide appropriate treatment. For example, intermediate-level resistant strains of *S pneumoniae* can be treated with beta-lactam antibiotics if the infection is at a body site where the antibiotic is able to penetrate and reach concentrations substantially above the MIC (11). Meningitis caused by *S pneumoniae* with intermediate- or high-level resistance to penicillin and third-generation cephalosporins should not be treated with these agents because bactericidal concentrations of the drug in the cerebrospinal fluid (CSF) may not be attained (11).

MANAGEMENT OF RESISTANT *S PNEUMONIAE* MENINGITIS

Case reports of treatment failures using a third-generation cephalosporins (eg, cefotaxime or ceftriaxone) at appropriate doses to treat meningitis caused by cephalosporin-resistant *S pneumoniae* have been published (12,13). The failure of treatment in these cases was manifest by the delayed sterilization of CSF; the persistence of fever, irritability and lethargy; or the development of complications such as seizures and neurological deficits. These patients eventually responded to therapy after the addition of vancomycin or a change in therapy to vancomycin plus one other antibiotic (eg, rifampin or chloramphenicol). Although successful treatment of bacterial meningitis caused by intermediately cephalosporin-resistant bacteria has been reported in children, with cefotaxime at 200 to 225 mg/kg/day (14) and in adults at even higher doses (15), data in children suggest that even high dosage cefotaxime may not be sufficient to achieve bactericidal activity in the CSF for intermediate- and high-level cephalosporin-resistant pneumococcus (16). Therefore, at the present time, monotherapy with third-generation cephalosporin agents as empirical treatment for penicillin- or cephalosporin-resistant pneumococcus cannot be recommended.

Empirical therapy of meningitis should be based on knowledge of local resistance patterns. Chloramphenicol monotherapy (17) has been used in the past for penicillin- or cephalosporin-resistant pneumococcus, but treatment failures with chloramphenicol have occurred, and this therapy is no longer recommended (18,19). Pneumococcal strains that are resistant to penicillin and cephalosporins remain susceptible to vancomycin (20). Rifampin is also highly effective against most penicillin-resistant pneumococcus, but it is inadequate as monotherapy because of the rapid development of resistance when it is used alone (21).

DUAL THERAPY WITH VANCOMYCIN AND THIRD-GENERATION CEPHALOSPORINS

Currently, dual therapy using high dose vancomycin (60 mg/kg/day) and either a third-generation cephalosporin (cefotaxime or ceftriaxone) or rifampin has been proposed as the optimal empirical treatment for suspected pneumococcal meningitis until antibiotic susceptibilities are known (2, 20). In an experimental model of meningitis, the combination of vancomycin and ceftriaxone was shown to be synergistic, while vancomycin plus rifampin, and ceftriaxone plus rifampin showed no synergy when given in combination against penicillin- and cephalosporin-resistant pneumococcus (22, 23). Furthermore, when the combination of vancomycin plus ceftriaxone or rifampin plus ceftriaxone was used, there was significantly enhanced CSF bactericidal activity compared with the use of ceftriaxone alone against the resistant strains in these children (24). Thus, even though there is no obvious synergy between various antibiotics in vitro (22, 23), combinations of antibiotics appear to improve bactericidal effects in vivo (24). Experts recommend a dosage of cefotaxime for empirical use of 300 mg/kg/day (derived from experience in children who failed therapy with a cefotaxime dosage of 200 mg/kg/day) (2). The dosage recommended for ceftriaxone is 100 mg/kg/day; an additional dose of 100 mg/kg is recommended at 12 h on the first day because this achieves CSF concentrations that are six- to10-fold above the MIC of cephalosporin-resistant pneumococcus during the first 24 h (2).

CURRENT EVIDENCE ON THE ROLE OF DEXAMETHASONE

Dexamethasone reduces the inflammatory response and has been recommended in Canada (25) and the United States (9, 26) as adjunctive therapy to reduce the complications of meningitis caused by Hib and *S pneumoniae*. Although, dexamethasone reduces the penetration of antibiotics, especially vancomycin and ceftriaxone, into the CSF, its use was not associated with a delay in the sterilization of CSF cultures (23).

These double-blind, placebo controlled trials of dexamethasone therapy in meningitis were performed before the advent of penicillin- and cephalosporin-resistant pneumococcus (27,28). In a survey of paediatric infectious diseases specialists and microbiologists in Canada conducted in 1999, about one-half of respondents recommended the use of dexamethasone for Hib meningitis, and only one-third of respondents recommended it for pneumococcal meningitis. Those who did not recommend dexamethasone use for either pathogen cited the theoretical concern about the reduced penetration of antibiotics into the CSF as a major reason for not recommending dexamethasone (29).

A recent review published in the Cochrane Library (30) has shed more reassuring light on the controversy. In the review eligible published and non-published RCTs on corticosteroids as adjuvant therapy in acute bacterial meningitis for all ages over 6 weeks of age, were included. Eighteen studies involving 2750 people met criteria for inclusion. Overall, adjuvant corticosteroids were associated with lower case fatality (relative risk (RR) 0.83, 95% Confidence Interval (CI) 0.71 to 0.99), lower rates of severe hearing loss (RR 0.65, 95% CI 0.47 to 0.91) and lower rates of long-term neurological sequelae (RR 0.67, 95% CI 0.45 to 1.00). In children, corticosteroids reduced severe hearing loss (RR 0.61, 95% CI 0.44 to 0.86). Subgroup analysis of adult and childhood cases showed that corticosteroids reduced mortality in patients with meningitis due to *S pneumoniae* (RR 0.59, 95% CI 0.45 to 0.77) and reduced severe hearing loss in children with meningitis due to *H influenzae* (RR 0.37, 95% CI 0.20 to 0.68); subgroup analysis for patients with meningococcal meningitis showed a favourable, though nonsignificant, trend in mortality (RR 0.71, 95% CI 0.31 to 1.62). Sub analyses for high-income and low-income countries of the effect of corticosteroids on mortality showed RRs of 0.83 (95% CI 0.52 to 1.05) and 0.87 (95% CI 0.72 to 1.05), respectively. Corticosteroids were protective against short-term neurological sequelae in patients with bacterial meningitis high-income countries (RR 0.56, 95% CI 0.3 to 0.84). For children with bacterial meningitis admitted in high-income countries, corticosteroids showed a protective effect on severe hearing loss (RR 0.61, 95% CI 0.41 to 0.90) and favourable point estimates for severe hearing loss associated with non-*H influenzae* meningitis (RR 0.51, 95% CI 0.23 to 1.13) and short-term neurological sequelae (RR 0.72, 95% CI 0.39 to 1.33). Overall, adverse events were not increased significantly with corticosteroids. The authors' concluded that corticosteroids significantly reduced rates of mortality, severe hearing loss and neurological sequelae. The data support the use of adjunctive corticosteroids in children in high-income countries like Canada.

MANAGING OTHER PATHOGENS OF MENINGITIS

N meningitidis with reduced susceptibility to penicillin has been reported in Saskatchewan, but the clinical significance of this is unknown (32). These strains remain susceptible to third-generation cephalosporins and rifampin (32). Meningitis caused by these strains of meningococcus can still be treated with high-dose penicillin (33).

Third-generation cephalosporins continue to be effective against Hib, and may be used for the empirical therapy of suspected Hib meningitis (25). Ampicillin monotherapy is not recommended for the empirical therapy of Hib meningitis because about 10% to 40% of Hib strains produce beta-lactamase and are, therefore, resistant to ampicillin (34).

RECOMMENDATIONS FOR LABORATORY DIAGNOSIS AND MANAGEMENT

In the work-up of a suspected case of bacterial meningitis, a blood culture should be collected and a lumbar puncture should be performed to obtain CSF for a Gram stain and a culture to determine the cause of infection. The Gram stain, if it is examined by an experienced reader, may help point to the bacterial species involved. However, therapy should not be based on the results of the Gram stain alone. Previous oral antibiotic use can reduce the yield in finding the etiological bacterial agent in both the CSF Gram stain and culture (35,36). Table 1 summarizes suggested empirical antibiotics and appropriate doses. Once the responsible organism is subsequently identified from blood or CSF and the antibiotic susceptibilities are known, the most appropriate antibiotic treatment may be selected to complete the full course of therapy, see Table 2. If the responsible organism is not isolated on culture, then the antibiotic treatment chosen for empirical therapy may be used to complete the course of therapy.

Table 1: Recommended empirical antibiotics for suspected bacterial meningitis*

Vancomycin 60 mg/kg/day given intravenously divided every 6 h (aiming for a peak serum vancomycin level of 30 to 40 mg/L and a trough level of 5 to 10 mg/L daily adult dose, 2 - 4 grams)
plus either
cefotaxime 300 mg/kg/day given intravenously divided every 6 to 8 h

(daily adult dose, 8-10 grams)
or
ceftriaxone 100 mg/kg intravenously divided in two doses in the first 24 h and then 100 mg/kg every 24 h (daily adult dose, 4 grams)
**For patients who cannot be given either vancomycin or a third-generation cephalosporin due to a contraindication (eg, allergies), expert infectious diseases opinion should be sought. In all patients, treatment should continue until susceptibility results return. If early cultures indicate a Gram-negative organism, vancomycin may be dropped and an aminoglycoside added. If Listeria monocytogenes is suspected because of age (under 3 months of age) or an outbreak setting, IV Ampicillin should be added.*

A repeat lumbar puncture to determine the effectiveness of treatment (eg, sterilization of CSF) within 24 to 36 h of starting empirical antibiotic therapy may be indicated for the following patients: patients who fail to improve clinically within that time period; immunocompromised patients in whom the success of antibiotic therapy for bacterial meningitis cannot be assured; patients with meningitis that is caused by a penicillin- or cephalosporin-resistant pneumococcus in situations in which the eradication of bacteria from the CSF may be delayed; and patients with meningitis caused by Gram-negative enteric bacilli (2,9). Patients who are receiving dexamethasone may appear to be improving, despite delayed CSF sterilization. Patients with positive CSF cultures in the second CSF sample may require the addition or alteration of antibiotics for successful treatment. Consequently, consultation with an infectious diseases specialist is strongly recommended.

Table 2: Antibiotics that may be used to complete therapy for bacterial meningitis once antibiotic susceptibility testing is available

Etiological agent and antibiotic susceptibility	**Antibiotics that can be used to complete therapy**	**Recommended total duration of therapy for uncomplicated meningitis***
Streptococcus pneumoniae		
Fully susceptible to penicillin or third-generation cephalosporins (MIC<0.1 µg/ml)	Penicillin G 250,000- 400,000 U/kg/day divided in 4 to 6 doses (maximum adult dose 24,000,000 U/24 h. ***or*** cefotaxime (doses as specified in Table 1)† ***or*** ceftriaxone (doses as specified in Table 1)†	10 days
Intermediate- (0.12 to1.0 µg/ml), resistant- (1.0 to 2.0 µg /ml) or high-level resistance (> 2.0 µg/ml) to penicillin or third-generation cephalosporins (MIC >2.0 µg/ml):	Intravenous vancomycin 60 mg/kg/day divided every 6 hours (aiming for a peak serum vancomycin level of 30 to 40 mg/L and a trough level of 5 to 10 mg/L) ***plus either*** cefotaxime ***or*** ceftriaxone (doses as specified in Table 1)†	10 to 14 days

Neisseria meningitidis		
	Penicillin G 250,000 to 400,000 U/kg/day divided in 4 to 6 doses (daily adult dose 24,000,000 U)	5 to 7 days
***Haemophilus influenzae* type b**		
Beta-lactamase negative	Ampicillin 300-400 mg/kg/day divided in 4 doses (daily adult dose, 6-12 grams)	10 days
Beta-lactamase positive	cefotaxime (doses as specified in Table 1) ***or*** ceftriaxone (doses as specified in Table 1)	10 days
Group B streptococcus (May cause bacterial meningitis in infants up to 3 months of age)		
	Penicillin G 400,000 U/kg/day divided in 4 doses	14 to 21 days
	or ampicillin 300 - 400 mg/kg/day divided in 4 doses	14 to 21 days
	plus gentamicin 7.5 mg/kg/day divided every 8 hours	first 7 days
Enteric Gram-negative organism (May cause bacterial meningitis in infants up to 3 months of age)		
	Either of cefotaxime 200-300 mg/kg/day divided in 3 or 4 doses ***or*** ceftriaxone (doses as specified in Table 1)† **plus** gentamicin 7.5 mg/kg/day divided every 8 hours	21 days after sterilization of CSF
Culture is negative but bacterial etiology is suspected or cannot be ruled out (Note that antigen detection testing of cerebrospinal fluid for pneumococcus, meningococcus and *H influenzae* type b is not considered sensitive or specific enough to be helpful in these situations)	Cefotaxime 200 mg/kg/day divided in 3 to 4 doses ***or*** ceftriaxone (doses as specified in Table 1)† ***with or without*** vancomycin (depending on the clinical level of suspicion) 60 mg/kg/day intravenously divided every 6 hours (aiming for a peak serum vancomycin level of 30 to 40 mg/L and a trough level of 5 to 10 mg/L)	7 to 10 days
**Minimum durations for uncomplicated meningitis; †Expert opinion from an infectious diseases specialist regarding the need for*		

an alternative antibiotic should be sought if a patient has any contraindication to cefotaxime or ceftriaxone. MIC Minimum inhibitory concentration

RECOMMENDATIONS

- The current recommended empirical treatment of bacterial meningitis in infants six weeks of age and older consists of a combination of vancomycin and a third-generation cephalosporin (Table 1). *(Category of recommendation: A-II)*.
- Definitive therapy and the duration of therapy should be guided by susceptibility results of the organism identified (Table 2) *(Category of recommendation: A-II)*.
- Dexamethasone can be used as adjunctive treatment for suspected bacterial meningitis. *(Category of recommendation: A-I)*. The evidence for benefit of its use is strongest in cases with *H influenzae type b* strains in children *(Category of recommendation: A-I)*. It has also been shown to be beneficial for other bacterial causes in children and in adults especially when administered before the first dose of antibiotic. Dexamethasone has been well tolerated when used in the recommended dose and duration. Because the causative organism is usually not known initially, a decision must often be made before all laboratory results are available. If used, the dose of dexamethasone given should be 0.6 mg/kg/day in four divided doses or 0.8 mg/kg/day in two divided doses for two to four days. It should be given only to children with suspected bacterial meningitis older than six weeks of age, and before or within 1 hour of antibiotic administration.
- A repeat lumbar puncture to determine the effectiveness of treatment (eg, sterilization of CSF) within 24 to 36 h of starting empirical antibiotic therapy may be considered for the following patients: patients who fail to improve clinically within that time period; immunocompromised patients in whom the success of antibiotic therapy for bacterial meningitis cannot be assured; patients with meningitis that is caused by a penicillin- or cephalosporin-resistant pneumococcus, in whom the eradication of bacteria from the CSF can not be assured; patients with meningitis caused by Gram-negative enteric bacilli. *(Category of recommendation: B-III)*.

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