CANADIAN PAEDIATRIC SOCIETY STATEMENT

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

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. In the early 1990s, monotherapy with third-generation cephalosporins, such as cefotaxime and ceftriaxone, was a recommended option for the empirical antibiotic treatment of suspected bacterial meningitis in children one month of age and older (1,2). The third-generation cephalosporins were effective against the three major pathogens that caused 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 has changed.

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 (3). There was a further decline in cases after the vaccines were approved in 1991/92 for use during infancy (3). In 1985 (during the prevaccine era), 485 cases of invasive Hib cases were reported in Canada, while only eight cases were reported each year from 1996 to 1997 in 11 of the current 12 Canadian paediatric tertiary care centres that participate in the Immunization Monitoring Program, Active (IMPACT) surveillance network (4-6). Thus, in the late 1990s, bacterial meningitis in Canada was mostly caused by *S pneumoniae* and *N meningitidis*, with a 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 mg/L or less are considered to be susceptible; strains with a MIC of 0.1 to 1 mg/L are considered to have intermediate-level resistance and strains with a MIC of 2 mg/L or more are considered to be resistant (7). Strains of *S pneumoniae* with intermediate-level resistance and strains that are resistant are usually considered to have 'reduced susceptibility' to penicillin (7). Approximately 50% of penicillin-resistant strains of *S pneumoniae* are also resistant to cefotaxime and ceftriaxone; strains with a MIC of 0.5 to 1.0 mg/L to either cephalosporin are defined as having intermediate-level resistance, and strains with a MIC of 2.0 mg/L or more are considered to have high-level resistance (8). The rates of resistance of *S pneumoniae* to penicillin and other antibiotics are increasing in the United States and Canada. 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 (8). In Canada, by December 31, 1998, the 11 paediatric centres participating in the IMPACT surveillance system had screened more than 1800 strains of *S pneumoniae* that were cultured from sterile body sites, and determined that the rate of penicillin-resistance among these strains was gradually increasing over time: 2.5% in 1991, 4% in 1992/93, 7% in 1994 to 1996, 11.6% in 1997 and 13% in 1998 (D Scheifele, personal communication). Intermediate-level penicillin resistance

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) *plus either*

- cefotaxime 300 mg/kg/day given intravenously divided every 6 h

or

- ceftriaxone 100 mg/kg intravenously at diagnosis; repeat the dose of 100 mg/kg at 12 h and 24 h, and then 100 mg/kg every 24 h

**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*

predominated in each study period, but in 1998, one-third of the 13% (4.4%) of the penicillin-resistant isolates were highly resistant. All IMPACT centres, except two, had found high-level, penicillin-resistant isolates. Of particular interest, 26 of 295 (8.8%) isolates associated with meningitis demonstrated penicillin-resistance, with 1.1% of the isolates revealing high-level resistance (D Scheifele, personal communication). The MIC of an organism to penicillin and third-generation cephalosporins should be used, along with other data such as tissue penetration, by clinicians as a guide to determine 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 (9). 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 (9).

MANAGEMENT OF RESISTANT *S PNEUMONIAE* MENINGITIS

Case reports of treatment failures using previously recommended 'meningitic' doses of third-generation cephalosporins (eg, 200 to 225 mg/kg/day of cefotaxime and 100 mg/kg/day of ceftriaxone) in meningitis caused by cephalosporin-resistant *S pneumoniae* have been published (10-12). 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). The successful treatment of bacterial meningitis with cefotaxime at doses of 200 to 225 mg/kg/day in children has also been reported, especially those cases involving intermediate-level cephalosporin resistance (ie, with MICs between 0.5 to 2.0 mg/L) (13). A higher dose of cefotaxime (300 mg/kg/day) has been used successfully to treat adult patients with cephalosporin-resistant pneumococcal meningitis (14). However, data in children suggest that even this high dose of cefotaxime may not be sufficient to achieve bactericidal activity in the CSF for intermediate-level and high-level cephalosporin-resistant pneumococcus (15). 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 (16) 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 (17,18). Currently, pneumococcal strains that are resistant to penicillin and cephalosporins are susceptible to vancomycin (19). 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 (20).

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 (1,19). 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 were indifferent (showed no synergy) when given in combination against penicillin- and cephalosporin-resistant pneumococcus (21,22). 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 (23). Thus, even though there is no obvious synergy between various antibiotics in vitro (21,22), combinations of antibiotics appear to improve bactericidal effects in vivo (23). 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) (1). 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- to 10-fold above the MIC of cephalosporin-resistant pneumococcus during the first 24 h (1).

The use of dexamethasone as an adjunctive therapy to help reduce the complications of meningitis caused by

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 mg/L)	Penicillin G 250,000 U/kg/day divided every 4 to 6 h *or* cefotaxime 200 mg/kg/day divided every 6 to 8 h *or* ceftriaxone 100 mg/kg/day divided every 24 h	7 to 14 days
Intermediate- or high-level resistance to penicillin or third-generation cephalosporins (MIC≥0.1 mg/L)	Intravenous vancomycin 60 mg/kg/day 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) *plus either* cefotaxime *or* ceftriaxone (doses as specified in Table 1)†	7 to 14 days
Neisseria meningitidis	Penicillin G 250,000 U/kg/day divided every 4 to 6 h	5 to 7 days
Haemophilus influenzae type b		
Beta-lactamase negative	Ampicillin 300 mg/kg/day divided every 6 h	7 to 10 days
Beta-lactamase positive	Cefotaxime 200 mg/kg/day divided every 6 to 8 h *or* ceftriaxone 100 mg/kg/day divided every 24 h	7 to 10 days
Group B streptococcus (May cause bacterial meningitis in infants up to 3 months of age)	Penicillin G 450,000 U/kg/day divided every 6 h *or* ampicillin 300 mg/kg/day divided every 6 h *plus* gentamicin 7.5 mg/kg/day divided every 8 h for first week	14 to 21 days
Enteric Gram-negative organism (May cause bacterial meningitis in infants up to 3 months of age)	*Either of* cefotaxime 200 mg/kg/day divided every 6 to 8 h *or* ceftriaxone 100 mg/kg/day divided every 24 h *plus* gentamicin 7.5 mg/kg/day divided every 8 h	21 days
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 every 6 to 8 h *or* ceftriaxone 100 mg/kg/day divided every 24 h *with or without* vancomycin (depending on the clinical level of suspicion) 60 mg/kg/day 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)	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*

Hib and *S pneumoniae* has been recommended in Canada (24) and the United States (8,25). Dexamethasone has the effect of reducing the inflammatory response in the CSF in bacterial meningitis, but it also reduces the penetration of antibiotics, especially vancomycin and ceftriaxone, into the CSF (23,26).

CURRENT EVIDENCE ON THE ROLE OF DEXAMETHASONE

Double-blind, placebo controlled trials of dexamethasone therapy in meningitis were performed before the advent of penicillin- and cephalosporin-resistant pneumococcus (27, 28). Dexamethasone use in those earlier studies was not associated with a delay in the sterilization of CSF cultures. However, further information is needed to determine whether dexamethasone use can lead to the delayed sterilization of CSF and poorer outcomes in meningitis caused by penicillin- and/or cephalosporin-resistant pneumococcus. Because most of the patients enrolled in studies of dexamethasone had Hib meningitis, the best evidence showing the reduction of complications (primarily hearing loss) pertains to this organism. There is only fair to moderate evidence for dexamethasone use in reducing the risk of hearing loss in meningitis due to *S pneumoniae*, and no evidence to support dexamethasone use for the other causes of meningitis (29). 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 (29). The first dose of dexamethasone should be given before the first dose of antibiotics or within 1 h of the first dose of antibiotics for maximum benefit. In a 1999 survey of paediatric infectious diseases specialists and microbiologists in Canada, about one-half of respondents recommended the use of dexamethasone for Hib meningitis, and only one-third of respondents recommended it for pneumococcal meningitis (B Tan, personal communication). Those respondents who did not recommend dexamethasone use for either pathogen cited the theoretical concern about the reduced penetration of antibiotics (especially vancomycin) into the CSF as a major reason for not recommending dexamethasone.

TABLE 3: Rating system for strength of recommendation and quality of evidence supporting the recommendation

Categories for the strength of each recommendation

Category	Definition
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

Categories for the quality of evidence on which recommendations are made

Stage	Definition
I	Evidence obtained from at least one properly randomized controlled trial
II	Evidence from at least one well designed, clinical trial without randomization, from cohort or case-controlled analytic studies preferably from more than one centre, from multiple time series or from dramatic results in uncontrolled experiments
III	Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies or reports of expert committees

Data from reference 37

MANAGING OTHER PATHOGENS OF MENINGITIS

N meningitidis with reduced susceptibility to penicillin has been reported in the prairie region of Canada, but the clinical significance of its reduced susceptibility is currently unknown (30). These strains of *N meningitidis* remain fully susceptible to third-generation cephalosporins and rifampin (31). Meningitis caused by these strains of meningococcus can still be treated with high-dose penicillin (32).

Third-generation cephalosporins continue to be effective against Hib, and may be used for the empirical therapy of suspected Hib meningitis (24). 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 (24).

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 (34,35). 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 (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.

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; patients with meningitis caused by Gram-negative enteric bacilli, and patients who are receiving dexamethasone (1,36). Patients who are receiving dexamethasone may erroneously 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.

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,* see Table 3 for descriptions).
- Definitive therapy and the duration of therapy should be guided by susceptibility results of the organism identified (Table 2) *(Category of recommendation: A-II)*.
- No recommendation for the routine use of dexamethasone for suspected bacterial meningitis can be made at this time because of the near eradication of *H influenzae (Category of recommendation: A-1).* The evidence is moderate for susceptible *S pneumoniae* strains *(Category of recommendation: B-1I)*. For all other diagnoses, the evidence is poor *(Category of recommendation: C-II)*. If the decision is made to give dexamethasone, it should be given only to children older than six weeks of age, and before or within 1 h of antibiotic

administration. Because, in most cases, the causative organism is not known and the initial dose of steroids is only effective for *S pneumoniae* if given before the first dose of antibiotics, the recommendation for the overall use of steroids is controversial *(Category of recommendation: C-III)*.

- 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 situations in which the eradication of bacteria from the CSF may be delayed; patients with meningitis caused by Gram-negative enteric bacilli; and patients who are receiving dexamethasone *(Category of recommendation: B-III)*.

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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