CANADIAN PAEDIATRIC SOCIETY STATEMENT

ID 98-05

Invasive group A streptococcal infections

Since the mid-1980s, there have been reports from around the world of an increase in the incidence of severe invasive group A streptococcal (*Streptococcus pyogenes*) infections, and associated morbidity and mortality (1-3). Furthermore, there is increasing recognition of a syndrome, designated streptococcal toxic shock syndrome (STSS), in which patients develop rapidly progressive hypotension and multiorgan failure (1,4,5). The news media have been especially fascinated with and have dramatized this illness, with reports of 'flesh-eating disease' or 'flesh-eating virus' dominating the headlines of numerous newspapers, magazines, radio and television reports. The purpose of this brief review is to comment on the current state of knowledge and management of invasive group A streptococcus disease in children and close contacts of persons with invasive group A streptococcus disease.

Invasive group A streptococcus disease refers to illness associated with the isolation of group A streptococcus from a normally sterile site such as blood, cerebrospinal fluid or pleural fluid. The more serious STSS case definition consists of the isolation of group A streptococcus from a normally sterile site in association with hypotension and multisystem organ failure (Table 1) (5). The cause of the noted increase in invasive group A streptococcus infections is probably multifactorial, but the majority of the infections have been due to strains expressing M-protein types M-1 and M-3 and producing the pyrogenic exotoxins A or B, or both (2,4,6,7). There have been suggestions of a single clonal ancestry for many isolates of group A streptococci causing invasive disease (8). In a recent report of an outbreak in Minnesota during which seven cases of invasive streptococcal disease were identified, a single clone of group A streptococcus was shown to be responsible for all cases as well as for 25% of pharyngitis cases from which group A streptococcus was isolated (compared with 0% to 10% of isolates of pharyngitis from neighbouring schools in which there was no outbreak) (9). Furthermore, there was an increase in pharyngeal carriage rates of this clone among the outbreak community's school-aged children.

There are numerous case reports, case series and in the past few years population-based studies on invasive group A streptococcus disease involving children (3,4,6,7). Whereas it is recognized that invasive disease is most common at the extremes of age (younger than 10 years of age and older than 74 years of age), STSS and necrotizing fasciitis are most common in older individuals with underlying medical problems (7). In a prospective population-based study completed in Ontario during 1992 and 1993, cases of invasive diseases occurred at a rate of 1.5/100,000 population annually in the general population, but the incidence in children younger than 10 years was slightly greater at two/100,000 population (7). In contrast, children between 10 years and 19 years of age had rates less than 0.75/100,000 population. Whereas only 5% of invasive disease in children up to 14 years old was associated with the STSS, 17% of adults (45 to 74 years of age) and 29% of the elderly with invasive disease developed the syndrome. STSS accounted for only 6% of cases of invasive disease among persons younger than 10 years of age compared with 21% of those older than 60 years of age. The rate of STSS was also increased among those with underlying illness. Pneumonia was associated with a case-fatality rate of 33%, while necrotizing fasciitis was fatal in 45% of cases. The most common primary sites of infection in children are soft tissue (39%), upper respiratory (17%) and joints (11%). Compared with adults, children are more likely to have bacteremia without focus and upper respiratory tract infection, and are less likely to have pneumonia (10). In two population-based studies, the overall case fatality rate for invasive group A streptococcus disease was 15%, with case fatality rates for persons with STSS ranging from 44% in American

TABLE 1: Case definition for streptococcal toxic shock syndrome

Isolation of group A streptococcus (*Streptococcus pyogenes*) from a normally sterile site (eg, blood, cerebrospinal fluid, pleural fluid)*

and

Hypotension (fifth percentile of systolic blood pressure for children or less than 90 mmHg for adolescents)

and two or more of:

1. Renal impairment (creatinine greater than two times the upper limit for age)
2. Coagulopathy (platelets less than 100,000 $\times 10^6$ U/L or evidence of disseminated intravascular coagulopathy)
3. Liver involvement (alanine aminotransferase, aspartate aminotransferase or bilirubin greater than two times upper limit of normal)
4. Adult respiratory distress syndrome (pulmonary infiltrates and hypoxemia without heart failure or generalized edema)
5. Generalized erythematous rash that may desquamate
6. Soft tissue necrosis in the form of necrotizing fasciitis, myositis or gangrene

**If group A streptococcus is isolated from a nonsterile site (eg, throat, sputum, vagina) but the patient has hypotension and two of the other criteria 1 to 6 above, it is considered a probable case if no other etiology for the illness is found*

TABLE 2: Early diagnostic clues for severe invasive group A streptococcal infections*

Clinical

- Influenza-like symptoms such as fever, aches, pains and chills
- Severe pain
- Rapid breathing, signs of pleural effusion
- Secondary fever following varicella infection suggests invasive group A streptococcus disease

Laboratory

- Normal or elevated white blood cell count, with marked 'left shift' (high number of immature neutrophils)
- Prolonged prothrombin time and partial prothrombin time
- Low platelet count
- Low albumin
- Low calcium
- High creatinine phosphokinase (CPK)†
- Magnetic resonance imaging (MRI) (or computed tomography scan or ultrasound if MRI not available). This should not delay surgical consultation

**None of the signs and laboratory features are specific, and all the features noted in Table 1 can occur at any time. †CPK elevation may be a sign of early necrotizing fasciitis with muscle involvement (myositis), but fasciitis may still occur in the presence of a normal CPK if there is no muscle involvement*

surveillance to 65% in Canada (7,11). When necrotizing fasciitis occurs without STSS, the risk of death is similar to that of all patients with invasive group A streptococcal disease.

The clinical presentation of patients with invasive group A streptococcus disease is not very specific, and many patients may make multiple visits to the health care system before being diagnosed. Skin or soft tissue infections account for 48% of presentations, bacteremia with no septic focus for 14%, and pneumonia for 11% (7). In children, the respiratory tract is the most common disease focus. There may be a recent history of an upper respiratory tract infection or strep throat. Pleural effusions are particularly common as a manifestation of group A streptococcus pneumonia, and tend to organize rapidly into empyema. However, many children also present with soft tissue infections that quickly progress to necrotizing fasciitis. Because early fasciitis mostly involves the subcutaneous tissue and the overlying skin is often normal, an important clue to the diagnosis is excruciating pain not in keeping with the clinical findings. Another common finding on presentation (reflecting the entry point of the group A streptococcus) is local evidence of an abrasion, cut or contusion at a body site. Prominent symptoms at presentation may include fever, influenza-like symptoms, aches, pains and chills. There may be a scarlatiniform rash in up to 20% of patients. Children younger than 10 years of age with chickenpox have a 39-fold increase in risk of developing invasive group A streptococcus disease during the two weeks after the onset of skin lesions. Hospital-based series have identified between 6% and 16% of invasive group A streptococcal infections in children as associated with varicella (3,12). However, cases complicating chickenpox and other cases in children do not differ in the proportion of children with underlying illness or in case fatality (13). Other types of skin lesions including eczema also appear to increase risk of invasive disease, presumably because they provide a portal of entry for the bacteria. Hypotension can develop within 24 h or as late as four weeks after the precipitating event.

The laboratory features of severe invasive group A streptococcus disease are nonspecific (Tables 1,2). The association of a normal or elevated white blood cell count with a left shift in association with severe pain may be the only early clue to the diagnosis of necrotizing fasciitis. Patients suspected of having invasive group A streptococcus disease must be admitted to hospital and monitored very closely, preferably under the supervision of an expert in infectious diseases. Blood cultures, as well as cultures of other normally sterile sites that appear to be involved clinically must be obtained, and the child should be started on intravenous clindamycin 40 mg/kg divided into three or four doses a day and intravenous penicillin in high doses (250,000 to 400,000 units/kg/day divided into six doses). Clindamycin should be added because it has been shown in mouse models of group A streptococcus myositis to be more effective than penicillin in preventing death. However, it should not be used as monotherapy because of the potential for a small percentage of group A streptococcus isolates to be resistant. Antibiotics should be given for a full 10 days. There is also evidence from case reports and one stratified case-control study that normal immunoglobulin may be life saving in patients

meeting the case definition for STSS (14,15). Doses of 400 mg/kg up to 2 g/kg/day for one to five days have been used, but the most efficacious dosing and frequency of administration have not been determined. For patients with suspected necrotizing fasciitis, an early surgical consultation should be sought; the fascia may need to be incised for decompression and assessment of whether debridement is needed to save the affected area or the patient's life. Often, multiple debridements are needed. Although imaging with magnetic resonance induction and computed tomography scanning have been noted to be of value in diagnosing necrotizing fasciitis, surgical management should not be unduly delayed in favour of these.

The risk of secondary related invasive group A streptococcal disease in household members of patients with invasive disease is 2.9/1000, a rate almost 200 times that of the general population. This risk of disease among close contacts and the overall case fatality rate of invasive group A streptococcus disease of 15% are similar to those for sporadic meningococcal infections. For this reason, it is currently recommended by most public health authorities in Canada that close household contacts (Table 3) of persons with severe invasive disease should receive chemoprophylaxis. The ideal chemoprophylactic regimen has not been determined, but monotherapy with rifampin, the usual chemotherapeutic agent for meningococcemia and *Haemophilus influenzae* disease is poor at eradicating group A streptococcus carriage (16). Most authorities in Canada recommend prophylaxis with drugs such as penicillin, amoxicillin, first generation cephalosporins, clindamycin or erythromycin for 10 days. However, definitive studies of chemoprophylaxis remain to be done. There is no role for doing throat cultures to determine if the contacts require chemoprophylaxis because a negative culture does not negate the indication for chemoprophylaxis.

TABLE 3: Definition of close household contact

- More than 4 h a day or
- 20 hours a week of contact or
- Sharing sleeping arrangements or
- Having direct mucous membranes contact with oral or nasal secretions within seven days of illness of index patient

Nonsteroidal anti-inflammatory drugs (NSAIDS) have been implicated as possibly provoking the onset of necrotizing fasciitis. Whether this reflects a real increased risk with NSAIDS or reflects the likelihood that patients with severe pain who are more likely to receive NSAIDS are also more likely to have subclinical necrotizing fasciitis remains to be determined. In the meantime, caution is suggested in the use of this class of medications in patients presenting with undiagnosed severe pain where necrotizing fasciitis is a part of the differential diagnosis.

In summary, invasive group A streptococcus infections appear to be on the increase (17). Early diagnosis requires awareness of the presenting features and a high index of suspicion. Chemoprophylaxis should be given in cases of STSS and necrotizing fasciitis, and the recommendations of local public health departments in the area of residence of the practitioner involved should be sought.

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Consultants: *Drs Noni MacDonald, Division of Infectious Diseases, Children's Hospital of Eastern Ontario, Ottawa, Ontario; Victor Marchessault, Cumberland, Ontario*

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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.