Time to reconsider routine high-dose amoxicillin for community-acquired pneumonia in all Canadian children

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Community-acquired pneumonia (CAP) is one of the most common reasons for hospitalization in otherwise healthy Canadian children. The introduction of effective vaccinations, such as the pneumococcal conjugate vaccines, to the routine immunization schedule, has led to decreased rates of illness and, possibly, changes in the epidemiology of CAP in Canada. Unfortunately, in many children diagnosed with pneumonia, no causative agent can be isolated and up to date local data regarding the most common causes of pneumonia are difficult to obtain. The 2011 national guideline from the Canadian Paediatric Society (CPS) (1) and international guideline from the Infectious Diseases Society of America (2) recommend high-dose amoxicillin as the first-line treatment for otherwise healthy children with CAP who can be treated with oral antibiotics (1,2). This recommendation was initiated before the widespread introduction of the 13-valent pneumococcal conjugate vaccine to immunization schedules, when penicillin-resistant serotype 19A disease was a rising concern. We sought to determine the appropriateness of this recommendation in our setting based on our current local *Streptococcus pneumoniae* susceptibility patterns.

WHAT ARE THE MAJOR CAUSES OF CAP IN CHILDREN?

Data regarding the etiology of CAP in Canadian children, especially outpatients, are limited. Most data that are available are outdated and were collected before pneumococcal vaccines were introduced to the routine immunization schedule in Canada in the early 2000s. A recent, active, population-based surveillance study in the United States detected ≥1 viruses in 66% of children admitted to hospital with CAP, as well as ≥1 bacteria in 8% and both bacterial and viral pathogens in 7% (3). The most common causes of pneumonia in infants and preschool children are viruses (eg, respiratory syncytial virus, rhinovirus, human metapneumovirus, influenza) (3-8). With the exception of influenza, viruses are less likely to be the sole cause of pneumonia in older children (9).

Before the widespread use of pneumococcal conjugate vaccines, epidemiological studies cited *S pneumoniae* as the most commonly documented bacterial pathogen in children with CAP, with the organism isolated from 4% to 44% of all children examined (4-12). More recent studies suggest that the incidence of bacterial pneumonia is now lower, likely owing to the success of conjugate vaccines, and changes in laboratory sampling and diagnostic methods (3). Among bacteria, *S pneumoniae* was, and may still be, the most significant pathogen in children of all ages (1,3,10). Empirical oral antimicrobial therapy is selected to provide effective treatment for the bacterial pathogens most likely to cause CAP, with particular emphasis on *S pneumoniae*. If left untreated or treated inadequately, *S pneumoniae* may lead to serious sequelae including empyema, sepsis and, rarely, death (13).

WHAT DO CURRENT TREATMENT GUIDELINES FOR MILD TO MODERATE CAP IN CHILDREN RECOMMEND FOR EMPIRICAL THERAPY?

The 2011 CPS's practice point, "Pneumonia in healthy Canadian children and youth: Practice points for management" (1), recommends high-dose oral amoxicillin (75 mg/kg/day to 100 mg/kg/day divided three times per day) or intravenous ampicillin for most cases of nonsevere pneumonia. As described in the practice point, the primary goal is to offer good coverage for *S pneumoniae*. The most current CPS guideline indicates a dosage range of 40 mg/kg/day to 90 mg/kg/day and does not provide recommendations on when to use high dose (14).

The Infectious Diseases Society of America's guideline, "The management of community-acquired pneumonia in infants and children older than 3 months of age" (2), was published in July 2011. It recommends that high-dose amoxicillin (90 mg/kg/day divided two times per day) be used as first-line therapy for previously healthy, appropriately immunized infants and children with mild to moderate CAP suspected to be of bacterial origin.

WHAT IS THE EVIDENCE FOR THE USE OF EMPIRICAL HIGH-DOSE AMOXICILLIN IN CHILDREN WITH COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA?

Amoxicillin is the most common antibiotic prescribed by primary care providers in Canada (15). There are no randomized controlled trials examining clinical outcomes of high-dose versus standard-dose amoxicillin for treatment of CAP in Canada or the United States (16). The Infectious Diseases Society of America's recommendation for the routine use of high-dose amoxicillin is based on expert opinion due to concerns regarding the emergence of the antibiotic-resistant serotype 19A strain of *S pneumoniae* after the introduction of the 7-valent pneumococcal conjugate vaccine (this serotype was not covered by this vaccine). This recommendation has not been re-evaluated since the introduction of the 13-valent pneumococcal conjugate vaccine (which provides coverage for serotype 19A) into the routine immunization schedule in the United States and Canada.

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TABLE 1
***Streptococcus pneumoniae* susceptibility to amoxicillin from all paediatric and adult invasive and lower respiratory tract specimens in Calgary, Alberta from 2008 to 2014**

	Lower respiratory tract	Invasive	Total
Amoxicillin susceptible, MIC ≤2 µg/mL	509 (99.4)	717 (99.3)	1226 (99.4)
Amoxicillin intermediate, MIC 4 µg/mL	3 (0.6)	5 (0.7)	8 (0.6)
Amoxicillin resistant, MIC ≥8 µg/mL	0 (0)	0 (0)	0 (0)
Total, n	512	722	1234

Data presented as n (%) unless otherwise indicated. MIC Minimum inhibitory concentration

WHAT ARE THE SUSCEPTIBILITY PATTERNS OF *STREPTOCOCCUS PNEUMONIAE* IN CALGARY, ALBERTA?

Population-based surveillance of invasive and lower respiratory tract *S pneumoniae* infections has been conducted in the Calgary area since January 1, 1998, by the Calgary *Streptococcus pneumoniae* Epidemiology Research (CASPER) surveillance system (17). The surveillance system covers an estimated population of 1.3 million individuals. Susceptibility data for *S pneumoniae* isolates from all invasive and lower respiratory tract specimens collected from adults and children from January 1, 2008 to December 31, 2014 were reviewed. The most common lower respiratory tract specimens included endotracheal tube aspirates (46%), broncheoalveolar lavage (26%) and sputum samples (21%). The majority of invasive isolates (isolated from a normally sterile site) were found in blood (86%), with cerebrospinal fluid (4%) and pleural fluid (4%) the next most common sources. Amoxicillin susceptibility testing (E-test) was only performed on isolates with a penicillin minimum inhibitory concentration (MIC) >0.12 µg/mL. Isolates with penicillin MIC ≤0.12 µg/mL are susceptible to amoxicillin. Of note, the Clinical and Laboratory Standards Institute revised the penicillin breakpoints for *S pneumoniae* in 2008 because treatment with standard doses of penicillin were found to be effective for the treatment of noncentral nervous system infections.

Of 1234 isolates tested, only 8 (0.6%) were found to have intermediate resistance to amoxicillin and none were found to be resistant (Table 1).

CONCLUSIONS

Despite the recommendations in the 2011 national and international guidelines, review of our local *S pneumoniae* resistance rates suggest that high-dose amoxicillin is unnecessary for the treatment of mild to moderate CAP in most children in our area. Special consideration may need to be given to children with risk factors associated with resistant *S pneumoniae* (eg, antimicrobial use in the past three months, unimmunized or incompletely immunized, daycare attendance) who may be at higher risk for infection with resistant *S pneumoniae* serotypes.

Although amoxicillin is generally well tolerated among children, the unjustified use of higher doses (double the standard dose) leads to increased costs, side effects (eg, gastrointestinal symptoms) and total antibiotic exposure. Harmful effects on the patient's microbiome should be considered as well. Using the minimum appropriate duration of antibiotic treatment for mild to moderate pneumonia would further help to mitigate some of these effects. The 2011 guidelines suggest a duration of seven days is adequate in most cases (1,2).

These findings highlight the importance of incorporating local data, where available, into treatment guidelines, especially when local variations in susceptibility patterns may exist. Clinicians should be familiar with their local antibiograms and use this valuable resource when making decisions about antimicrobial prescribing. We encourage other communities across the country to review their local epidemiology and determine whether high-dose amoxicillin is truly required as first-line therapy in children with CAP in their setting.

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