Successful Shortening from Seven to Four Days of Parenteral Beta-Lactam Treatment for Common Childhood Infections: A Prospective and Randomized Study

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ABSTRACT

Objectives: To explore whether 4-day parenteral β-lactam therapy is as effective as 7-day therapy for children hospitalized for parenteral antimicrobials.

Methods: A series of patients aged 3 months to 15 years who fulfilled strict criteria for bacterial pneumonia, other respiratory infections, sepsis-like infections, and other acute infections were prospectively randomized to receive parenteral penicillin or cefuroxime randomly for 4 or 7 days. Besides blood and throat cultures, the etiology was searched by serology for 23 different agents.

Results: Of 154 children analyzed, a probable etiology was established in 96. Of those, a bacterial infection, with or without concomitant viral infection, was disclosed in 80% and 94% in the 4-day and 7-day treatment groups, respectively, pneumococcus being the commonest agent. There was one possible treatment failure in the 4-day group, but with a questionable relation to the short course. Three patients in the 4-day and two in the 7-day group underwent treatment changes, or were rehospitalized within 30 days. All children recovered entirely.

Conclusions: Shortening parenteral β-lactam treatment to 4 days in infections for which most parenteral antimicrobials are instituted, is not only safe, but reduces costs, is ecologically sound, and minimizes the risks of nosocomial infections and other adverse effects of treatment.

Key Words: antimicrobic, bacteremia, cefuroxime, penicillin, pneumonia, short treatment


Pneumonia, other acute lower respiratory infections, and various other bacteremic or nonbacteremic processes are the most common indications for hospitalization and administering a 7- to 10-day course of parenteral antimicrobials. Little is known about whether a treatment period of this length is needed. Curiously, even with the best laboratory and other facilities, most of these commonly seen patients are discharged without the etiology determined, in contrast to those with meningitis or osteoarticular or urinary tract infections. However, except for the latter infections, those diseases are rare. Among other undesirable effects, long treatments increase resistance problems; a good example is the reduced susceptibility of Streptococcus pneumoniae to penicillin, which is increasing at alarming rates in Europe and elsewhere.

In response to the urgent need for new therapeutic approaches, the authors established a prospective and randomized study focusing on children, who form the overwhelming majority of patients for whom parenteral antimicrobials are given. A β-lactam antimicrobial, procaine penicillin (50,000 IU/kg once daily intramuscularly) or cefuroxime (100 mg/kg per day in 3 divided doses intravenously), was always used, and the duration of medication was randomized to last 4 or 7 days. This degree of the treatment shortening was deemed justified on the basis of what is known of the short duration of treatment proven successful in lower urinary tract infections in adults and meningococcal meningitis.

PATIENTS AND METHODS

Patients and Inclusion Criteria

A total of 178 infants and children were enrolled prospectively from Helsinki University Central Hospital, Hospital for Children and Adolescents, and Aurora Hospital, Helsinki, Finland. To ensure that all common agents circulating periodically in the community were included,
According to the clinical presentation and the radiographic and laboratory findings, the patients were divided into four categories: pneumonia (acute respiratory symptoms and alveolar consolidation), sepsis-like infections (clinically ill enough to receive antimicrobial treatment), bacterial infections (clinically ill enough to receive antimicrobials but no respiratory symptoms, fever at least 38.5°C, and an initial CRP 100 mg/L), and other likely bacterial infections (clinically ill enough to receive antimicrobials but no respiratory symptoms, low fever, or only marginally increased CRP), cellulitis and lymphadenitis were examples in this category.

The exclusion criteria were the following: age less than 3 months or more than 15 years, immunocompromise, meningitis, osteoarticular or urinary tract infections, or a condition requiring surgery or intensive care.

Disease Manifestations and Treatment

According to the clinical presentation and the radiographic and laboratory findings, the patients were divided into four categories: pneumonia (acute respiratory symptoms and alveolar consolidation in chest radiograph), other respiratory infections (as for pneumonia, but without alveolar consolidation), sepsis-like infections (clinically ill but no respiratory symptoms, fever at least 38.5°C, and an initial CRP 100 mg/L), and other likely bacterial infections (clinically ill enough to receive antimicrobials but no respiratory symptoms, low fever, or only marginally increased CRP), cellulitis and lymphadenitis were examples in this category.

The randomization of medication for 4 days or 7 days was done by a computer-generated list kept at the University Hospital, to assign patients in the four groups. The randomization of medication for 4 days or 7 days was used to test potential differences between the means for testing category variables. The tests were two-sided, of continuous variables, and chi-squared tests were used for testing category variables. The tests were two-sided, and the level of significance was set at P < 0.05.

The primary endpoint for successful treatment was uneventful recovery (no change in the scheduled treatment). Sample size calculations showed that, with two treatment groups, a total of 142 patients would be required to detect a 20% difference in effectiveness at a level of P < 0.05 (two-sided test) with a power of 80%. Student's unpaired two-tailed t-test or analysis of variance (ANOVA) was used to test potential differences between the means of continuous variables, and chi-squared tests were used for testing category variables. The tests were two-sided, and the level of significance was set at P < 0.05.

RESULTS

In all, 178 patients were enrolled, of whom 24 (13%), 14 in the 4-day and 10 in the 7-day group, were excluded for...
the following reasons: 8 had an underlying disease,11 in 5 cases the scheduled antimicrobial was discontinued within 24 hours because the clinician was convinced of viral illness; 4 developed otitis and 2 streptococcal tonsillitis (which required prolonged treatment with another oral agent); 1 case was considered to be listeriosis, and in another case, opening of an intravenous line was not successful. Finally, parents withdrew two children from the study, and in one case the protocol was not followed for unknown reasons. Hence, 154 patients were analyzed; 73 (47%) were in the 4-day and 81 (53%) in the 7-day treatment groups. There were 86 males and 68 females.

Initial Characteristics

At presentation, the groups were comparable (Table 1). Slightly more irritable (33% vs 17%; P = 0.03) patients were randomized to the 4-day group.

The laboratory and radiographic indices used did not differentiate the groups. C-reactive protein levels exceeded 80 mg/L in 82% of children in the 4-day and in 78% of 7-day group. This strongly suggests that the majority of children had an invasive bacterial infection.9,10 A 50% increase within 8 to 12 hours was found in an additional 8% in the short- and 10% in the long-treatment group. The mean CRP values were 131 mg/L and 132 mg/L, and erythrocyte sedimentation rates 59 mm/h and 50 mm/h, respectively. Pneumonia was found in 48%, and 49% respectively. Pretreatment antimicrobials had been given in eight and seven cases, respectively.

Disease Manifestation and Microbiologic Etiology

Pneumonia (46%), other respiratory infections (15%), sepsis-like infections (25%), and other acute infections (14%) were diagnosed in the 4-day treatment group; in the 7-day group, the corresponding figures were 47%, 17%, 21%, and 15%. Overall, a probable etiology was established in 62% (45/73) of cases in the short- and 63% (51/81) in the long-treatment groups (Table 2).

Serologic findings established most etiologic diagnoses, since bacteriologic confirmation was achieved in only 10 cases, as is typical in the industrialized world.17,18 In eight cases, blood culture proved positive (6 yielded S. pneumoniae, 2 H. influenzae type b), whereas the throat culture identified two cases of group A streptococcal tonsillitis. Overall, evidence for bacterial infection, alone or with viruses, was obtained in 80% (36/45) and 94% (48/51) of the cases with the probable etiology disclosed in the short- and the long-treatment group, respectively. There were more mixed bacterial-viral infections in the 4-day group (22% vs 4%; P = 0.02).

Streptococcus pneumoniae was overwhelmingly the most common agent found, being identified in 25 and 34 cases in the 4-day and 7-day treatment groups, respectively. Adenoviruses were detected in six cases in which concomitant bacterial infections were unlikely. The distribution of the etiologic agents identified is summarized in Table 2.

### Table 1. Pretreatment Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>4-Day (n = 73)</th>
<th>7-Day (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Boys (n)</td>
<td>37</td>
<td>49</td>
</tr>
<tr>
<td>Girls (n)</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>3.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Previous antimicrobials (n)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely ill (n)</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Impaired consciousness (n)</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Irritability (n)</td>
<td>24*</td>
<td>14*</td>
</tr>
<tr>
<td>Temperature (mean)</td>
<td>39.1°C, 102.4°F</td>
<td>39.2°C, 102.6°F</td>
</tr>
<tr>
<td>Cough (n)</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Respiratory symptoms (n)</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Diarrhea (n)</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting (n)</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td><strong>Laboratory studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>131</td>
<td>132</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>59</td>
<td>50</td>
</tr>
<tr>
<td>White blood cell count (x 10^3/L)</td>
<td>21.6</td>
<td>22.4</td>
</tr>
<tr>
<td>Thrombocytes (x 10^5/L)</td>
<td>324</td>
<td>339</td>
</tr>
<tr>
<td>Pneumonia on chest x-ray (n)</td>
<td>34</td>
<td>36</td>
</tr>
</tbody>
</table>

*P < 0.05; * Chest radiograph obtained in 71 and 78 cases, respectively.
### Table 2. Microbial Etiology and Clinical Outcome of Patients

<table>
<thead>
<tr>
<th>Probable microbial etiology</th>
<th>4-Day (n = 73)</th>
<th>7-Day (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Percentage</td>
<td>Number</td>
</tr>
<tr>
<td>S. pneumoniae alone</td>
<td>15</td>
<td>33*</td>
</tr>
<tr>
<td>S. pneumoniae with any other agent</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Other bacteria, alone or in combinations</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Mixed bacterial-viral infections</td>
<td>10*</td>
<td>22</td>
</tr>
<tr>
<td>Etiology disclosed in all</td>
<td>45</td>
<td>62</td>
</tr>
</tbody>
</table>

**Clinical Outcome**

There was no difference in clinical outcome between the treatment groups (see Table 2). The course was completed parenterally as scheduled in 97% (71/73) of the 4-day and 62% (50/81) of the 7-day group; 38% of children in the latter group completed their medication orally because of the refusal of parents to have their children stay longer in hospital.

One potential treatment failure was found in the 4-day group (see Table 2), but was probably not in relation to the short treatment. A girl at the age of 4 years with bilateral pneumonia responded well to cefuroxime, but new respiratory symptoms and signs developed 2 days after discontinuation of medication. Procaine penicillin led to an uneventful recovery. Cultures proved negative on both occasions, but serology suggested a combined pneumococcal and HHV 6 infection. Concomitant viral infection makes it difficult to interpret whether the case was a true failure.

Sensitive *S. pneumoniae* (minimal inhibitory concentration [MIC] = 0.1 μg/mL) grew from the blood culture, and the patient responded well to a 7-day course of procaine penicillin. However, a new respiratory infection developed after cessation of treatment. Further blood cultures remained negative. Uneventful recovery followed treatment with cefuroxime. It is unlikely that pneumococcal pneumonia would not have been cured by a week-long treatment, such a case has probably never been documented. The authors deemed the relapse to be attributable to an unidentified secondary infection.

**Follow-up**

Two other children were readmitted within 1 month of discharge: an 18-month-old boy in the 4-day group developed diarrhea and was rehospitalized for rehydration, and a 6-year-old boy in the 7-day group developed pneumonia 4 weeks after discharge. In both instances, a causal relation to the primary infection was unlikely.

In all, 133 children (86%) attended the control visit 2 to 3 weeks following hospital discharge. In the majority, all symptoms and signs had subsided. Ten children, four in the short- and six in the long-treatment group, revisited the outpatient department spontaneously within 1 month after hospitalization. There was not any reason to suspect failure of earlier treatment. All patients returned home. The diagnoses were fever without focal signs (n = 5), acute otitis media (n = 2), nasopharyngitis (n = 1), obstructive bronchitis (n = 1), and gastroenteritis (n = 1). Another four children consulted a private physician within 30 days, two for acute otitis media, one...
for streptococcal tonsillitis, and one for pharyngitis; otitis and tonsillitis were treated with antimicrobials. Distribution of all these 14 children is summarized in Table 2.

DISCUSSION

Many bacterial infections are treated for unnecessarily long periods, solely based on criteria that are more subjective than objective. Sometimes shorter courses have become well established. Medication for staphylococcal osteomyelitis has been reduced to 3 weeks; a 3-day course of cotrimoxazole or a 5-day course of a β-lactam is as efficacious as any treatment for acute cystitis in women; and a perforated appendix may be treated anywhere from 1 to 10 days. Another example is neonatal bacterial meningitis (in an immunocompetent host): no benefit is achieved with more than 7 days of antibiotic treatment in meningococcal meningitis, whereas in meningococcal meningitis, a single intramuscular injection of long-acting penicillin or chloramphenicol suffices.

The authors’ conclusions might be challenged because the etiology remained sometimes unproven, despite intense search for microbiologic causes (23 bacterial, viral, or protozoal agents). However, in 62% of cases the probable etiology was disclosed, and this result compares favorably with virtually all earlier series. Furthermore, all children were considered ill enough to require costly hospitalization and parenteral antimicrobials, and the laboratory parameters performed (see Table 1) strongly favored this decision. An invasive bacterial infection was most likely in almost all children recruited in this particular study.

The results also highlight the difficulties in the microbiologic diagnosis of infections for which most antimicrobials in hospital are ordered. Even in the best centers the majority of these patients remain without settled etiology. Series on pneumonia and bacteremia have been published, but this study is the first that compared alternative duration of treatment in children with a wide disease spectrum. The variability of patients reflects the existing realities in the on-call circumstances throughout the world.

Uneventful recovery was the primary endpoint for successful treatment. Duration of fever alone was not used as an outcome measure because antipyretics are given frequently to pediatric patients, and the same agents also are used as analgesics. Although not all patients had a follow-up visit after discharge, the results were valid because had any relapse occurred, it would have been treated in the participating centers.

Since children in the 4-day group were no less ill than those in the 7-day group (see Table 1), it is concluded that prolonging β-lactam treatment for longer than 4 days provides no added benefits. Instead, short-term antimicrobial treatment decreases the general costs of treatment and the risks of nosocomial infection, allergy, and other adverse outcomes, and is ecologically sound. Although penicillin-resistant pneumococci were not encountered in this study, they should not be a problem for short-term treatment of nonmeningeal diseases, because these strains still respond well to penicillin, at least if used in high doses. Beta-lactamase-positive strains restrict the use of penicillin in several countries, but in Finland, and in many other countries as well, isolation of those from invasive infections is rare. Curiously enough, even the β-lactamase-positive strains have not been shown to be unresponsive to ampicillin or amoxicillin treatment in immunocompetent patients.

The data might be relevant for the treatment of children throughout the world, although more studies along these lines are warranted, and these results might not be directly applicable to other settings. Nevertheless, short-duration treatments have been found effective in pediatric urinary tract infections. The present results should also raise questions about traditional treatment policies in other common infections. Long courses promote antimicrobial resistance, and in the developing world, many patients are left without adequate treatment because costly antimicrobials are reserved for families affluent enough to afford the costs. Inexpensive drugs and treatments are a necessity. Shortening of treatment from 7 to 4 days in children hospitalized for parenteral antimicrobials seems often justified.

REFERENCES


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