Antibiotic treatment schemes for very severe community-acquired pneumonia in children: a randomized clinical study

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Objective. To compare clinical response to initial empiric treatment with oxacillin plus ceftriaxone and amoxicillin plus clavulanic acid in hospitalized children diagnosed with very severe community-acquired pneumonia (CAP).

Methods. A prospective randomized clinical study was conducted among children 2 months to 5 years old with a diagnosis of very severe CAP in the pediatric ward of São Paulo State University Hospital in Botucatu, São Paulo, Brazil, from April 2007 to May 2008. Patients were randomly divided into two groups by type of treatment: an oxacillin/ceftriaxone group (OCG, n = 48) and an amoxicillin/clavulanic acid group (ACG, n = 56). Analyzed outcomes were: time to clinical improvement (fever and tachypnea), time on oxygen therapy, length of stay in hospital, need to widen antimicrobial spectrum, and complications (including pleural effusion).

Results. The two groups did not differ statistically for age, sex, symptom duration before admission, or previous antibiotic treatment. Time to improve tachypnea was less among ACG patients than OCG patients (4.8 ± 2.2 versus 5.8 ± 2.4 days respectively; P = 0.028), as was length of hospital stay (11.0 ± 6.2 versus 14.4 ± 4.5 days respectively; P = 0.002). There were no statistically significant differences between the two groups for fever improvement time, time on oxygen therapy, need to widen antimicrobial spectrum, or frequency of pleural effusion.

Conclusions. Both treatment plans are effective in treating very severe CAP in 2-month- to 5-year-old hospitalized children. The only analyzed outcome that favored amoxicillin/clavulanic acid treatment was time required to improve tachypnea.

Trial registration. ClinicalTrials.gov ID: NCT01166932

Key words Pneumonia; anti-bacterial agents; randomized clinical trial; child, preschool; infant; ceftriaxone; oxacillin; amoxicillin; clavulanic acid; Brazil.

Community-acquired pneumonia (CAP) is the main cause of death in children under 5 years old (1). While the global Control of Acute Respiratory Infection (CARI) program initiated by the World Health Organization (WHO) in 1983 has helped reduce pneumonia-related mor-

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one) (12–14). However, various studies have linked third-generation cephalosporins with an increased prevalence of extended-spectrum beta-lactamase (ESBL)-producing bacteria, and increased mortality, longer inpatient time, and higher hospital costs (15–18).

Faced with this problem, an alternative is to use beta-lactamase antibiotics associated with beta-lactamase inhibitors (amoxicillin plus clavulanic acid), which provide the same bacterial cover (19, 20). Clavulanic acid acts as a “suicide” inhibitor, forming a complex with beta-lactamase, and making it inactive (21).

Together, amoxicillin and clavulanic acid preserve amoxicillin activity against S. pneumoniae and restore its activity against methicillin-sensitive S. aureus, H. influenzae, and M. catarrhalis (22). This was confirmed by the SENTRY Antimicrobial Surveillance Program (23).

There have been no clinical studies comparing amoxicillin plus clavulanic acid with oxacillin plus ceftriaxone in treating children diagnosed with very severe CAP. The hypothesis of the current study is that amoxicillin/clavulanic acid is as effective as oxacillin/ceftriaxone for inpatient treatment of severe CAP and, because it can be administered orally, allows for a reduced hospital stay.

The objective of this study was to compare clinical response to initial empiric treatment with oxacillin plus ceftriaxone and treatment with amoxicillin plus clavulanic acid in 2-month- to 5-year-old children diagnosed with very severe CAP who required hospital admission.

MATERIALS AND METHODS

Study sample

This was a randomized prospective clinical study of 2-month- to 5-year-old children admitted to the pediatric ward of São Paulo State University Hospital (“University Hospital”) in Botucatu, São Paulo, Brazil, between April 2007 and May 2008 with very severe CAP, diagnosed according to the criteria of the WHO CARI program (24, 25). According to these criteria, CAP was defined as severe inflammation of the pulmonary parenchyma, affecting alveolar space and interstitial tissue, caused by an infectious community agent, associated with the signs and symptoms of pneumonia, accompanied by pulmonary infiltrate at thoracic X-ray or pulmonary auscultation compatible with pneumonia (increase or reduction in vesicular murmur; localized crackling), in outpatients or patients who had been discharged more than 14 days before symptom onset (26). CAP was considered severe when tachypnea (respiratory frequency ≥ 60 mpm in those under 2 months old, ≥ 50 mpm in 2-month- to 1-year-olds, and ≥ 40 mpm in those between 1 and 5 years old) was accompanied by substernal retractions, nostril flaring, or grunting. The disease state was considered very severe when the clinical picture described above was associated with one or more of the following signs or symptoms: convulsion, sleepiness, expiratory wheezing during sleep, severe malnutrition, inability to feed, or central cyanosis. Analyzed outcomes were: time to clinical improvement (fever and tachypnea), time on oxygen therapy, length of stay in hospital, need to widen antimicrobial spectrum, and complications.

The study was approved by University Hospital’s institutional research ethics committee, and written consent was obtained from each patient’s parents or guardians before inclusion in the study.

A form was completed for each patient and included data on identity, sex, admission date, comorbidities, diagnosis at admission and discharge, disease duration before admission, clinical picture at admission, type and duration of oxygen treatment, complication, discharge date, culture results, etc. Along with the standard exams, hemoculture was obtained at admission for all patients included in the study.

It is estimated that University Hospital serves 1.5 million people from 68 municipal areas. The hospital has 415 beds, with 52 in intensive care. The pediatric ward has 80 beds.

Patients were excluded from the study if they: 1) had immunodeficiency (primary or secondary) or renal insufficiency (acute or chronic), 2) were referred to the hospital while already receiving the proposed antibiotics, or 3) were allergic to the proposed treatments.

Randomization

Patients were randomly assigned to two different groups by type of treatment: an oxacillin/ceftriaxone group (OCG) and an amoxicillin/clavulanic acid group (ACG). A computerized random sequence generator (Research Randomizer version 3.0, www.randomizer.org) was used to assign patients to the two groups. The sequence was placed in an opaque envelope, making it impossible to predict to which group patients would be allocated. Physicians involved in assessment were blinded to the treatment.

Antibiotic schemes and treatment time

OCG patients received intravenous (IV) oxacillin (Staficilin®) at 200 mg/kg/day every 6 hours for 10 days and ceftriaxone IV (Rocefin®) at 100 mg/kg/day every 12 hours for 10 days (12). ACG patients received amoxicillin/clavulanic acid IV (Clavulin®) at 100 mg/kg/day every 8 hours at the beginning of amoxicillin base treatment (27, 28). If there was clinical improvement after 48 hours, defined as improved tachypnea with a drop of at least 20% in initial respiratory frequency and fever remission, ACG patients were changed to the same antibiotic by oral route (OR) at 50 mg/kg/day (split into three doses) until 10 days treatment was completed (29, 30). Also, if clinical improvement was maintained for the next 24 hours, the patient was discharged. OCG antibiotic was given by parenteral route throughout treatment. Any requirement to change initial antibiotic treatment was evaluated on an individual basis according to clinical, laboratory, and radiological data.

Antibiotics were administered as per the hospital’s pediatric ward nursing standards and the doctor’s prescription.

Oxygen treatment was prescribed according to the following international criteria: Patients with very severe pneumonia with central cyanosis, inability to eat, substernal retraction, respiratory frequency > 70 mpm, wheezing (31), or SaO₂ < 92%, measured by sputometer (Dixtal Biomédica Indústria e Comércio Ltda., Manaus, Brazil), received oxygen by nasal catheter at 3 L/min, providing an inspired oxygen fraction (FiO₂) of 28%–35%, or by facial mask providing 35%–50% FiO₂. If there was no improvement, patients were put on a mask with reservoir (FiO₂ = 100%) until stabilization (decreased respiratory rate and substernal retractions, and increased SaO₂). Oxygen treatment was maintained until the patient showed clinical improvement.

Oxygen weaning was gradual. In patients with an O₂ nasal catheter, when
SaO₂ reached values over 92%, oxygen flow was reduced 1 L/min every 12 hours. In those with a mask, FiO₂ was reduced 10%–20% every 8–12 hours, and when it reached 35%, treatment was changed to an O₂ nasal catheter, and reduced as previously described.

Simple parapneumonic pleural effusion (PPE) was defined as a buildup of fluid in the pleural cavity, containing a small number of inflammatory cells. Empyema was defined as the presence of pus in the pleural cavity (32). Patients with pleural effusion were initially submitted to thoracic puncture and draining, according to indication (large volumes, loculations, or trabeculations; purulent aspect, pH < 7.2; lactic dehydrogenase (LDH) > 1,000 IU/L; and glucose < 40 mg/dL) (33).

Statistical analysis

Groups were compared for age, sex, symptom duration before admission, comorbidities, previous antibiotic treatment, time for improvement in fever and tachypnea, and time in hospital. Variables presenting normal probability distribution were analyzed by the Student’s t-test and results expressed as mean ± standard deviation, and those presenting non-normal distribution by the Mann-Whitney test and results expressed as median (range). The chi-square test was used to compare distribution by sex, previous antibiotic treatment, the need to change initial antibiotic treatment, comorbidity, and frequency of evolution for pleural effusion/empyema. Significance level was 5%.

Sample size was determined to detect a 15% difference between the groups. With a test power of 80% (Type II error [β] = 0.20) and 95% confidence interval (Type I error [α] = 0.05), 70 patients were needed for each group.

RESULTS

Patient inclusion and exclusion

In the period chosen for the study, 218 patients diagnosed with very severe CAP were admitted to the hospital’s pediatric ward. A total of 114 patients were excluded or self-eliminated from the study: 72 who did not meet the age requirement, 17 who refused to participate, 16 who transferred from another health facility and had already received the proposed antibiotic treatment, 4 who were described as previously described.

The final study sample of 104 patients was randomly distributed into the two treatment groups for a total of 56 ACG patients and 48 OCG patients (Figure 1).

Patient characteristics

Table 1 shows the characteristics of the 104 randomized patients. There was no statistical difference between groups for age, sex, symptom time before admission, and previous antibiotic treatment. Comorbidities were found in 6.7% of patients (three with nonprogressive neurological disease; two with congenital cardiology; one with endocrinopathy, among OCG patients; and one with congenital cardiology, among ACG patients). However, all of these patients presented stability from the point of view of the base disease, none of them evolved with complications, and in no case were the comorbidities responsible for the need to widen the antimicrobial spectrum. A significantly large proportion of patients from both groups (71.1%) had received previous antibiotic treatment (prior to their referral to the hospital), with no significant difference between groups.

Table 2 shows no statistical difference between groups for O₂ catheter or mask, or fever subsidence. However, tachypnea improvement time was significantly lower among the ACG patients, as was hospitalization time. Sixteen patients (15.3%) evolved with pleural effusion and empyema, but with no statistical difference between groups. Analyzing the need for widening the antimicrobial spectrum revealed that the frequency of patients from both groups in whom it was not necessary to change initial treatment schemes (ACG, 85.5%; OCG, 85.4%) was greater than the frequency of patients in whom the initial antibiotics were changed, with no significant difference between groups.

The microbial agent was isolated in six patients (5.8%) from hemoculture taken at admission. Enterobacter, S. aureus was isolated in three OCG patients; S. coagulase negative in two ACG patients; and Pseudomonas aeruginosa negative in one ACG patient.

DISCUSSION

This is the first randomized prospective clinical study of children under 5 years old diagnosed with very severe CAP that has compared the amoxicillin/clavulanic acid and oxacillin/ceftriaxone antibiotic treatment schemes. There was a significant reduction in time for tachypnea im-
A prospective multicenter study compared other antibiotic schemes for children with CAP in developing countries. In India, a 3-month- to 12-year-old children with severe lower respiratory tract infection were equally effective as no difference was found between treatment groups for time on IV antibiotics, improvement in tachypnea, or improvement in oral eating ability. The differences between the results of the current study and those cited above may be at least partially attributed to the antibiotic dosage level. The current study used a much higher dose of amoxicillin/clavulanate acid (100 mg/kg/day, based on the amoxicillin component) at the start of treatment. The studies cited above used doses between 30 and 75 mg/kg/day (based on the amoxicillin component).

### TABLE 1. Age, sex, symptom duration before admission, previous antibiotic treatment, and comorbidities by type of treatment (ACG and OCG) in study of hospitalized children with very severe community-acquired pneumonia (CAP), Botucatu, São Paulo, Brazil, April 2007–May 2008

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACG (n = 56)</th>
<th>OCG (n = 48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in months (range)</td>
<td>11.5 (3–60)</td>
<td>10.5 (2–60)</td>
<td>0.748&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>1.000&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Mean no. of days with symptoms before admission (± SD)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.9 ± 3.0</td>
<td>5.8 ± 4.0</td>
<td>1.000&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Previous antibiotic treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>13</td>
<td>0.195&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td>0.075&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>55</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> ACG: amoxicillin + clavulanic acid group.<br><sup>b</sup> OCG: oxacillin + ceftriaxone group.<br><sup>c</sup> Mann-Whitney test.<br><sup>d</sup> Chi-square test.<br><sup>e</sup> SD: standard deviation.<br><sup>f</sup> Student’s t-test.

### TABLE 2. Time on oxygen catheter/mask, time for improvement in fever and tachypnea, hospital length of stay, evolution to pleural effusion/empyema, and need to widen antibiotic spectrum by type of treatment (ACG and OCG) in study of hospitalized children with very severe community-acquired pneumonia (CAP), Botucatu, São Paulo, Brazil, April 2007–May 2008

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACG (n = 56)</th>
<th>OCG (n = 48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time with O2 catheter in days (range)</td>
<td>1 (0–7)</td>
<td>1 (0–16)</td>
<td>0.073&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean time with O2 facial mask in days (range)</td>
<td>0 (0–8)</td>
<td>0 (0–7)</td>
<td>0.993&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean time for fever improvement in days (range)</td>
<td>3 (1–8)</td>
<td>3 (0–7)</td>
<td>0.606&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean time for tachypnea improvement in days (± SD)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.8 ± 2.2</td>
<td>5.8 ± 2.4</td>
<td>0.028&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean length-of-stay in hospital in days (± SD)</td>
<td>11.0 ± 6.2</td>
<td>14.4 ± 4.5</td>
<td>0.002&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Evolution to pleural effusion/empyema</td>
<td></td>
<td></td>
<td>1.001&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>49</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Need to widen antibiotic spectrum</td>
<td></td>
<td></td>
<td>1.000&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>48</td>
<td>41</td>
<td></td>
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<tr>
<td>Yes</td>
<td>8</td>
<td>7</td>
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</tr>
</tbody>
</table>

<sup>a</sup> ACG: amoxicillin + clavulanic acid group.<br><sup>b</sup> OCG: oxacillin + ceftriaxone group.<br><sup>c</sup> Mann-Whitney test.<br><sup>d</sup> SD: standard deviation.<br><sup>e</sup> Student’s t-test.<br><sup>f</sup> Chi-square test.
lin component), which could have influenced patient clinical evolution.

In the current study, hospital length of stay was significantly lower for the amoxicillin/clavulanic treatment group (ACG). This can be explained in part by the transition from IV to OR antibiotic treatment among ACG patients presenting clinical improvement, but still suggests ACG patients improved more quickly than OCG patients, especially with respect to tachypnea. This result may be at least partially due to the protocol of the current study, which required oxacillin/ceftriaxone patients to remain in the hospital until the end of the treatment. In a multicenter randomized trial of 246 children with CAP admitted to eight hospitals in the United Kingdom, Atkinson et al. (29) compared oral amoxicillin and IV benzylpenicillin and found that length of hospital stay was reduced in the group randomized to oral antibiotics. As in the current study, time for fever improvement was not influenced by either antibiotic scheme.

Oxygen use frequency in the current study (74%) was close to that in Michelow et al. (60%) (36). The current study found no significant difference between groups for oxygen use via catheter or mask. A similar result was reported by Atkinson et al. (29) with oxygen treatment times of 1.2 (0.9–1.6) days for the OR amoxicillin group and 1.3 (1.1–1.7) days for the IV benzylpenicillin group in children with CAP.

Mean frequency of the need to widen the antibiotic spectrum in the current study was 14.4%, without statistical difference between groups for oxygen use via catheter or mask. A similar result was reported by Atkinson et al. (29) with oxygen treatment times of 1.2 (0.9–1.6) days for the OR amoxicillin group and 1.3 (1.1–1.7) days for the IV benzylpenicillin group in children with CAP.

Limitations

An important limitation in the current study is the small size of the study sample. Sample size analysis indicated that to reach an 80% test power with a 95% confidence interval, 70 children were needed in each group. The actual number included in each group guaranteed a 74% test power and 80% confidence interval. Another study limitation is the different number of patients in the two groups (48 versus 56). This might have happened by chance due to simple randomization. However, if block randomization were used this problem could be minimized. Considering the difficulties in conducting this type of study in a general pediatric ward of a university hospital, the authors of the current research recommend additional, collaborative studies with different types of health facilities to obtain more reliable results.

Conclusion

Both treatment plans—oxacillin/ceftriaxone and amoxicillin/clavulanic acid—are effective in treating very severe CAP in 2-month- to 5-year-old hospitalized children. The only analyzed outcome that favored amoxicillin/clavulanic acid treatment was time required for tachypnea improvement.

Acknowledgments. The authors thank all members of the pediatric ward team at São Paulo State University Hospital for their help during this study, and Carlos Roberto Padovani for his help with the statistical analysis.
REFERENCES


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Objetivo. Comparar la respuesta clínica al tratamiento empírico inicial con oxacilina más ceftriaxona frente a amoxicilina más ácido clavulánico en niños hospitalizados con diagnóstico de neumonía extrahospitalaria muy grave.

Métodos. Se llevó a cabo un estudio clínico prospectivo aleatorizado en niños de 2 meses a 5 años de edad con diagnóstico de neumonía extrahospitalaria muy grave en la sala de pediatría del Hospital Universitario del Estado de São Paulo en Botucatu, São Paulo, Brasil, entre abril del 2007 y mayo del 2008. Los pacientes se dividieron aleatoriamente en dos grupos según el tratamiento administrado: un grupo recibió oxacilina/ceftriaxona \((n = 48)\) y otro amoxicilina/ácido clavulánico \((n = 56)\). Los criterios de valoración analizados fueron el tiempo hasta la mejoría clínica (de la fiebre y la taquipnea), el tiempo de administración de oxigenoterapia, la duración de la internación, la necesidad de ampliar el espectro antibiótico y las complicaciones (como el derrame pleural).

Resultados. Los dos grupos no presentaban diferencias estadísticas con respecto a la edad, el sexo, la duración de los síntomas antes de la internación o el tratamiento previo con antibióticos. El tiempo hasta la mejoría de la taquipnea fue menor en los pacientes tratados con amoxicilina/ácido clavulánico que en los que recibieron oxacilina/ceftriaxona \((4,8 \pm 2,2\) días frente a \(5,8 \pm 2,4\) días, respectivamente; \(P = 0,028)\), y también fue menor la duración de la internación \((11,0 \pm 6,2\) días frente a \(14,4 \pm 4,5\) días, respectivamente; \(P = 0,002)\). No hubo diferencias estadísticamente significativas entre los dos grupos en relación con el tiempo hasta la mejoría de la fiebre, el tiempo de administración de oxigenoterapia, la necesidad de ampliar el espectro antibiótico ni la frecuencia de derrame pleural.

Conclusiones. Ambos esquemas de tratamiento son eficaces para tratar la neumonía extrahospitalaria muy grave en niños de 2 meses a 5 años de edad hospitalizados. El único criterio de valoración analizado que favoreció el tratamiento con amoxicilina/ácido clavulánico fue el tiempo hasta la mejoría de la taquipnea.

Resumen

Esquemas de tratamiento antibiótico para la neumonía extrahospitalaria muy grave en niños: estudio clínico aleatorizado

Palabras clave

Neumonía; agentes antibacterianos; ensayo clínico aleatorio; preescolar; lactante; ceftriaxona; oxacilina; amoxicilina; ácido clavulánico; Brasil.