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

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ABSTRACT

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 mortality worldwide, the numbers are still alarming, especially in developing countries, where 2–3 million children die from pneumonia each year (2, 3). Clinical disease severity is most frequent with bacteria as etiological agents (4–6).

Various studies concur that the most frequent bacterial etiological agents for CAP in the 2-month to 5-year age group are *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Staphylococcus aureus* (7). Nontypical bacteria such as *H. influenzae* and *Moraxella catarrhalis* (8, 9) have also been implicated, even though they are considered nonpathogenic for the respiratory system.

The WHO recommendation for 2-month- to 5-year-old children diagnosed with very severe CAP is admission to hospital and immediate empiric parenteral antibiotic therapy (10, 11). According to recent publications, the standard treatment in these cases is oxacillin plus a third-generation cephalosporin (ceftriax-

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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. influenza*, 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 subcostal 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, subcostal retractions, respiratory frequency > 70 mpm, wheezing (31), or SaO_2 < 92%, measured by saturometer (Dixtal Biomédica Indústria e Comércio Ltda., Manaus, Brazil), received oxygen by nasal catheter at 3 L/min, providing an inspired oxygen fraction (FiO_2) of 28%–35%, or by facial mask providing 35%–50% FiO_2. If there was no improvement, patients were put on a mask with reservoir (FiO_2 = 100%) until stabilization (decreased respiratory rate and subcostal retractions, and increased SaO_2). Oxygen treatment was maintained until the patient showed clinical improvement.

Oxygen weaning was gradual. In patients with an O_2 nasal catheter, when

SaO_2 reached values over 92%, oxygen flow was reduced 1 L/min every 12 hours. In those with a mask, FiO_2 was reduced 10%–20% every 8–12 hours, and when it reached 35%, treatment was changed to an O_2 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, time on oxygen therapy, 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 presented with immunodeficiency, and 5 who presented with renal insufficiency. 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 cardiopathy; one with endocrinopathy, among OCG patients; and one with congenital cardiopathy, 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 O_2 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-

FIGURE 1. Flow diagram for patient inclusion and randomization by treatment group in study of hospitalized children with very severe community-acquired pneumonia (CAP), Botucatu, São Paulo, Brazil, April 2007–May 2008

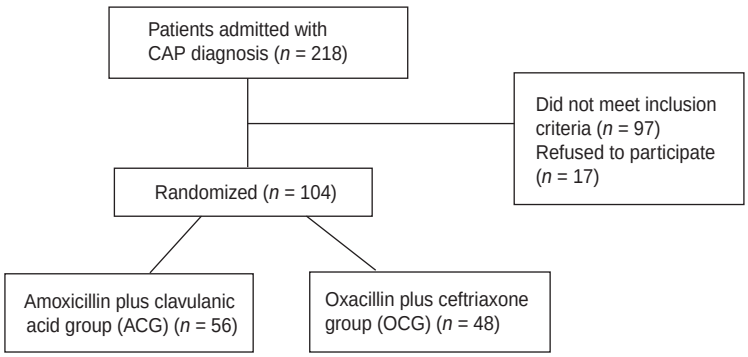

TABLE 1. Age, sex, symptom duration before admission, previous antibiotic treatment, and comorbidities by type of treatment (ACG[a] and OCG[b]) in study of hospitalized children with very severe community-acquired pneumonia (CAP), Botucatu, São Paulo, Brazil, April 2007–May 2008

Variable	ACG (*n* = 56)	OCG (*n* = 48)	*P*
Median age in months (range)	11.5 (3–60)	10.5 (2–60)	0.748[c]
Sex			1.000[d]
Male	29	29	
Female	27	19	
Mean no. of days with symptoms before admission (± SD[e])	4.9 ± 3.0	5.8 ± 4.0	0.195[f]
Previous antibiotic treatment			1.000[d]
No	17	13	
Yes	39	35	
Comorbidities			0.075[d]
No	55	42	
Yes	1	6	

[a] ACG: amoxicillin + clavulanic acid group.
[b] OCG: oxacillin + ceftriaxone group.
[c] Mann-Whitney test.
[d] Chi-square test.
[e] SD: standard deviation.
[f] 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[a] and OCG[b]) in study of hospitalized children with very severe community-acquired pneumonia (CAP), Botucatu, São Paulo, Brazil, April 2007–May 2008

Variable	ACG (*n* = 56)	OCG (*n* = 48)	*P*
Mean time with O_2 catheter in days (range)	1 (0–7)	1 (0–16)	0.073[c]
Mean time with O_2 facial mask in days (range)	0 (0–8)	0 (0–7)	0.993[c]
Mean time for fever improvement in days (range)	3 (1–8)	3 (0–7)	0.606[c]
Mean time for tachypnea improvement in days (± SD[d])	4.8 ± 2.2	5.8 ± 2.4	0.028[e]
Mean length-of-stay in hospital in days (± SD)	11.0 ± 6.2	14.4 ± 4.5	0.002[e]
Evolution to pleural effusion/empyema			1.001[f]
No	49	39	
Yes	7	9	
Need to widen antibiotic spectrum			1.000[f]
No	48	41	
Yes	8	7	

[a] ACG: amoxicillin + clavulanic acid group.
[b] OCG: oxacillin + ceftriaxone group.
[c] Mann-Whitney test.
[d] SD: standard deviation.
[e] Student's *t*-test.
[f] Chi-square test.

provement and hospital length of stay for the group of patients who underwent the first treatment scheme (ACG) versus the latter scheme (OCG). The two groups did not differ statistically for time on oxygen therapy, fever subsidence, need for widening the antimicrobial spectrum, or complications.

Two previous randomized trials compared other antibiotic schemes for children with CAP in developing countries. In India, a prospective multicenter study of 3-month- to 12-year-old children with severe lower respiratory tract infection comparing amoxicillin/clavulanate treatment with cefotaxime/sulbactam found no statistical differences between groups for improvements in coughing, tachypnea, and fever (34). In another Indian study (35) that compared crystalline penicillin plus gentamicin with amoxicillin plus clavulanic acid in children 2–59 months old with severe or very severe CAP, in which patients received IV antibiotics for at least three days and were changed to OR amoxicillin/clavulanate after clinical stabilization, the authors concluded the two antibiotic schemes 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/clavulanic 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 amoxicil-

lin component), which could have influenced patient clinical evolution.

In the current study, hospital length of stay was significantly lower for the amoxicillin/clavulanate 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. In a prospective observational study conducted in India by Tiewsoh et al. (37) on hospitalized children with severe CAP treated with penicillin plus aminoglycoside, this frequency was 56.5% for all patients, indicating that penicillin plus aminoglycoside is probably less effective than the two medications used in the current study.

The frequency of pleural effusion/empyema in the current study was 15.3%, a rate similar to that found in a non-interventional prospective study by Kin Key et al. in Brazil (38) that evaluated CAP severity and radiological findings in children. The current study found no statistical difference between treatment groups for this or any other complication, as in Kin Key et al. and three other trials (29, 39, 40).

In the current study, the ACG patients received amoxicillin/clavulanic acid orally after clinical stabilization, whereas oxacillin/ceftriaxone was maintained intravenously from the beginning to end of OCG patients' treatment. Therefore, the effectiveness of oral versus IV antibiotics for treating CAP in children should be taken into account when considering the current results. A randomized clinical trial conducted by Addo-Yobo et al. (39) in eight developing countries compared oral amoxicillin and IV penicillin G treatment among children with CAP, and a similar trial by Campbell et al. (40) in Gambia compared oral co-trimoxazole and intramuscular procaine penicillin. Both studies concluded that oral antibiotics are likely to be equivalent in clinical outcomes to IV antibiotics. An editorial by Wilder (41) reviewing these trials concluded that oral antibiotics are as efficacious as IV antibiotics in the treatment of CAP in children. Therefore, it can be assumed that the different forms of administration (oral versus IV) used in the current study did not influence the results.

In addition to the specific outcomes selected for analysis in the current research, some other findings were notable. For example, age distribution in the current study coincided with the age of major CAP prevalence in Brazil and other countries (42, 43). Similarly, duration of symptom(s) before hospital admission did not differ between groups, which was similar to observations by other authors (29, 36). Antibiotic frequency before hospital admission was elevated (71%) in both groups, in contrast to findings from a prospective observational study conducted in the United States by Michelow et al. (36) evaluating the clinical characteristics of 6-month- to 18-year-old patients diagnosed with CAP, which found a rate of 40%. This range of results is probably due to differences in the study populations, and cultural differences in antibiotic use, as well as type of health facility. For example, the hospital where the current study was carried out is a reference (highly specialized/equipped) university hospital and thus accepts patients from other health facilities who are very often already on antibiotic treatment.

On the other hand, comorbidities most likely did not affect the current results by interfering with the response to clinical treatment, as all patients selected for the study presented as stable from the point of view of base disease. Unlike the current study, in which only 6.7% of patients had comorbidities, Michelow et al. (36) found a comorbidity rate of 20% in their study. The low frequency of comorbidities in the current study made analyzing their influence on patient evolution difficult.

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.

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RESUMEN

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

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 ± 2,2 días frente a 5,8 ±2,4 días, respectivamente; P = 0,028), y también fue menor la duración de la internación (11,0 ± 6,2 días frente a 14,4 ± 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.

Registro del ensayo. ClinicalTrials.gov ID: NCT01166932.

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