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Original Article

Oxacillin or Cefalotin Treatment of Hospitalized Children with Cellulitis

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SUMMARY: Cellulitis is an important cause of hospitalization in pediatrics. Because *Staphylococcus aureus* is the main pathogen of cellulitis, medicinal therapeutics should take the changing resistance profile of this organism into consideration. The aim of this study was to evaluate the progression and outcomes of children hospitalized for cellulitis and treated with oxacillin or cefalotin. This retrospective cohort study enrolled 218 children, hospitalized between 2001 and 2008 in Salvador, Northeast Brazil. All were diagnosed with cellulitis and treated with oxacillin or cefalotin ($\geq$100 mg/kg/day). The median age was 2 years and 56.9% were males. Frequencies of signs and symptoms used in the clinical diagnoses were as follows: swelling (91.3%), redness (81.7%), warmth (47.2%), and tenderness (31.7%). All patients were discharged due to clinical recovery and the mean length of hospitalization was 7 $\pm$ 4 days. None of the patients died, needed intensive care, or had sequelae. By comparing the daily frequency of clinical findings during hospitalization, significant decreases were found in the frequencies of fever (admission day [42.2%], first day [20.8%], second day [12.9%], third day [8.3%], fourth day [6.1%]), toxemia, irritability, somnolence, vomiting, tachycardia, and need for intravenous hydration. In conclusion, oxacillin or cefalotin remain the drugs of choice for treating uncomplicated cellulitis in regions where community-acquired methicillin-resistant *S. aureus* is infrequent ($<$10%).

INTRODUCTION

Cellulitis is a soft tissue infection with clinical findings that include tenderness, swelling, redness, and warmth. Inflammation of the regional lymph nodes and systemic manifestations can also occur. The pathogenesis is related to inflammation of subcutaneous tissue due to bacterial infection (1,2). Risk factors for cellulitis include those that cause loss of skin integrity, such as small traumatic injuries secondary to insect bites, abrasions, lacerations, and other primary skin infections (1,3,4).

The causative microorganism depends mainly on the affected area of the body, the mechanism of injury, the environment, and the host (5). In general, *Staphylococcus aureus* is the most common infectious agent of cellulitis (5–8). Facial cellulitis without loss of skin integrity is more frequently related to *Streptococcus pneumoniae* or *Haemophilus influenzae* type b (less common in vaccinated children) infections (1,9,10). Other possible bacterial pathogens are *Pasteurella* spp., resulting from animal bites; these are often mixed aerobic and anaerobic infections (1,5).

Physicians must be aware of the potential for emergence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) as an agent of skin and soft tissue infections (SSTI); these pathogens, primarily known as hospital-acquired infectious agents, have been increasing as important causes of community cellulitis in the last two decades (11,12). For this reason, prescribing practices have changed to accommodate this new bacteriologic profile in several countries (13). In a revised opinion, Kaplan does not recommend empirical use of β-lactam antibiotics in areas were the prevalence of CA-MRSA isolates accounts for $\geq$10% of infections (14).

It is difficult to define the etiology of infections and antimicrobial susceptibility patterns on an individual basis. This is because blood cultures often have low microbial titers, and wound cultures are rarely performed (1,5,7,15). Therefore, in both outpatients and inpatients, parenteral therapy is frequently initiated with empirically determined antibiotics based on local epidemiology and characteristics of the infection (5).

These facts are particularly important in the treatment of children because of the high frequency of infections caused by CA-MRSA in some countries, and the fact that this infectious agent has been recognized as the cause of invasive and severe infections (12,14,16).

Our aim was to evaluate the progression and outcomes of children hospitalized because of cellulitis and treated with oxacillin or cefalotin.

MATERIALS AND METHODS

The Ethics Committee of the university hospital at the Federal University of Bahia, Salvador, Northeast Brazil, approved this study. The retrospective cohort study enrolled all children (age, $<$14 years) who were hospitalized with cellulitis and treated with oxacillin or cefalotin ($\geq$100 mg/kg/day) between October 2001 and July 2008 at the Professor Hosannah de Oliveira Pediatric Center, Federal University of Bahia, as shown in Fig. 1. Exclusion criteria included the presence of collection, abscesses, foreign bodies, necrosis, or osteo-

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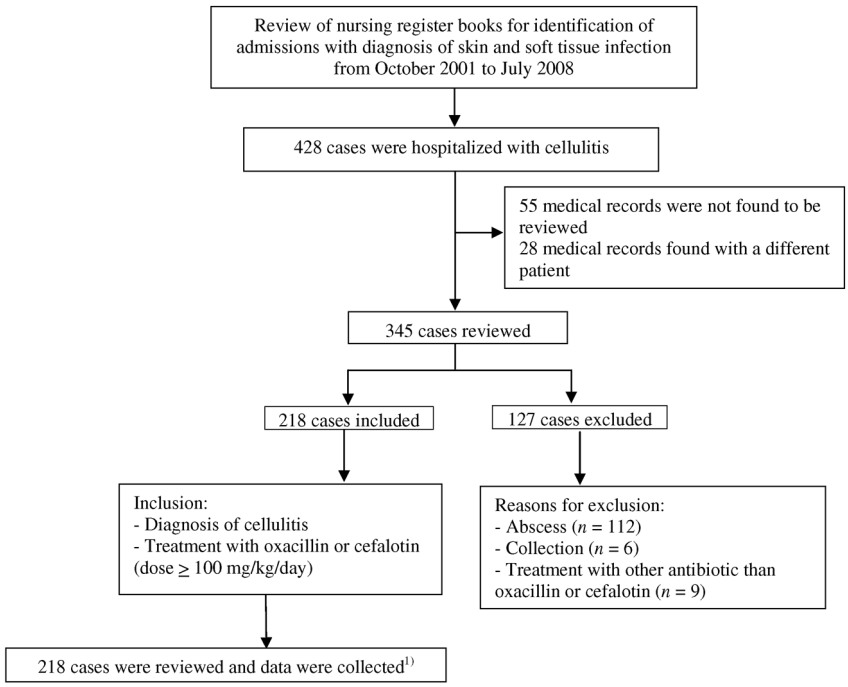

1): Two patients were hospitalized twice because of cellulitis, then resulted in two cases each.

Fig. 1. Procedure of sample construction of the retrospective cohort on cellulitis in Salvador, Northeast Brazil.

Table 1. Cut-off values for defining fever, tachycardia, and tachypnea among children hospitalized with cellulitis (18,19)

Age	Tachycardia	Tachypnea	Fever
1 week–1 mo	heart rate >180 beats/min	respiratory rate >40 breaths/min	axillary temperature >37.5°C
1 mo–1 y	>180 beats/min	>34 breaths/min	
2–5 y	>140 beats/min	>22 breaths/min	
6–12 y	>130 beats/min	>18 breaths/min	
13–14 y	>110 beats/min	>14 breaths/min	

The higher values registered in the medical records each day were collected.

myelitis detected on admission.

Data collected from a review of the medical records were registered in a standardized form and included the following: age, gender, data on admission (weight, height, clinical findings, location of the cellulitis, precipitating cause, blood culture results, underlying medical conditions, previous hospitalization or surgery, antimicrobial therapy, previous burning episodes, immunodeficiency, previous corticosteroid therapy, history of vaccinations, and presence of indwelling central venous catheter). The data recorded for progression during hospitalization included the following: toxemia, food refusal, vomiting, diarrhea, sensory state, bulging fontanelle, cyanosis, breathing discomfort, seizure, fever, tachycardia or tachypnea, presence of localized or distant complications, results of complete blood cell count with differential analysis, and erythrocyte sedimentation rate. The patient outcome was recorded considering factors such as hospital discharge, intensive care assistance, sequelae, or death. Data from the records for treatment during the first 5 days of hospitalization included which antibiotics were prescribed, whether oxygen was administered, and if the patient received intravenous hydration.

Nutritional evaluation was performed using World Health Organization (WHO) Anthro, version 3, and WHO AnthroPlus software. Severe malnutrition was defined as z-score for weight-for-age index or body mass index (BMI) under −3 using the WHO standard (17). The definitions of the clinical signs used are presented in Table 1.

Statistical methods: SPSS software, version 9.0, for Windows, was utilized to build the database and perform the statistical analyses. Two-tailed P values of <0.05 were considered statistically significant. Sample description was performed with descriptive statistics, such as distribution, central tendency, and dispersion. Comparison of frequencies of clinical progression between the days of hospitalization was performed using the McNemar test. Kaplan-Meier survival analysis was utilized to evaluate the duration of prognostic factors.

RESULTS

Of the 428 patients hospitalized with cellulitis, 218 were included in the study (Fig. 1). The characteristics of the patients on admission are described in Table 2. The detected risk factors for MRSA infections are listed

Table 2. Demographic and clinic characteristics on admission among children hospitalized with cellulitis

Variable	
Male no. (%)	124 (56.9)
Age (y)	
Mean ± SD	2.8 ± 2.5
Median (range)	2 (18 d–14 y)
Signs and symptoms on admission	no. (%)
Swelling	199 (91.3)
Redness	178 (81.7)
Warmth	103 (47.2)
Tenderness	69 (31.7)
Report of fever	65 (29.8)
Cellulitis location	no. (%)
Periorbital	104 (47.7)
Head (non periorbital)	51 (23.4)
Members	58 (26.6)
Trunk	3 (1.4)
Head and trunk	2 (0.9)
Total	218 (100)
Precipitating cause of cellulitis	no. (%)
Trauma	35 (37.2)
Insect bite	16 (17.0)
Conjunctivitis	13 (13.8)
Sinusitis	7 (7.4)
Conjuntivitis + Sinusitis	6 (6.4)
Scabies	8 (8.5)
Skin infection	4 (4.3)
Varicella	2 (2.1)
Mastoiditis	2 (2.1)
Dental caries	1 (1.1)
Total	94 (100)

Table 3. The frequency of risk factors for MRSA among children hospitalized with cellulitis

Risk factor	No. (%) of patients	% Proportion of overall patients (n = 218)
Underlying illness		
Lung	9 (37.5)	4.1
Genetic disorders	6 (25)	2.8
Gastrointestinal tract	4 (16.7)	1.8
Nervous system	2 (8.3)	0.9
Upper respiratory tract	2 (8.3)	0.9
Sickle cell disease	1 (4.2)	0.5
Total	24 (100)	11
Previous hospitalization		
Previous year	35 (51.5)	16.1
More than 1 year	33 (48.5)	15.1
Total	68 (100)	31.2
Severe malnutrition	4	1.9
Previous surgery	19	8.7
Previous burning	1	0.5
Corticosteroids use[1)]	2	0.9
Antibiotics use in the previous 3 months		
Beta-lactam	35 (85.4)	16.1
Macrolides	4 (9.8)	1.8
Chloramphenicol	1 (2.4)	0.5
Trimethoprim-sulfamethoxazole	1 (2.4)	0.5
Total	41 (100)	18.9

[1)]: 1 patient used for 7 days and 1 patient used in asthma crisis.

Table 4. Proportions of daily frequencies of significant clinical findings during hospitalization of patients with cellulits (n = 218)

Clinical finding	Day of hospitalization				
	D0	D1	D2	D3	D4
Fever %	42.2	20.8	12.9	8.3	6.1
Irritability %	9.4	6.1	4.9	3	2
Tachycardia %	7.4	4.3	1.2	0	0.7
Toxemia %	7.3	3	0.5	0.5	0
Somnolence %	5.6	4.1	2	1	1.5
Vomiting %	4.8	1	2	2.5	3.1
Intravenous hydration %	4.6	1.8	2.8	1.4	0.9

in Table 3. No temporary or permanent central venous catheters were required in any of the patients. The tested bacterial strains were susceptible to methicillin, aminoglycosides, quinolone, clindamycin, rifampicin, glycopeptide, and trimethoprim-sulfamethoxazole; two strains were resistant to penicillin and one to erythromycin.

The antibiotics used in the treatment of cellulitis were as follows: oxacillin, in 185 cases (84.9%); cefalotin, in 10 cases (4.6%); and oxacillin plus ceftriaxone, in 23 cases (10.5%). In all cases where ceftriaxone and oxacillin were concomitantly used, the localization of cellulitis was in the head. Of these, 18/23 (78.3%) were located periorbitally. There was a precipitating cause in 15/23 (65.2%) of these cases with the causes including sinusitis (n = 5, 33.3%), conjunctivitis (n = 3, 20%), and sinusitis accompanied by conjunctivitis (n = 3, 20%), mastoiditis (n = 2, 13.3%), and dental caries and trauma (n = 1, 6.7%, each).

All patients were discharged due to clinical recovery and hospitalization ranged from 1 to 25 days, with the mean length of stay being 7 ± 4 days; none of the patients died, needed intensive care, or had sequelae. Of the 218 patients, 40 (18.3%) had a complication in the course of hospitalization: abscess or purulent collection (n = 35, 87.5%) and ocular complications (n = 5, 12.5%). The ocular complications included 2 proptoses, 1 pseudostrabismus due to edema, 1 diplopia, and 1 hemorrhagic conjunctivitis with pseudomembrane formation.

Overall, by comparing the daily frequency of specific clinical findings during hospitalization, significant differences were found (Table 4). These clinical findings and their related comparisons included the following: fever: D0 versus D1, D2, D3, D4 ($P < 0.01$), D1 versus D3, D4 ($P = 0.02$), and D1 versus D2 and D2 versus D3 ($P = 0.04$, respectively); toxemia: D0 versus D1 ($P = 0.02$), and D0 versus D2, D3, D4 ($P < 0.01$)); irritability: D0 versus D2 ($P = 0.03$), D0 versus D3, D4 ($P < 0.01$), and D1 versus D3, D4 ($P = 0.02$); tachycardia: D0 versus D2, D3, D4 ($P \leq 0.03$); somnolence: D0 versus D4, or D1 versus D3 ($P = 0.04$ in both cases); vomiting: D0 versus D1 ($P = 0.03$); and use of intravenous hydration: D0 versus D1 and D0 versus D4 ($P \leq 0.04$).

By analyzing only the patients who received oxacillin

Table 5. Proportion of daily frequencies of significant clinical findings during hospitalization of patients with cellulitis treated concomitantly with oxacillin plus ceftriaxone

Clinical finding	Day of hospitalization				
	D0	D1	D2	D3	D4
Fever %	40.9	14.3	19.0	0.0	0.0
Food refusal %	20.0	27.3	8.7	0.0	4.5

plus ceftriaxone, significant differences were found on the frequencies (Table 5): fever: D0 versus D1 ($P = 0.03$), D0 versus D3 ($P < 0.01$), D0 versus D4 ($P < 0.01$); and food refusal: D1 versus D3 ($P = 0.03$). By excluding the patients who also received ceftriaxone, the previously observed significant differences in the frequency of somnolence and use of intravenous hydration were not found.

Overall, no significant difference was found in the daily frequency of food refusal, diarrhea, breathing discomfort, and tachypnea (data not shown). No patient had bulging of the fontanelle, cyanosis, or seizures.

The prognostic factors analyzed were underlying illnesses, previous use of antibiotics, localization of cellulitis, and concomitant use of ceftriaxone during hospitalization. None of these showed significant differences between the groups, with or without these factors, in time of survival to predict reduction of fever (data not shown).

DISCUSSION

On the basis of the aforementioned data, it is possible to observe the clinical effectiveness of oxacillin or cefalotin on patients hospitalized with cellulitis. No patient had the antibiotics changed based upon the spectrum of activity of oxacillin. All patients were discharged due to clinical recovery; no patients died, needed intensive care, or had sequelae. Complications were detected in 18% of the cases; however, these were acute intercurrences that resolved during hospitalization. The exclusion criteria and the nutritional evaluation of the patients were combined to avoid confounding variables with respect to patient progression during antibiotic treatment.

Although we have found clinical effectiveness for the treatment of cellulitis with oxacillin or cefalotin in all cases, Nascimento-Carvalho et al. showed, in a previous study (20) performed in the same hospital, that the frequency of CA-MRSA was 4.9%. The results of these two studies are consistent with other previous studies (8,21,22), which suggest that it is possible to achieve good outcomes in the treatment of uncomplicated SSTI caused by CA-MRSA, even using inappropriate antibiotic therapy. In a revision on the management of SSTI in emergency situations, the authors comment that it is not yet clear as to the need for CA-MRSA antimicrobial coverage in SSTI. This need depends on infection characteristics and local epidemiological data (5).

Different data were found in other studies regarding the characteristics and outcomes of patients with either CA-MRSA or community-acquired methicillin-susceptible *S. aureus* (CA-MSSA) infections (23–25). In these, SSTI caused by CA-MRSA was an independent predictor of clinical failure in patients who received inappropriate initial antimicrobial therapy. Ruhe et al. (23) compared patients with CA-MRSA infections who received active antimicrobial therapy with those who received inactive antimicrobial therapy, and treatment failure was the primary outcome. Characteristics of the population that differed from the present study were median age (47 years), injectable drug use (5%), diabetes mellitus (17%), and the inclusion of patients with abscesses, which was the most frequent SSTI. Davis et al. (24) included, in a case-controlled prospective study, patients with positive cultures for *S. aureus*. It was conducted in four teaching hospitals located in the midwestern United States. They compared outcomes of patients with CA-MRSA to those with CA-MSSA; the median ages of the two groups were 46 and 53 years, respectively. By multivariate regression analysis, clinical failure was significantly associated with MRSA infection. In a subset analysis of patients with CA-MRSA SSTI, the cure rates were higher in those who received concordant antimicrobial therapy, and surgical treatment did not influence this result. Cohen and Kurzrock (25) retrospectively reviewed the records of undergraduate and graduate school students with CA-MRSA infections who sought health center services at a Texas university. This study included a small sample of 10 patients who had positive bacterial cultures for MRSA. Ages ranged from 19 to 45 years (median, 23 years); abscesses were present in 8 cases; and half of the patients received surgical treatment.

It is important to note that the favorable outcome reported herein occurred in patients with uncomplicated infections. Nevertheless, when CA-MRSA is a possible pathogen in severe infections, such as complicated pneumonia or sepsis, it is essential to consider initial treatment with antibiotics that are effective against this bacterium (14,16).

CA-MRSA strains are spread in several countries and these microorganisms are the most prevalent causes of SSTI in some geographic areas, such as the Asian-Pacific region and the United States (6,8). In Latin America, CA-MRSA infections have been reported since 2003 (26). The first report in Brazil was in the year 2005, and severe infections have been described since then (27–29).

S. aureus is the main etiologic agent of cellulitis; however, other pathogens that are susceptible to oxacillin and cefalotin (or the related cephalosporin, ceftriaxone), such as *Streptococci* sp., may cause this infection. It is possible, therefore, that these other pathogens may have been implicated in some of our cases, and may have influenced the favorable outcome reported in this investigation (7–9).

We observed several parameters that define the severity of SSTI and pediatric systemic inflammatory response syndrome that were used to evaluate the clinical recovery of patients treated with oxacillin or cefalotin in the first 4 days (19,30). Fever, tachycardia, toxemia, vomiting, somnolence, irritability, and use of intravenous hydration were parameters that significantly decreased in daily frequency, suggesting favorable disease progression.

When ceftriaxone was concomitantly administered

with oxacillin, the daily frequency of food refusal decreased significantly; all these children had facial cellulitis and this localization probably interferes with food acceptance. To the best of our knowledge, there is no other study on children with facial cellulitis treated with ceftriaxone plus oxacillin. In a study in Saudi Arabia, 90% of the patients with orbital cellulitis received cephalosporins, of which 3% also received penicillins; however, their clinical progression was not assessed (31). In addition, the majority of our cases of facial cellulitis were periorbital, which differs from orbital cellulitis in anatomy, risk factors, complications, and management (32,33).

Of our cases, 71% were localized in the head, and among all cases, 48% were periorbital. This is consistent with previous studies in which children hospitalized because of cellulitis were analyzed (7,15). This is most likely due to the presence of several factors that indicate hospitalization to be appropriate for patients with facial cellulitis (1,5,7).

All blood cultures were negative. The low microbial titer of blood cultures in uncomplicated SSTI has been recognized (1,5,15). The positive cultures grew *S. aureus*. The strains were susceptible to a large spectrum of antibiotics, such as methicillin (MSSA) and the antibiotics that have been used as first choice in emergency departments where the prevalence and importance of CA-MRSA is high, such as clindamycin, trimethoprim-sulfamethoxazole, quinolone, and glycopeptide (11–13).

In conclusion, oxacillin or cefalotin remain the drugs of choice for the treatment of uncomplicated cellulitis in regions were CA-MRSA is infrequent ($<10\%$).

Conflict of interest None to declare.

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