Empiric Antibiotic Therapy in Children with Community-acquired Pneumonia

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ABSTRACT

Objective: *To assess the possible change of clinical response to empiric antibiotic therapy among children survivors hospitalized with community-acquired pneumonia at a teaching hospital during 1991-2001.* ***Methods:*** *This was a retrospective observational study. The medical records of children (aged 29 days to 12 years) with diagnosis of presumed bacterial pneumonia at hospital discharge were reviewed and patient's data were extracted, using standardized forms. The principal outcome was patient's response to empiric antibiotic therapy. The secondary outcome was length of hospital stay.* ***Results:*** *893 patients were included for this study. Penicillin and derivatives were the most commonly used empiric antibiotics throughout the studied period. There was a slight but statistically significant increase in the mean rate of antibiotic failure from 1991-1998 to 1999-2001 (3.8% vs 11.4%, P<0,001). The most common causes for antibiotic failure were inadequate coverage of initial antibiotics between 1991-1998 and presumed antibiotic resistance between 1999-2001. No significant difference was observed regarding the means of length of hospital stay during the whole studied period (P=0.08).* ***Conclusion:*** *Empiric antibiotic therapy was effective among children with community-acquired pneumonia treated at a teaching hospital between 1991-2001, inspite of a slight increase in the rate of presumed antibiotic resistance in later years.*

Key words: *Antibiotic, Children, Community-acquired pneumonia.*

INTRODUCTION

Antibiotic therapy is the mainstay of treatment for children with pneumonia requiring hospitalization. The choice of antibiotics for hospitalized children with community-acquired pneumonia (CAP) is usually empiric, based on clinical and radiological findings and knowledge of the etiology of CAP at different ages. Penicillin and derivatives are still the first line antibiotics recommended by most guidelines in developing countries as well as in developed countries(1-3). However, the rapid global spread of antibiotic resistance may cast doubts on the effectiveness of empiric antibiotic therapy in these patients(4-5).

We conducted this study to assess the possible change of clinical response to empiric antibiotic therapy among children survivors hospitalized with CAP at a teaching hospital during a period of 11 years.

METHODS

This retrospective observational study was conducted at the teaching hospital (30-bed pediatric inpatient ward) of the Federal University of Rio Grande, Brazil. This is one of the two general hospitals covering a population of approximately 200000 in a southern region of Brazil. The study protocol was approved by the Ethics Committee of the University.

Patient selection: An electronic search of the Hospital Registration Database (January 1991-December 2001) was performed to identify children, aged 29 days to 12 years, with diagnosis of presumed bacterial pneumonia at hospital discharge. The diagnosis codes used for this search (J13-J18) were based on the 10th edition of the International

Classification of Diseases (ICD-10)(6). After obtaining a complete list with patient's name and registration number, the medical records during hospitalization were reviewed by the investigators. Patients were excluded from the study if they had pneumonia 48 hours or more after hospital admission, chronic cardiac or pulmonary diseases, immunodeficiency, and had initial admission at the intensive care unit. If respiratory rate (breaths per minute) at hospital admission was less than the upper limits for age (60, <2 months; 50, 2-12 months; 40, >1yr-5yr; 30, >5yr)(7), the diagnosis of pneumonia was rejected and patients were excluded from the study, unless *X*-ray showed infiltrates, or other signs compatible with pneumonia. The death cases were not included because of inability to access the death registry of the hospital at the time of study.

***Data extraction*:** Data were extracted from the medical records, using a standardized form. The extracted data included: demographic variables, clinical, laboratory and radiological findings at hospital admission (body temperature, respiratory symptoms and signs, white blood cell count and chest *X*-ray), etiological investigations; antibiotic use and clinical evolution during hospitalization (body temperature, respiratory symptoms and signs), and length of hospitalization.

Outcome definition: The principal outcome of this study was patient response to empiric antibiotic therapy. It was defined as 'antibiotic failure' if the initial antibiotics were changed due to no clinical improvement 72 hours or more after their use or clinical worsening at any time during the course. The secondary outcome was length of hospital stay in days.

***Statistical analysis*:** Data were analyzed with Stata 8.0 for Windows (Stata Co., College Station, TX, USA). In the most of cases, descriptive statistical analyses (summary statistics) were performed. Chi square test was used for analysis of categorical data and one-way analysis of variance was used to compare the means of length of hospital stay in each year (1991-2001).

RESULTS

A total of 1007 medical records were reviewed, of which 24 were excluded due to incomplete data and 90 were excluded because of diagnosis error. Finally, 893 patients were included for this study (***Table* I**). The mean age was 2.4 years and 56.9% of patients were male. On admission, more than 84% of the patients had fever, cough, rales and infiltrate in the chest *X*-ray.

Etiological investigation was performed in 4.1% of patients (36/893). Among 36 patients who had blood culture and/or culture of pleural fluid, 22 (61.1%) had evidence of presence of microorganism and *Staphylococcus aureus* was the most commonly identified agent (8/22, 36.4%).

***Table* II** shows empiric antibiotic therapy and antibiotic failure among 893 hospitalized children with CAP. Penicillin and derivatives were the most commonly used antibiotics as monotherapy during the whole studied period. However, the use of cephalosprins (2nd and 3rd generation) had increased since 1999 while penicillins were less frequently used. Combination antibiotic therapy was not common in this group of patients, varied from 2.4 to 17.9% of total antibiotic courses between 1991 and 2001.

The failure of empiric antibiotic therapy was uncommon event between 1991 to 1998, varied from

TABLE I CHILDREN ADMITTED WITH PNEUMONIA (1991-2001)

Year	Patients of CAP	Excluded due to incomplete data	Excluded due to error in diagnosis	Included patients
1991	98	0	5	93
1992	96	3	11	82
1993	120	4	14	102
1994	105	2	5	98
1995	141	6	12	123
1996	139	5	11	123
1997	88	1	9	78
1998	83	2	10	71
1999	42	0	3	39
2000	49	1	6	42
2001	46	0	4	42
Total	1007	24	90	893

2.2 to 7.7% of total antibiotic courses, with a mean rate of 3.8% (29/770). Among 29 cases of antibiotic failure, all used penicillin initially and their derivatives as the mono- or combination empiric antibiotic therapy. In 17 (58.6%) cases, the initial antibiotics (penicillin G or ampicillin) were substituted by oxacillin as the clinical, radiological and laboratory findings during hospitalization suggested *S.aureus* as a pathogen. In 2 cases, the initial antibiotic was oxacillin and it was substituted by vancomycin due to clinical suspicion of oxacillin-resistant *S. aureus*. In the remaining 10 cases, the initial antibiotics (penicillin G or ampicillin) were changed to cephalosprins (*n*=8, 27.6%) for presumed resistant pathogens (*Streptococcus pneumoniae* and *Hemophilus influenzae*) and erythromycin (*n*=2, 6.9%) for atypical pneumonia.

In spite of considerable variation, the frequency of empiric antibiotic failure had increased during the period 1999-2001, with a mean rate of 11.4% (14/123). This rate was significantly higher that the mean rate of 3.8% in the period 1991-1996 ($P<0.001$). Penicillin and their derivatives were used as the initial antibiotics in all 14 patients with antibiotic failure. In 3 (21.4%) cases, the initial antibiotics (penicillin G) were substituted by oxacillin for *S. aureus*. In 2 (14.3%) cases, the initial antibiotics

(oxacillin, penicillin G) were substituted by vancomycin because of presumed antibiotic resistant *S. aureus*. In the remaining 9 cases (64.3%), the initial antibiotics (penicillin G) were changed to cephalosprins because of presumed resistant pathogens (*Streptococcus pneumoniae* and *Hemophilus influenzae*).

No significant difference was observed regarding the mean length of hospital stay during the study period 1991-2001 (P=0.08), varying from 8.2 to 9.5 days.

DISCUSSION

The number of children admitted to our hospital with a diagnosis of pneumonia decreased dramatically since 1999. This reduction may reflect improvement of primary care of children with pneumonia due to nationwide implementation of Brazilian Guideline for diagnosis and treatment of pneumonias in 1998(9). The introduction of routine *Hemophilus influenzae* type b as vaccination for children in Brazil since 1999 may have also contributed.

Etiological investigation was rarely available in this group of patients. Among 36 patients with etiological approach, 32 (88.9%) had complicated

TABLE II   EMPIRIC ANTIBIOTIC USE AND ANTIBIOTIC FAILURE AMONG 893 HOSPITALIZED CHILDREN WITH COMMUNITY ACQUIRED PNEUMONIA

Year	Number of patients	Monotherapy *n* (%)			Combination therapy *n* (%)	Antibiotic failure *n* (%)
		Penicillins	Cephalosporins	Others		
1991	93	83 (89.2)	3 (3.2)	4 (4,3)	3 (3.2)	2 (2.1)
1992	82	72 (87.8)	5 (6.1)	2 (8.5)	3 (3.7)	3 (3.7)
1993	102	88 (86.3)	3 (2.9)	4 (3.9)	7 (6.9)	4 (3.9)
1994	98	89 (90.8)	3 (3.1)	1 (1.0)	5 (5.1)	3 (3.1)
1995	123	93 (75.6)	4 (3.3)	4 (3.3)	22 (17.9)	4 (3.2)
1996	123	96 (78.0)	5 (4.1)	4 (3.3)	18 (14.6)	6 (4.9)
1997	78	59 (75.6)	10 (12.8)	7 (8.9)	2 (2.7)	6 (7.7)
1998	71	50 (70.4)	7 (9.9)	3 (4.2)	11 (15.5)	1 (1.4)
1999	39	21 (53.8)	14 (35.9)	2 (5.1)	2 (5.1)	7 (17.9)
2000	42	27 (64.3)	9 (21.4)	2 (4.8)	4 (9.5)	2 (4.8)
2001	42	21 (50.0)	16 (38.1)	4 (9.5)	1 (2.4)	5 (11.9)
Total	893	699 (78.3)	80 (8.9)	36 (4.0)	78 (8.7)	43 (4.8)

pneumonia with pleural effusion. *Staphylococcus aureus* was the most common identified agent. However, this finding may not be extrapolated to the whole group regarding etiological profile as most of the patients with etiological investigation had more severe pneumonia with pleural effusion. Limited available etiological studies in Brazil point out *S. pneumoniae* and *H. influenzae* as the most common infectious agents in children with CAP(8, 9). Penicillin and derivatives were the most commonly used empiric antibiotics during the whole study period. However, the use of cephalosprins (2nd and 3rd generation) increased after 1999. This may reflect the change of profile of hospitalized children with pneumonia in later years. Probably these patients were treated with intramuscular penicillin G or oral amoxicillin before hospitalization as suggested by the Brazilian guideline. It sounds reasonable to select the second line antibiotics, such as cephalosprins for children who presented with therapeutic failure to penicillins and needed hospital admission.

Empirical antibiotic therapy failed in 43 cases among 893 hospitalized children with CAP between 1991 and 2001. The overall rate of empiric antibiotic failure (4.8%) in this group of patients was low. However, the mean rate of antibiotic failure had increased from 3.8% between 1991 and 1998 to 11.4% between 1999 to 2001. The presumed causes of antibiotic failure had also changed since 1999. During the period 1991-1998, the most common cause (58.6%) of empiric antibiotic failure was inadequate coverage of initial antibiotics for *S. aureus*. Only 27.6% had clinical suspicion of antibiotic resistance, representing 0.13% of 770 hospitalized children with CAP between 1991-1998. In contrast, during the period 1999-2001, 64.3% of patients with antibiotic failure had clinical clues of antibiotic resistance, representing 7.3% of the total number of patients admitted to hospital with CAP in this period. These data indicate a possible trend of increase in antibiotic resistance between 1991 and 2001. However, as the presumed cases of antibiotic resistance represented a small proportion of hospitalized children throughout the studies period, their impact on effectiveness of empiric antibiotics in this group of patients appears to be limited.

Some methodological limitations of this study should be taken into account in interpreting the results. Firstly, due to retrospective nature of the study, the data extracted from medical records might be incomplete and inaccurate. However, as the study setting was a university teaching hospital, the academic discipline might reduce heterogeneity among observers in terms of patient's assessment and recording of clinical findings, and consequently, enhance the validation of the extracted data of this study. Secondly, presumed antibiotic resistance in this group of patients was not confirmed by antibiotic susceptibility tests. This limitation might over-estimate the rate of antibiotic resistance as other causes of antibiotic failure might mimic antibiotic resistance(10). It means that the real rate of antibiotic resistance in this group of patients may be lower than that estimated by this study. In this sense, the potential bias may not confound the interpretation of the results, that is, antibiotic resistance was uncommon in this group of patients over a period of 11 years. Thirdly, the death cases were not included in this study and antibiotic use in theses patients may be different from that in the survivors. Based on the database of Brazilian Ministry of Health (DATASUS), a total of 54 children aged 29 days to 12 years died from pneumonia in two hospitals of our municipality between 1991-2001 and only 5 deaths occurred between 1999-2001. We believe that the data of this small number of deaths may not alter significantly the overall results of this study.

In conclusion, empiric antibiotic therapy remains effective among children with CAP treated at a teaching hospital between 1991-2001, in spite of a slight increase in the rate of presumed antibiotic resistance in later years.

WHAT IS ALREADY KNOWN?

• Antibiotics are the mainstay of treatment of pneumonia in hospitalized children.

WHAT THIS STUDY ADDS?

• Empiric antibiotic therapy remains effective among hospitalized children with community-acquired pneumonia.

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