

## Original Research Article

# EVALUATION OF THE USE OF ANTIMICROBIALS IN THE TREATMENT OF BACTERIAL PNEUMONIA IN PEDIATRIC PATIENTS AT A TERTIAR HOSPITAL

### ABSTRACT

**Aims:** The present study aims to evaluate the use of antibiotics in the management of bacterial pneumonia in the pediatric sector of a teaching hospital.

**Study design:** a retrospective and descriptive cross-sectional study.

**Place and Duration of Study:** The pediatrics sector of the Julio Bandeira University Hospital (HUJB) from September 2017 to December 2021

**Methodology:** A total of 734 medical records were analyzed, which were divided into those who adhered to the protocol (AP) and those who did not (DP), according to agreement with the scheme used and recommended by hospital guidelines. The data were analyzed in a descriptive and exploratory way to evaluate the distribution and characterize the study population, so that the categorical variables were presented in the form of absolute (n) and relative (%) frequencies, while the continuous variables were evaluated through measures of central tendency and dispersion.

As the data distribution did not adhere to normality, the differences between the proportions of categorical variables were evaluated by the Chi-square test (5% significance level), while the differences between the medians by the U-Mann-Whitney test.

**Results:** The results found indicate greater effectiveness in the group that followed the institution's protocol (95.93%), as well as less use of antibiotics in therapy, making the majority use of monotherapy (74%), and adequacy to the duration of therapy (OR=1.49). In addition, there was an increase in the use of azithromycin during the Covid-19 pandemic

**Conclusion:** The group that adhered to the protocol stood out over the group that did not adhere to the protocol in terms of greater effectiveness. of treatment, less use of antibiotics and adequate length of stay for the prescribed treatment. Furthermore, a growth in the use of azithromycin was observed during the years of the Covid-19 pandemic.

Comment [VS1]: Length of use?

*Keywords: pneumonia; antibiotics; drug resistance; pediatrics.*

## 1. INTRODUCTION

Pneumonia is an acute inflammatory disease that affects the Lower Respiratory Tract (LRT), and can affect both the pulmonary alveoli and the interstitium, so that dyspnea, productive cough, fever and chest pain are common manifestations of the disease<sup>1</sup>. It acquires importance in the global public health scenario because it is the cause of high morbidity and mortality in the world, especially in children under 5 years old, representing 18% of deaths in the pediatric public in this age group<sup>2,3</sup>. In Brazil, the disease was responsible for more than 50,000 deaths in children under 5 years of age in 2017 and was the second cause of hospitalization for children in the same year, representing an important cause of hospitalization<sup>4,5</sup>.

Comment [VS2]: IRV or LRT?

In addition, it is important to draw attention to the North and Northeast states, which have high mortality rates due to pneumonia<sup>1,6</sup>. However, the mortality and infection rate due to this disease has been decreasing over the years, much as a result of the child's health being a priority in public health programs, with emphasis on vaccination<sup>7,8</sup>.

Another effective measure to reduce morbidity and mortality is early and correct diagnosis, followed by adequate treatment of pneumonia. This is based on the initial identification of the pathogen causing the disease, which in this case may be viral, bacterial or fungal; being the majority of cases of viral origin, however the bacterial ones tend to be more serious<sup>9,3</sup>. These are treated with the use of antibiotics, which is empirically based on three pillars: epidemiology; resistance profile; rational use of antimicrobials<sup>10</sup>.

Comment [VS3]: Being in the majority ?

The importance of knowledge about these pillars is important not only for effective therapy, but also to prevent the development of multiresistant bacteria, which are already becoming a worldwide problem, and, according to WHO estimates, deaths resulting from these agents will exceed deaths from oncological causes<sup>11</sup>.

Therefore, the use of targeted antibiotic therapy, in the case of childhood pneumonia - *Streptococcus pneumoniae*, and which aims at the rational use of this pharmacological class is fundamental, since pneumonia caused by resistant bacteria is more difficult to clinically manage, have longer hospital stays and worse outcome<sup>10,12</sup>.

In this context, in view of the above, there is a need for studies that help combat the development of multidrug-resistant bacteria, focusing on inadequate prescription of use, in order to reduce the impacts that this act has on public health. Thus, this study aims to evaluate the prescriptions of antimicrobials used in the management of bacterial pneumonia in the pediatric sector of a public hospital in Brazil.

## 2. MATERIAL AND METHODS

### 2.1 Characterization of the Study

This research consists of a research involving human beings elaborated through a retrospective and descriptive cross-sectional study in order to evaluate the use of antibiotics in patients hospitalized in the pediatric sector of the Hospital Universitário Júlio Bandeira (HUJB), Cajazeiras-Paraíba, reference for the municipalities of the Ninth Health Region of Paraíba, from September 1, 2017 to December 31, 2021.

### 2.2 Target Population/Sample

The study included patients treated at the pediatrics sector of the Hospital Universitário Júlio Bandeira (children and adolescents up to 17 years and 11 months old) diagnosed with pneumonia and who received antibiotic therapy, admitted to the university hospital from September 2017 to December 2021.

Data collection was carried out at HUJB through medical prescriptions and electronic medical records available through the Management Application for University Hospitals (AGHU), which were carefully analyzed and placed in a spreadsheet containing the following information: antibiotics used; hospitalization time; treatment effectiveness; follow the hospital protocol.

Comment [VS4]: This can be broken up into 3 sentences. Repetition of words could be avoided

### 2.3 Procedures and Data Collection

The medical records were divided into those who adhered to the protocol (AP) and those who did not (DP), according to agreement with the scheme used and recommended by hospital guidelines. Regarding the number of drugs, the use of only one antibiotic throughout the treatment was considered monotherapy, while in polytherapy two or more were used. Finally, the treatment was considered effective when the patient was discharged from the hospital and did not return to the hospital in less than a month with the same diagnosis.

The data were analyzed in a descriptive and exploratory way to evaluate the distribution and characterize the study population, so that the categorical variables were presented in the form of absolute (n) and relative (%) frequencies, while the continuous variables were evaluated through measures of central tendency and dispersion.

To assess whether the data were close to a Normal Distribution, the Kolmogorov-Smirnov test was used. As the data distribution did not adhere to normality, the differences between the proportions of categorical variables were evaluated by the Chi-square test (5% significance level), while the differences between the medians by the U-Mann-Whitney test. For the analysis of associated factors, simple non-conditional logistic regression was used, presenting the crude odds ratios and their respective 95% confidence intervals. For all analyses, the IBM® SPSS® v.26 software was used.

## 2.4 Protocol

Therapeutic options for hospitalization:

0-21 days:

1st option: Ampicillin 100-200mg/kg/day 6/6hs + gentamicin 5mg/kg/day;

2nd option: Oxacillin 50mg/kg/day (newborns 25mg/kg/day) every 6 hours + Gentamicin 5mg/kg/day 10-14 days.

21 days – 3 months:

1st option: Oxacillin 50mg/kg/day (newborns 25mg/kg/day) every 6 hours + gentamicin 5mg/kg/day;

2nd option: Ampicillin (100-200mg/kg/day) + gentamicin (5mg/kg/day).

>3 months:

Crystalline penicillin 100000 to 200000iu/kg/day or ampicillin (100-200mg/kg/day) + gentamicin (5mg/kg/day) 7-10 days;

4 months – 4 years:

1st option: Ampicillin 100-200mg/kg/day IV every 6h for 7 days;

2nd option: Crystalline penicillin 100000 to 200000iu/kg/day 6/6hs;

3rd option: Ceftriaxone 100mg/kg/ day 12/12h (IV or IM).

> 5 years:

1st option: Ampicillin 100-200mg/kg/day IV every 6h for 7 days;

2nd option: Ceftriaxone 100mg/kg/day 12/12h (IM or IV);

Atypical pneumonia (*M. pneumoniae*, *C. pneumoniae*, *Legionella* sp. and *B.pertussis*) Azithromycin (ped) 5-12mg/kg/day, or 500mg 1x day for 5 days (adults), or Levofloxacin 20mg/kg/day, maximum dose 750mg (for teenagers).

Adults with admission criteria:

1st option: Ceftriaxone 2 g/day or Ampicillin 200mg/kg/day (divided into 6/6 hours), \*assess the need for the association of macrolides in case of risk for pneumonia due to atypical germs;

2nd option: Levofloxacin 500-750mg/day; for 7 days (therapeutic regimen must be bypassed to oral route in case of improvement of the patient and discharge conditions).

### 3. RESULTS AND DISCUSSION

A total of 734 medical records were analyzed, with ampicillin being the most used antibiotic, 55.4% (CI 51.8%-59%) followed by azithromycin and ceftriaxone, respectively, with 37.4% and 38.4% (Table 1).

**Table 1. Distribution of medical records according to the antibiotics used in the period from 2017 to 2021.**

Antibiotics	n	%	CI95%
Ampicillin	400	55,4	51,8 - 59,0
Ceftriaxone	277	38,4	34,9 - 42,0
Azithromycin	270	37,4	33,9 - 41,0
Oxacillin	35	4,8	3,5 - 6,6
Gentamicin	29	4,0	2,8 - 5,6
Penicillin G	16	2,2	1,3 - 3,5
Clindamycin	8	1,1	0,5 - 2,1
Cefepime	7	1,0	0,4 - 1,9
Vancomycin	6	0,8	0,3 - 1,7
Amoxicillin	5	0,7	0,3 - 1,5
Piperacillin + Tazobactam	5	0,7	0,3 - 1,5
Cephalothin	4	0,6	0,2 - 1,3
Metronidazole	4	0,6	0,2 - 1,3
Sulfamethoxazole + Trimethoprim	4	0,6	0,2 - 1,3

Amikacin	3	0,4	0,1 - 1,1
Meropenem	3	0,4	0,1 - 1,1
Ciprofloxacin	1	0,1	0,0 - 0,6

CI 95%: 95% Confidence Interval

Regarding compliance with institutional guidelines for the treatment of pediatric patients with bacterial pneumonia, 17 did not use any antibiotics, due to the initial diagnosis of pneumonia being changed after a detailed clinical investigation during hospitalization, 295 followed the protocol and 420 did not followed. It was found that in the AP group, effectiveness was achieved in 283 (95.93%) of the cases, while in the DP group, the effectiveness was lower, being obtained in 367 (87.38%) of the medical records, so that those medical records that followed the protocol had 3.41 more chances of having an effective treatment compared to a failed treatment ( $P < 0,001$ ).

As shown in Table 2, it was verified that 74% of the prescriptions in the AP group were based on monotherapy, unlike the DP group, where there was equivalence of prescriptions with monotherapy and polytherapy, respectively, 48.8% and 51.2% of prescriptions. In addition, it was found that the AP group stands out positively in several parameters, such as: lower chance of using polytherapy (OR = 0.33;  $P < 0,001$ ); use of a smaller number of antibiotics (OR = 0.38 for two and OR = 0.19 for three or more antibiotics; both  $P < 0,001$ ); and an adequate length of stay (OR = 1.49;  $P < 0,049$ ) during clinical treatment.

**Table 2 - Association between protocol follow-up and transit, number of antibiotics and length of stay.**

Variables	Protocol				OR	CI 95%	p-value
	Yes		No				
	n	%	n	%			
<b>Effectiveness</b>							
Not effective	12	18,5	53	81,5	1		
Effective	283	43,5	367	56,5	3,41	1,79 - 6,49	< 0,001
<b>Therapy</b>							



2017 e 2018	60	24,5	185	75,5	1		
2019	73	29,1	178	70,9	1,27	0,85 - 1,88	0,249
2020	53	46,1	62	53,9	2,64	1,65 - 4,21	< 0,001
2021	84	75,7	27	24,3	9,59	5,69 - 16,17	< 0,001
<b>Year</b>							
2017 a 2019	133	26,8	363	73,2	1		
2020 e 2021	137	60,6	89	39,4	4,20	3,01 - 5,86	< 0,001

Source: Own authorship (2023).

OR: Odds Ratio. Indicates the chance of one. CI 95%: 95% Confidence Interval. P-value: Significance level with which the null hypothesis is excluded - in this case, 5% or 0.05 was adopted.

The choice of antibiotic to treat a disease should consider the type of pathogen and the region of the body commonly affected, the individual comorbidities, the local epidemiology and the cost-effectiveness for each patient. In addition, the investigation of mild pneumonia is clinical and outpatient, considering the epidemiology and effectiveness of certain antibiotics for empirical treatment, reserving etiological research for severe and refractory cases<sup>13</sup>.

Regarding bacterial pneumonia, the main etiological agents isolated in patients include: *Streptococcus pneumoniae* (pneumococcus), prevalent in up to 70% of cases, followed by atypical bacteria - *Mycoplasma*, *Legionella* and *Chlamydia*, in approximately 10 to 48% and *Haemophilus influenzae*, in up to 18% of patients. Thus, through epidemiological knowledge associated with the clinical context of the patient and the most prevalent agent, it is possible to estimate the cause and the need for the use of antimicrobials. Furthermore, since pneumococcus is the most common and considering the sensitivity of this microorganism to beta-lactams, initial therapy with penicillin is recommended, with the association with a macrolide such as azithromycin reserved for severe cases, evidencing the exceptionality polytherapy in these situations<sup>14</sup>.

Therefore, the present study ratifies the literature regarding the use of beta-lactams as initial choices in the treatment of bacterial pneumonia, as shown in table 1, represented by ampicillin, with 55.8%, and by ceftriaxone, with 38.4%, with confidence intervals (CI) of 51.8 - 59.0 and 34.9 - 42.0, respectively. Next, the use of a macrolide (azithromycin) is observed, generally used in association and in more severe cases, corresponding to 37.4% (CI 33.9 - 41) of therapy, which demonstrates the safety of this therapy in accordance with the guidelines.

Regarding the duration of antibiotic therapy, there is no established consensus. However, short-term treatment seems to be more appropriate, which is explained by the shorter exposure time to antibiotics, thus reducing adverse effects and the development of

resistance by pathogens, as well as minimizing the risk of prolonged exposure, hospitalization and hospital costs<sup>13</sup>.

It is important to highlight that the complications of Community-Acquired Pneumonia, especially pleural effusion and empyema, are related to prolonged hospitalization, and may even progress to its most severe form, which is pulmonary necrosis. In this context, therapeutic failure in groups that developed complications was exponentially greater, although the initial choice of antimicrobials followed national and international protocols and guidelines for the treatment of pneumonia in children and adolescents<sup>15</sup>.

Therefore, according to one meta-analysis<sup>16</sup>, the duration of treatment sufficient to guarantee efficacy against CAP is usually 5 to 7 days, especially in mild to moderate infections. In another meta-analysis, there were no significant differences between short-term regimens (less than 7 days) compared to longer-term regimens (with 2 days or more days apart) in terms of good clinical response<sup>13</sup>.

Thus, the data found in this study corroborate the literature, since there was a prevalence in the period from 3 to 6 days (61% of the records), compared to periods of less than 3 days (18.6%) and more of 7 days (17.9%). When referring to the group with less than 3 days, monotherapy is recommended for an average of 5 days, that is, antibiotic therapy for less than 3 days would not be sufficient to bring about clinical improvement. In contrast, with regard to the group of more than 7 days, a prolonged duration of treatment, in addition to maximizing financial costs, favors the development of resistant strains, such as *Clostridium difficile* infections, as well as exposing the patient to risks of the potentially serious adverse effects of drugs<sup>13</sup>.

The organized protocols must follow what is recommended by the Ministry of Health and updated studies in the area, considering the pathology and the age group being treated, but must, mainly, consider the epidemiology of the region, in order to avoid the unnecessary prescription of antibiotics, which, as it is an infectious disease, has the possibility of developing resistant bacteria, which are associated with greater clinical complications. Thus, the studies show, as well as the results found, that following the norms and protocols are associated with greater effectiveness of the treatment<sup>16,17</sup>.

As for following the protocol and prescribed treatment, the findings of this study differ from those provided in the literature, one study<sup>18</sup> highlight that the recommendations regarding the choice of antibiotic were followed in 91.8% of cases and another<sup>19</sup> in 92.31%, while only 41.5% of the analyzed prescriptions adopted the hospital's recommendations.

The data obtained in the present study (Table 2) also demonstrate that the records of the AP group had a lower chance (OR=0.33) of using polytherapy, in a found research<sup>20</sup> state that, of the patients who used monotherapy, 65.3% had a scheme in agreement with the institution, on the other hand, only 51.56% of those who used polytherapy followed the protocol of the institution in question, it should be noted that the protocols vary between institutions and age groups.

In this context, studies that analyze the impact of polytherapy on bacterial resistance report that the use of a greater number of antibiotics is related to a greater risk of developing drug interactions (DI). Thus, it should be noted that a complication of great importance to global public health is the emergence of resistant bacteria, directly linked to the inappropriate use of antibiotics, with DI induced by polytherapy, one of the factors that corroborate the development of resistant strains, for interfering with the effectiveness of the drug<sup>21</sup>. In addition, one of its possible results for the patient's health is the potentiation of the adverse effects of a given drug, which increases the rate of treatment abandonment<sup>21,22</sup>.

Azithromycin is part of the group of macrolides, which are drugs used in the treatment of airway infections. However, this class of drugs, in addition to the bacteriostatic property, also has anti-inflammatory and immunomodulatory actions, reducing the exacerbated production of cytokines, a fact that was a driver for the beginning of the development of research on its effect against COVID-19<sup>23</sup>.

Comment [VS5]: Corroborates with the?

Thus, in the pandemic period of COVID-19, azithromycin had a leap in the number of prescriptions with the discourse of strengthening the immune system, being the second most prescribed class of drug after analgesics<sup>24</sup>. However, studies<sup>25</sup> point out that the use of this drug did not change the clinical outcome of severe patients with coronavirus, it only spread the indiscriminate use of yet another antimicrobial.

In this context, the use of azithromycin for the treatment of lower airway diseases was also widespread, and this impact was observed in the study with the increased use of this drug, which had a significant increase during the pandemic period when compared to the period pre-pandemic ( $p < 0.001$ ).

#### 4. CONCLUSION

After analyzing the collected data, it is possible to conclude that most of the analyzed prescriptions did not adhere to the institution's protocol regarding the treatment of pneumonia, but the group that adhered to the protocol stood out over the group that did not adhere to the protocol in terms of greater effectiveness. of treatment, less use of antibiotics and adequate length of stay for the prescribed treatment. Furthermore, a growth in the use of azithromycin was observed during the years of the Covid-19 pandemic.

#### ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee with opinion number 3,686,831 and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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