

Original Research Article

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

Comment [AK1]: Tertiary

Comment [AK2]: Title: A retrospective cohort analysis of the treatment of Bacterial pneumonia paediatric cases

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), Brazil from September 2017 to December 2021.

Methodology: A total of 734 medical records were analyzed, based on two groups: a) For those subjects who adhered to the protocol (AP) and b) for those who did not (DP), which were already recommended in the agreement described in the guidelines of hospital. 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.

Keywords: pneumonia; antibiotics; drug resistance; pediatrics.

1. INTRODUCTION

Pneumonia is linked to the lower respiratory tract infection and inflammation that can affect both the alveoli and interstitium of lungs. The common manifestations are dyspnea, productive cough, fever and chest pain¹. This disease acquires attention in the global public health scenario because of high morbidity and mortality across the world, especially in children under 5 years old represented the total of 18% of death cases in the pediatric public^{2,3}.

In 2017, the disease was responsible for attaining more than 50,000 deaths in children in Brazil and was representing an important cause of hospitalization in same age group of children^{4,5}. In addition, it has also drawn the attention in North and Northeast states, which have high mortality rates due to pneumonia^{1,6}. 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^{7,8}.

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^{9,3}. These are treated with the use of antibiotics, which are empirically based on three pillars: epidemiology; resistance profile; rational use of antimicrobials¹⁰.

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 causes¹¹.

Rephrase the following paragraph as:

Pneumonia caused by the resistant bacteria is difficult to manage clinically, especially in patients who stay longer in hospitals often show worse outcome. Therefore, the targeted antibiotic therapy is fundamentally required for rational use of pharmacological in childhood pneumonia caused by *streptococcus pneumoniae*.^{10,12}

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 retrospective and descriptive cross-sectional study was conducted to evaluate the antibiotic usage in patients hospitalized from 1 September 2017 to 31 December 2021 in the pediatric sector of the Hospital Universitário Júlio Bandeira (HUJB), Cajazeiras-Paraíba, reference for the municipalities of the Ninth Health Region of Paraíba.

2.2 Target Population/Sample

The study included patients treated at the pediatrics sector of the Hospital Universitário Júlio Bandeira (children and adolescents aged from 11 months old to 17 years old) diagnosed with

Comment [AK3]: Add more reference precisely explain the estimation of WHO regarding mortality comparison.

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Paediatric infections caused by *Streptococcus pneumoniae* include otitis media, sinusitis, occult pneumonia, meningitis, bacteremia, osteomyelitis, septic arthritis, peritonitis and pericarditis.

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 on the Management Application for University Hospitals (AGHU).

The data was carefully analyzed and a spreadsheet is prepared containing the following information: antibiotics used; hospitalization time; treatment effectiveness; followed the hospital protocol.

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 passed to oral route in case of improvement of the patient and discharge conditions).

Note:

1. Tabulated for of the protocol and also mention for pneumonia cases including community acquired pneumonia, atypical pneumonia alongside the cases of *Streptococcus pneumoniae*.
2. Please recheck the protocol and ask other reviewers from medical background.
3. Authors have mentioned the drug resistant bacteria so it is imperative to explain the observed antibiotic resistance in patients who followed the treatment regimen fully.
4. Please specify the protocol for Pneumonia cases only. Check the time period for pneumonia cases treatment.
5. *Legionella* infection is generally linked to 50+ aged groups. You can mention specifically in discussion if any case found with *Legionella* and others as multifactorial infection.
6. Protocol number or any specific guideline.

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	%			
Effectiveness							
Not effective	12	18,5	53	81,5	1		
Effective	283	43,5	367	56,5	3,41	1,79 - 6,49	< 0,001
Therapy							
Monotherapy	219	51,8	204	48,2	1		
Polytherapy	77	26,5	214	73,5	0,33	0,24 - 0,46	< 0,001
Number of antibiotics							
One	219	51,8	204	48,2	1		
Two	67	28,8	166	71,2	0,38	0,27 - 0,53	< 0,001
Three or more	10	17,2	48	82,8	0,19	0,10 - 0,39	< 0,001
Length of stay							
Less than 3 days	49	35,8	88	64,2	1		

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Comment [AK6]: Change the heading: Patients did not adhered to the protocol

3 to 6 days	203	45,3	245	54,7	1,49	1,01 - 2,21	0,049
7 days or more	44	33,3	88	66,7	0,90	0,54 - 1,49	0,675

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.

Finally, it is possible to observe in table 3 that there was a significant increase in the prescription of azithromycin in the years 2020 and 2021 (pandemic period), with OR of 2.64 and OR of 9.59 ($P < 0,001$), respectively, and OR of 4.20 ($P < 0,001$) of the period, when compared to the pre-pandemic period (2017, 2018 and 2019).

Table 3 - Association between Azithromycin and year

Variables	Azithromycin				OR	CI 95%	
	Yes		No				
	n	%	n	%			
Year							
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
Year							
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

Comment [AK7]: Patients adhered to the protocol

Comment [AK8]: Patients did not adhere to the protocol

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.

- Note: 1. Graphical representation of this data will be more visible instead of tables.
2. During monotherapy and polytherapy what are the antibiotic resistance patterns observed.
3. If authors like to mention of operations and protocols of antibiotic resistance pattern for those patients who haven't shown any improvement.
4. Azithromycin is used massively for both AP and DP group. Any impact. If these were not available then you might wish to add more as how can that be contributed to the effective operation.
5. It is worthwhile to mention the therapeutic failure in any of patients linked to AP or DP group.

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 cases¹³.

Apart from bacterial pneumonia of *Streptococcus pneumoniae* (pneumococcus), the main etiological agents isolated in patients, prevalent in up to 70% of cases, had been 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 situations¹⁴.

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 costs¹³.

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 adolescents¹⁵.

Therefore, according to one meta-analysis¹⁶, 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 response¹³.

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 drugs¹³.

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^{16,17}.

As for following the protocol and prescribed treatment, the findings of this study differ from those provided in the literature, one study¹⁸ highlight that the recommendations regarding the choice of antibiotic were followed in 91.8% of cases and another¹⁹ 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 research²⁰ 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 drug²¹. 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^{21,22}.

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-19²³.

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 analgesics²⁴. However, studies²⁵ 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, the growing use of azithromycin was observed during the years of the Covid-19 pandemic.

Please edit couple of more lines as what was the accurate outcome and how it has contributed for the safer treatment. What can be done for further improvements!

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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