Original Research Article

A retrospective cohort analysis of the treatment of Bacterial pneumonia pediatric 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 pain[1]. 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[3,9] . These are treated with the use of antibiotics, which are empirically based on three pillars: epidemiology; resistance profile; rational use of antimicrobials [10].

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 be comparable to deaths from oncological causes in 2020[11,12]. Also, pediatric infections caused by Streptococcus pneumonae include otitis media, sinusitis, occult pneumonia, meningitis, bacteremia, osteomyelitis, septic arthritis, peritonitis and pericarditis[10,13].

Pneumonia caused by the resistant bacteria is difficult to manage clinically, especially in patients who stay longer in hospitals often show worse outcomes. Therefore, the targeted antibiotic therapy is fundamentally required for rational use of pharmacological in childhood pneumonia caused by *streptococcus pneumoniae*.[10,14].

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

2.1Characterization 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 . 2Target 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 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 (PROTOCOL FOR THE RATIONAL USE OF ANTIMICROBIALS PRT.SVSSP.001 V.3-HUJB)

2.4.1 Therapeutic options for hospitalization for bacterial pneumonia:

2.4.1.1 Community acquired pneumonia:

0-21 days:

1st option: Ampicillin 100-200mg/kg/day 6/6hs + gentamicin 5mg/kg/day for 10-14 days;

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

21 days – 3 months:

1st option: Oxacillin 50mg/kg/day (newborns 25mg/kg/day) every 6 hours + gentamicin 5mg/kg/day for 10-14 days;

2nd option: Ampicillin (100-200mg/kg/day) + gentamicin (5mg/kg/day) for 10-14 days.

>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 7-10 days;

2nd option: Crystalline penicillin 100000 to 200000iu/kg/day 6/6hs for 7-10 days;

3rd option: Ceftriaxone 100mg/kg/ day 12/12h (IV or IM) for 7-10 days.

> 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) for 7 days;

2.4.1.2 Atypical pneumonia:

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

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.Unfortunately, due to the lack of cultures, it was not possible to analyze the etiological profile or the occurrence of resistant bacteria

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

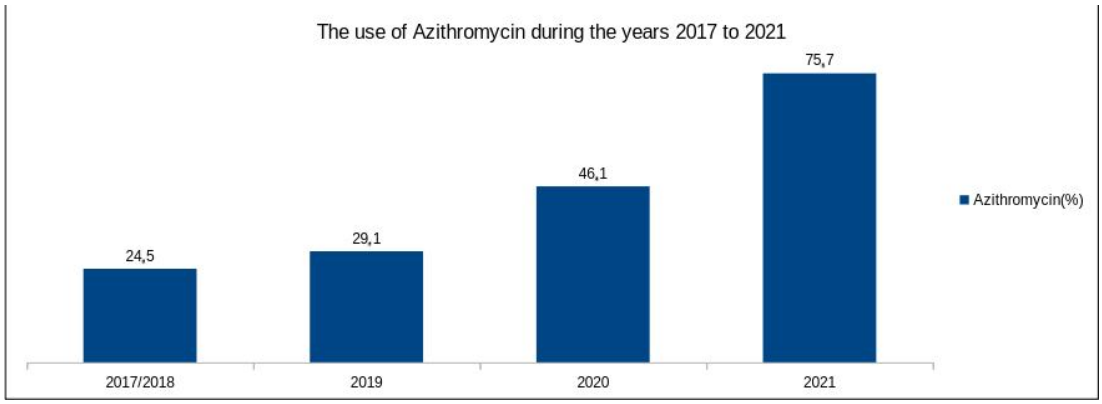
Variables	**Protocol**						
	Patients Adhered to the Protocol		Patients did not Adhered to the Protocol				
	n	**%**	**n**	**%**	**OR**	**CI 95%**	**p-value**
Effectiveness							
Not effective	12	18,5	53	81,5	1		
Effective	283	43,5	367	56,5	3,41	1,79 - 6,49	< 0,001
Therapy							
Monotherapy	219	51,8	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		
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).

Grafic 1 – The use of Azithromycin during the years 2017 to 2021.



Source: Own authorship (2023).

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[15].

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 situations [16].

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[15].

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[17].

Therefore, according to one meta-analysis[18], 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[15].

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[15].

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[18,19].

As for following the protocol and prescribed treatment, the findings of this study differ from those provided in the literature, one study[20] highlight that the recommendations regarding the choice of antibiotic were followed in 91.8% of cases and another[21] 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[22] 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[23]. 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[23,24].

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[25].

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[26] . However, studies[27] 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 ($p < 0.001$), such unreasonable use poses a future risk due to unnecessary exposure to a broad-spectrum antibiotic.

.

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 (RC=3,41); less use of antibiotics,with less chance of indicating monotherapy(RC=0,33), or making use of 2(RC=0,38), or three or more antibiotics (RC=0,19); and adequate length of stay for the prescribed treatment, with greater chances of hospitalization time of 3 to 6 days (RC=1,49) and smaller chances of hospitalizations longer than 7 days (RC=0,90), these factors associated with shorter hospital stay, complications and costs, in addition to reducing exposure to multiple antibiotics, therefore, checking the compliance of the antibiotic with the protocol ,by the pharmacy ,before dispensing the medication can be beneficial.. Furthermore, the growing 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, due to the research demanding access to private data from the medical record, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

REFERENCES

1. Ferreira Bueno NF, Soares de Sousa B, Negreiros Santos M, Ataídes França L, Martins Reis Junior P. EPIDEMIOLOGICAL PROFILE OF HOSPITALIZATION DUE TO

PNEUMONIA IN CHILDREN IN TOCANTINS BETWEEN 2014 AND 2018. Revista de Patologia do Tocantins. 2020 Oct 18;7(3):3–6. Accessed 02 March 2023. Available: https://sistemas.uft.edu.br/periodicos/index.php/patologia/article/view/8200.

2. Gaspar MAR, Barros PHS, Costa ASV, Soares FA, Oliveira BLCA de. Social inequality and hospitalizations for pneumonia in children under five years of age in the State of Maranhão, Brazil. Brazilian Journal of Mother and Child Health [Internet]. 2020 May 11 20(1):81–9. Accessed 02 March 2023. Available from: https://www.scielo.br/j/rbsmi/a/MtvWvKSRk9YSRW4mTdrfFJw/abstract/?lang=pt
3. Community-acquired pneumonia in childhood. Scientific Department of Pulmonology of the Brazilian Society of Pediatrics.2018; 3:1-8. Accessed 02 March 2023. Available from: https://www.sbp.com.br/fileadmin/user_upload/Pneumologia_-_20981d-DC_-_Pneumonia_adquirida_na_comunidade-ok.pdf.
4. Da Silva CH, Oliveira RX de, Gomes AP, Moreira TR, Braga LM. Antimicrobial resistance in community-acquired pneumonia: literature review. VITTALLE - Journal of Health Sciences. 2021 Dec 20;33(3):76–88. Accessed 02 March. Available: https://periodicos.furg.br/vittalle/article/view/12659
5. Fuchs Bahlis L, Diogo L, De Souza Kuchenbecker R, Fuchs S, Fuchs L. Mailing address. J bras pneumol [Internet]. 2018 Jun;44(04). Accessed 02 March 2023. Available: https://www.scielo.br/pdf/jbpneu/v44n4/pt_1806-3713-jbpneu-44-04-00261.pdf
6. Nascimento RT, Farah LE. Epidemiological profile of pneumonia patients in the State of Sergipe. Brazilian Journal of Health Review. 2020;3(5):13292–9. Accessed 02 March 2023. Available: https://www.brazilianjournals.com/index.php/BJHR/article/view/17254
7. Pimenta AGD, Mendes AP de S, Braga BSC, Silva BV da C, Teixeira D, Ramos EC, et al. Health education as a tool to prevent childhood pneumonia: experience report. Research, Society and Development. 2021 Feb 7;10(2):e13410212039. Accessed 02 March 2023. Available: https://rsdjournal.org/index.php/rsd/article/view/12039
8. Cardoso de Oliveira I, Fernandes Moreira EA, Barbosa de Andrade F. EVALUATION OF CHILD MORBIDITY AND MORTALITY DUE TO RESPIRATORY CAUSES IN THE AGE GROUP FROM 1 TO 4 YEARS IN NORTHEAST BRAZIL. Plural Science Magazine. 2020 Jun 13;6(2):140–55. Accessed 02 March 2023. Available: https://periodicos.ufrn.br/rcp/article/view/19910.
9. Assunção RG, Pereira WA, Abreu AG. BACTERIAL PNEUMONIA: EPIDEMIOLOGICAL ASPECTS, PATHOPHYSIOLOGY AND ADVANCES IN DIAGNOSIS. Journal of Biomedical Investigation [Internet]. 2018 Jul 31;10(1):83–91. Accessed 02 March 2023. Available: http://www.ceuma.br/portalderevistas/index.php/RIB/article/view/211
10. Alfayate Miguélez S, Garcia-Marcos L. Rational use of antimicrobials in the treatment of upper airway infections. Journal of Pediatrics. 2020 Mar;96(1):111–9. Accessed 02 March 2023. Available: https://www.scielo.br/j/jped/a/R88T8szYzBGGcjHHgRsTdVM/?format=html&stop=next&lang=en.
11. Lanks CW, Musani AI, Hsia DW. Community-acquired Pneumonia and Hospital-acquired Pneumonia. Medical Clinics of North America. 2019 May;103(3):487–501. Accessed 02 March 2023. Available: https://www.medical.theclinics.com/article/S0025-7125(18)30173-1/fulltext.
12. Teresa C, Graham D, Amy P, So A, Topp E. Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance. 2023. Accessed 03 May 2023. Available: https://www.unep.org/resources/superbugs/environmental-action?gclid=Cj0KCQjw9deiBhC1ARIsAHLjR2C4HFMwzJ-p0LKtXdE5Affr3cuZ_xmGgJ2Ow_WspqvtwNLlAk4TYtMaAh-oEALw_wcB.
13. Martinón-Torres F, Salas A, Rivero-Calle I, Cebey-López M, Pardo-Seco J, Herberg JA, et al. Life-threatening infections in children in Europe (the EUCLIDS Project): a prospective cohort study. The Lancet Child & Adolescent Health [Internet]. 2018 Jun 1

;2(6):404–14. Accessed 03 May 2023.Available: https://pubmed.ncbi.nlm.nih.gov/30169282/
14. Fritz CQ, Edwards KM, Self WH, Grijalva CG, Zhu Y, Arnold SR, et al. Prevalence, Risk Factors, and Outcomes of Bacteremic Pneumonia in Children. Pediatrics [Internet]. 2019 Jun 19;144(1):e20183090. Accessed 02 March 2023. Available: https://pediatrics.aappublications.org/content/pediatrics/144/1/e20183090.full.pdf
15. Corrêa R de A, Costa AN, Lundgren F, Michelin L, Figueiredo MR, Holanda M, et al. 2018 recommendations for the management of community acquired pneumonia. Brazilian Journal of Pulmonology [Internet]. 2018 Oct;44(5):405–23. Accessed 03 March 2023. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6467584/
16. SYRIAN BENEFICENT ASSOCIATION - HCOR. Emergency Care Protocol - Community-Acquired Bacterial Pneumonia [Internet]. Syria: HCOR, 2021. Accessed 02 March 2023. Available:https://www.hcor.com.br/area-medica/wp-content/uploads/sites/3/2021/12/PROTOCOLOS_PROTOCOLOS_SOCORRO_PNEUMONIA_BACTERIANA_ACQUIRIDA-web.pdf
17. Krapiec AB. Complications of community acquired pneumonia in children: associated factors and therapeutic failure association. Pediatric Residence. 2022;12(1). Accessed 02 March 2023. Available: https://residenciapediatrica.com.br/detalhes/1072/complicacoes%20da%20pneumonia%20adquirida%20na%20comunidade%20em%20criancas-%20fatores%20associados%20e%20a%20associacao%20com%20falha%20terapeutica.
18. Fonseca Lima E, Lima D, Serra GH, Abreu e Lima MA, Mello MJ. Prescription of antibiotics in community-acquired pneumonia in children: are we following the recommendations? Therapeutics and Clinical Risk Management. 2016 Jun;12:983. Accessed 02 March 2023. Available: https://www.tandfonline.com/doi/full/10.2147/TCRM.S101709.
19. Nascimento LCGB do, Alves Junior GL, Pereira VM, Rodrigues G da S, Silva Júnior AB da, Lemos ALC, et al. Bacterial resistance in the treatment of pneumonia in hospital unit patients: a systematic review. Research, Society and Development. 2022 Sep 26;11(13):e25111334930. Accessed 02 March 2023. Available: https://rsdjournal.org/index.php/rsd/article/view/34930.
20. Tannous R, Haddad RN, Torbey P-H. Management of Community-Acquired Pneumonia in Pediatrics: Adherence to Clinical Guidelines. Frontiers in Pediatrics. 2020 Jun 19;8. Accessed 02 March 2023. Available: https://www.frontiersin.org/articles/10.3389/fped.2020.00302/full.
21. Di Pietro P, Della Casa Alberighi O, Silvestri M, Tosca MA, Ruocco A, Conforti G, et al. Monitoring adherence to guidelines of antibiotic use in pediatric pneumonia: the MAREA study. Italian Journal of Pediatrics. 2017 Dec;43(1). Accessed 02 March 2023. Available: https://link.springer.com/article/10.1186/s13052-017-0432-2.
22. Del Risco Zevallos J, Olivas Via MA. Characterization of the prescription and use of antimicrobials and the occurrence of adverse reactions attributable to patients hospitalized in five departments of a Hospital level III-1 in Lima-Perú in 2017. repositorioupchedupe[Internet]. 2017. Accessed 02 March 2023. Available: https://hdl.handle.net/20.500.12866/602
23. Santos B da S, Silva MS da, Pereira IO e, Lemos LB, Lemos G da S. Potential drug interactions and profile of antimicrobials prescribed for outpatient use in the interior of Bahia. Research, Society and Development. 2021 Apr 17;10(4):. Accessed 02 March 2023. Available: https://rsdjournal.org/index.php/rsd/article/view/14250.
24. Cortes ALB, Silvino ZR. Factors associated to potential drug interactions in one Intensive Care Unit: a cross-sectional study. Escola Anna Nery. 2019;23(3). Accessed 02 March 2023. Available: https://www.scielo.br/j/ean/a/ct9jpdg5WQv3qF6HNzQPmrJ/?lang=en.

25. Pani A, Lauriola M, Romandini A, Scaglione F. Macrolides and viral infections: focus on azithromycin in COVID-19 pathology. International Journal of Antimicrobial Agents [Internet]. 2020 Aug 1;56(2):106053. Accessed 02 March 2023. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7286256/
26. ALVIM M. Uso desenfreado de antibióticos na pandemia pode levar a 'apagão' contra bactérias resistentes. BBC News [Internet]. 2020 Out 17. Accessed 03 March 2023. Available: https://www.bbc.com/portuguese/geral-54532598.
27. Horby PW, Roddick A, Spata E, Staplin N, Emberson JR, Pessoa-Amorim G, et al. Azithromycin in Hospitalised Patients with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Medrxiv. 2020 Dec 14. Accessed 03 March 2023