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Pharmacokinetics optimization of antimicrobials: a stewardship approach for pediatric patients with pneumonia and hypoalbuminemia

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Abstract

Objective: To evaluate whether pharmacokinetic optimization of beta-lactam antibiotics highly bound to plasma proteins prevent escalation to broader-spectrum antibiotics in pediatric patients with complicated CAP. **Methods:** Retrospective cohort study in a pediatric tertiary hospital, involving patients with complicated CAP treated with optimized doses of ceftriaxone and/or oxacillin, monitored by the antimicrobial stewardship program between 2023 and 2024. Patients admitted to the wards were included, excluding those in ICUs, hemato-oncology or with treatment time less than 48 hours. Data were collected from clinical records and analyzed using SPSS v2.0, including descriptive analyses (means, standard deviation, frequencies) and inferential tests (Mann-Whitney, Student's t-test, Chi-Square/Fisher, $p<0.05$). The outcomes evaluated were clinical/microbiological cure, treatment failure, and augmented renal clearance. The study followed the STROBE guidelines and was approved by the Ethics Committee (CAAE: 77560624.9.0000.0097). **Results:** The sample included 53 patients, of which 96.2% had complicated CAP, high prevalence of hypoalbuminemia (92.5%) and augmented renal clearance (91.3%). There was a significant reduction in escalation in 2024 (from 48.3% to 8.3%; $p=0.001$), decreased in the time to intervention for therapy optimization (5th vs. 3rd day, $p=0.004$), and reduction in total treatment duration (12.2 vs. 9.5 days, $p=0.011$) after protocol implementation. No adverse reactions occurred, and clinical cure without escalation was observed in 69.8% of patients. **Conclusion:** Pharmacokinetic optimization of beta-lactam antibiotics was effective in reducing escalation in patients with complicated CAP. The pharmacist's role in stewardship, contributed to better clinical outcomes and safety, with positive impacts on clinical practice and adherence to the protocol.

Keywords: pneumonia, pharmacokinetics, antimicrobial stewardship, pediatrics.

Otimização farmacocinética de antimicrobianos: uma estratégia de *stewardship* em pacientes pediátricos com pneumonia e hipoalbuminemia

Resumo

Objetivo: Avaliar se a otimização farmacocinética de antibióticos beta-lactâmicos altamente ligados a proteínas plasmáticas evitou o escalonamento para antibióticos de maior espectro de ação em pacientes pediátricos com PAC (pneumonia adquirida na comunidade) complicada. **Métodos:** Estudo de coorte retrospectivo em hospital pediátrico terciário, envolvendo pacientes com PAC complicada tratados com doses otimizadas de ceftriaxona e/ou oxacilina, acompanhados pelo programa de *stewardship* de antimicrobianos entre 2023 e 2024. Foram incluídos pacientes internados em enfermarias, excluindo-se aqueles em UTIs, hemato-oncologia ou com tempo de tratamento menor que 48 horas. Os dados foram coletados a partir de registros clínicos e analisados no SPSS v2.0, incluindo análises descritivas (médias, desvio-padrão, frequências) e testes inferenciais (*Mann-Whitney*, *T-Student*, *Qui-Quadrado/Fisher*, $p<0,05$). Os desfechos avaliados foram cura clínica/microbiológica, falha terapêutica e *hiperclearance* renal. O estudo seguiu as diretrizes STROBE e foi aprovado pelo Comitê de Ética (CAAE: 77560624.9.0000.0097). **Resultados:** A amostra incluiu 53 pacientes, dos quais 96,2% apresentaram PAC complicada, alta prevalência de hipoalbuminemia (92,5%) e *hiperclearance* renal (91,3%). Houve redução significativa no escalonamento em 2024 (de 48,3% para 8,3%; $p= 0,001$), diminuição do tempo de intervenção para otimização da terapia (5º vs 3º dia, $p=0,004$) e redução na duração total do tratamento (12,2 vs 9,5 dias, $p=0,011$)

após a implementação do protocolo de otimização. Não ocorreram reações adversas, e a cura clínica sem escalonamento foi observada em 69,8% dos pacientes. **Conclusão:** A otimização farmacocinética de antibióticos beta-lactâmicos foi eficaz na redução do escalonamento em pacientes com PAC complicada. A atuação do farmacêutico no *Stewardship*, contribuiu para melhores desfechos clínicos e segurança, com impactos positivos na prática clínica e adesão ao protocolo.

Palavras-chave: pneumonia bacteriana, farmacocinética, gestão de antimicrobianos, pediatria.

Introduction

Community-acquired pneumonia (CAP) is a common respiratory infection in the pediatric population and, globally, is the leading infectious cause of childhood mortality, responsible for over 700,000 deaths annually in children under five years of age, including approximately 190,000 newborns. Most of these deaths are considered preventable[1]. A study conducted by the CHAMPS network analyzed 1,120 child deaths that occurred between 2016 and 2022 in seven low- and middle-income countries, identifying pneumonia in up to 40.6% of the deaths based on clinical data and minimally invasive tissue sampling (MITS)[2].

Complicated CAP is characterized by the presence of pleural effusion (PE) and other associated signs and symptoms, requiring hospitalization and intravenous antimicrobial therapy[3]. Regarding hospital treatment, the Pediatric Infectious Diseases Society (PIDS) recommends ampicillin or penicillin G as first-line regimens for immunized infants or school-aged children, provided local epidemiology does not indicate high levels of penicillin resistance among *Streptococcus pneumoniae* strains, which is considered the main etiologic agent of pediatric CAP[4].

In Brazil, data from the epidemiological bulletin published in 2024 by the regional vaccine surveillance system (SIREVA) showed that approximately 33% of *Streptococcus pneumoniae* strains (non-meningitis cases) are resistant to penicillins in patients under five years of age[5]. This scenario underscores the need to assess local epidemiology to guide empirical therapy in the treatment of pneumococcal diseases.

In cases of penicillin resistance, third-generation cephalosporins (ceftriaxone or cefotaxime) are recommended, in combination with oxacillin, which is the first-line treatment for *Staphylococcus aureus*, another important etiologic agent responsible for complicated CAP in children. Both antimicrobials have a pharmacokinetic feature of high plasma protein binding rates (between 85% and 95%), such as to serum albumin, which may be decreased in cases of complicated pneumonia[6]. The severity of the disease and the response time to first-line antimicrobials may lead to the decision to add vancomycin[7].

Hypoalbuminemia has been associated with various inflammatory conditions, including pneumonia, rheumatoid arthritis, severe bacterial infections, and sepsis. When present, this condition shows a direct correlation with disease severity, as well as increased morbidity and mortality. It is believed that the cause of acute hypoalbuminemia results from a combination of two pathophysiological mechanisms: albumin loss into the pleural effusion due to intravascular leakage and increased C-reactive protein (CRP) at the expense of albumin[8].

In the study by Porat et al. (2002), pleural effusion samples from patients revealed a substantial amount of protein due to intravascular leakage. Furthermore, according to the authors, high CRP levels may suggest a shift in hepatic biosynthesis favoring CRP production over albumin. In a sick child who is adequately nourished and shows no signs of protein malabsorption or albumin loss, acute hypoalbuminemia can be considered a marker of severe disease[8].

After the COVID-19 pandemic, an increase in cases of complicated community-acquired pneumonia (CAP) in pediatrics was observed, due to the low circulation of *Streptococcus pneumoniae* during the period of social restrictions, which left the pediatric population immunologically "naive" to pneumococcal serotypes not covered by vaccines but with high pathogenic potential[9]. With the challenge of the growing number of complicated CAP cases and the possibility of therapeutic failure with ceftriaxone and oxacillin regimens, antimicrobial stewardship programs play a key role in supporting the clinical team in decision-making to improve the quality of care and achieve positive patient outcomes, in addition to promoting the rational use of antimicrobials[10].

Within the multidisciplinary stewardship team, the pharmacist plays an essential role, as they possess knowledge of clinical pharmacology, including the pharmacokinetics of antimicrobials, and act as a communication facilitator among attending physicians, infectious disease specialists, microbiologists, and the nursing team[10]. One of the clinical pharmacist's responsibilities is to facilitate the application of the pharmacokinetic and pharmacodynamic (PK/PD) profile of beta-lactams, which is based on the percentage of time that the free drug concentration remains above the minimum inhibitory concentration (%fT>MIC) of the target bacteria[11].

Due to the hydrophilic nature of oxacillin and ceftriaxone, the PK/PD profile should be considered in clinical practice to optimize pharmacotherapy. The therapeutic effect of these antibiotics depends on their free (unbound) fraction, and conditions such as hypoalbuminemia and augmented renal clearance increase the risk of therapeutic failure, especially with beta-lactams that are highly bound to plasma proteins[11].

Real-world data revealed that hypoalbuminemia was common (over 80%) among pediatric patients with CAP, with or without pleural effusion (PE), suggesting that albumin levels should be assessed in all patients with this diagnosis to allow timely pharmacokinetic optimization and reduce the risk of treatment failure[12].

In this context, in cases of hypoalbuminemia, the pharmacokinetic optimization of hydrophilic beta-lactams highly bound to plasma proteins—through increased doses or administration frequency—represents an opportunity for pharmacist intervention within antimicrobial stewardship. This action helps prevent therapeutic failure during CAP treatment and avoids the need to escalate to broader-spectrum antibiotics, contributing to reduced bacterial selective pressure and more rational use of this drug class[13].

The antimicrobial stewardship model led by clinical pharmacy is based on institutional protocols and aims to disseminate clinical reasoning focused on the judicious use of these drugs[10]. Accordingly, the main measure implemented at the institution under study was the update and dissemination of the protocol for managing CAP, including guidelines for pharmacokinetic optimization.

To assess the benefits of this intervention in pharmacotherapeutic follow-up, this study aimed to evaluate whether the pharmacokinetic optimization of beta-lactam antibiotics prevented the need for escalation to broad-spectrum antibiotics in pediatric patients with complicated CAP. Additionally, secondary objectives included determining the rate of hypoalbuminemia in pediatric patients with complicated CAP; analyzing infectious cure outcomes in patients who received pharmacokinetic antimicrobial optimization; and evaluating whether the implementation of the CAP protocol improved adherence to the pharmacokinetic suggestions proposed by pharmacists. Real-world data were used to demonstrate how such interventions can increasingly influence changes in medical practice, especially in the pediatric population, given the scarcity of studies in this group.

Methods

This was a descriptive retrospective cohort study involving pediatric patients diagnosed with complicated community-acquired pneumonia (CAP) who received optimized doses of hydrophilic antibiotics (oxacillin and/or ceftriaxone). These patients were followed by a clinical pharmacist as part of the antimicrobial stewardship program over a 2-year period (from January 2023 to December 2024). The study was conducted at a tertiary philanthropic pediatric hospital in southern Brazil, with 369 beds (283 general ward beds, 76 intensive care unit beds, and 10 bone marrow transplant beds), 32 pediatric subspecialties, and 26 residency programs. The hospital serves patients from the public healthcare system (SUS), private health insurance, and private consultations, with emergency and outpatient services available.

Inclusion criteria were: patients under 18 years of age; hospitalized patients with a diagnosis of CAP; patients followed by the stewardship program in the general wards; and patients who received oxacillin and/or ceftriaxone in doses or frequencies optimized based on the PK/PD profile of the drugs. Patients were identified through the stewardship program's daily monitoring list and the hospital ward census. Those diagnosed with CAP and treated with optimized ceftriaxone and/or oxacillin therapy were considered eligible for inclusion. Exclusion criteria included: treatment with oxacillin or ceftriaxone for less than 48 hours; and patients admitted to intensive care units or hematology-oncology units.

The variables analyzed were: number of patients diagnosed with CAP who received optimized doses of ceftriaxone and/or oxacillin; patient sex and age; monotherapy or combination therapy regimens; diagnosis of complicated CAP; need for surgical intervention; positive cultures; albumin levels; creatinine clearance; need for escalation; days of treatment and therapeutic failure; time to optimization; total treatment duration; and outcome (clinical cure).

The diagnosis of complicated community-acquired pneumonia was made by the attending physician based on clinical signs and imaging findings. Hypoalbuminemia was defined as serum albumin levels ≤3.9 g/dL. Optimized doses of oxacillin were considered to be greater than 200 mg/kg/day; for ceftriaxone, doses greater than 100 mg/kg/day and/or adjusted administration frequency to three times daily. Clinical cure was defined as the resolution of infectious signs and symptoms during monotherapy treatment with optimized doses of ceftriaxone and oxacillin. Microbiological cure was defined as a negative follow-up culture after an initial positive microorganism isolation[14]. Therapeutic failure was defined as the onset or persistence of fever associated with worsening laboratory markers and the subsequent need to escalate initial pharmacotherapy. Escalation was defined as the replacement of ceftriaxone or oxacillin with a broader-spectrum antimicrobial[15]. Augmented renal clearance was analyzed based on 24-hour urinary output, defined as values >3 mL/kg/h[16]. The year 2023 corresponded to the protocol implementation phase, while 2024 represented the post-implementation period.

Data were recorded in a Microsoft Excel® spreadsheet with anonymization of patient information, and statistical analysis was performed using IBM® SPSS Statistics Software, version 2.0. For the purposes of this study, descriptive analysis included absolute frequencies (n), means, medians, standard deviations (SD), interquartile ranges (IQR), and relative frequencies (%) for qualitative variables. Normality of the data was assessed using the Shapiro-Wilk test. The Mann-Whitney U test was applied for non-normally distributed numerical variables, and the Student's t-test for normally distributed data. Additionally, the Chi-square test was used to assess independence between categorical variables, with the Fisher's exact test applied when frequencies were below 5 in more than 20% of cells. A significance level of $p<0.05$ was considered for all inferential analyses.

The study was approved by the Research Ethics Committee under the number CAAE: 77560624.9.0000.0097. This study was conducted in accordance with the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) for observational studies.

Results

During the study period, 53 patients diagnosed with CAP were included and treated with optimized doses of ceftriaxone and/or oxacillin, according to the institutional protocol (Figure 1). Detailed results are presented in Table 1. The study population consisted mainly of female patients (n = 27; 50.9%), with a median age of 4 years (IQR 3.2–4.8) at the time of treatment.

The distribution of therapeutic regimens included 9 patients receiving ceftriaxone monotherapy (17.0%), 20 receiving the combination of ceftriaxone and clindamycin or antivirals (37.7%), 20 receiving the combination of ceftriaxone and oxacillin (37.7%), and 4 treated with oxacillin in combination with clindamycin or antivirals (7.6%), totaling 53 analyzed treatments - Figure 2.

Of the 53 patients, 51 (96.2%) were diagnosed with complicated pneumonia, of whom 29 (54.7%) required procedures for infectious focus control, including pleural drainage and thoracotomy. In 44 patients (83.0%), no bacterial growth was observed in blood cultures or pleural fluid cultures. Hypoalbuminemia was identified in 49 patients (92.5%), with a mean serum albumin level of 2.5 g/dL. Additionally, augmented renal clearance was detected in 21 of these patients (91.3%).

The majority of patients (n = 44; 83.0%) received combined antibiotic treatment with clindamycin or antivirals, mainly due to the low rate of bacterial isolation. In total, 49 ceftriaxone dose optimizations were performed, resulting in a final mean dose of 150 mg/kg/day, and 24 oxacillin dose optimizations were performed, with a final mean dose of 291 mg/kg/day.

In the first and second years of the study, 29 and 24 patients were included, respectively. A greater need for antimicrobial spectrum escalation was observed in patients treated in 2023 compared to 2024 (48.3% vs. 8.3%, p = 0.001). The escalation mainly consisted of replacing the initial regimen with vancomycin or cefepime due to treatment failure associated with persistent fever or worsening laboratory parameters during therapy. Treatment failure was identified, on average, on the 9th day of treatment.

With the implementation of the institutional treatment protocol for CAP in 2023—which included the recommendation for serum albumin measurement and the optimization of antibiotic doses or administration frequencies—therapy optimization was performed on the 5th day of treatment (median). In 2024, a significant reduction in the time to therapy optimization was observed, occurring on the 3rd day of treatment (IQR 2.4–3.7; p = 0.004), reflecting greater effectiveness in the implementation and adherence to the protocol, which supported clinical discussions and stewardship team recommendations within the institution.

This antimicrobial therapy review, or "time-out," carried out on day 3 of antibiotic use, encourages the adjustment or continuation of therapy based on the patient's clinical signs and laboratory and microbiological data at an earlier stage, contributing to the definition of the optimal treatment approach at the onset of illness.[17]

In this context, it was noted that in the second year there was a considerable increase (in 2023 and 2024, respectively: 35.7% vs. 64.5%, p = 0.015) in dose or frequency optimizations before the first time-out, on the 3rd day of treatment, demonstrating greater clinical adherence to the protocol.

Additionally, there was a reduction in the total duration of CAP treatment between the two years analyzed (12.2 vs. 9.5 days, p = 0.011, 95% CI 0.64–4.73), representing a decrease of 2.7 treatment days, which is considered an appropriate duration for cases of complicated CAP.

Clinical cure was attributed to 37 patients (69.8%) who did not require therapeutic escalation with ceftriaxone or oxacillin. Considering that most patients were not treated based on pathogen isolation from cultures, and that the therapeutic regimens employed included coverage for the main etiological agents of CAP—including the combination with oseltamivir—it is not possible to attribute clinical cure solely to the pharmacokinetic optimization proposed in this study.

Discussion

The contribution of the pharmacokinetic optimization of ceftriaxone and/or oxacillin implemented through the institutional protocol was evident in the observation that most treatments did not require antimicrobial escalation, thereby avoiding the emergence of potential resistant bacteria to broader-spectrum antibiotics. Hypoalbuminemia was confirmed in the majority of cases, reinforcing the need for careful consideration of optimization strategies when using antimicrobials with high plasma protein binding. Comparing the years 2023 and 2024, a reduction in therapy escalation was observed, attributed to the dissemination of this clinical reasoning combined with the early implementation of pharmacokinetic adjustments.

When defining antimicrobial therapy, it is important to consider the impact of hypoalbuminemia in inflammatory conditions such as CAP. We observed that most patients in this study presented with this clinical condition, which may influence treatment outcomes.

In the adult population, there is evidence of a correlation between hypoalbuminemia and negative clinical outcomes. The present study confirms the prevalence of hypoalbuminemia in the pediatric population as well, suggesting it may be a contributing factor to beta-lactam treatment failure in these cases.[18]

Among the collected data, the low yield of blood cultures and pleural drainage fluid cultures in CAP cases stands out, with no bacterial growth observed in approximately 83% of patients. This represents a significant challenge for medical decision-making, interventions, and the selection of optimal treatment strategies.

In this context, the evidence-based pharmacokinetic optimization of beta-lactam antibiotics (ceftriaxone and/or oxacillin), supported by the confirmation of hypoalbuminemia associated with augmented renal clearance, helps prevent therapeutic failures due to underdosing during CAP treatment. It also offers a viable alternative to the commonly performed escalation of antimicrobial spectrum in these cases.

Regarding the study population, the lack of approved pediatric indications for many medications—resulting in a high rate of off-label use—is another obstacle in clinical practice. Furthermore, dose optimization not only improved treatment effectiveness, avoiding escalation due to persistent fever or worsening laboratory parameters, but also ensured safe and rational drug use. None of the patients experienced adverse reactions or changes in liver or kidney function, and therapeutic windows for beta-lactam antibiotics were respected.

Adherence to the CAP protocol can be demonstrated by the significant reduction in antimicrobial escalation when comparing the initial implementation year (2023) with the following year. The data on the timing and day of therapy optimization also reflect progressive adherence to the protocol, along with a shift in prescriber behavior, marked by proactive engagement and direct intervention with each healthcare professional.

Furthermore, beyond limiting the use of broad-spectrum antimicrobials, the primary goal should be the patient's recovery. In this study, more than half of the patients achieved clinical cure without the need for therapeutic escalation. A reduction in the total duration of CAP treatment between the two analyzed years was also observed, highlighting pharmacokinetic optimization as a strategy to avoid prolonged clinical courses, increase medical acceptance, and promote a change in prescribing approaches.

The findings of this study demonstrate that the role of the clinical pharmacist within the antimicrobial stewardship program, focused on optimization, was effective in preventing unnecessary escalations. The main escalation observed in CAP treatments was to vancomycin, an antimicrobial with a narrow therapeutic index, which can lead to severe adverse effects such as nephrotoxicity if not properly monitored. The clinical pharmacist's involvement in promoting adherence to the CAP protocol and preventing unnecessary use of vancomycin represents not only a stewardship initiative but also a value-based healthcare contribution for these patients.

Real-world data studies like this one have become increasingly relevant in the healthcare field, especially when aiming to inform and transform clinical practice. Unlike traditional clinical trials, which are often conducted in controlled environments with highly selected populations, real-world studies utilize data collected from everyday settings—such as hospitalizations for CAP—reflecting the complexity and diversity of patients monitored by antimicrobial stewardship programs.

With a solid foundation of real-world evidence, care teams can make informed decisions in clinical practice, tailor approaches to meet individual patient needs, and improve clinical outcomes.

The main limitations of this study include its retrospective data collection, which may compromise the completeness of information, such as the inability to calculate creatinine clearance for all patients. Additionally, the single-center approach limits the generalizability of the results to other institutions.

Conclusion

Pharmacokinetic optimization prevented escalation in the treatment of CAP, demonstrating the importance of the pharmacist's role within the stewardship program in protocol management. One year after the implementation of the institutional protocol, results showed clear adherence and dissemination of the recommended practices.

This intervention proved impactful, as the vast majority of patients with serum albumin measurements presented confirmed hypoalbuminemia, making pharmacokinetic optimization an effective and safe strategy. The predominant clinical outcome observed was cure, with no reports of adverse reactions to the optimized doses used.

Finally, emphasizing the importance of real-world data research is essential, as it not only enhances existing knowledge but also catalyzes practical changes and improvements in the quality of patient care through evidence-based healthcare. This approach allows medicine to become more adaptive, patient-centered, and effective.

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Contributors

BDA, FLC, TLS, MMC, and DB collected the data and compiled the results. BDA, DB, SSS, and BS analyzed the results and wrote the manuscript. BDA was responsible for the statistical analysis. FAM and MCR analyzed the results and supervised the development of the work.

Conflict of Interest Statement

The authors declare no conflicts of interest related to this article.

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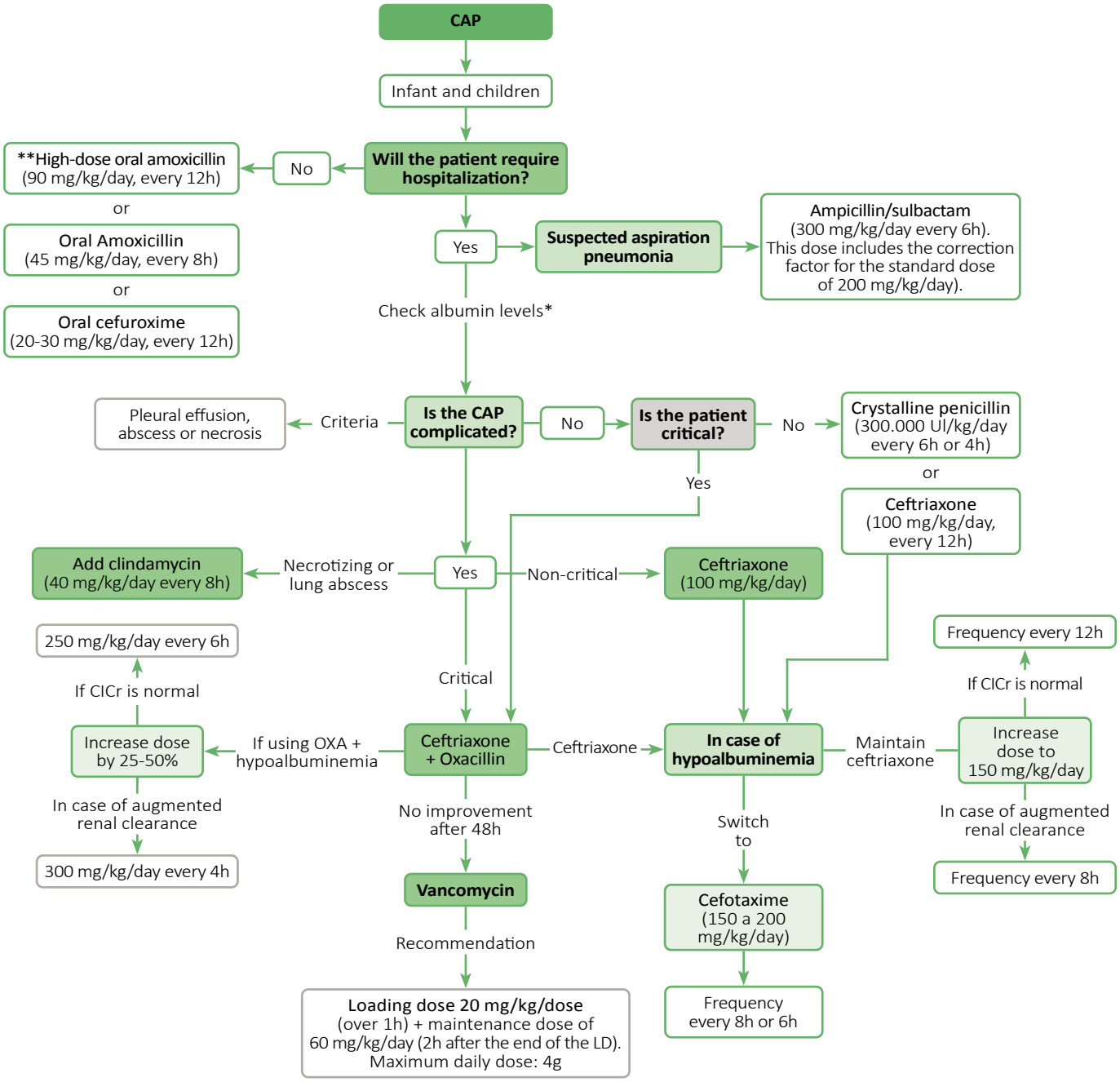
Table 1. Results obtained from treatment with optimized doses of ceftriaxone and oxacillin

Variables (n=53)	N (%)	*p*
Female Sex	27 (50.9)	
2023 (n=29)	16 (55.2)	
2024 (n=24)	11 (45.8)	
Age, median (IQR)	4.0 (3.2-4.8)	
2023	4.0 (2.0-5.0)	0.41
2024	3.0 (1.25-5.75)	
Source control (surgical procedure)	29 (54.7)	
2023	17 (58.6)	0.53
2024	12 (50.0)	
Hypoalbuminemia (serum albumin level < 3.9 mg/dL)	49 (92.5)	
2023	29 (100)	
2024	20 (100)1	
***Augmented renal clearance* in patients with hypoalbuminemia**	21 (91.3)2	
2023	10 (83.3)	
2024	11 (100)	
Clinical cure among patients who did not undergo treatment escalation	37 (69.8)	
2023	18 (62.1)	0.18
2024	19 (79.2)	
Clinical cure in patients treated with monotherapy (ceftriaxone or oxacillin) or combination therapy with both	15 (28.3)	
2023	3 (10.3)	0.006
2024	12 (50)	
Patients with escalated treatments	16 (30.2)	
2023	14 (48.3)	0.001
2024	2 (8.3)	
Treatment duration, mean (SD)	11 (4.5)	
2023	12.2 (4.8)	0.011
2024	9.5 (3.6)	
Optimization within 72 hours of treatment initiation (n=73)[3]	35 (47.9)	
2023(n=42)	15 (35.7)	0.015
2024 (n=31)	20 (64.5)	
Optimization after 72 hours of treatment initiation (n=73)[3]	38 (52.1)	
2023(n=42)	27 (64.3)	0.015
2024 (n=31)	11 (35.5)	
Day of dose or frequency optimization, median (IQR)	4.0 (3.4-4.6)	
2023	5.0 (3.9-5.6)	0.004
2024	3.0 (2.4-3.7)	

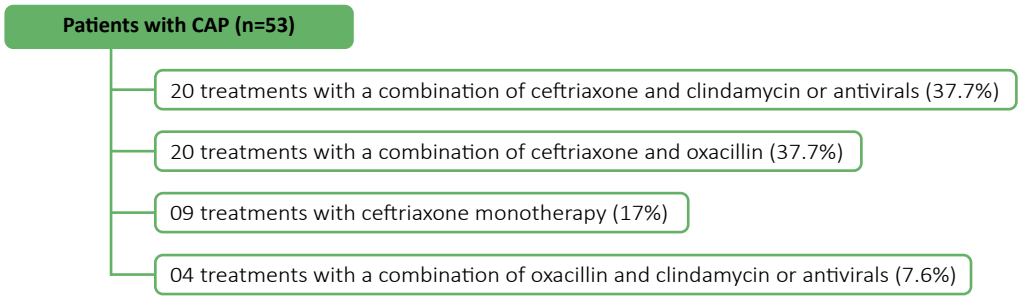
[1]Four patients were excluded from the analysis due to the absence of serum albumin measurements.
[2]The *n* for this variable would be 49, corresponding to patients with hypoalbuminemia; however, 28 patients were excluded due to missing data required for clearance calculation, leaving 12 eligible patients in 2023 and 11 in 2024. Of these, 2 patients in 2023 did not present with hypoalbuminemia.
[3]Number of treatments.

Figure 1. Institutional protocol: decision-making algorithm for antibiotic therapy in CAP.



* The albumin level measurement is strictly for the purpose of optimizing the dosage of antimicrobials that are highly protein-bound. This does not indicate that albumin replacement therapy should be performed.
** If the treatment intention is primarily to cover *S. pneumoniae*, the use of amoxicillin/clavulanate does not provide additional clinical benefit.

Figure 2. Distribution of therapeutic regimens.



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