Majalah Farmaseutik
ISSN-e: 2614-0064 | ISSN-p: 1410-590x
Volume 22(2) 2026: 177-184

Empirical Use of Cephalosporins in Pediatric Infections in Indonesia: A Systematic Review

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Submitted: 12-08-2025 *Revised: 22-02-2026* *Accepted: 06-03-2026*

ABSTRACT
Cephalosporins, particularly third-generation agents like ceftriaxone, remain widely used in pediatric populations in Indonesia despite declining effectiveness due to high rates of ESBL-producing pathogens. This systematic review synthesized evidence on cephalosporin use, resistance patterns, and effectiveness in Indonesian children across various clinical settings, based on five studies published between 2021–2023. Data included study characteristics, patient profiles, indications, and effectiveness. Ceftriaxone was the most common empirical choice for infections such as sepsis, pneumonia, and urinary tract infections. However, susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* was often below 30%, whereas amikacin and meropenem maintained over 90% activity. Notably, one tertiary pediatric ward observed a decrease in ESBL prevalence following ceftriaxone restriction, which may be associated with targeted antimicrobial stewardship programs. The findings suggest an opportunity to further align prescribing practices with current resistance patterns, highlighting the importance of real-time microbiological surveillance, and regularly updated pediatric empirical therapy guidelines. Strengthening pediatric antimicrobial stewardship is crucial to preserving antibiotic effectiveness and optimizing clinical outcomes in children amid rising resistance.
Keywords: Antibiotic; Antimicrobial resistance; Antimicrobial stewardship; Ceftriaxone; Effectiveness

INTRODUCTION
Cephalosporins, a class of β-lactam antibiotics, are among the most frequently prescribed and well-tolerated agents for empirical therapy in pediatric patients (Alshammari et al., 2025; Sillcox et al., 2024). Across five generations, cephalosporins are indicated for infections caused by both Gram-positive and Gram-negative bacteria, including meningitis, acute bacterial arthritis, skin and soft tissue infections, pneumonia, and other severe bacterial diseases (Bui et al., 2024). Third-generation cephalosporins, particularly ceftriaxone and cefotaxime, continue to serve as the cornerstone of empirical therapy for pediatric infections in Indonesia. National and institutional surveillance data consistently report that these agents represent 44–50% of systemic antibiotic prescriptions in pediatric wards (Kurniawati et al., 2023; Limato et al., 2021; Norcahyanti et al., 2021).

The pediatric population represents a uniquely vulnerable group due to their immature immune systems, altered pharmacokinetics, and limited antibiotic options. Consequently, empirical antibiotic therapy is often initiated prior to microbiological confirmation, underscoring the critical importance of selecting appropriate and effective antimicrobial agents (Versporten et al., 2016). Inappropriate empirical antibiotic selection in pediatric patients may lead to treatment failure. This may result in prolonged hospitalization and increased healthcare costs, with the most critical consequence being the emergence of antimicrobial resistance (AMR) (Girma et al., 2018; Xavier et al., 2022; Yonts et al., 2018).

AMR has emerged as a global health crisis, contributing to an estimated 1.27 million deaths worldwide in 2019. This alarming burden has prompted its designation as a “silent pandemic” (World Health Organization, 2023). In Indonesia, AMR was associated with an estimated 133,753 deaths in 2019, including 36,508 deaths directly attributable to resistance, underscoring its serious national health burden (Gach et al., 2024; Institute for Health Metrics and Evaluation, 2021). These findings highlight the urgent need for rational antibiotic use and effective antimicrobial stewardship

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to mitigate the growing impact of AMR. Within this context, cephalosporins warrant particular attention because of their predominant use as empirical therapy for pediatric infections in Indonesia.

Despite their widespread use, evidence regarding the effectiveness of cephalosporins as empirical therapy in Indonesian pediatric populations remains fragmented. While several studies have reported favorable microbiological susceptibility profiles, data linking these findings to meaningful clinical outcomes are limited and inconsistent. Furthermore, variations in local resistance patterns and prescribing practices across healthcare settings may influence therapeutic effectiveness. This systematic review aims to evaluate the effectiveness of cephalosporins when used as empirical therapy in pediatric patients in Indonesia, based on studies published from 2021 onward. By consolidating current data, this review seeks to clarify existing evidence, identify knowledge gaps, and support more rational and evidence-based antibiotic use in pediatric care.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). Literature searches were conducted in Scopus, PubMed, and Google Scholar using the keywords: ("empirical antibiotic" OR "empiric antibiotic" OR "empirical antimicrobial" OR "empiric antimicrobial") AND ("cephalosporins") AND ("effectiveness" OR "efficacy" OR "outcome") AND ("pediatric" OR "paediatric" OR "child" OR "infant" OR "adolescent") AND ("Asia" OR "Indonesia" OR "Southeast Asia").

This review will include original research articles evaluating empirical cephalosporin therapy in pediatric populations. Eligible designs comprise randomized controlled trials, cohort studies, and cross sectional. Inclusion is restricted to articles published in English from 2019 onwards. Previous systematic reviews will be consulted solely for reference tracking. Studies will be excluded if they present incomplete data, were published prior to 2019, or are classified as reviews, case series, letters, notes, conference abstracts, or opinion articles. Additional exclusions apply to studies not involving pediatric subjects or empirical cephalosporin interventions. The Joanna Briggs Institute (JBI) will be employed to assess the quality of the included articles (Zingg et al., 2016).

Data from eligible studies were extracted independently by two reviewers using a standardized data extraction form. Extracted information included study characteristics (author, year of publication, region, and study design), sample size, clinical setting, type and generation of cephalosporin used and indication for empirical treatment. Any discrepancies between reviewers were resolved through discussion.

MRP (first author) contributed to conceptualization, drafting, reviewing, and editing the manuscript. TMC (second author) participated in drafting, reviewing, and editing. AEN (third author) and IPS (fourth author) served as supervisors and investigators, providing critical guidance throughout the research process.

RESULT AND DISCUSSION

A total of five studies met the established inclusion and exclusion criteria, identified following a comprehensive screening of 3,115 articles. These studies applied diverse methodological approaches, including retrospective designs and cross-sectional descriptive analyses, enabling a multidimensional understanding of the topic. The research was conducted across multiple regions in Indonesia (Semarang, Bangil, Yogyakarta, and Surabaya) with one study adopting a multi-center design involving several hospitals. All included articles were published within the 2021–2023 period. The risk of bias of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools. This systematic review was undertaken to consolidate and critically evaluate the existing body of evidence concerning cephalosporin use, antimicrobial susceptibility trends, and therapeutic effectiveness in varied clinical contexts throughout Indonesia.

Pattern of Cephalosporin Use

Cephalosporins represent a key group of antibiotics, commonly prescribed in pediatric patients due to their strong antibacterial efficacy and favorable safety profile (Tauzin et al., 2019). Across the included studies, third-generation cephalosporins particularly ceftriaxone were consistently the most frequently prescribed agents for both prophylactic and empirical purposes in

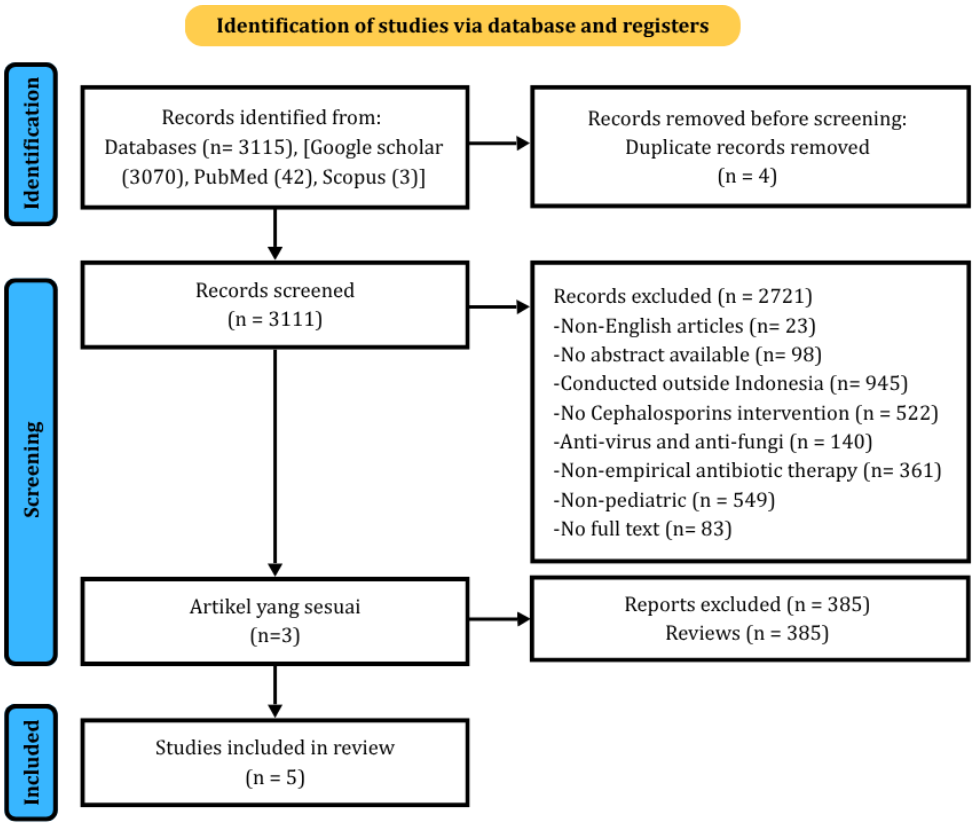

Figure 1. Research Flow Schematic

various clinical contexts in Indonesia. In the Surabaya urologic surgery cohort, ceftriaxone was used in 69.3% of procedures, predominantly as a single-dose prophylaxis administered one day before surgery, despite local bacterial cultures showing low susceptibility among Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa isolates (Asmarawati et al., 2023). In the pediatric inpatient setting in Bangil, ceftriaxone had the highest defined daily dose (DDD) value (10.3 DDD/100 bed-days) among all antibiotics, indicating substantial utilization even though the study did not assess clinical effectiveness (Norcahyanti et al., 2021).

In neonatal intensive care units (NICUs), the prescribing pattern was influenced by facility capabilities. Hospitals without microbiology culture facilities tended to rely heavily on third-generation cephalosporins for early-onset sepsis (EOS), while those with culture facilities more often used ampicillin/amoxicillin in combination with aminoglycosides (Salsabila et al., 2022). Similarly, in pediatric urinary tract infection (UTI) cases at Dr. Kariadi Hospital, a high prevalence of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-pE) was observed, yet cephalosporins remained in use despite markedly reduced susceptibility (Farida et al., 2023).

In the Yogyakarta UTI study, various cephalosporins were employed as part of empirical regimens; however, appropriateness of use according to guidelines did not correlate significantly with better clinical outcomes ($p = 0.64$)(Kurniawati et al., 2023). This finding suggests that reliance on cephalosporins, even when guideline-concordant, may not translate into improved patient recovery in areas with high resistance rates.

Overall, the evidence demonstrates a persistent trend of high cephalosporin consumption across multiple Indonesian healthcare settings, often in contexts where resistance data suggest limited effectiveness. This pattern underscores the need for ongoing antimicrobial stewardship interventions, including revisiting prophylaxis protocols and empirical therapy choices to align with up-to-date local antibiogram data.

Susceptibility Pattern of Cephalosporin

The reviewed studies consistently report susceptibility pattern of cephalosporins, particularly third-generation agents such as ceftriaxone, among common uropathogens and other bacterial isolates in Indonesian healthcare settings. In the Surabaya urologic surgery, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* demonstrated low susceptibility to ceftriaxone and cefazolin, with ESBL-pE strains accounting for 64% of E. coli and 89% of *K. pneumoniae* isolates. In contrast, aminoglycosides such as amikacin retained higher activity, with susceptibility rates reaching 97% for *E. coli* (Asmarawati et al., 2023).

In pediatric urinary tract infections, the prevalence of ESBL-pE was substantial 56.4% in 2018 and 62.9% in 2019 resulting in markedly reduced cephalosporin efficacy. Susceptibility to ceftriaxone in these strains was poor, whereas amikacin, meropenem, and fosfomycin demonstrated higher activity profiles (Farida et al., 2023). This resistance pattern was consistent with findings in neonatal sepsis cases, where gram negative pathogens dominated and cephalosporin susceptibility was limited, further supporting the use of aminoglycosides in empirical regimens in certain facilities (Salsabila et al., 2022).

Clinically, diminished microbiological efficacy of cephalosporins may lead to inconsistent therapeutic results. Such variability is shaped by multiple determinants, including the cephalosporin generation administered, prevailing bacterial resistance patterns, and the infection's clinical setting. Increasing resistance to third-generation cephalosporins, such as ceftriaxone, has been associated with higher rates of treatment failure in infections like pediatric urinary tract infections and nosocomial pneumonia (Muramatsu et al., 2024). In the Yogyakarta UTI study, guideline-concordant empirical antibiotic use, often involving cephalosporins, did not show a statistically significant association with improved patient outcomes ($p = 0.64$), indicating that appropriateness of drug selection alone may be insufficient in high-resistance settings (Kurniawati et al., 2023).

Collectively, these findings highlight that in the context of rising ESBL prevalence and multidrug resistance, cephalosporins offer limited effectiveness for certain infections in Indonesia. Alternative agents such as amikacin and meropenem, which consistently demonstrated >90% susceptibility in several studies, may provide better clinical outcomes when guided by local resistance data (Asmarawati et al., 2023; Farida et al., 2023; Salsabila et al., 2022).

The widespread use of third-generation cephalosporins in Indonesian hospitals, despite mounting resistance, underscores the urgent need for effective antimicrobial stewardship programs. Several studies within this review emphasize the mismatch between prescribing practices and local resistance data. In Surabaya, ceftriaxone was the primary prophylactic agent for urologic surgeries, even though local *E. coli* and *K. pneumoniae* isolates demonstrated high rates of ESBL production and resistance to cephalosporins (Asmarawati et al., 2023). Similar prescribing patterns were observed in pediatric and neonatal care, where cephalosporins continued to be used empirically despite evidence of limited susceptibility (Farida et al., 2023; Salsabila et al., 2022).

A notable example of stewardship intervention was the ceftriaxone restriction policy implemented at Dr. Kariadi Hospital in Semarang. This policy, enacted in January 2019, limited ceftriaxone uses to specific indications such as central nervous system infections, severe leptospirosis, sepsis, and typhoid fever in pregnant patients. Following the implementation, the overall prevalence of ESBL-pE decreased from 71.7% to 55.5%, demonstrating that targeted restriction policies can yield measurable improvements in resistance profiles (Farida et al., 2023). However, the persistence of inappropriate cephalosporin use in other institutions suggests that policy changes must be coupled with broader stewardship measures. These include regular updates to hospital antibiotic formularies, mandatory adherence to empirical treatment guidelines informed by local antibiogram data, and continuous clinician education on resistance trends. The Yogyakarta UTI study further highlighted that guideline adherence alone does not guarantee improved clinical outcomes if the guidelines are not adapted to reflect current resistance patterns (Kurniawati et al., 2023).

Considering these findings, stewardship programs should prioritize integrating real-time microbiological surveillance into empirical therapy decision-making. This would allow for the rational use of cephalosporins, reserving them for cases where susceptibility is confirmed, and promoting alternative agents such as aminoglycosides or carbapenems when resistance rates exceed

e I. Summary of included studies on cephalosporin use and effectiveness in Indonesia

uthors	Year	Region	Study Design	Sample Size	Pathological Condition	Cephalosporin Use	Effectivenes
Pudy arawati .	2023	Surabaya, Indonesia	Retrospective, descriptive	179 procedure s	Patients undergoing urologic surgeries	Ceftriaxone was most used (69.3%) for prophylaxis, despite low susceptibility in *E. coli*, *K. pneumoniae*, and *P. aeruginosa*	Low effectiveness due to high resistance; aminoglycosides suggest as alternative
 niawati et	2023	Yogyakarta, Indonesia	Retrospective, cross-sectional	196 patients	Hospitalized UTI patients	Ceftriaxone, Cefixime, Cefotaxime, Ciprofloxacin, Cefuroxime, Cefoperazone	No significant relationsh between guideline-appropriate cephalospor uses and improved outcomes (p=0.64)
nsa abila et al.	2022	Multi-center, Indonesia	Retrospective, cross-sectional	2,509 neonates (242 with EOS)	Early-onset neonatal sepsis	3rd-generation of cephalosporins commonly used in hospitals without culture facilities	Cephalosporins showed lower effectiveness than aminoglycosides
 cahyanti	2021	Bangil, Indonesia	Retrospective, cross-sectional	402 pediatric inpatients	Various bacterial infections (diarrhea, bronchopneum onia, TB)	Ceftriaxone showed the highest DDD (10.3/100 bed-days) among cephalosporins	Ceftriaxone was found to be the most used antibio
mia Farida .	2023	Semarang, Indonesia	Retrospective, cross-sectional	318 confirmed pediatric UTI cases	UTI caused by extended-spectrum β lactamase-producing Enterobacteriac eae (ESBL-pE)	The antimicrobial susceptibility pattern remained sensitive to ciprofloxacin	Cephalosporins demonstrated low effectiveness, whereas amikacin, meropenem, a fosfomycin showed high activity.

acceptable thresholds (Asmarawati et al., 2023; Farida et al., 2023; Salsabila et al., 2022). However, several important considerations must be taken into account when using aminoglycosides and carbapenems as empirical therapy in pediatric patients.

Aminoglycosides, such as amikacin and gentamicin, are associated with nephrotoxicity, posing significant safety concerns in pediatric patients. Recent epidemiological studies show that Acute Kidney Injury (AKI) may occur in 20-33% of children to exposed aminoglycosides. To prevent nephrotoxicity from aminoglycoside may be carried out by choice of aminoglycoside, extended interval dosing, therapeutic drug monitoring, nebulised aminoglycosides, daily monitoring of serum creatinine, time of dosing, pharmacological interventions, and inhibition of megalin-mediated endocytosis of aminoglycoside (Mcwilliam et al., 2025).

Furthermore, carbapenem use in children should be carefully optimized, as they are often considered a therapeutic option for last-line treatment in multidrug-resistant infections (Ramalingam, 2016). Carbapenem administration is not straightforward, as these agents are classified within the reserve group and require careful clinical consideration prior to initiation (Kementerian Kesehatan RI, 2021). The emergence of carbapenem-resistant organisms, such as carbapenem-resistant *Acinetobacter baumannii* (CRAB), is also associated with increased treatment complexity and higher healthcare costs. Therefore, antimicrobial stewardship is essential to preserve their effectiveness in pediatric populations (Cohen et al., 2023; Lashari, 2022)

Implication for Practice

The findings from this review highlight several important considerations for clinical practice. First, the selection of cephalosporins, particularly third-generation agents should be guided by up-to-date local resistance data rather than solely by national or historical guidelines. In multiple Indonesian settings, high ESBL prevalence and low susceptibility rates have rendered cephalosporins less effective for common pathogens such as *E. coli* and *K. pneumoniae* (Asmarawati et al., 2023; Farida et al., 2023). Second, aminoglycosides such as amikacin and carbapenems such as meropenem have consistently demonstrated superior *in vitro* activity, with susceptibility rates exceeding 90% in several studies. Therefore, they may be considered alternative empirical options in high-resistance settings, provided that their use is guided by strict clinical judgment and antimicrobial stewardship principles (Farida et al., 2023; Salsabila et al., 2022). Third, sustainable improvement in prescribing practices will require comprehensive antimicrobial stewardship interventions, including regular updates to hospital formularies. In addition, prescribing decisions should be guided by local bacterial susceptibility patterns and supported by real-time microbiological surveillance (Kurniawati et al., 2023; Norcahyanti et al., 2021). By aligning antibiotic selection with current local epidemiology and ensuring prescribers are equipped with the latest resistance data, healthcare facilities can improve treatment outcomes while mitigating the further spread of multidrug-resistant organisms.

Limitations

This review has several important limitations. Most of the included studies primarily reported microbiological outcomes. Only a few evaluated clinically meaningful endpoints, such as symptom resolution, mortality, or length of hospital stay. As a result, the true clinical effectiveness of cephalosporin therapy cannot be fully determined. The findings may also be influenced by publication bias. Studies reporting significant resistance patterns or notable microbiological results are more likely to be published. This could lead to an overestimation of the burden of antimicrobial resistance. In addition, the majority of the included studies were retrospective and conducted in single centers. This limits the generalizability of the findings across diverse healthcare settings in Indonesia. Future research should prioritize prospective, multicenter designs that integrate both microbiological and clinical outcomes to generate more robust and clinically relevant evidence for guiding empirical antibiotic therapy.

CONCLUSION

Third-generation cephalosporins, particularly ceftriaxone, remain widely used in Indonesia despite increasing evidence of resistance among ESBL-producing pathogens. The persistence of high consumption in the context of reduced susceptibility highlights gaps in antimicrobial stewardship

practices. Strengthening guideline adherence, surveillance integration, and culture-guided therapy is urgently needed to optimize antibiotic use and mitigate the spread of multidrug-resistant organisms.

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