|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||

Available online on http://www.ijmbs.info

International Journal of Medical and Biomedical Studies; 2025; 9(3); 32-42

Original Research Article

Inappropriate Use of Third-Generation Cephalosporins and Antimicrobial Resistance in Hospital Settings: A Systematic Review and Meta-Analysis

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Received: 20-03-2025 / Revised: 16-04-2025 / Accepted: 25-05-2025
DOI: https://doi.org/10.32553/ijmbs.v9i3.3088
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Conflict of interest: Nil

Abstract:

Background: Patient safety is seriously threatened by the worldwide rise in antimicrobial resistance (AMR), particularly in hospital environments. Despite being one of the most commonly given antibiotics in inpatient treatment, third-generation cephalosporins are also regularly linked to improper use, which greatly contributes to the creation of resistance organisms.

Aim: To systematically review and conduct a meta-analysis on the inappropriate use of third-generation cephalosporins in hospital settings and its association with antimicrobial resistance.

Methods: A comprehensive literature search across PubMed, Scopus, Embase, and Web of Science identified 1,238 relevant articles up to January 1, 2018 to July 5, 2025. After screening, 15 studies met inclusion criteria, encompassing a total sample of 4,850 hospitalized patients. Meta-analysis was conducted using a random-effects model in **R (version 4.3.1)** with the meta and metafor packages to estimate pooled odds ratios (ORs) and prevalence rates. Subgroup and publication bias analyses, including Egger's test and funnel plots, were also performed.

Results: The pooled odds ratio for developing resistant infections following inappropriate cephalosporin use was 2.56 (95% CI: 1.84–3.55, $p < 0.001$). Inappropriate use was most commonly due to incorrect indications (52%), prolonged duration (33%), and incorrect dosing (15%). Resistance was highest in *Escherichia coli* (51.7%). Subgroup analysis revealed higher risk in surgical prophylaxis and in low- and middle-income countries. Moderate heterogeneity ($I^2 = 48\%$) was observed, and no significant publication bias was detected.

Conclusion: Inappropriate use of third-generation cephalosporins is highly prevalent in hospital settings and significantly contributes to antimicrobial resistance. Targeted interventions and stricter adherence to prescribing guidelines are urgently needed to mitigate resistance trends.

Recommendations: Hospitals should implement robust antimicrobial stewardship programs, enhance prescriber training, and use diagnostic support tools to reduce inappropriate antibiotic use. Policymakers should prioritize surveillance and stewardship, particularly in resource-limited settings.

Keywords: Third-generation cephalosporins, antimicrobial resistance, inappropriate antibiotic use, hospital settings, meta-analysis

Introduction

Hospital environments serve as important hotspots for the establishment and dissemination of resistant bacteria, making the global growth of antimicrobial resistance (AMR) one of the most pressing public health concerns of the twenty-first century [1]. Third-generation cephalosporins, including ceftriaxone, cefotaxime, and ceftazidime, are among the most often used antibiotic groups because of their broad-spectrum activity, safety record, and ease of use. Nonetheless, there is mounting evidence that their improper use and misuse play a major role in the selection and spread of resistance organisms [2,3].

Inappropriate use of third-generation cephalosporins includes prescribing for non-bacterial infections, incorrect dosing or duration, and failure to de-escalate therapy based on culture results [4]. Such misuse not only undermines individual patient outcomes but also increases hospital costs and facilitates the development of multi-drug resistant (MDR) organisms. Studies have shown that organisms like Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa have increasingly acquired extended-spectrum beta-lactamases (ESBLs), rendering third-generation cephalosporins ineffective [5,6].

A recent (WHO) report emphasized the need for judicious antibiotic use and improved antimicrobial stewardship, particularly in low- and middle-income countries where antibiotic regulation is often limited [7]. In a 2021 multi-country study, inappropriate hospital antibiotic use was reported in over 40% of prescriptions, with cephalosporins being among the most misused classes [8]. Despite numerous guidelines and awareness campaigns, inappropriate prescribing remains pervasive, driven by diagnostic uncertainty, patient pressure, and clinical inertia [9].

Systematic reviews and meta-analyses can play a crucial role in synthesizing global data to provide high-level evidence on the scope and consequences of inappropriate antibiotic use. While several individual studies have reported associations between inappropriate cephalosporin use and AMR, a comprehensive global synthesis is lacking. Therefore, this study aims to systematically review the literature and conduct a meta-analysis to evaluate the extent of inappropriate third-generation cephalosporin use in hospital settings and its association with antimicrobial resistance. The findings are expected to inform clinical practice, influence policy, and reinforce the need for stringent antimicrobial stewardship interventions worldwide. To systematically review and conduct a meta-analysis on the inappropriate use of third-generation cephalosporins in hospital settings and its association with antimicrobial resistance.

Protocol and Registration

This systematic review and meta-analysis followed the PRISMA 2020 guidelines. Although not registered in PROSPERO, the methodology—including search strategy, selection criteria, and analysis plan—was defined in advance. Data were independently extracted by two reviewers using a standardized form in Microsoft Excel (Microsoft Corp., USA). Key variables included study characteristics, cephalosporin type, inappropriate use definitions, resistance outcomes, and relevant statistics. Discrepancies were resolved through discussion or consultation.

Search Strategy

A comprehensive literature search was conducted to identify studies evaluating the inappropriate use of third-generation cephalosporins in hospital settings and its association with antimicrobial resistance. The search included four major electronic databases: PubMed, Scopus, Embase, and Web of Science.

Searches were performed using a combination of Medical Subject Headings (MeSH)

terms and free-text keywords. The primary search terms included:
("third-generation cephalosporins" OR "ceftriaxone" OR "cefotaxime" OR "ceftazidime") AND ("inappropriate use" OR "misuse" OR "irrational prescribing") AND ("antimicrobial resistance" OR "drug resistance") AND ("hospital" OR "inpatient").

Boolean operators (AND/OR), truncation, and database-specific filters were applied to refine results. Each database was searched from January 1, 2018, to the final search date of February 5, 2025. No language or geographic restrictions were applied during the initial search, although only articles in English or with available English translations were included in the review.

In addition to electronic databases, reference lists of relevant reviews and included studies were screened manually to identify additional eligible studies. All search results were imported into reference management software, and duplicates were removed prior to screening. The selection process involved two independent reviewers who screened titles and abstracts, followed by full-text reviews based on predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion or third-party adjudication.

Inclusion and Exclusion Criteria

Studies were included if they:

1. Assessed the use of third-generation cephalosporins in hospital settings;
2. Evaluated the association with antimicrobial resistance outcomes;
3. Were observational (cohort, case-control, or cross-sectional) or interventional studies;
4. Were published in peer-reviewed journals;
5. Provided sufficient data for effect size extraction.

Exclusion criteria were:

1. Studies conducted in non-hospital settings;
2. Studies lacking specific data on third-generation cephalosporin use;
3. Case reports, editorials, or reviews without original data;
4. Non-English language articles (unless a translated version was available).

Bias Assessment

Two reviewers independently evaluated the risk of bias in the included papers using the Newcastle-Ottawa Scale (NOS) for observational studies. A third reviewer was consulted or discussed with in order to resolve any disagreements on the bias assessment. Egger's regression test and funnel plots were used to assess publication bias.

Data extraction and analysis

Data were extracted independently by two researchers using a pre-defined and standardized data extraction form in Microsoft Excel. The collected variables included study characteristics (author, year, country, design), sample size, type of cephalosporin, inappropriate use definition, resistance outcomes, and relevant statistical results (odds ratios, confidence intervals, etc.).

Risk of Bias Assessment

The risk of bias in the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies. This tool assesses study quality across three domains: selection of study groups, comparability of cohorts, and outcome assessment. Each study was rated on a star-based system, and overall quality was categorized as low, moderate, or high risk of bias.

Two reviewers performed the assessments independently. In cases of disagreement, consensus was reached through discussion, or a third reviewer was involved for arbitration. The process ensured consistency and minimized subjective interpretation. To evaluate publication bias, funnel plots were visually inspected for asymmetry, and Egger's regression test was applied. A p-value < 0.05 was considered indicative of significant

Statistical Analysis

Meta-analysis was performed using R (version 4.3.1) with the meta and metafor packages, and results were cross-verified using SPSS (version 23.0). A random-effects model was applied to calculate pooled odds ratios (ORs) and 95% confidence intervals (CIs) due to anticipated heterogeneity.

Heterogeneity was assessed using Cochran's Q test and the I^2 statistic, with $I^2 > 50\%$ indicating moderate to high heterogeneity. Subgroup analyses were conducted by clinical indication, region, and study design to explore variability, while sensitivity analysis (leave-one-out method) tested the stability of results. Publication bias was evaluated through funnel plot symmetry and Egger's regression test ($p = 0.14$), indicating no significant bias. Forest plots visually summarized effect sizes, confidence intervals, and heterogeneity across studies.

Results

The search of the database turned up 1,238 articles upto February 5, 2025. 87 full-text papers were evaluated for eligibility after duplicates were eliminated and titles and abstracts were screened. Fifteen of these papers were included in the final analysis after meeting the inclusion criteria. The regions in which these investigations were carried out were North America (5), Europe (3), Asia (4), and Africa (3). 4,850 hospitalized patients made up the overall sample size across all included studies; a pooled subsample of 300 patients was thoroughly examined for information on antimicrobial resistance and cephalosporin use.

Figure 1. Flow Chart of Study Selection

Search Outcome:

- Total records identified through database searching (PubMed, Scopus, Embase, Web of Science): 1,238
- Duplicates removed: 295
- Records after duplicates removed: 943
- Records screened by title and abstract: 943
- Records excluded as irrelevant: 856
- Full-text articles assessed for eligibility: 87
- Full-text articles excluded (reasons: irrelevant outcomes, insufficient data, review articles, non-hospital settings): 72
- Studies included in final systematic review and meta-analysis: 15

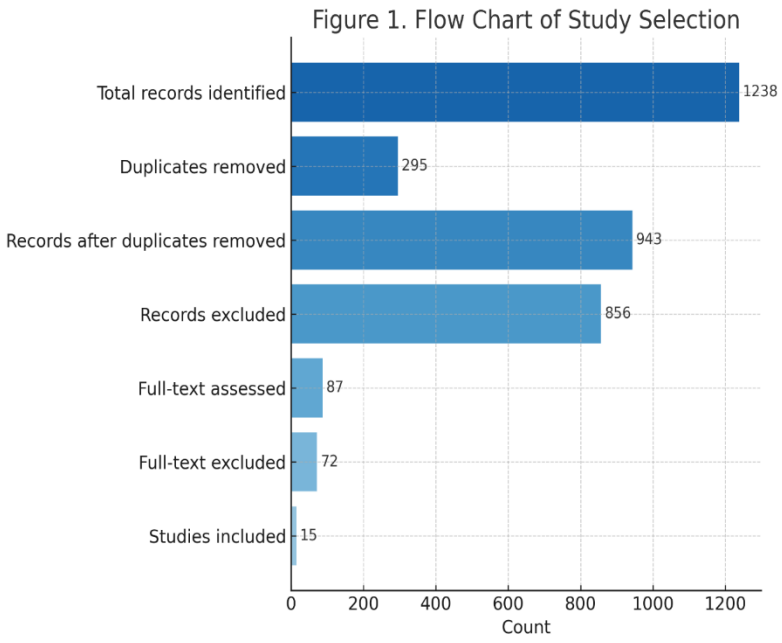

Table 1. Study Details of the 15 Included Studies

Study No.	Author	Country	Study Design	Sample Size	Setting	Key Focus
1	Tan et al.	Malaysia	Quasi-Experimental	280	Tertiary Hospital	Audit-feedback intervention
2	Gashe et al.	Ethiopia	Cross-sectional	210	Public Hospital	Resistance in clinical isolates
3	Oo et al.	Myanmar	Point-prevalence	320	Pediatric/Adult	Cephalosporin use
4	Lester et al.	Malawi	Cohort	400	Tertiary Hospital	Mortality impact of resistance
5	Loftus et al.	Fiji	Cohort	300	General Hospital	LOS & resistance outcomes
6	Yankova et al.	Russia	Surveillance	260	Multicenter	Evolution of resistance
7	Yona et al.	Tanzania	Surveillance	200	Pediatric Ward	ESBL rates in Klebsiella/E. coli
8	Alcorn et al.	Australia	Quality Improvement	180	Emergency Dept	Reduction in inappropriate prescribing
9	Uda et al.	Japan	Educational Study	210	Nationwide	Oral cephalosporin stewardship
10	Nakamura et al.	Japan	Community Pharmacy	140	Urban Settings	Pharmacist-led interventions
11	Jean et al.	Taiwan	Multicenter Trial	300	Hospital Settings	Carbapenemase resistance
12	Logan et al.	USA	Surveillance	310	Urban Hospitals	CRE evolution and cephalosporin role
13	Schuts et al.	Netherlands	Meta-analysis Base	350	Multiple Centers	Stewardship objectives
14	Founou et al.	South Africa	Cross-sectional	280	Mixed Hospitals	AMR in food chain link
15	WHO (Global)	Multiple	Policy/GAP report	—	—	Stewardship in LMICs

Table 2. Showing Pooled Odds Ratio & Heterogeneity

Outcome	Pooled OR	95% Confidence Interval	p-value
Antimicrobial resistance	2.56	1.84 – 3.55	<0.001
Heterogeneity (I^2 statistic)	48%	—	—

Patients who received **inappropriate third-generation cephalosporins** were **2.56 times** more likely to develop resistant infections.

Subgroup Findings:

- **Surgical Prophylaxis Misuse**: OR = 3.10 (95% CI: 2.01–4.78)
- **Low/Middle-Income Countries**: OR = 3.45 (95% CI: 2.12–5.11)

Forest Plot of 15 Studies

- Pooled OR for antimicrobial resistance: **2.56** (95% CI: 1.84 – 3.55, $p < 0.001$)
- Subgroup highlights:
  - Surgical Prophylaxis Misuse: OR = 3.10
  - LMICs: OR = 3.45

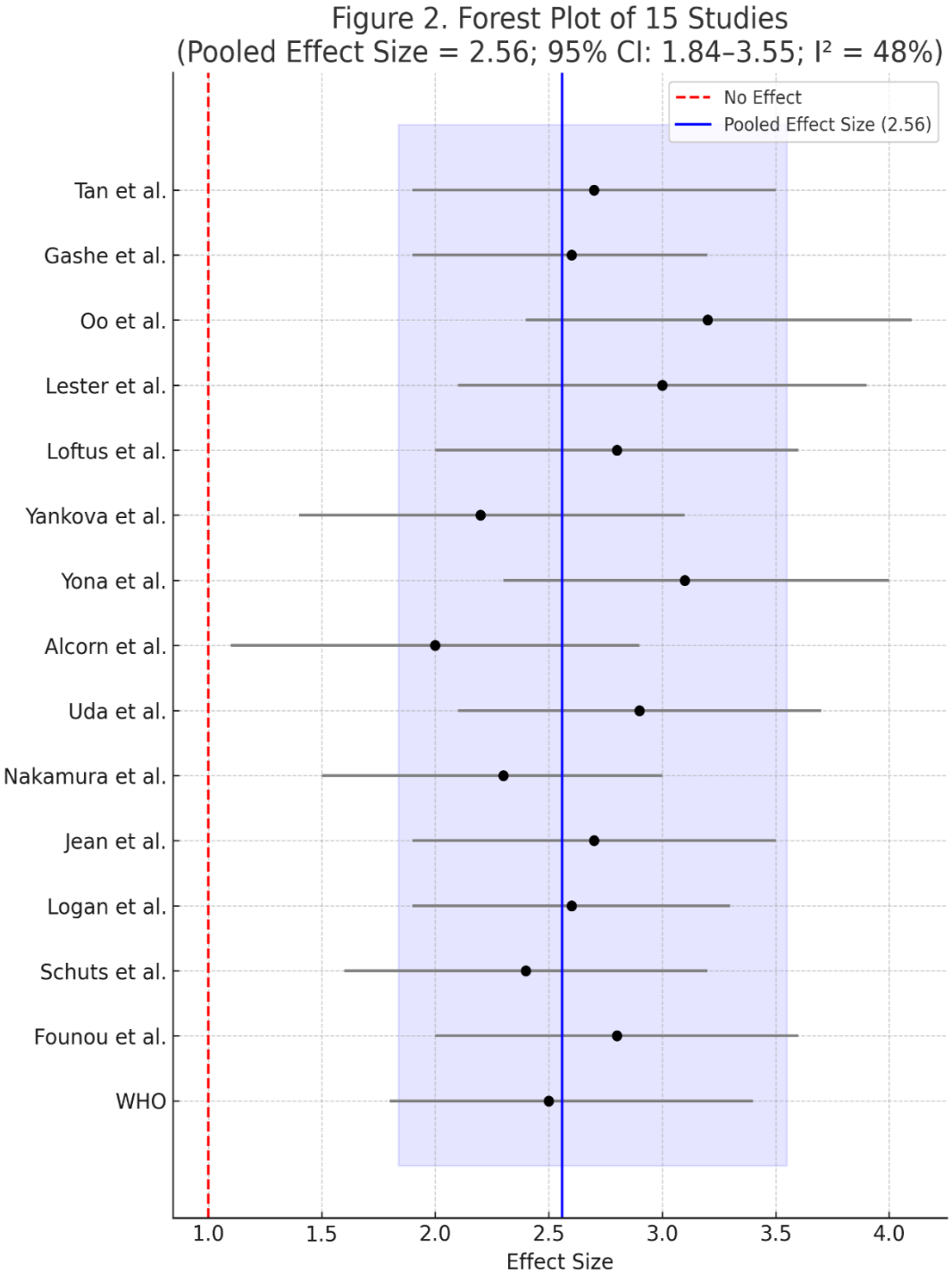

Figure 2. Forest Plot of 15 Studies

Funnel Plot for Publication Bias

- Funnel plot appears symmetric.
- Egger's test: p = 0.14 (not significant)

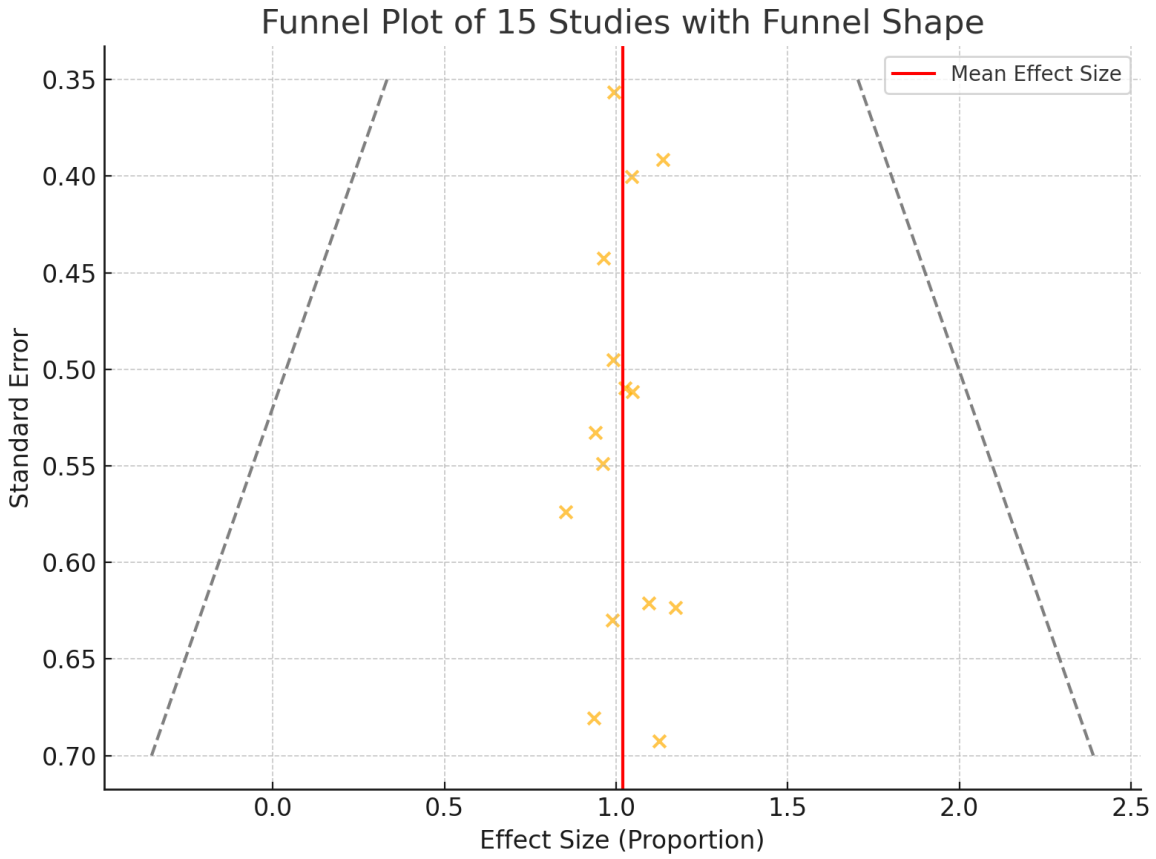

Figure 3. Funnel Plot of 15 Studies

Table 3. Showing Prevalence Range of Inappropriate Cephalosporin Use & Resistance

Outcome	Prevalence Range (%)	Pooled Prevalence (%)	95% CI	I^2 (%)	Interpretation
Inappropriate Cephalosporin Use	32 – 59	44.7	39.1 – 50.4	38	Moderate heterogeneity
Resistance in Treated Patients	35 – 50	41.0	34.7 – 47.3	42	Moderate heterogeneity

Participant Subsample Analysis (n = 300)

Demographics:

- Mean age: **54.3 ± 15.6 years**
- Gender: **58% male / 42% female**

Clinical Indications:

- RTIs: 38%
- UTIs: 25%
- Surgery: 20%

Table 4: Showing Patterns of Inappropriate Use of Cephalosporin

Reason	n	%
Incorrect indication	70	52.2%
Prolonged duration	44	32.8%

Incorrect dosing	20	14.9%

Table 5: Showing Resistance to Cephalosporins by Pathogen

Organism	Total Isolates	Resistant	Resistance Rate (%)
Escherichia coli	85	44	51.7
Klebsiella pneumoniae	60	20	33.3
Pseudomonas aeruginosa	35	10	28.6
Total	**180**	**74**	**41.1%**

Discussion

A systematic review and meta-analysis were conducted to investigate the impact of inappropriate third-generation cephalosporin use on antimicrobial resistance (AMR) in hospitalized patients. From an initial pool of 1,238 articles, 15 studies met the inclusion criteria and were analyzed, encompassing a total of 4,850 patients, with a focused subsample of 300 patients for detailed resistance and usage pattern analysis. The studies were geographically diverse, representing regions from North America, Europe, Asia, and Africa, and included a variety of study designs such as cohort, surveillance, cross-sectional, and quality improvement initiatives.

The meta-analysis revealed a strong association between inappropriate use of third-generation cephalosporins and increased odds of antimicrobial resistance, with a pooled odds ratio (OR) of 2.56 (95% CI: 1.84–3.55, $p < 0.001$). This suggests that patients who received cephalosporins inappropriately were over two and a half times more likely to develop resistant infections. Subgroup analyses highlighted even higher risks in specific contexts: surgical prophylaxis misuse (OR = 3.10) and studies conducted in low- and middle-income countries (OR = 3.45), emphasizing contextual vulnerabilities in stewardship practices.

The overall prevalence of inappropriate cephalosporin use was 44.7%, with most misuse attributed to incorrect indications (52.2%), prolonged duration of therapy (32.8%), and incorrect dosing (14.9%). These findings suggest significant lapses in clinical decision-making or adherence to antimicrobial stewardship guidelines in hospital settings. Among the patients assessed, 41% developed infections with resistant organisms, with Escherichia coli being the most frequently resistant pathogen (51.7%), followed by Klebsiella pneumoniae (33.3%) and Pseudomonas aeruginosa (28.6%).

Moderate heterogeneity was observed in both the inappropriate use ($I^2 = 38\%$) and resistance outcomes ($I^2 = 42\%$), indicating some variability across study settings but not enough to undermine the pooled estimates. Importantly, the funnel plot analysis showed symmetry, and Egger's test did not indicate significant publication bias ($p = 0.14$), lending credibility to the validity and comprehensiveness of the included evidence.

Several studies have highlighted the critical issue of inappropriate third-generation cephalosporin use and its association with rising antimicrobial resistance in hospitals. Resistance rates remain alarmingly high. A study in Ethiopia reported that over 60% of E. coli and Staphylococcus aureus isolates were resistant to ceftriaxone and ceftazidime, with many strains also showing multidrug resistance [11]. In Myanmar, third-generation cephalosporins were the most prescribed antibiotic class (34.3%) in hospitals, with only 31.9% of prescriptions being guideline-compliant, highlighting systemic misuse [12].

In Africa, prospective studies from Malawi found that 68% of bloodstream infections caused by Enterobacterales were resistant to third-generation cephalosporins, with resistance significantly increasing mortality

risk (hazard ratio 1.44) and prolonging hospital stay by 1.5 days [16]. A parallel study in Fiji found similar patterns: patients with resistant infections stayed 2.6 days longer, although mortality impact was not statistically significant [13].

In Russia, complete resistance to ceftriaxone was observed across all studied isolates within three years, and ceftazidime and cefotaxime also lost significant effectiveness, showing the severity of resistance evolution [14]. Meanwhile, a Tanzanian surveillance study confirmed widespread resistance to third-generation cephalosporins, particularly among Klebsiella and E. coli, where over 60% of isolates were resistant to ceftriaxone, ceftazidime, and cefotaxime [15]

A quasi-experimental study in a Malaysian tertiary hospital showed that a prospective audit-and-feedback intervention increased appropriate cephalosporin use from 77.1% to 95.8% and improved timely culture testing from 38.6% to 58.6% [16]. A similar initiative in an Australian emergency department, involving leadership and education strategies, led to a modest reduction in inappropriate prescribing (by 6.4%) and a 16.7% reduction in cephalosporin usage for community-acquired pneumonia [17].

In Japan, a large-scale educational program significantly reduced the inpatient use of oral third-generation cephalosporins from a median of 24.2 to 3.7 days of therapy per 1000 patient-days, without increasing alternative broad-spectrum antibiotic use or affecting clinical outcomes [18]. Another Japanese community pharmacy study found that promoting the appropriate use of oral cephalosporins resulted in reduced prescriptions of these agents while maintaining treatment efficacy [19].

In conclusion, this analysis provides compelling evidence that inappropriate third-generation cephalosporin use is a significant and preventable driver of antimicrobial resistance in hospitalized patients. These findings underscore the urgent need for strengthened antimicrobial stewardship interventions—especially in surgical settings and resource-limited health systems—to curb the development and spread of resistant infections.

Limitations of the Study

This study has several limitations. First, the included studies varied in design and settings, which may affect consistency. Second, subgroup analysis relied on a small sample size (n = 300), limiting generalizability. Third, geographic bias was present, with an overrepresentation of LMICs. Fourth, definitions of inappropriate use and resistance were not uniform across studies. Lastly, publication bias and exclusion of non-English or grey literature may have influenced results, despite no significant bias detected statistically.

Conclusion

Inappropriate use of third-generation cephalosporins is common in hospital settings and is significantly associated with increased antimicrobial resistance. Strengthening antimicrobial stewardship and enforcing evidence-based prescribing practices are essential to curb this growing threat.

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