



Original Article



A Study on Formulary Restriction and Preauthorization of Reserved Antibiotics: Adherence, Posology, and Consumption in Adult Inpatients

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ABSTRACT

Background: Antimicrobial resistance (AMR) is a global threat owing to the overuse and inappropriate use of antibiotics, including the WHO's 'Reserve' category of antibiotics. Antimicrobial stewardship strategy of formulary restriction and preauthorization is an important intervention in curbing the developing resistance, however, the effectiveness of such interventions must be periodically assessed.

Objectives: To verify adherence to the formulary restriction and preauthorization process for reserved antibiotics in adult inpatients, assess prescribing practices including posology, and evaluate consumption trends of both reserved and non-reserved antibiotics.

Methods: This prospective, cross-sectional audit was conducted at a tertiary care teaching hospital in India between April and July 2024. A total of 225 consecutive reserved antibiotic prescriptions were reviewed. Appropriateness of indication, dose, route and method of administration were assessed through bedside validation. Culture practices, empirical vs. definitive use, and de-escalation patterns were recorded. Antibiotic consumption was measured in Days of Therapy (DOT) per 1000 patient-days from 2020 to 2024 and analyzed using Mann-Whitney U and Kendall's Tau tests.

Results: Among the 225 prescriptions, 96.88% were initiated with clinically appropriate indications. However, 22.94% had incorrect selection of predefined indications within the software system. Empirical therapy accounted for 76.45% of prescriptions; cultures were sent in 95.34% of these, with 56.70% yielding growth. Of these, 33.34% were resistant to the empirical agent. Among cases eligible for de-escalation, 74.19% underwent therapy de-escalation, while the remaining 25.81% were not de-escalated despite susceptibility data supporting it, indicating a potential gap in antimicrobial stewardship practices. Dose and administration were appropriate in 89.77% and 100% of cases, respectively. Meropenem was the most used agent (67.11%), predominantly in critical care units (97.77%). Respiratory tract infections were the most common indication (33.33%). DOT for reserved antibiotics decreased over five years (from 80.81 to 65.55), with a significant downward trend ($p=0.016$), but no significant compensatory rise in non-reserved use ($p=0.9$).

Conclusion: The study demonstrated a strong compliance to the formulary restriction and preauthorization intervention process and a sustained reduction in reserved antibiotic consumption. Indication selection, dose adjustment, and de-escalation exhibited few gaps requiring continuous prescriber education, real-time audits, and feedback mechanisms to optimize antimicrobial use.

KEYWORDS: Antimicrobial Stewardship; Formulary Restriction; Preauthorization; Reserved Antibiotics; Antibiotic Consumption

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INTRODUCTION

The rise of antimicrobial resistance (AMR) has already been identified a global health threat, due to injudicious and irrational use of antimicrobial agents leading to a large volume in its consumption.¹ India, Pakistan, and Bangladesh, are among the largest consumers of antimicrobial agents, contributing disproportionately to the global AMR burden.^{2,3} As per the available literature India alone ranks among the highest in both antibiotic consumption and emergence of antimicrobial resistance.⁴

Antimicrobial stewardship programs (ASPs) are the most effective means of optimizing antimicrobial use, preserving drug efficacy, and improving clinical outcomes, especially when there is a scarcity of effective options available as well as the time consuming process of drug discovery and development.⁵ As a part of ASP several strategies have been formulated, including formulary restriction, where certain identified antimicrobial agents, also known as reserved antimicrobial agents are prescribed only for predefined indications. Preauthorization, is a process where an ID specialist or ASP member verifies the prescriptions of reserved antimicrobial agents and their indications before approving them for the use.^{5,6}

Although the procedure has several advantages of reducing the consumption of reserved antimicrobial agents, it also has several challenges. For example, formulary restrictions may be bypassed by inappropriate indication selection, especially in institutions lacking understanding of its purpose.⁶ In addition, it can delay care during after-hours, or can give rise to a tendency to shift prescribing toward unreserved agents.⁶⁻¹⁰

The Prospective Audit and Feedback (PAF) model offers a post-prescription approach, allowing tailored recommendations based on clinical context and microbiology results. Despite implementation hurdles, PAF has shown promise in reducing inappropriate therapy.^{11,12}

At our institution, a formulary restriction and preauthorization system for reserved antibiotics has been implemented. This study aimed to evaluate adherence to these stewardship protocols by verifying the appropriateness of selected clinical indications and assessing the role of the approver through a prospective audit. We also sought to compare the consumption of reserved and non-reserved antibiotics before and after implementation of these measures. Additionally, the study aimed to identify commonly prescribed reserved antibiotics, the most frequent clinical indications and hospital areas where they are used. The appropriateness of posology—including dose, route, method of administration and

de-escalation was assessed as part of the antimicrobial stewardship quality indicators.

MATERIAL AND METHODS

Study Design and Setting: This prospective, cross-sectional audit was conducted at Shree Krishna Hospital affiliated with Pramukhswami Medical College, Bhaikaka University, Karamsad, a tertiary care teaching hospital in Gujarat, India, from April 1, 2024 to July 7, 2024, following approval from the Institutional Ethics Committee (IEC/BU/145/Faculty/04/168/2023).

Data Sources: Clinical data were obtained from inpatient medical records and the Laboratory Information System (LIS). Antimicrobial consumption data were retrieved through a module that extracts the consumption data from the Hospital Information System (HIS).

Study Population and Sample Size: All adult inpatients who were prescribed a reserved antibiotic during the study period were eligible. A total of 225 consecutive prescriptions were audited.

A sample size calculation was performed using an expected adherence rate of 75% (based on previous literature), 95% confidence level, and 5% precision. Using the standard formula for proportions and applying finite population correction for an estimated population of approximately 450 prescriptions, the minimum required sample size was 176 prescriptions. The final sample of 225 prescriptions exceeded this requirement and was therefore considered scientifically adequate.

No exclusion criteria were applied.

Definitions

- Antimicrobial Stewardship (AMS):** Optimal selection, dosage, and duration of antimicrobial therapy to achieve the best clinical outcomes with minimal toxicity and minimal contribution to resistance.⁵
- Reserved Antibiotics:** WHO AWaRe “Reserve” category agents used as last-line therapy for multidrug-resistant infections.¹³
- Formulary Restriction:** Policy limiting the use of specific antimicrobials to predefined clinical indications or specific authorizations.⁵
- Preauthorization:** Mandatory approval by the AMS team or infectious disease specialist before release of certain antimicrobials.⁵

Reserved Antibiotics Included: The following antibiotics are listed under the hospital's Reserve category:

1. Imipenem
2. Meropenem
3. Vancomycin
4. Teicoplanin
5. Colistin
6. Polymyxin B
7. Linezolid
8. Ceftazidime–Avibactam

These are incorporated into the Shree Krishna Online Application for Clinical Excellence (SOLACE) with predefined clinical indications for each drug created by Microbiologists and Intensivists, and audited for appropriateness. When a reserved antibiotic is prescribed, the system sends an automated alert to an approver team (five microbiologists and three intensivists), who are expected to approve or disapprove the order within 48 hours. Prescribers may initiate therapy immediately, but disapproved drugs are subsequently removed from the online chart and pharmacy access.

Approval times are monitored, and delays beyond 48 hours are investigated.

Audit Procedure: For each prescription, the investigators conducted bedside verification of:

- Accuracy of the clinical indication selected in SOLACE
- Appropriateness of:
 - o Dosage (weight-based; renal/hepatic adjustments)
 - o Route and method of administration
- Use of the drug as empirical or definitive therapy
- Whether culture samples were sent prior to empirical initiation
- Whether empirical therapy was susceptible on culture
- Appropriateness and timeliness of de-escalation based on microbiology results
- Adherence to the 48-hour approval time

All observations were recorded in a structured audit proforma.

Antibiotic Consumption Analysis: Antibiotic use was quantified using Days of Therapy (DOT), defined as the aggregate number of days a patient receives any amount of a given antimicrobial agent.

- DOT per 1000 patient-days was calculated for reserved and non-reserved antibiotics.
- The mean DOT of 2020–2022 was used as a baseline.
- Consumption in 2023 and 2024 was compared to this baseline to evaluate the impact of preauthorization implementation.

Statistical Analysis: The following indicators were calculated:

- Percentage of prescriptions with appropriate indication
- Percentage of culture sampling before empirical therapy
- Percentage of empirical prescriptions matching susceptibility
- Percentage of cases where de-escalation was performed when indicated
- Percentage of prescriptions with appropriate dosing

Ethical Considerations: A waiver of informed consent was granted as the audit involved no direct patient interventions. In cases of incorrect dosing identified during audit, the treating team was immediately notified and the dose of the prescribed antibiotic was corrected. Privacy and confidentiality were maintained throughout the study. No external funding was required.

RESULTS

Patient Demographics and Antibiotic Use Patterns:

During the study period, a total of 18,003 patients were admitted to the hospital, of whom 17,310 were adults and 693 were pediatric patients. Among adult patients, 196 individuals who had received 225 prescriptions of reserved antibiotics were included in the study.

Among these, 48.96% (n = 95) were males and 51.04% (n = 101) were females. The mean age of the patients was 58.42 years (SD = 17.82), with males averaging 60.24 years and females 56.72 years.

Most patients (85.20%) received a single reserved antibiotic prescription. A smaller proportion received two (13.26%), three (0.51%), or four (1.02%) reserved antibiotics.

Length of Hospital Stay (LOS): The mean total hospital stay for 196 patients was 13.75 days, and the mean duration before initiating a reserved antibiotic was 6.93 days.

Of the 225 prescriptions, 97.77% were issued to patients in critical care units, where the mean hospital stay was

12.68 days, and the average time to start a reserved antibiotic was 5.97 days.

Reserved Antibiotic Utilization: The most commonly prescribed reserved antibiotic was Meropenem, accounting for over two-thirds of all prescriptions. The complete frequency distribution of reserved antibiotics is provided in Table 1.

Table 1. Frequency of Reserved Antibiotics Prescribed

Antibiotic	Frequency (n)	Percentage (%)
Meropenem	151	67.11%
Teicoplanin	19	8.44%
Polymyxin B	17	7.55%
Vancomycin	11	4.88%
Linezolid	11	4.88%
Ceftazidime–Avibactam	10	4.44%
Colistin	5	2.22%
Imipenem–Cilastatin	1	0.44%
Total	225	100%

Prescribing Location and Purpose: A majority of prescriptions originated from critical care units, while a few were issued from the medicine ward, surgery ward, and dialysis unit.

In terms of purpose, most prescriptions were for empirical therapy, with fewer used as definitive therapy. These data are summarized in Table 2.

Table 2. Empirical vs. Definitive Use of Reserved Antibiotics

Use Type	Frequency (n)	Percentage (%)
Empirical Therapy	172	76.45%
Definitive Therapy	53	23.55%

Infection Site and Organ System Involved: Reserved antibiotics were most commonly prescribed for respiratory tract infections, followed by bloodstream and urogenital infections. Full details are presented in Table 3.

Table 3. Reserved Antibiotics by Infection Site

Organ System	Frequency (n)	Percentage (%)
Respiratory Tract Infections	75	33.33%
Bloodstream Infections	47	20.88%
Urogenital Infections	41	18.22%
Gastrointestinal Infections	26	11.55%
Central Nervous System Infections	15	6.66%
Skin & Soft Tissue Infections	8	3.55%
Bone & Joint Infections	8	3.55%
Miscellaneous Infections	3	1.33%
Hepatobiliary Infections	2	0.88%
Total	225	100%

Appropriateness of Reserved Antibiotic Use: Out of the 225 prescriptions of reserved antibiotics audited, 96.88% (n = 218) were found to have a clinically

appropriate indication present in the patient's medical records, as per the predefined criteria. The remaining 3.12% (n = 7) prescriptions lacked an appropriate clinical indication. Among these seven, 57.14% (n = 4) were disapproved by the authorizing team during the preauthorization process, while 42.86% (n = 3) were inappropriately approved despite the absence of a justifiable indication.

When evaluating the accuracy of indication selection by the prescriber (i.e. whether the selected indication matched the actual clinical scenario), only 77.06% (n = 168) of prescriptions had the correct indication selected. In the remaining 22.94% (n = 50), the prescriber had selected an incorrect indication, although a different appropriate indication was present in the patient's profile. These prescriptions were approved after either a clinical review or discussion. In the 80% (n = 40) of the cases where an incorrect indication was selected, the approving authority documented the inappropriateness of the indication in only 20% (n = 10) of the cases.

Microbiological Culture Practices: Clinical specimens for culture and antimicrobial susceptibility were sent in 95.34% (n = 164) of the 172 prescriptions initiated as empirical therapy indicating a strong adherence to diagnostic stewardship principles.

Pathogen Susceptibility to Empirical Reserved Antibiotics: Among the 164 empirical prescriptions where clinical samples were sent for culture prior to initiating therapy, 56.70% (n = 93) generated a positive culture with identifiable pathogens. Among these 93 cases, the reserved antibiotic that had been empirically prescribed was found to be susceptible in 66.66% (n = 62) of cases whereas in 33.34% (n = 31) of cases, the prescribed reserved antibiotic was found to be resistant.

De-escalation Based on Culture Results: In the present study, there were 62 cases in whom the empirical reserved antibiotic was confirmed to be appropriate based on susceptibility testing. Among them 74.19% (n = 46) underwent de-escalation to a narrower-spectrum or non-reserve antibiotic whereas in 25.81% (n = 16) of these cases, de-escalation was not carried out. It was observed that the reasons for not de-escalating the antibiotic were not documented in the clinical notes, indicating a potential gap in the antimicrobial stewardship process.

Appropriateness of Dose, Route, and Administration: Out of all 225 prescriptions, the correct dose was prescribed in 89.77% (n = 202) prescriptions taking into

account patient weight and necessary renal or hepatic adjustments. However, 10.23% (n = 23) of prescriptions had dosing errors, primarily due to missed adjustments for renal or hepatic impairment. The clinicians were immediately informed about the missed dosing adjustments and the dose was corrected subsequently. The method of administration for all prescriptions was appropriate, with 100% compliance to standard institutional protocols for each reserved antibiotic.

Antibiotic Consumption Measurement: The Days of Therapy (DOT) metric was used to measure the consumption of antimicrobial agents. Consumption was standardized per 1000 patient-days.

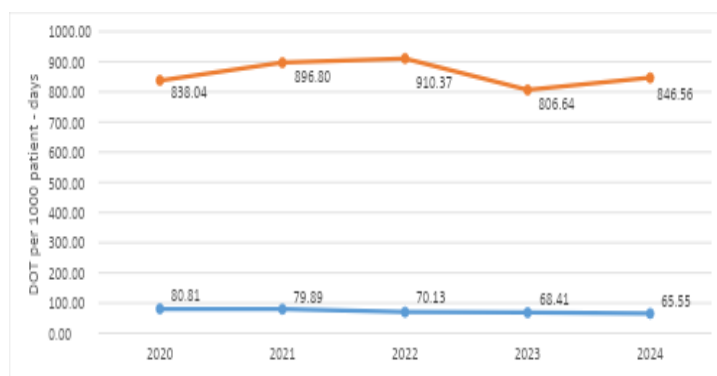


Figure 1 demonstrates the year-wise consumption trends for reserved and non-reserved antibiotics over the five-year period, with implementation of the formulary restriction and preauthorization protocol in 2023

Baseline DOT data for reserved and non-reserved antibiotics were collected for the years 2020, 2021, and 2022, prior to implementation of the preauthorization protocol. These were used as the pre-intervention period. Post-intervention data were collected for the years 2023 and 2024.

Reserved Antibiotic Consumption Trends: A reduction in reserved antibiotic consumption (DOT per 1000 patient-days) was observed following implementation of the preauthorization protocol. A Mann–Whitney U test comparing DOT between the pre-intervention and post-intervention periods yielded a U-statistic of 6.0 with a p-value of 0.2. A Kendall’s Tau test for trend analysis over the entire five-year period (2020–2024) produced a Tau value of –1.0 with a p-value of 0.016.

Non-Reserved Antibiotic Consumption Trends: To evaluate any change in non-reserved antibiotic use, a one-tailed Mann–Whitney U test comparing pre- and post-intervention periods yielded a U-statistic of 5.0 and a p-value of 0.9. The Kendall’s Tau correlation for non-reserved antibiotics over the five-year period

showed a Tau value of 0.0 and p-value of 1.0, indicating no significant trend.

DISCUSSION

This study evaluated the adherence to the process of formulary restriction and preauthorization system for reserved antibiotics at a tertiary care hospital along with its impact on antibiotic consumption.

The WHO AWaRe classification includes agents such as Cefiderocol, Ceftazidime-Avibactam, Linezolid, Colistin, and Polymyxin B under the ‘Reserve’ category.¹⁴ However, depending upon the local policies various nations, such as England, have expanded this list to include Carbapenems (e.g., Imipenem, Meropenem, Doripenem). The intention is to prevent its overuse and preserve their efficacy for a longer period, especially against multidrug-resistant Gram-negative organisms.¹⁵ In line with the similar principle our institutional policy has also included Carbapenems as well as Glycopeptides (Vancomycin, Teicoplanin) under the ‘Reserved’ category.

In the present study, a high adherence, with 96.88% (n = 218/225) of prescriptions, was observed to the clinical indications when prescribing reserved antibiotics. This demonstrates a fairly successful implementation of the stewardship protocols, supported by the SOLACE system, an in house software for electronic medical records. Within this high adherence to the clinical indication, 22.94% (n = 50) of prescriptions had an indication selection that did not match with the patient’s condition. In such cases the indication present in the patient justified the use of reserved antibiotic but the prescriber had selected a different indication from the selection panel. Among these, 80% were approved without documentation by the authorizing team member. Majority of the times junior doctors generates a prescription of the reserved antibiotics following approval from the senior consultants. The high adherence to the indication is explained by the fact that the prescriptions are supervised by the senior consultants. However, the selection of the indication from the dropdown list is solely done by the junior doctors, who sometimes, end up selecting an inappropriate indication. This suggests a lack of awareness among the junior doctors regarding the process of preauthorization and the importance of selection of appropriate indication. The findings of the present study align with those by Felix et al. (77.3% appropriate indication use),¹⁶ Jayalakshmi et al. (77.1% initial, improving to 88.3% post-intervention),¹⁷ and Teli et al. (82.11% overall appropriateness).¹⁸

The reserved antibiotics were given in the right dose in 89.77% of cases. In majority of the patients, the dose of the reserved antibiotics were adjusted as per

renal/hepatic impairment. Jayalakshmi et al. and Jose et al. observed frequent errors related to dose and duration.^{13, 17} whereas, Velu et al. reported a lower rate of indication appropriateness (44.44%) but similar dosing accuracy (86.11%).¹⁹

The antibiotic consumption did not show a statistically significant reduction in reserved antibiotic use following implementation of preauthorization ($p = 0.2$). However, the trend analysis over five years using Kendall's Tau test showed encouraging results demonstrating a significant downward trajectory (Kendall's $\tau = -1.0$, $p = 0.016$).

Persisting with the preauthorization system, the consumption trend is expected to improve over the next few years. While trying to restrict the use of reserved antibiotics, the consumption of non-reserved antibiotics tend to increase as the clinicians simply switch over to the other available options. Importantly, no compensatory increase in non-reserved antibiotic use was observed ($p = 0.9$). These trends are consistent with those reported by Aiesh et al.,²⁰ Tiwari et al.,²¹ Mahmoudi et al.,²² Ya et al.,²³ and Karanika et al.,²⁴ Singh et al.,²⁵ and Ababneh et al.²⁶ who documented reductions in reserve antibiotic use following ASP interventions. In contrast, studies conducted by Doltario et al. and Al-Omari et al., reported either a rise or unsustained decline in reserve antibiotic use post-intervention.^{27, 28} A high adherence to indication for reserved antibiotics in the present study with lack of significant reduction in its consumption also points to the fact that the prescribing pattern of the reserved antibiotic before the preauthorization process (baseline) was already rationale to a large extent.

In the present study, Meropenem was the most commonly prescribed reserve antibiotic (67.11%). The choice of antibiotic depends on the antibiotics included in the reserve list. Studies that included Carbapenems in their reserve lists (Jayalakshmi et al.,¹⁷ Felix et al.,¹⁶ Saxinger et al.,²⁹ Krishna Kumar et al.,³⁰ and Sekar et al.³¹) also found Meropenem or Imipenem to be the most frequent agents while studies excluding Carbapenems identified other drugs such as Piperacillin-Tazobactam^{13, 21}, Linezolid³² or Colistin³³ as most common antibiotic prescribed.

Adult ICUs was the most common location (97.77%) for reserved antibiotic prescriptions. Sekar et al.,³¹ described similar findings whereas Kumar et al. and Mahmoudi et al. found high usage in wards such as Orthopedics or General Surgery, respectively.^{12, 22} ICUs cater critically ill patients with several comorbidities, immunocompromized state and long standing clinical conditions requiring multiple exposure to antibiotics. The higher prevalence of infections resistant to non-reserved antibiotics in ICU patients leads to

increased use of reserved antibiotics in these locations. In the present study, reserved antibiotics were most commonly used for respiratory tract infections (33.33%). Jose et al.,¹³ Kumar et al.,³² and Bhattacharjee et al.³³ observed similar findings whereas sepsis and soft tissue infections were more prominent in studies by Felix et al.,¹⁶ Velu et al.,¹⁹ and Sekar et al..³¹ In the present study 76.45% of reserve antibiotics were prescribed empirically, owing to a high prevalence of multidrug-resistant organisms (MDROs). Prior studies conducted at our center have described high MDRO rates in VAP and bloodstream infections.^{34 - 37} Among the patients in whom reserved antibiotics were started empirically, cultures were sent in 95.34% patients. Among these 56.70% cultures revealed a growth of a pathogen of which 33.34% were resistant to the empirical agent started in these patients. Implementation of antimicrobial stewardship is highly complex in settings where there is a high prevalence of MDRO infections, often challenging even the best practices. Samarkos et al. described a similar predictive value of hospitalization history in MDRO risk.³⁸

LIMITATIONS

Formulary restriction and preauthorization is a continuous process. The present study evaluated the adherence to this system for a short duration and therefore it remains to see the compliance over a longer period of time, especially, in a medical college where there is a high turnover of doctors such as resident doctors. As antimicrobial stewardship targets a behaviour change, which takes a long time, the resulting effect in the consumption of the antibiotics may not be evident in the initial years and a longer follow – up might be required. The present study was designed primarily as an antimicrobial stewardship audit to evaluate adherence to formulary restriction and preauthorization processes for reserved antibiotics. Therefore, patient-level clinical outcomes such as mortality, clinical cure, and indication-specific length of stay were not assessed.

CONCLUSIONS

The present study represents a well implemented formulary restriction and preauthorization process using an in house designed electronic medical record system (SOLACE) and which has resulted in a consistent consumption of reserved antibiotics without unnecessary escalation in the use of non – reserved antibiotics. Although the adherence to the system was high, there were gaps in selection of indications for reserved antibiotics which could be improved by continuing awareness about the selection process. To

further improve the consumption trends other interventions such as prospective audits, antibiotic time out and microbiological feedback has to be strengthened along with education and behavior-change strategies.

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None

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest

SOURCE OF FUNDING

None

ETHICS STATEMENT INCLUDING PATIENT CONSENT

The study was approved by the Institutional Ethics Committee (IEC/BU/145/Faculty/04/168/2023) with a waiver of consent.

AUTHOR'S CONTRIBUTION

CM: Conceptualization, Methodology, Formal Analysis, Writing – Review & Editing

RD: Ethics Approval, Data Curation, Investigation, Formal Analysis, Writing – Original Draft

CD: Methodology, Data Curation, Investigation, Formal Analysis

AI DECLARATION

No AI tool was used to generate research data, perform data analysis, interpret findings, formulate scientific conclusions, or make editorial decisions. All AI-assisted content was critically reviewed, verified, and revised by the authors. The authors take full responsibility for the accuracy, originality, integrity, and final content of the manuscript.

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