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SYSTEMATIC REVIEW: THE IMPACT OF ANTIMICROBIAL STEWARDSHIP PROGRAM IMPLEMENTATION IN HOSPITAL INTENSIVE CARE UNITS

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ABSTRACT

Antimicrobial resistance represents a significant challenge in clinical settings, particularly in intensive care units (ICUs). The incidence of antimicrobial resistance in the ICUs has reached 30% of all hospital patients. Furthermore, over 71% of patients on the unit were using antibiotics. Consequently, infections contribute substantially to the elevated mortality and morbidity rates in patients with critical status. The Antimicrobial Stewardship Program (ASP) is a program that refers to a multidisciplinary approach to optimize the appropriate use of antimicrobials. This systematic review aims to identify ASP policies implemented in hospital ICUs, utilizing various parameters for assessment. This systematic review was conducted using PubMed, Scopus, Google Scholar, and the Cochrane Database of Systematic Reviews, focusing on publications from January 1, 2015, to June 1, 2024. A comprehensive review of 4,419 articles identified 12 studies that met the inclusion and exclusion criteria. The primary goal of ASP is to enhance the appropriateness of antimicrobial use, ensuring accurate prescribing practices in terms of indication, antimicrobial selection, route of administration, and therapy duration. The outcomes of ASP implementation are evaluated based on decreased in antimicrobial use, increased in the number of recommendations, decreased in treatment costs, and a decrease in multidrug-resistant organism (MDRO) incidence. Although numerous articles have provided positive results regarding the implementation of ASP in ICU settings, there remains a need for extensive and structured research to validate these findings comprehensively.

KEYWORDS *Antimicrobial Stewardship Program; Antimicrobial Resistance; Intensive Care Unit; Antimicrobial Use; Audit and Feedback*

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INTRODUCTION

Infectious diseases remain a major public health issue in communities, particularly in developing countries. These diseases arise from microorganisms that provoke immune responses, manifesting in symptomatic conditions. Antimicrobials, including antibacterials/antibiotics, antifungals, antivirals, and antiprotozoals, constitute the cornerstone of treatment for these conditions. Antibiotics, specifically designed to combat bacterial infections, play a crucial role in medical practice. However, inappropriate use of antibiotics contributes to the emergence of resistance (Kemenkes RI, 2021).

Antimicrobial resistance is defined as the ability of microorganisms to withstand exposure to antimicrobials. This phenomenon renders the administered antimicrobials ineffective in inhibiting the growth of these microorganisms (Chowdhury et al., 2020; Klein et al., 2018; Pulingam et al., 2022). The World Health Organization (WHO) has identified antimicrobial resistance as one of the foremost global public health challenges. It is projected that by 2050, antimicrobial resistance could lead to 10 million deaths annually worldwide, significantly impacting healthcare expenditures (El-Sokkary et al., 2022). This issue persists due to ongoing gaps in knowledge, attitudes, and practices related to antimicrobial use. Additionally, the sluggish pace of new drug development to combat multidrug-resistant organisms (MDROs) contributes to the exacerbation of this problem (Alfraij et al., 2023; Falcone et al., 2014).

Antimicrobial resistance can occur in various cases, notably in the intensive care units (ICUs). Studies indicate that antimicrobial resistance affects approximately 30% of all hospitalized patients in ICUs (Lindsay et al., 2019; Timsit et al., 2019). Moreover, over 71% of ICU patients receive antibiotics. Consequently, infections contribute significantly to the high mortality and morbidity rates observed among critically ill patients (Haseeb et al., 2021; Jantarathaneewat et al., 2022). Several factors contribute to antimicrobial resistance in ICUs, including advanced age of patients, compromised immune systems, prolonged hospital stays, extensive antibiotic therapies, and various invasive medical procedures. Patients in ICUs face a heightened risk of infection, being 5-10 times more susceptible compared to non-hospitalized individuals. Nosocomial infections caused by multidrug-resistant organisms (MDROs) further exacerbate morbidity, mortality, treatment costs, and prolong ICU admissions (Steinmann et al., 2018; Ture et al., 2023). Given these substantial challenges and potential impacts, stringent antimicrobial stewardship practices are essential to curtail the emergence and transmission of MDROs (Raphael et al., 2021; Wall, 2019).

The Antimicrobial Stewardship Program (ASP) is a multidisciplinary approach designed to optimize the appropriate use of antimicrobials in various healthcare institutions (Chiotos et al., 2023; Sofro et al., 2022; Tacconelli et al., 2018). Furthermore, ASP aims to enhance the accuracy of antimicrobial prescriptions, including indications, antimicrobial selection, administration routes, and therapy duration (Roca et al., 2015; Timsit et al., 2019). ASP indirectly contributes to enhancing antimicrobial utilization and potentially extending the efficacy of existing agents, while fostering the development of new therapeutic options. Variations in ASP policies across institutions exist, yet core implementation standards typically encompass: (1) monitoring patterns of antimicrobial prescribing; (2) surveillance of microbial resistance; and (3) post-prescription assessment (Lindsay et al., 2019; Mokrani et al., 2023). In light of these considerations, this systematic review aims to delineate ASP policies implemented in hospital ICUs, evaluated across multiple criteria.

RESEARCH METHODS

Search Strategy

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The publication search was performed using the databases, namely PubMed, Scopus, Google Scholar, and the Cochrane Database of Systematic Reviews from January 1, 2015, to June 1, 2024. The combination of keywords used included “stewardship AND intensive care,” “stewardship AND critical care,” “stewardship AND acute care,” “antimicrobial stewardship AND intensive care,” “antimicrobial stewardship AND critical care,” and “antimicrobial stewardship AND acute care.”

Inclusion and exclusion criteria

The study will include research conducted in hospital intensive care units (ICUs) where ASP interventions are implemented. The definition of ASP is based on guidelines from the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA). Only quantitative studies such as randomized controlled trials, controlled and non-controlled before-and-after studies, controlled and non-controlled interrupted time series analyses, and cohort studies will be included. The previous systematic reviews will be exclusively utilized for cross-referencing purposes. Exclusion criteria were reviews, case series, letters, notes, conference abstracts, and opinion articles. Other exclusion criteria were interventions in patients in units other than ICUs, the use of antiviral and antifungal interventions, and studies published in languages other than English and Indonesian.

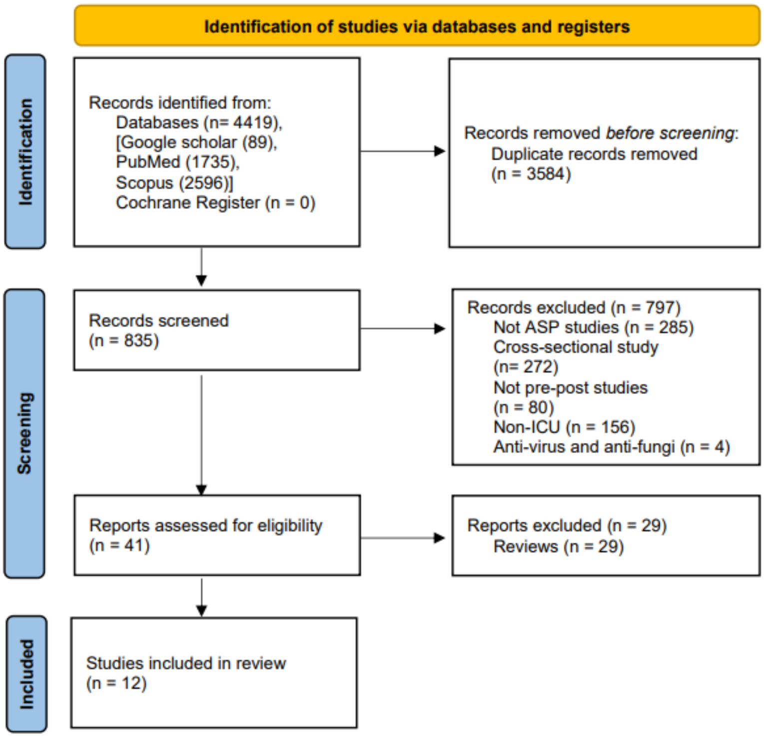

Figure 1. Research Flow Schematic

Quality assessment and risk of bias

The quality of the articles will be evaluated utilizing the Integrated Quality Criteria for Systematic Review of Multiple Study Designs (ICROMS) (Zingg et al., 2016).

Data Extraction

Data will be extracted by summarizing the details of the studies conducted, followed by an evaluation of their outcomes. Inappropriate antimicrobial use is defined as the use of broad-spectrum antibiotics when treatment with narrow-spectrum antibiotics would be sufficient, or when the duration of treatment exceeds the recommended period.

RESULTS AND DISCUSSION

A total of 12 studies met the inclusion and exclusion criteria, identified after reviewing 4,419 articles. These studies include interrupted time series analyses and uncontrolled before-after studies. The majority of studies were conducted within single hospital settings, with some involving multiple hospitals. Furthermore, all reviewed articles spanned ten regions, consisting of nine countries and one region in Latin America. This systematic review focuses on scientific articles published between 2015 and 2024. The objective of this study is to examine the implementation and impact of antimicrobial stewardship programs (ASPs) across various metrics, including antibiotic usage rates, changes in prescribing practices, and recommendation frequencies (Álvarez-Lerma et al., 2018; Vahidi et al., 2018).

The intensive care unit (ICU) stands out as a high-risk environment for infections, often characterized by a notable prevalence of multidrug-resistant (MDR) colonization. Patients in this setting, particularly those with specific risk factors and undergoing extensive medical interventions, face heightened susceptibility to infections. Arena et al. (2015) conducted research at a hospital in Siena, Italy, where they implemented an Antimicrobial Stewardship Program (ASP) featuring a Clinical Microbiology-Intensive Care Partnership (CMICP). This initiative involved daily rounds conducted by clinical microbiologists in collaboration with intensive care specialists. Discussions during these rounds focused on optimizing the use of empirical antibiotics, conducting definitive testing, diagnosing and treating infections, addressing infection control needs, and optimizing infection management strategies (Arena et al., 2015; Papan et al., 2021).

This discussion process represents a pivotal intervention strategy also utilized by Taggart et al. (2015). During the ASP intervention, a team of doctors and pharmacists reviewed patient conditions. The outcomes of these group discussions were documented and provided as verbal recommendations for patient treatment (Magdalena & Bachtiar, 2018; Taggart et al., 2015). Similarly, Ruiz-Ramos et al. (2017) and Jones et al. (2019) implemented ASP interventions involving collaboration among intensive care specialists, clinical microbiologists, and pharmacists. These initiatives featured daily discussions and feedback sessions focused on treatment recommendations and adjustments (Jones et al., 2019; Ruiz-Ramos et al., 2017). Likewise, Ruiz et al. (2017) and Kitano et al. (2019) assembled teams comprising intensive care physicians, infectious disease specialists, and pharmacists. Their discussions focused on antimicrobial prescriptions for various antibiotic classes, treatment durations exceeding recommendations, patient dosing conditions, potential interactions, and side effects (Kitano et al., 2019; Ruiz et al., 2018).

Other studies by Hohn et al. (2015), Panditrao et al. (2021), and Elsawah et al. (2022) used ASP teams consisting of intensive care specialists, clinical microbiologists, and pharmacists. The policies from these ASP groups included prescription restrictions, evaluations of antimicrobial usage, educational discussions, and guideline dissemination (Elsawah et al., 2022; Hohn et al., 2015; Panditrao et al., 2021). Devchand et al. (2019) and Haseeb et al. (2021) similarly organized ASP teams consisting of intensive care and infectious disease specialists, clinical microbiologists, and pharmacists. These studies implemented the "5 Moments" policy, which involves initiating or broadening antimicrobial use, replacing broad-spectrum antimicrobials, discontinuing antimicrobial therapy, switching from intravenous to oral antimicrobials, and optimizing dosing regimens (Devchand et al., 2019; Haseeb et al., 2021). A similar policy was observed by Quiros et al. (2022) in 77 ICUs, based on self-evaluation of ASP team composition. The ASP teams included intensive care and infectious disease specialists, clinical microbiologists, and pharmacists. Self-evaluation measurements covered leadership and coordination, institutional intervention strategies, monitoring, and education (Prestinaci et al., 2015; Quirós et al., 2022).

In general, the role of ASPs is crucial in preventing antibiotic resistance. Education is a vital element of these programs, complemented by considerations of underlying cultural and behavioral factors (Karuniawati et al., 2021; Roca et al., 2015).

ASP activities encompass a wide array of strategies, including the establishment of multidisciplinary teams, prospective audit and feedback mechanisms, antibiotic reviews, prescription constraints, dosage optimization, antimicrobial escalation and de-escalation protocols, adjustments in administration routes, guideline formulation, creation of antibiotic order forms, educational campaigns, integration of artificial intelligence for decision support, and utilization of laboratory findings for treatment decisions (Elshenawy et al., 2023; Livorsi et al., 2023).

Implementing ASPs in healthcare facilities has numerous benefits, from preventing antimicrobial resistance to reducing MDRO incidents. Arena et al. (2015) reported that ASP interventions increased appropriate empirical treatments by 34%, guideline adherence by 28%, de-escalation rates by 42%, and reduced antimicrobial use (Arena et al., 2015; Tamma et al., 2021). Hohn et al. (2015) found a 21.2% reduction in antimicrobial use and a 43% decrease in treatment costs (Hohn et al., 2015). Taggart et al. (2015) observed a 28% reduction in monthly antimicrobial use in trauma and neurosurgery ICUs but a 14% increase in medical-surgical ICU (Taggart et al., 2015). Ruiz et al. (2017) noted a 22.4% reduction in antimicrobial use, prescriptions of penicillin and β-lactamase inhibitors, linezolid, cephalosporins, and aminoglycosides, along with a reduction in treatment costs (Ruiz et al., 2018).

Similar findings were reported by Kitano et al. (2019), with a 76.2% reduction in antimicrobial use, decreased long-term antimicrobial use, and reduced MRSA levels (Kitano et al., 2019; Mokrani et al., 2023). Jones et al. (2019) reported a 6.5% reduction in antimicrobial use and a 17.6% decrease in broad-spectrum antimicrobial use (Hikaka et al., 2019). A 25% reduction in antimicrobial use was observed following ASP intervention by Haseeb et al. (2021) (Haseeb et al., 2021), while Elsawah et al. (2022) reported a significant reduction in carbapenem antibiotic use and a 37% decrease in *carbapenem-resistant Klebsiella* incidence (Elsawah et al., 2022).

Other outcomes documented in the literature include recommendations, as highlighted by Ruiz-Ramos et al. (2017) and Devchand et al. (2019). Ruiz-Ramos et al. (2017) reported 121 cases where recommendations for antimicrobial changes were made, and 55 instances where antimicrobial therapy was discontinued (Ruiz-Ramos et al., 2017). Devchand et al. (2019) noted that 42% of ASP team recommendations achieved an acceptance rate of 83.8%, contributing to a significant improvement in prescription accuracy ranging from 46.7% to 76.9% (Devchand et al., 2019). Additional observed outcomes encompassed reductions in treatment durations, antibiotic usage, and incidents of ventilator-associated pneumonia (VAP) as reported by Panditrao et al. (2021), alongside a notable enhancement in appropriate antimicrobial utilization across 26% of units by Quiros et al. (2022) (Panditrao et al., 2021; Quirós et al., 2022).

Table 1. Summary of the included studies

Authors	Country	Study Design	Outcomes	Patients	Types of ASPs
Arena et al. (2015)	Italy	Before-after	34% increase in appropriate empirical treatment, 28% adherence to guidelines, 42% de-escalation rate, reduction in antimicrobial use	18 (pre) and 19 (post)	Discussion and feedback with healthcare professionals (ICU doctors, infectious disease specialists, and clinical microbiologists)
Hohn et al. (2015)	Germany	Retrospective quasi-experimental	21.2% reduction in antibiotic use and 43% reduction in treatment costs	2422	Direct feedback to ICU doctors, including procalcitonin protocol implementation, restrictions
Taggart et al. (2015)	Canada	Interrupted time series analysis	Medical-Surgical ICU: 14% monthly increase in antimicrobial use; Trauma and Neurosurgery ICU: 28% monthly decrease in antimicrobial use	1305 (pre) and 1369 (post) Medical-Surgical ICU 1330 (pre) and 1387 (post) Trauma-Neurosurgery ICU	Discussion and feedback with healthcare professionals (ICU doctors, infectious disease specialists, and pharmacists)
Ruiz-Ramos et al. (2017)	Spain	Before-after	121 cases with antimicrobial change recommendations and 55 instances of discontinued antimicrobial use	169	Discussion and feedback with healthcare professionals (ICU doctors, infectious disease specialists, clinical microbiologists, and pharmacists)
Ruiz et al. (2017)	Spain	Before-after	22.4% reduction in antimicrobial use, changes in prescriptions of penicillin and β-lactamase inhibitors, linezolid, cephalosporins, and aminoglycosides, reduction in treatment costs	182	Discussion and feedback with healthcare professionals (ICU doctors, infectious disease specialists, clinical microbiologists, and pharmacists)
Devchand et al. (2019)	Australia	Interrupted time series analysis	42% recommendations from ASP team with 83.8% acceptance rate; 46.7% to 76.9% improvement in prescribing accuracy	202	Recommendations based on the 5 moments of antimicrobial prescribing (escalation, de-escalation, discontinuation, substitution, optimization) adhered to by doctors
Kitano et al. (2019)	Japan	Before-after	76.2% reduction in antimicrobial use, decrease in long-term	913 (pre) and 194 (post)	Daily antimicrobial management, antibiotic

			antimicrobial use, and MRSA rates		stop-order policy protocols
Jones et al. (2019)	England	Before-after	6.5% reduction in antimicrobial use and 17.6% reduction in broad-spectrum antimicrobial use	554 reports	Positive feedback at each ASP process
Haseeb et al. (2021)	Saudi Arabia	Quasi-experimental study	25% reduction in antimicrobial use	135 (pre) and 169 (post)	10 ASP strategies including education and training, antimicrobial prescribing policies, IV to oral conversion, dose optimization, audit and feedback, routine review
Panditrao et al. (2021)	India	Before-after	Reduction in treatment duration, antibiotic use, and incidence of ventilator-associated pneumonia (VAP)	337	Discussion and feedback with healthcare professionals (ICU doctors, infectious disease specialists, clinical microbiologists, and pharmacists)
Elsawah et al. (2022)	Egypt	Before-after	Significant reduction in carbapenem antibiotic use and 37% reduction in incidence of *carbapenem-resistant Klebsiella*	205	Discussion and feedback with healthcare professionals (ICU doctors, infectious disease specialists, clinical microbiologists, and pharmacists)
Quiros et al. (2022)	Latin America	Quasi-experimental prospective with continuous time seris	Significant increase in appropriate antimicrobial use for comprehensive ASP treatment in 26% of units	77 ICUs	ASP interventions including coordination, institutional intervention strategies, monitoring, and education

CONCLUSION

Antimicrobial stewardship programs (ASPs) are designed to optimize the appropriate use of antimicrobials, enhancing the accuracy of antimicrobial prescribing in terms of indications, antimicrobial selection, administration routes, and therapy duration. The outcomes of ASP implementation can be assessed through metrics such as reductions in antimicrobial use, increases in the number of recommendations, decreases in treatment costs, and reductions in the incidence of multidrug-resistant organisms (MDROs). Although numerous articles have reported positive outcomes of ASP implementation in various intensive care unit settings, there is a lack of comprehensive and structured studies to validate these data. The heterogeneity and suboptimal designs of existing studies pose challenges in evaluating the impact of ASPs. Both qualitative and quantitative evaluations are necessary to achieve optimal antibiotic outcomes.

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