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Review

A systematic review of antimicrobial stewardship interventions implemented in intensive care units

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SUMMARY

Antimicrobial stewardship (AS) is essential to ensure appropriate antimicrobial usage and subsequently reduce the emergence of microbial resistance. The intensive care unit is a crucial place for monitoring antimicrobial usage due the frequent exposure to infections. This review provides an update on the current status of AS intervention utilized in intensive care settings. A comprehensive search was performed in Cochrane, Web of Science, and PubMed using keywords grouped into Antimicrobial, Stewardship, and Intensive care unit. The search was restricted to original articles published from April 2015 to November 2024. Of 1234 records retrieved from the databases, 55 studies were included in this systematic review. Most of the studies were conducted in the USA ($N = 9$), followed by China ($N = 8$), India ($N = 5$), and Italy ($N = 4$). We identified seven key AS strategies: multi-intervention AS programmes (22 studies, 40%), prospective feedback and audit (11 studies, 20%), procalcitonin (PCT) protocols for guiding antimicrobial use (12 studies, 21.8%), protocols for antimicrobial de-escalation (four studies, 7.3%), antimicrobial restrictions or preapprovals (four studies, 7.3%), diagnostic stewardship (one study, 1.8%), and guidelines for antimicrobial prescription (one study, 1.8%). A reduction in targeted or overall antimicrobial usage was reported in most studies (34/42). Specifically, all studies implementing multi-invention AS programmes reported a successful reduction in antimicrobial utilization. Some AS interventions significantly enhanced the appropriateness of antimicrobial prescriptions. In addition, patient health outcomes were not compromised by antimicrobial reduction. Nonetheless, future studies at a larger scale over a longer time are recommended to accurately assess the impact of AS programme on patient health outcomes.

Introduction

Antimicrobials have been a revolutionary advancement in the field of medicine, transforming infection treatments and continuing to save millions of lives [1,2]. However, the rise of antimicrobial resistance (AMR) has empowered most human pathogens to evade the activity of antimicrobial drugs, posing a significant threat to public health [3,4]. This issue was foreseen

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by Alexander Fleming, who warned of a future where antimicrobials would be readily available and accessible to anyone at any time leading to them being overused and misused [5]. Indeed, the lack of policies and guidelines governing antimicrobial use has led to their widespread misuse and overexploitation. Contributing factors include self-medication, inappropriate prescription, over-the-counter availability, inadequate dosing, and agricultural use [5–8]. As AMR continues to rise, available treatment options for infections are limited and lives are put at risk. To preserve the integrity and effectiveness of currently available antimicrobials, it is essential to implement targeted mitigation strategies. These efforts should aim to reduce unnecessary antimicrobial use, especially in clinical settings.

The Infectious Disease Society of America (IDSA) advocates for antimicrobial stewardship programmes (ASPs) in hospitals, ensuring appropriate antimicrobial consumption through policies and guidelines [8,9]. Antimicrobial stewardship (AS) is a co-ordinated programme that guides physicians in appropriately selecting, dosing, and administering antimicrobial drugs [9]. The main aim of these interventions is to minimize antimicrobial misuse, improve patient outcomes, and combat microbial resistance.

Intensive care units (ICUs) are hotspots for hospital-acquired infections, necessitating excessive antimicrobial use [10]. However, many antimicrobials used in ICUs are inappropriate, unnecessary, and suboptimal [11,12]. Having said this, the ICU becomes a critical focus area for implementing ASPs. Previous systematic reviews have established that AS strategies are associated with a reduction in antimicrobial utilization and cost in intensive care settings [13,14]. Given the significant impact, it is important for hospitals to implement and maintain ASPs. To inform these strategies, this systematic review aims to summarize existing data on AS intervention, providing an updated overview of the current state of ASP programmes in ICUs globally.

Methods

Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. Using tailored search terms, we conducted a comprehensive search in Cochrane, Web of Science, and PubMed databases. Search terms were grouped into Antimicrobial, Stewardship, and Intensive care unit.

In Cochrane and Web of Science, search terms combined keywords such as ("Antimicrobial" OR "antibiotic") AND ("stewardship" OR "restriction" OR "pre-approval" OR "reassessment" OR "consultation" OR "audit" OR "feedback" OR "de-escalation" OR "optimization" OR "procalcitonin" OR "education" OR "policy" OR "guideline" OR "decision support") AND ("critical care unit" OR "critical care settings" OR "intensive care unit" OR "intensive care settings" OR "ICU").

In PubMed, the search strategy utilized Mesh term and relating keywords, forming ("Antimicrobial stewardship" [Mesh] OR "Antibiotic stewardship") AND ("Critical Care" [Mesh] OR "Critical care settings" OR "Intensive Care Units" [Mesh] OR "Intensive care settings" OR "ICU").

The search was restricted to articles published from April 2015 to November 2024. Open access and Free full-text filters were applied in Web of Science and PubMed, respectively.

Study selection criteria

Inclusion criteria

This study included all study designs, including observational, quasi-experimental, quality improvement, and clinical trials that described the implementation and outcomes of AS interventions in ICUs. This review focused on evaluating the effect of AS by comparing intervention and non-intervention groups.

Exclusion criteria

Full-text articles were excluded based on the following criteria: non-peer-reviewed sources such as preprints, editorials, and study protocols; studies involving patients from non-ICU settings or those that combined data from ICU and non-ICU units; studies that did not specify the number of ICU patients or non-intervention participants; and studies that lacked outcome data following interventions. Additionally, studies comparing two interventions without a non-intervention group were excluded.

Data extraction

Relevant data from the included studies were extracted and managed using Microsoft Excel 365. The extracted data included various study descriptions described in Table I. The main interventions and outcomes reported in the included studies were extracted. $P<0.05$ was defined as statistically significant.

Results

Database search results

A total of 1234 records were retrieved after the extensive database search. Two hundred and eighty-five duplicate records were removed, leaving 1527 unique records to be screened. Of the 1527 unique records, 1385 were excluded upon title and abstract screening, and the remaining 142 records were sought for full-text retrieval and assessment for eligibility. Finally, 55 studies were included in the systematic review following a thorough full-text screening (Figure 1).

Description of eligible studies

The included studies represented twenty-four different countries spanning five continents, including Asia (27 studies, 49.1%), Europe (13 studies, 23.6%), North America (10 studies, 18.2%), Africa (three studies, 5.5%) and South America (two studies, 3.6%). Most of the studies were conducted in the USA (nine studies, 16.4%), followed by China (eight studies, 14.5%), India (five studies, 9.1%), and Italy (four studies, 7.3%) (Figure 2). Interventions were implemented within a single or multiple ICUs. Most studies implemented AS interventions in neonatal ICUs (10 studies, 18.2%) followed by paediatric (seven studies, 12.7%) and surgical (six studies, 10.9%). Ten studies implemented AS interventions in two or more specified ICUs whiles 18 studies did not specify the types of ICUs included. The

Table I
Study characteristics

Study	Study period	Country	Study design	Type of ICU	Patients		Key intervention	Duration of intervention
					NIG	IG		
Agarwal *et al.* [16]	2019–2020	India	Quality improvement	Neonatal	290	2002	Multi-interventions	24 months
Aldardeer *et al.* [17]	2022	Saudi Arabia	Retrospective cohort	Not specified	125	125	Guidelines for antimicrobial de-escalation	3 months
Alfraij *et al.* [18]	2018–2020	Kuwait	Retrospective cohort	Paediatric	272	156	Multi-interventions	12 months
Álvarez-Lerma *et al.* [19]	2007–2015	Spain	Prospective interventional cohort	Surgical and Medical	1971	3031	Multi-interventions	60 months
Bobillo-Perez *et al.* [20]	2011–2018	Spain	Prospective interventional	Paediatric	371	515	PCT-guided AS	24 months
Campos *et al.* [21]	2018–2021	Brazil	Quasi experimental	Not specified	114	102	Diagnostic stewardship	12 months
Cappanera *et al.* [22]	2016	Italy	NA	Surgical	300	92	Prospective audit and feedback	10 months
Chen *et al.* [23]	2000–2010	Taiwan	Longitudinal	Surgical and Medical	27499	33834	Computer-based decision support system	60 months
Chomba *et al.* [24]	2014–2015	South Africa	Controlled clinical trial	Surgical trauma	40	40	PCT-guided AS	6 months
Chowdhury *et al.* [25]	2017	India	Prospective intervention	Surgical	140	140	Prospective audit and feedback	6 months
Chu *et al.* [26]	2014–2016	China	Retrospective cohort	Neonatal	76	90	Antimicrobial restrictions	12 months
Custódio *et al.* [27]	2017–2018	Brazil	Quasi-experimental	Surgical	1056	1323	Multi-interventions	5 months
Daubin *et al.* [28]	2010–2016	France	Randomized multi-centre	Not specified	151	151	PCT-guided AS	NA
de Jong *et al.* [29]	2009–2013	The Netherlands	Randomized intervention trial	Not specified	761	785	PCT-guided AS	60 months
El-Bardan *et al.* [30]	2020	Egypt	Quasi-experimental	Surgical/Trauma	226	153	Prospective audit and feedback	6 months
Elsawah *et al.* [31]	2017–2019	Egypt	Retrospective observational	Not specified	61	144	Multi-interventions	11 months
Fan *et al.* [32]	2016–2020	China	Retrospective single centre	Paediatric	165	122	Multi-interventions	36 months
Go *et al.* [33]	2018–2022	Japan	Clinical trial	Neonatal	737	686	PCT-guided AS	24 months
Gu *et al.* [34]	2017–2019	China	Retrospective cohort	Surgical and Medical	270	291	Multi-interventions	12 months
Gustavsson *et al.* [35]	2014–2018	Sweden	Before and After study	Neonatal	82	63	Multi-interventions	12 months
Han *et al.* [36]	2015–2017	China	Not specified	Paediatric	70	70	Guidelines for antimicrobial de-escalation	24 months
Haseed *et al.* [37]	2016–2017	Saudi Arabia	Quasi-experimental	Not specified	684	623	Multi-interventions	9 months
Hashimoto *et al.* [38]	2016–2017	Japan	Retrospective	Not specified	2583	2540	Multi-interventions	12 months
Huang *et al.* [39]	2002–2009	Taiwan	Retrospective	Neurosurgical	2208	2619	Computer-based decision support system	36 months

Hussain *et al.* [40]	2017–2018	Pakistan	Quasi-experimental	Surgical	123	125	Multi-interventions	4 months
Yu *et al.* [41]	2022	China	Pre and post cohort intervention	Neurosurgical	487	526	Multi-interventions	6 months
Jeon *et al.* [42]	201–2015	South Korea	Randomized controlled trial	Not specified	29	23	PCT-guided AS	12 months
Jones *et al.* [43]	2017–2018	United Kingdom	Quality improvement	Paediatric	704	696	Multi-interventions	6 months
Jover-Sáenz *et al.* [44]	2013–2017	Spain	Prospective intervention	Not specified	34560	32802	Multi-interventions	60 months
Katz *et al.* [45]	2018–2019	United States	Randomized clinical trial	Paediatric	133	137	PCT-guided AS	13 months
Khdour *et al.* [46]	2015	Palestine	Pre- and post-intervention	Not specified	115	142	Prospective audit and feedback	4 months
Kim *et al.* [47]	2018–2019	South Korea	Retrospective	Surgical	182	149	Multi-interventions	12 months
Le Terrier *et al.* [48]	2014–2015	Guadeloupe	Retrospective before and after intervention	Surgical and Medical	738	803	Antimicrobial restrictions	12 months
Li *et al.* [49]	2014	China	Prospective cohort	Multiple	224	353	Prospective audit and feedback	2 months
Ma *et al.* [50]	2010–2013	China	Pre- and post-intervention	Multiple ICUs	433	545	Multi-interventions	12 months
Maalouf *et al.* [51]	2017–2022	Lebanon	Quality improvement	Neonatal	153	532	Multi-interventions	72 months
Mandelli *et al.* [52]	2017–2020	Italy	Pre- and post-intervention	Multiple	2901	3389	Prospective audit and feedback	36 months
Najafi *et al.* [53]	2012–2013	Iran	Randomized	Not specified	30	30	PCT-guided AS	12 months
Nazer *et al.* [54]	2019	Jordan	Randomized controlled	Oncological	76	77	PCT-guided AS	N/A
Onorato *et al.* [55]	2017–2018	Italy	Interrupted time series	Multiple ICUs	227	402	Prospective audit and feedback	18 months
Panditrao *et al.* [56]	2017	India	N/A	Surgical	94	243	Prospective audit and feedback	6 months
Payton *et al.* [57]	2015–2017	United States	Quality improvement	Neonatal	28	104	Multi-interventions	18 months
Renk *et al.* [58]	2017–2018	Germany	Pre- and post-implementation cohort	Paediatric	183	207	Prospective audit and feedback	6 months
Roper *et al.* [59]	2018–2019	United States	Retrospective cohort	Surgical, medical, neurosurgical, and cardiovascular	135	38	Guidelines for antimicrobial de-escalation	16 months
Seidelman *et al.* [60]	2017–2018	United States	Cluster-randomized cross-over trial	Surgical, medical, cardiothoracic, cardiac, neurologic	2353	2330	Prospective audit and feedback	12 months
Shah *et al.* [61]	2013	India	Cross-sectional	Medical	75	75	Guidelines for antimicrobial prescription	6 months
Singh HP *et al.* [62]	2018–2020	United States	Quality improvement	Neonatal	183	207	Multi-interventions	36 months

(*continued on next page*)

Table I (*continued*)

Study	Study period	Country	Study design	Type of ICU	Patients		Key intervention	Duration of intervention
					NIG	IG		
Singh *et al.* [63]	2008–2017	England	Retrospective observational	Surgical and Medical	75	325	Multi-interventions	18 months
Subedi *et al.* [64]	2016–2017	United States	Pre- and post-intervention	Surgical and Medical	37	37	PCT-guided AS	12 months
Thampi *et al.* [65]	2011–2013	United States	Retrospective cohort	Neonatal	864	716	Prospective audit and feedback	12 months
Vishalashi *et al.* [66]	2018–2020	India	Randomized controlled	Multiple ICUs	45	45	PCT-guided AS	18 months
Vyas *et al.* [67]	2019–2021	United States	Quality improvement	Neonatal	250	264	Multi-interventions	12 months
Willmon *et al.* [68]	2017–2018	United States	Prospective cohort	Multiple ICUs	26	26	PCT-guided AS	3 months
Zhao *et al.* [69]	2018–2020	China	Retrospective cohort	Not specified	173	53	Guidelines for antimicrobial de-escalation	36 months
Zini *et al.* [70]	2011–2021	Italy	Retrospective	Neonatal	111	119	Multi-interventions	12 months

AS, antimicrobial stewardship; ICU, intensive care unit; IG, intervention group; NIG, non-intervention group; PCT, procalcitonin.

duration of the intervention ranged from 2 to 72 months. The majority of the studies implemented the AS interventions for 12 months (16 studies, 29.1%) followed by 6 months (nine studies, 16.4%). The overall description of each study included in this review is provided in Table I.

AS implemented in ICUs

Seven AS interventions were mainly described in the included studies (Table II). Most studies ($N = 22$, 40%) implemented a combination of two or more AS interventions in ICUs. Commonly implemented strategies included a prospective audit and feedback, antimicrobial treatment protocols, healthcare staff training, and antimicrobial restriction or preapproval. Twelve studies (21.8%) implemented procalcitonin (PCT) protocols to inform antimicrobial treatment decisions, either stopping, continuing, escalating, or de-escalating therapy. The cut-off PCT values varied among studies, ranging from 0.1 to 2 μg/L. Prospective audits and feedback involving regular ICU rounds by either an infectious disease physician, a pharmacist, or the AS team were described in 11 studies. Other interventions including guidelines for antimicrobial de-escalation ($N = 4$ studies, 7.3%), antimicrobial restriction or pre-approvals ($N = 4$ studies, 7.3%), diagnostic stewardship ($N = 1$ study, 1.8%), and guidelines for antimicrobial prescriptions ($N = 1$ study, 1.8%) were also identified. A detailed description of the identified AS interventions is provided in Supplementary Tables S1–S6.

Impact of AS on antimicrobial utilization and cost

Antimicrobial utilization was the primary outcome evaluated before and after the implementation of ASP. The impact of AS interventions on antimicrobial use was reported in 42 of 55 studies. Eighty-one per cent (34/42) of these studies reported a reduction in overall antimicrobial usage. Studies implementing guidelines for antimicrobial de-escalation reported a reduction in the use of certain broad-spectrum antimicrobials such as cefepime, meropenem, ceftazidime-avibactam, and piperacillin-tazobactam (Table III). Of the 33 studies evaluating days of antimicrobial treatment, 26 (78.8%) reported shorter days while six studies reported no difference in the days of antimicrobial treatment before and after the intervention. Appropriateness of antimicrobial prescription was improved by AS strategies including multi-interventions, prospective audit and feedback, antimicrobial restriction or preapproval, and guidelines for antimicrobial prescription. In terms of antimicrobial cost, seven studies (70%) reported a decrease in price, two studies reported an increase, and one study found no difference in the prices. Table III provides detailed information on the impact of each AS intervention on antimicrobial utilization and cost.

Impact of AS on patient health outcomes

Patient health was the secondary outcome evaluated by most of the studies (Table IV). Commonly reported outcomes were length of stay in ICU (44 studies) and ICU mortality (42 studies). Length of stay in ICU was reported to be shorter in 16 studies, longer in six studies, and similar in 22 studies. ICU mortality rate was lower in 20 studies, higher in five studies, and similar in 17 studies. Other health outcomes such as

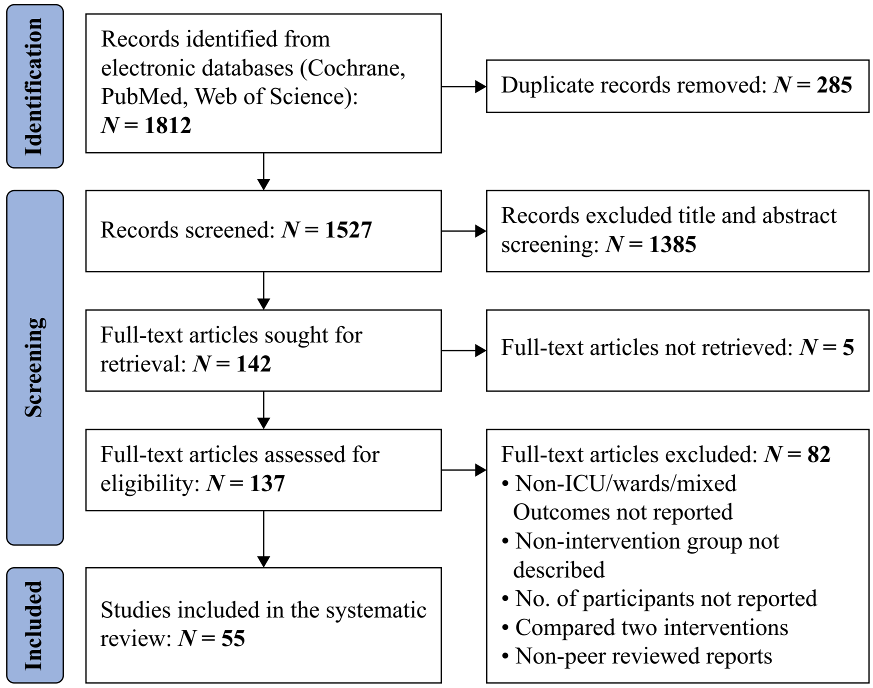

Figure 1. PRISMA flowchart of the screening process. ICU, intensive care unit.

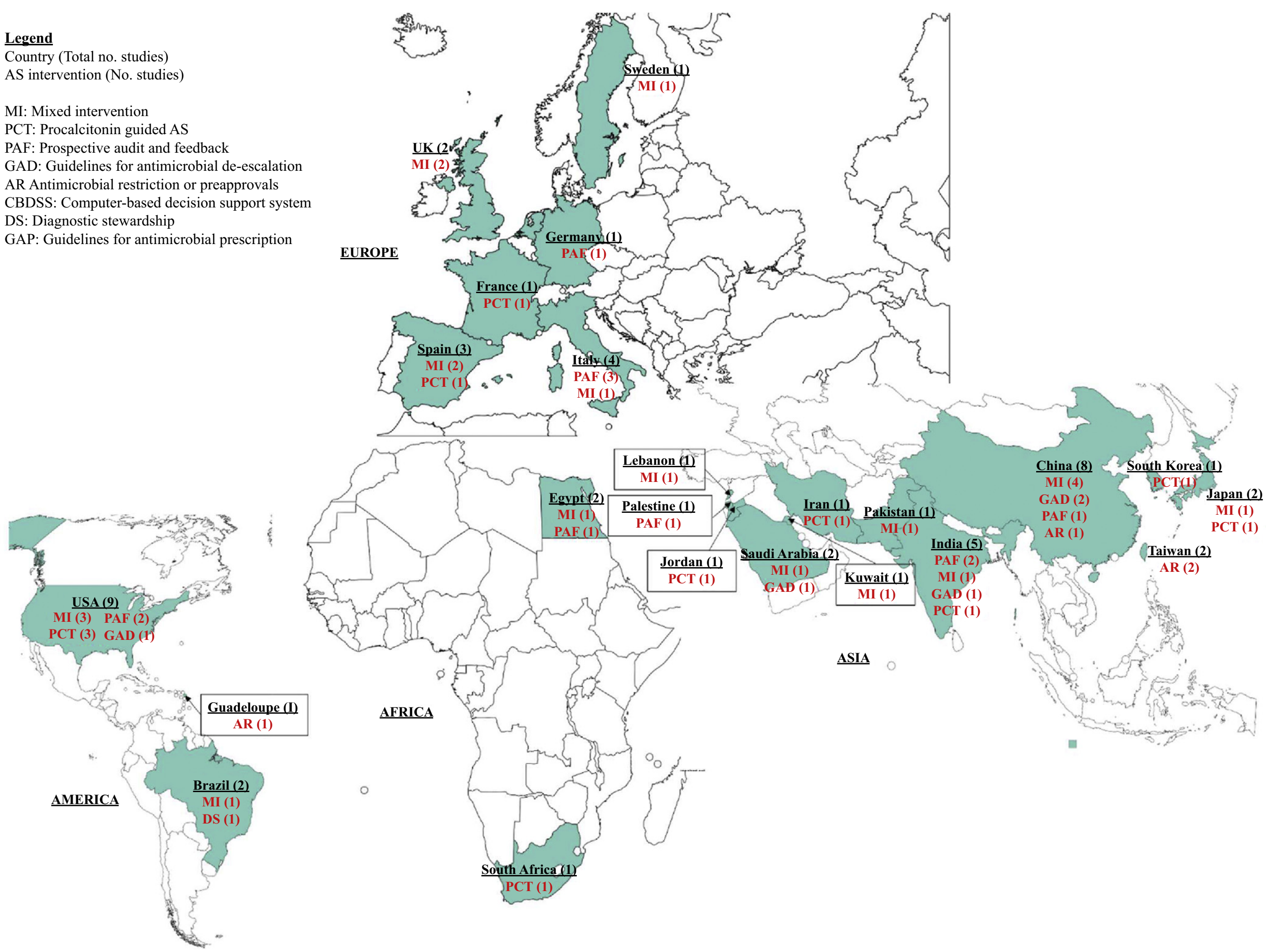

Figure 2. Geographical distribution of included studies and the antimicrobial stewardship (AS) interventions implemented.

Table II
Antimicrobial stewardship (AS) interventions identified

As interventions identified	No. of studies	Frequently implemented strategies
Multi-interventions	22	Prospective audit and feedback Protocols for antimicrobial treatment Antimicrobial restrictions or preapprovals Guidelines for antimicrobial de-escalation/escalation Treatment optimization protocols PCT protocols for antimicrobial discontinuation ID physician consultation Pharmacist-led AS recommendations Education and training of healthcare professionals Computer-based decision support system
Procalcitonin-guided AS	12	Stop antimicrobial when the PCT level is <0.5 μg/L or decrease by $\geq$ 80% from its peak Stop antimicrobial when the PCT level is <0.1 μg/L Stop antimicrobial when the PCT level is ≤ 2 μg/L Stop antimicrobial when the PCT level is ≤ 0.25 μg/L De-escalate antimicrobial when the PCT level is $<$ 0.5 μg/L or decrease by $\geq$80% from its peak.
Prospective audit and feedback	11	Weekly rounds by either an ID physician, a pharmacist, or the AS team
Guidelines for antimicrobial de-escalation	4	Replacing broad-spectrum antimicrobials with narrow-spectrum antimicrobials
Antimicrobial restriction or preapproval	4	Antimicrobials were assessed and approved by an ID physician Restriction of certain antimicrobials
Guidelines for antimicrobial prescription	1	Policies guiding antimicrobial prescriptions
Diagnostic stewardship	1	MALDI-TOF and detection of genes directly from blood culture bottles

ID, infectious disease; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight; PCT, procalcitonin.

readmission, rate of superinfection, and incidence of hospital-acquired infection was described in four, two, and two studies, respectively.

Discussion

The overexploitation of antimicrobials is the driving factor for the alarming rise of antimicrobial resistance. The World Health Organization (WHO) has established comprehensive standards for AS to address this growing global threat. This entails a strategy that focuses on improving awareness and understanding of AMR, strengthening knowledge and evidence-based practices, preventing infection, optimizing the use of antimicrobial drugs, and seeking alternative methods to fight AMR. This strategy will help preserve the effectiveness of antimicrobial agents and safeguard the public health for the future. Areas with elevated antimicrobial usage are primary focuses for stewardship initiatives. ICUs fall into this category, where infections frequently occur and typically necessitate antimicrobial treatment. However, some of these antimicrobials are unnecessary and inappropriate, exacerbating the AMR crisis [11,12]. Fortunately, AS strategies have shown significant effects in reducing overall antimicrobial utilization and to some extent improving patient outcomes. This systematic review aims to consolidate evidence from studies describing the implementation and impact of AS interventions in ICUs, providing valuable information for healthcare decision-makers, especially institutions yet to establish ASP.

The studies identified in this study were conducted in 24 countries across five continents. Seven key AS interventions reported in these studies were multi-interventions, prospective feedback, and audit, PCT protocols for guiding antimicrobial use, protocols for antimicrobial de-escalation, antimicrobial restrictions or preapprovals, diagnostic stewardship, and guidelines for antimicrobial prescription. Effective AS programmes rely on a thorough review of antimicrobial prescriptions. A key strategy in achieving this is prospective audit and feedback (PAF), which entails regular case-by-case reviews of antimicrobials prescribed by an infectious disease physician or a clinical pharmacist [71]. PAF is considered the gold standard stewardship intervention by the Infectious Disease Society of America [9]. Confirming the findings of Mertz *et al.* [14], our study found several studies utilizing audit and feedback in a critical care setting, revealing a positive impact on antimicrobial utilization. This supports PAF's status as a highly effective grade A-I AS intervention. Notably, PAF is widely accepted by physicians and offers educational opportunities, distinguishing it from other interventions. PCT is a valuable biomarker for detecting infections and guiding antimicrobial treatment decisions [72]. Our study identified research utilizing PCT value to recommend antimicrobial usage, with varying protocols and cut-offs. Some studies encouraged antimicrobial initiation, while others recommended cessation or de-escalation. In addition, the PCT cut-offs employed ranged from 0.1 μg/L to 2 μg/L, reflecting significant heterogeneity among studies. This variability in protocols and cut-offs may compromise the reliability of PCT as an AST strategy. To address this concern, further research is needed to optimize and standardize PCT protocols. This will help develop a universally applicable PCT protocol. One

Table III
Impact of antimicrobial stewardship (AS) interventions on antimicrobial utilization

As interventions	Outcome	No. of studies reporting outcome	Results	No. of studies (%)
Multi-interventions	Overall antimicrobial use	21	Reduced	19 (90)
			Increased	1 (5)
			No difference	1 (5)
	Days of antimicrobial treatment	8	Shorter	5 (62.5)
			No difference	2 (25)
			Longer	1 (12.5)
	Cost of antimicrobials	4	Reduced	3 (75)
			Increased	1 (25)
	Appropriateness of antimicrobial prescriptions	2	Improved	2 (100)
	Unnecessary antimicrobial days	1	Reduced	1 (100)
Procalcitonin-guided AS	Days of antimicrobial treatment	10	Shorter	9 (90)
			No difference	1 (10)
	Overall antimicrobial use	4	Reduced	1 (25)
			Increased	1 (25)
			No difference	2 (50)
Prospective audit and feedback	Overall antimicrobial use	11	Reduced	9 (81.8)
			No difference	2 (18.2))
	Days of antimicrobial treatment	8	Shorter	6 (75)
			No difference	2 (25)
	Cost of antimicrobials	3	Reduced	2 (66.7)
			No difference	1 (33.3)
	Appropriateness of antimicrobial prescriptions	1	Improved	1 (100)
Guidelines for antimicrobial de-escalation	Days of antimicrobial treatment	4	Shorter	3 (75)
			No difference	1 (25)
	Meropenem use	2	Reduced	2 (100)
	Cefepime use	2	Reduced	2 (100)
	Piperacillin-tazobactam use	2	Reduced	1 (50)
			Increased	1 (50)
	Ceftazidime-avibactam use	1	Reduced	1 (100)
	Ceftolozane/tazobactam use	1	Increased	1 (100)
Antimicrobial restriction or preapproval	Overall antimicrobial use	4	Reduced	4 (100)
	Days of antimicrobial treatment	3	Shorter	3 (100)
	Cost of antimicrobials	2	Reduced	2 (100)
	Appropriateness of antimicrobial prescriptions	1	Improved	1 (100)
Guidelines for antimicrobial prescription	Overall antimicrobial use	1	Reduced	1 (100)
	Appropriateness of antimicrobial prescriptions	1	Improved	1 (100)
Diagnostic stewardship	Overall antimicrobial use	1	Increased	1 (100)
	Cost of antimicrobials	1	Increased	1 (100)

interesting finding of our study is the implementation of multiple interventions in ICU settings. Close to half of the included studies employed a combination of interventions, suggesting that a bundle approach may maximize the overall success and effectiveness of an ASP [14]. This observation is supported by the evidence presented in our studies, where all included studies reported a successful reduction in antimicrobial utilization following the implementation of multi-intervention ASPs.

The main aim of an ASP is to reduce unnecessary antimicrobial use and ensure that the right antimicrobial is used in its rightful amount. A significant number of studies included in our study reported a reduction in antimicrobial utilization, confirming findings of a previous systematic review by Kaki *et al.* [13]. Decrease in broad-spectrum antimicrobial use was narrowly studied in AS programmes based on guidelines for antimicrobial de-escalation. All studies assessing the appropriateness of antimicrobial prescription reported an improvement after implementing the AS programme. This clearly indicates that an active AS intervention could positively impact antimicrobial utilization and ultimately play a crucial role in slowing down the rise of resistance. Secondarily, patient health

Table IV
Impact of antimicrobial stewardship (AS) interventions on patient health outcomes

As interventions	Outcome	No. of studies reporting outcome	Results	No. of studies (%)
Multi-interventions	ICU mortality	17	Lower	8 (47.05)
			No difference	8 (47.05)
			Higher	1 (5.9)
	Length of stay in ICU	16	No difference	8 (50)
			Shorter	6 (37.5)
			Longer	2 (12.5)
	Readmission	4	Higher	2 (50)
			Lower	1 (25)
			No difference	1 (25)
Procalcitonin-guided AS	Length of stay in ICU	11	No difference	7 (63.6)
			Shorter	3 (27.3)
			Longer	1 (9.1)
	ICU mortality	9	No difference	4 (44.4)
			Lower	3 (33.3)
			Higher	2 (22.2)
Prospective audit and feedback	Length of stay in ICU	8	No difference	6 (75)
			Shorter	1 (12.5)
			Longer	1 (12.5)
	ICU mortality	8	No difference	5 (62.5)
			Lower	2 (25)
			Higher	1 (12.5)
Guidelines for antimicrobial de-escalation	Length of stay in ICU	4	Shorter	2 (50)
			Longer	1 (25)
			No difference	1 (25)
	ICU mortality	3	Lower	3 (100)
	Superinfection	2	Lower	2 (100)
Antimicrobial restrictions and preapprovals	Length of stay in ICU	4	Shorter	3 (75)
			Longer	1 (25)
	ICU mortality	4	Lower	4 (100)
	Incidence of HAI	2	Lower	1 (50)
			No difference	1 (50)
Guidelines for antimicrobial prescription	None reported	—	—	—
Diagnostic stewardship	Length of stay in ICU	1	Shorter	1 (100)
	ICU mortality	1	Higher	1 (100)

HAI, hospital-acquired infection; ICU, intensive care unit.

outcomes were also evaluated by most of the studies. However, more than half of the studies reported no positive difference in patient health outcomes. The impact on patient health outcomes varied among studies similar to the findings by Mertz *et al.* [14]. This finding amplifies their recommendation that future studies are needed at a larger scale over a longer period which can accurately investigate the impact of AS programmes on patient health outcomes.

Antimicrobial overexploitation in clinical and veterinary medicine and agriculture is a serious problem in low- and middle-income countries where there are no or limited regulatory frameworks [73]. Some studies implementing AS programme in LMICs (10 countries) were identified in this review. It is appalling that more LMICs are implementing AS intervention compared to the number of countries reported by Kaki *et al.* [13]. Given LMICs' problematic history of antimicrobial misuse, it is recommended that efforts be put in place and resources be allocated to ensure that more of these countries are equipped to implement ASPs. This will strengthen the global strategy to reduce the burden of AMR through a One-Health regulation of the use of the old, newly, and yet-to-be-discovered antimicrobials.

In conclusion, this review presents AS interventions utilized in ICUs. Multi-intervention, prospective audit and feedback, and PCT-guided protocols were the commonly employed ASP strategies. AS interventions successfully contributed to the reduction in antimicrobial utilization in ICUs especially in programmes based on multi-interventions. ICU length of stay and mortality were not compromised by antimicrobial reduction. We therefore recommend a larger scale study over a longer time to better understand the impact on patient health outcomes. Our findings also emphasize the importance of implementing evidence-based ASPs, particularly in resource-limited regions, to promote appropriate antimicrobial use.

Author contributions
Conceptualization: O.K.N. and E.S.D. Data curation: O.K.N., B.O.-A., and E.S.D. Formal analysis: O.K.N., B.O.-A., and

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Conflict of interest statement

The authors have no competing interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2025.04.020.

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