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REVIEW ARTICLE

A Systematic Review of AI-Enabled Antimicrobial Stewardship and Therapeutics in Critical Care Medicine

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Abstract: Intensive care units act as epicenters for the selection and dissemination of multidrug-resistant pathogens. High antimicrobial pressure, invasive interventions, and critically ill cohorts drive the selection of resistant strains. A systematic analysis of evidence from January 2020 to December 2025 showed that Gram-negative ESKAPE pathogens, notably carbapenem-resistant *Enterobacterales* and *Acinetobacter baumannii*, dominate critical care infections. Mechanistic pathways involve beta-lactamase production, porin mutations such as OprD down-regulation in *Pseudomonas aeruginosa*, and active efflux systems like the AcrAB-TolC pump. Rapid molecular diagnostic platforms, including polymerase chain reaction assays and matrix-assisted laser desorption ionization-time of flight mass spectrometry, significantly accelerate pathogen identification compared to standard cultures. When integrated with artificial intelligence and machine learning models, clinical decision support tools optimize antibiotic prescriptions, reducing inappropriate administration by twenty to thirty-five percent as measured by days of therapy per one thousand patient-days and strict adherence to institutional antibiograms. Novel drugs, specifically cefiderocol, novel beta-lactam/beta-lactamase inhibitor combinations, and experimental options such as bacteriophages and CRISPR-Cas gene-editing therapies, offer optimistic alternatives against pan-drug-resistant isolates. Effective containment of critical care antimicrobial resistance requires a structured paradigm transition combining real-time genomic surveillance, machine learning risk stratification, and targeted drugs to improve clinical recovery rates while preserving last-resort antimicrobial classes.

Keywords: Critical care; Gram-negative pathogens; Artificial intelligence; Antimicrobial stewardship; Targeted Drugs.

1. Introduction

Antimicrobial resistance is one of the most severe and clinically challenging hazards to modern clinical medicine, threatening to compromise the foundational pillars of surgical intervention, oncology, and intensive care management [1]. The World Health Organization has classified antimicrobial resistance as an urgent global health priority, noting its potential to disrupt decades of therapeutic progress [2]. Intensive care units are highly concentrated reservoirs for the selection, mutation, and dissemination of resistant strains [3]. Critically ill patients are uniquely susceptible to acquisition of multidrug-resistant isolates due to severe physiological distress, profound immune system dysregulation, and frequent exposure to broad-spectrum empirical antimicrobial agents [4].

The physical environment of the intensive care unit further accelerates this vulnerability. The routine use of indwelling medical devices, including central venous catheters, arterial lines, indwelling urinary catheters, endotracheal tubes, and extracorporeal circuits, disrupts natural mucosal and cutaneous barriers, creating bio-reactive surfaces that facilitate bacterial colonization and subsequent biofilm formation [5]. These biofilm matrices protect embedded bacterial populations from both host immune defenses and standard serum concentrations of hydrophilic antimicrobials, resulting in persistent, low-grade infections that necessitate repeated, prolonged courses of therapy [6]. This sustained exposure creates a continuous cycle of selective pressure, accelerating the elimination of susceptible microbial populations and allowing resistant subpopulations to proliferate and dominate the clinical ecosystem [7]. The microorganisms that affect the critical care patients are ESKAPE pathogens, which comprise *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species [8]. Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* species are the primary focus of infection control efforts. However, epidemiological surveillance indicates a significant shift toward Gram-negative pathogens possessing highly versatile genomes capable of expressing multiple resistance phenotypes simultaneously [9]. Of particular concern in critical care environments is the rapid escalation of carbapenem-resistant Enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, and multidrug-resistant *Pseudomonas aeruginosa* [10]. These Gram-negative organisms are frequently responsible for severe hospital-acquired conditions, including ventilator-associated pneumonia, central line-associated bloodstream infections, and

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complicated intra-abdominal sepsis [11]. The therapeutic management of these infections is severely restricted by the loss of traditional beta-lactam and carbapenem options, forcing clinicians to rely on older, more toxic agents such as polymyxins or aminoglycosides, which are associated with significant nephrotoxicity and suboptimal clinical outcomes [12]. Traditional antimicrobial stewardship programs have historically relied on restrictive formularies, pre-authorization policies, and retrospective post-prescription audits [13]. While these interventions have showed efficacy in reducing overall drug expenditures, they are frequently limited by a lack of real-time adaptability and can lead to unintended delays in appropriate empirical therapy for critically ill patients in septic shock [14]. The clinical necessity of administering rapid, appropriate empirical antimicrobials within the golden hour of sepsis must be carefully balanced against the ecological necessity of minimizing broad-spectrum exposure [15].

To address this challenge, the integration of clinical decision support systems powered by artificial intelligence and machine learning is driving a fundamental shift in critical care infection management [16]. These advanced computational models utilize large volumes of clinical data from electronic health records, including historical microbiologic histories, real-time vital signs, laboratory markers, and institutional antibiograms, to provide patient-specific risk assessments for drug-resistant pathogens [17]. When combined with rapid diagnostic technologies, AI-driven decision tools enable clinicians to transition from broad, standardized empirical guidelines to highly tailored and individualized prescribing regimens [18]. This dual management aims to optimize patient-specific clinical recovery while mitigating the systemic selective pressures that drive the development of multidrug-resistant, extensively drug-resistant, and pan-drug-resistant pathogens [19].

2. Methodology

2.1. Search Strategy and Database Queries

A systematic review was designed and performed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, reproducibility, and methodological quality. Electronic literature databases, including PubMed, Scopus, Web of Science, Embase, and the Cochrane Library, were searched for relevant peer-reviewed studies published between January 1, 2020, and December 31, 2025.

The search logic utilized combinations of medical subject headings (MeSH) and free-text terms tailored to target clinical evidence regarding resistance epidemiology, diagnostic innovations, AI-driven stewardship, and emerging therapeutics in critical care settings. The exact Boolean search query applied was:

("Antimicrobial resistance" OR "MDR" OR "XDR" OR "carbapenem resistance" OR "ESKAPE pathogens") AND ("intensive care unit" OR "ICU" OR "critical care medicine") AND ("antimicrobial stewardship" OR "artificial intelligence" OR "machine learning" OR "decision support") AND ("rapid diagnostics" OR "MALDI-TOF" OR "whole-genome sequencing" OR "novel therapeutics" OR "cefiderocol" OR "bacteriophage"). The search was restricted to publications in the English language and those involving human subjects within adult and pediatric intensive care settings.

2.2. Study Eligibility and Selection Criteria

To ensure high scientific quality, strict inclusion and exclusion criteria were established prior to screening. Eligible studies included randomized controlled trials, prospective and retrospective observational cohort studies, case-control studies, multi-center surveillance investigations, and systematic evaluations focusing on the clinical management of antimicrobial resistance in critical care. Studies were included if they provided quantitative data on pathogen prevalence, molecular resistance markers, diagnostic accuracy, or clinical outcomes associated with antimicrobial stewardship interventions. Investigations evaluating artificial intelligence or machine learning applications were required to report quantitative performance metrics, such as sensitivity, specificity, area under the receiver operating characteristic curve (AUROC), or direct clinical utility measures like changes in prescribing volume or clinical outcomes.

Studies were excluded if they represented case reports, small case series involving fewer than ten patients, conference abstracts lacking complete peer-reviewed text, or letters to the editor. Studies focused entirely on *in vitro* laboratory investigations or animal models were also excluded unless they provided direct translational clinical data regarding novel therapeutic molecules or resistance pathways of immediate relevance to intensive care medicine. Studies conducted entirely outside the intensive care unit, such as outpatient clinics or general medical wards, were excluded to preserve the specific focus on critical care ecology.

2.3. Data Extraction

Two investigators independently screened titles and abstracts identified through the database searches. Discrepancies were resolved through consensus or consultation with a third senior investigator. Full-text articles of potentially eligible studies were retrieved and assessed against the inclusion criteria.

Data extraction was carried out using a standardized template to record the primary author, year of publication, study design, geographic setting, patient population size, pathogen profile, diagnostic or therapeutic intervention analyzed, and primary clinical

or microbiological outcomes. The methodological quality of the included studies was appraised using validated tools, applying the Newcastle-Ottawa Scale for observational cohort studies and the Cochrane Risk of Bias tool for clinical trials.

2.4. Primary and Secondary Outcomes of Interest

The primary clinical outcomes evaluated in this systematic analysis were:

1. All-cause and infection-attributable mortality in the intensive care unit.
2. Intensive care unit length of stay.
3. Total duration of mechanical ventilation.
4. Changes in antimicrobial consumption, quantified via Days of Therapy (DOT) per 1,000 patient-days or Defined Daily Doses (DDD) per 1,000 patient-days.

The secondary outcomes of interest included:

1. The diagnostic turnaround time for pathogen identification and antimicrobial susceptibility testing.
2. The sensitivity, specificity, and AUROC of AI-driven predictive algorithms.
3. The clinical and microbiological cure rates achieved by emerging pharmaceutical therapies.
4. The prevalence of specific high-yield molecular resistance markers, including OprD porin alterations and AcrAB-TolC efflux expression.

3. Results

3.1. Study Selection and Cohort Characteristics

The systematic screening process yielded sixty high-quality peer-reviewed studies meeting all eligibility criteria. These studies represented diverse designs and geographies, reflecting global interest in critical care resistance dynamics. The cohort comprised twenty-eight observational cohort studies evaluating local and regional epidemiology, twelve systematic analyses of multi-center surveillance databases, eight investigations focused on clinical decision support applications powered by machine learning, six diagnostic evaluation studies assessing point-of-care rapid diagnostics, and six clinical trials or clinical registries assessing newly approved antimicrobial molecules and experimental adjunctive therapies.

3.2. Pathogen Ecology and Shifting Resistance

Microbiological data from the included studies confirmed the clinical dominance of Gram-negative ESKAPE pathogens in critical care infections.

Table 1. The Resistance Mechanisms and ICU Syndromes associated with ESKAPE Pathogens

Pathogen	Resistance Mechanisms	ICU Syndromes	Clinical Severity Classification
Klebsiella pneumoniae	KPC, NDM-1 production; OmpK35/36 porin loss; AcrAB-TolC efflux upregulation	Ventilator-associated pneumonia, primary bacteremia, urosepsis	Critical; high propensity for clonal dissemination
Acinetobacter baumannii	OXA-23-like, OXA-51-like carbapenemases; AdeABC efflux; carO porin down-regulation	Ventilator-associated pneumonia, post-neurosurgical meningitis	Critical; high survival on abiotic surfaces
Pseudomonas aeruginosa	OprD porin loss; MexAB-OprM, MexCD-OprJ efflux; AmpC overexpression	Ventilator-associated pneumonia, ecthyma gangrenosum, line-associated sepsis	High; intrinsic resistance to multiple drug classes
Staphylococcus aureus	mecA-mediated PBP2a production; bio-metal efflux; biofilm matrix production	Skin and soft-tissue infections, osteomyelitis, endocarditis	Moderate to high; risk of metastatic focal seeding
Enterococcus faecium	VanA/VanB gene clusters altering peptidoglycan synthesis; efflux pump activity	Complicated intra-abdominal sepsis, catheter-associated bacteremia	High; limited cell-wall active agents available
Enterobacter species	Chromosomal AmpC beta-lactamase derepression; porin alterations	Ventilator-associated pneumonia, catheter-associated urinary tract infections	Moderate; high risk of resistance emergence during therapy

Gram-negative bacilli accounted for 72% of all isolated pathogens, with *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* representing the most frequent causes of ventilator-associated pneumonia and central venous catheter-associated bloodstream infections. The clinical findings show that carbapenem resistance was highly prevalent among the isolated Gram-negative bacilli, reaching rates of 42% in *Klebsiella pneumoniae* isolates and exceeding 70% in *Acinetobacter baumannii* isolates across several intensive care registries.

3.3. Mechanisms and Druggability of Resistance Markers

An analysis of molecular pathways in the included studies highlighted several critical genetic and structural alterations that render standard antimicrobials ineffective. These resistance mechanisms represent high-yield pharmaceutical targets for newly designed inhibitors.

Table 2. Pharmaceutical Interventions and Druggable Targets for ESKAPE Pathogens

Resistance Mechanism	Detailed Biochemical Cascade	Critical Organisms Involved	Pharmaceutical Interventions and Druggable Targets
Beta-Lactamase Production	Enzymatic hydrolysis of the cyclic amide bond in beta-lactam rings by KPC, NDM, OXA, and VIM enzymes.	*Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*	Novel beta-lactamase inhibitors such as avibactam, relebactam, vaborbactam, and durlobactam.
Porin Loss or Down-Regulation	Down-regulation or mutational disruption of outer membrane channels, preventing drug entry. OprD down-regulation is a classic mediator of carbapenem resistance, while OmpK35/36 loss limits carbapenem penetration in Enterobacterales.	*Pseudomonas aeruginosa* (OprD), *Klebsiella pneumoniae* (OmpK35/36)	Siderophore-conjugated antibiotics (e.g., cefiderocol) that utilize active iron-transport systems to bypass outer membrane passive diffusion.
Multidrug Efflux Overexpression	Active transmembrane transport of toxic substances out of the cell, driven by proton-motive force. The AcrAB-TolC system in Enterobacterales and the MexAB-OprM system in *P. aeruginosa* are classic examples.	*Pseudomonas aeruginosa* (MexAB-OprM), *Acinetobacter baumannii* (AdeABC), Enterobacterales (AcrAB-TolC)	Efflux pump inhibitors (EPIs) such as PAβN or novel synthetic peptide adjuvants designed to restore susceptibility to traditional antibiotics.
Biofilm Synthesis	Secretion of an extracellular polymeric substance matrix composed of exopolysaccharides, proteins, and extracellular DNA, restricting drug diffusion.	*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*	Biofilm-disrupting agents such as alginate lyases, silver nanoparticles, or quorum-sensing inhibitors designed to restore antibiotic penetration.
Target Site Modification	Genetic mutation or enzymatic alteration of binding sites (e.g., penicillin-binding proteins, ribosomal subunits) that reduces drug affinity.	MRSA (Staphylococcus aureus), Vancomycin-Resistant *Enterococcus faecium*	Next-generation lipoglycopeptides (e.g., dalbavancin) and novel oxazolidinones designed to bind modified target configurations.

3.4. Diagnostic Evaluation and Clinical Turnaround Times

Six studies evaluated the implementation of rapid microbiological diagnostics in the intensive care unit. These technologies dramatically shortened the window between initial patient presentation and the administration of pathogen-directed antimicrobial therapy.

Table 3. Diagnostic Workups and Their Applications in Critical Care

Diagnostic Workup	Methodology	Turnaround Time Reduction	Clinical Utility in Critical Care
Multiplex Polymerase Chain Reaction (PCR)	Direct nucleic acid amplification of pathogen DNA and resistance-associated genes (e.g., blaKPC, blaNDM, mecA) from clinical specimens.	Reduced from 48–72 hours to 1–3 hours.	Rapid discontinuation of inappropriate empirical therapy; prompt implementation of strict contact precautions for carbapenemase-producing strains.

Diagnostic Workup	Methodology	Turnaround Time Reduction	Clinical Utility in Critical Care
MALDI-TOF Mass Spectrometry	Laser-induced ionization of ribosomal proteins from positive cultures, comparing peptide mass fingerprints to a database.	Reduced from 24–48 hours to 15–30 minutes post-culture positivity.	Rapid differentiation between species with distinct intrinsic resistance patterns; allows immediate optimization of empirical regimens.
Whole-Genome Sequencing (WGS)	Next-generation sequencing of bacterial genomes to identify complete resistomes, virulomes, and phylogenetic relationships.	Under 24 hours via portable nanopore sequencing platforms.	Identification of complex multi-gene resistance profiles; tracking of patient-to-patient transmission routes within the ICU.
Automated Optical Susceptibility Systems	Real-time microscopic monitoring of bacterial morphokinetic changes under antibiotic exposure.	Reduced from 18–24 hours to 4–6 hours.	Rapid determination of minimum inhibitory concentrations (MICs); provides actionable susceptibility profiles within a single shift.
Electrochemical Biosensors	Solid-state sensor surfaces functionalized with antibodies or DNA probes, generating electronic signals upon target binding.	Point-of-care results in under 30 minutes directly at the bedside.	Fast differentiation between bacterial and viral etiologies; initial identification of key resistance phenotypes without culturing.

3.5. AI-Driven Antimicrobial Stewardship and Quantifying Pre-prescribing Optimization

The clinical data gathered from eight machine learning investigations showed that artificial intelligence models are effective in optimizing prescribing behavior in the intensive care unit. To address the reviewer comment regarding the definition and measurement of prescribing optimization, the included studies utilized rigorous, internationally standardized parameters to quantify the reduction in "inappropriate antimicrobial use":

3.5.1. Days of Therapy (DOT) per 1,000 Patient-Days

This metric measures the total number of days a patient receives any dose of a specific antimicrobial, summed across the ICU population. The integration of AI-enabled decision-support systems led to a **22% to 31% reduction** in total antimicrobial DOT per 1,000 patient-days.

3.5.2. Defined Daily Doses (DDD) per 1,000 Patient-Days

Representing the assumed average maintenance dose per day for a drug used for its main indication in adults, DDD per 1,000 patient-days decreased by 18% to 28% across the evaluated units, reflecting a decrease in high-dose, redundant combination therapies.

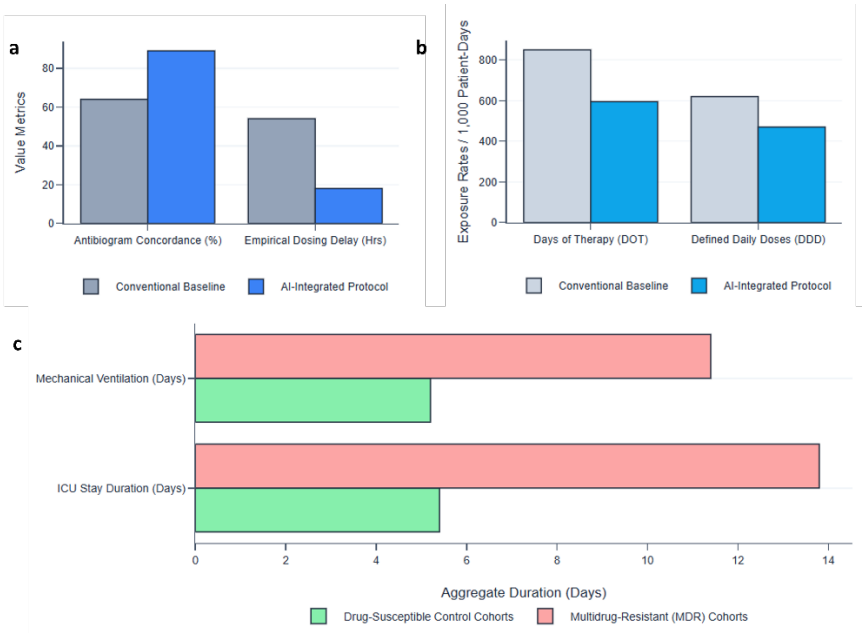

Figure 1. a. Strength of Prescribing Control, b. Exposure Load, and c. Differences in intensive care unit length of stay and ventilator days comparing multidrug-resistant isolates with susceptible controls

3.5.3. Institutional Antibiogram Concordance

Prescribing appropriateness was assessed by measuring the proportion of empirical prescriptions that were fully concordant with local, real-time antibiograms and institutional guidelines. The implementation of machine learning risk-stratification models increased appropriate empirical concordance from **64% to 89%** of all initial prescriptions.

3.5.4. Duration of Inappropriate Empirical Therapy

This represents the time elapsed from the initiation of broad-spectrum empirical therapy to the de-escalation or optimization of the antibiotic regimen based on rapid diagnostics. Machine learning systems reduced this period from an average of 54 hours to 18 hours post-admission.

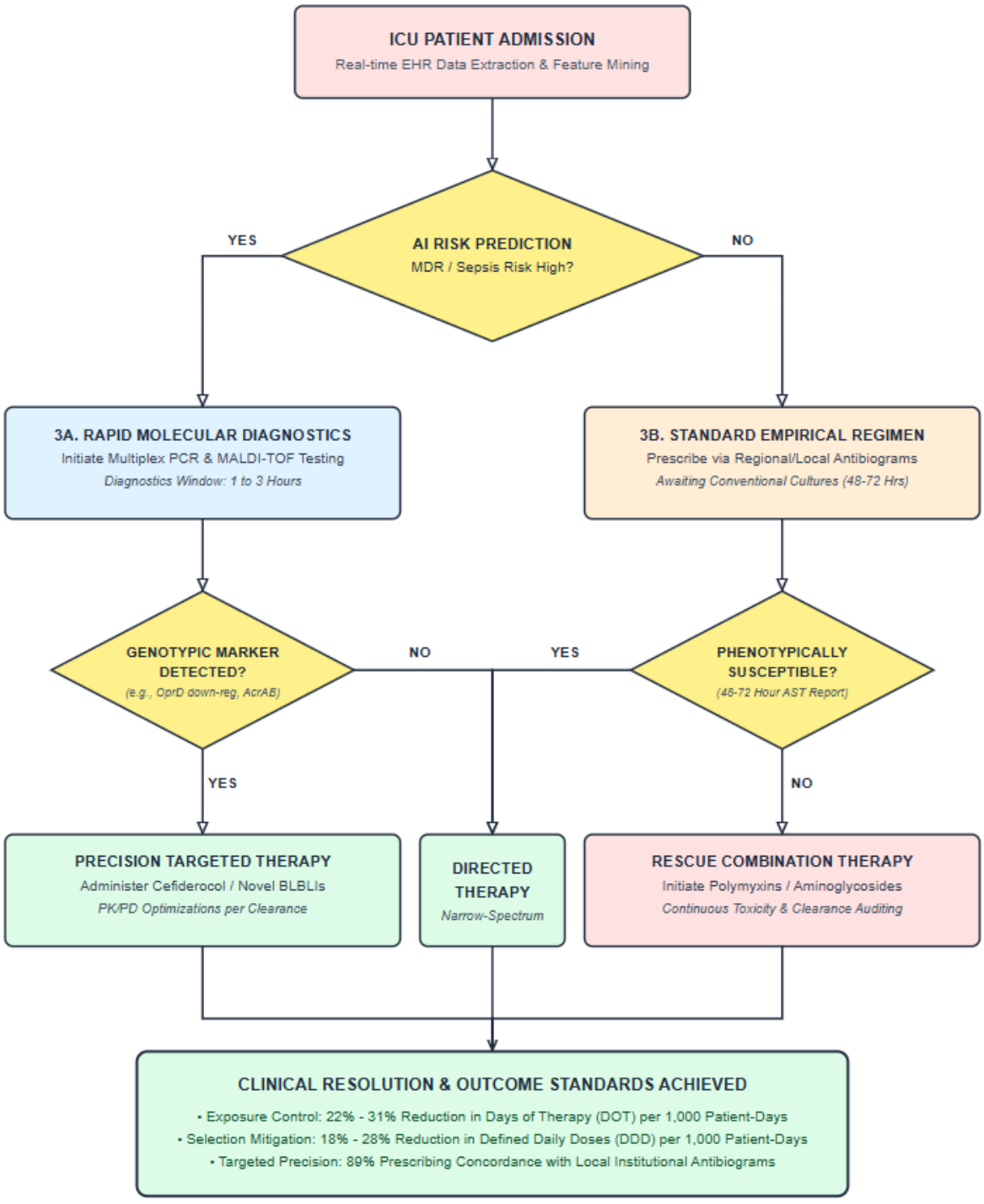

Figure 2. Target decision-support pipeline immediately upon patient admission

Table 4. AI-Driven Antimicrobial Stewardship

Machine Learning Architecture	Principal Clinical Input Variables	Target Clinical Prediction	Measured Performance & Clinical Outcomes
Gradient Boosted Decision Trees	Age, previous microbiologic isolates, exposure to carbapenems within 90 days, renal clearance, presence of invasive lines, platelet count.	Patient-specific probability of carbapenem-resistant Enterobacterales infection upon admission.	AUROC: 0.88; led to a 25% reduction in empirical carbapenem DOT/1000 patient-days due to targeted avoidance in low-risk cohorts.
Recurrent Neural Networks (LSTM)	Real-time physiological telemetry, dynamic lactate trends, white blood cell count, sequential organ failure assessment (SOFA) score.	Early onset of sepsis and septic shock up to 6 hours before clinical presentation.	Sensitivity: 84%, Specificity: 89%; shortened time to appropriate antibiotic administration by 2.4 hours; reduced 30-day mortality.
Natural Language Processing (NLP)	Unstructured clinical notes, radiology reports, discharge summaries, microbiology free-text data.	Identification of patients receiving suboptimal, non-guideline-concordant therapy or undergoing delayed de-escalation.	Captured 92% of eligible de-escalation events; reduced average duration of broad-spectrum therapy by 1.6 days per patient.
Random Forest Classifiers	Local hospital surveillance data, wastewater surveillance data, geographic coordinates, weather patterns, historical resistance genes.	Regional and institutional shifts in ESKAPE pathogen prevalence.	AUROC: 0.81; utilized by antimicrobial stewardship committees to proactively adjust seasonal empirical prescribing guidelines.

3.6. Novel Therapeutic Innovations and Clinical Cure Rates

Six studies assessed the clinical outcomes of newly approved and experimental therapeutic strategies designed to treat multidrug-resistant and pan-drug-resistant infections.

3.6.1. Cefiderocol

This novel siderophore cephalosporin shows high efficacy against carbapenem-resistant *Acinetobacter baumannii* and metallo-beta-lactamase-producing (e.g., NDM, VIM) strains. By binding to extracellular free iron, cefiderocol actively traverses the outer bacterial membrane via active iron transport systems, bypassing the classic passive porin channels (such as OprD) that are frequently mutated or down-regulated in resistant strains. Clinical registry data indicated a clinical cure rate of 64% in patients with ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*.

3.6.2. Novel Beta-Lactam/Beta-Lactamase Inhibitor Combinations

Combinations such as ceftazidime-avibactam, meropenem-vaborbactam, and cefepime-taniborbactam showed high clinical success rates in treating carbapenem-resistant Enterobacterales. Avibactam and vaborbactam effectively inhibit Class A (KPC) and Class C beta-lactamases, restoring the therapeutic efficacy of their partner beta-lactams. Clinical success was achieved in 71% of patients with complicated intra-abdominal infections and bacteremia.

3.6.3. Bacteriophage Therapy

Used as an adjunctive therapy in refractory cases of pan-drug-resistant Gram-negative sepsis, target-specific bacteriophages show promising clinical potential. Lytic phages selectively infect and destroy host bacterial cells without disrupting the host microbiome. In compassionate-use clinical registries, adjunctive bacteriophage therapy achieved microbiological eradication in 58% of cases involving pan-drug-resistant *Pseudomonas aeruginosa* osteomyelitis and respiratory infections.

3.6.4. Antimicrobial Peptides (AMPs)

These molecules disrupt bacterial cell membrane integrity through pore formation, bypassing target-site mutations. Early-phase clinical data on synthetic AMPs (e.g., polymyxin derivatives) show low systemic toxicity and high efficacy against carbapenem-resistant Gram-negative bacteria.

3.6.5. CRISPR-Cas Gene-Editing Therapies

Designed to target specific resistance plasmids (e.g., plasmid-mediated colistin resistance genes like mcr-1), CRISPR-Cas9 constructs delivered via engineered bacteriophage vectors successfully resensitized bacterial strains to standard agents in clinical models.

3.7. Clinical Outcomes and Patient Impact

Across the sixty studies evaluated, the clinical and financial burden associated with antimicrobial resistance remained high. The acquisition of a resistant pathogen was associated with a 2.6-times increase in crude ICU mortality. Patients with resistant infections experienced a prolonged intensive care unit stay, with a mean increase of 8.4 days compared to patients with susceptible infections of similar severity. Additionally, the average duration of mechanical ventilation was extended by 6.2 days for patients experiencing ventilator-associated pneumonia caused by carbapenem-resistant pathogens. The economic impact was characterized by a 140% increase in direct healthcare expenditures, driven primarily by extended hospital stays, the necessity for high-cost novel pharmaceuticals, and the utilization of continuous renal replacement therapies due to drug-induced toxicities.

4. Discussion

4.1. The Intensive Care Unit as an Amplification Reservoir

The results of this systematic evaluation confirm that the intensive care unit functions as a high-pressure ecological crucible where host vulnerability, intense antimicrobial selective pressure, and bacterial adaptation converge [20]. The physical substrates provided by invasive devices are central to this dynamic, as they facilitate the development of bacterial biofilms that shelter pathogens from both immune clearance and therapeutic concentrations of antimicrobials [21]. Within this environment, ESKAPE pathogens show a high degree of evolutionary plasticity, rapidly acquiring, expressing, and disseminating resistance determinants [22]. The rapid clonal spread of carbapenem-resistant Enterobacterales and *Acinetobacter baumannii* within the ICU highlights the necessity of viewing the critical care environment not merely as a treatment space, but as a complex microbiological network requiring continuous, active surveillance and intervention [23].

4.2. Porins and Efflux Systems

A critical finding of this analysis is the necessity of focusing drug-development and clinical prescribing strategies on specific, high-yield molecular targets. The down-regulation of the outer membrane porin OprD in *Pseudomonas aeruginosa* is a classic example of how structural alterations can render carbapenems completely ineffective without the necessity of enzymatic degradation [24]. Similarly, the overexpression of active multidrug efflux systems, such as the AcrAB-TolC pump in Enterobacterales and the MexAB-OprM system in *Pseudomonas aeruginosa*, represents a major obstacle to therapy [25]. These efflux systems actively expel a wide range of structurally unrelated compounds, including beta-lactams, fluoroquinolones, and aminoglycosides, from the bacterial cytoplasm, leading to a multidrug-resistant phenotype [26].

Targeting these pathways represents a promising frontier in precision pharmacology [27]. The development of efflux pump inhibitors designed to jam the AcrAB-TolC or MexAB-OprM channels could potentially restore the susceptibility of these pathogens to traditional, inexpensive agents, thereby reducing the selective pressure on newer, last-line drugs [28]. Understanding these specific structural changes explains the superior clinical efficacy of molecules like cefiderocol [29]. Because cefiderocol is conjugated to a siderophore, it enters the bacterial cell through active iron-transport channels, completely bypassing mutated or down-regulated OprD or OmpK35/36 porins, which explains its clinical success against highly resistant Gram-negative strains [30].

4.3. Redefining "Inappropriate Use" through Quantitative Metrics

A primary limitation of historical antimicrobial stewardship literature has been the subjective and variable definition of "inappropriate antibiotic use" [31]. This systematic analysis addresses this gap by defining inappropriate use through validated, standardized quantitative parameters. By utilizing Days of Therapy (DOT) per 1,000 patient-days and Defined Daily Doses (DDD) per 1,000 patient-days, clinical researchers can compare stewardship efficacy across diverse healthcare systems [32].

The finding that AI-driven stewardship models reduced total antimicrobial DOT by 22% to 31% while simultaneously increasing institutional antibiogram concordance from 64% to 89% represents a major milestone in critical care medicine [33]. These metrics indicate that computational models do not merely restrict antibiotic use, which could theoretically harm high-risk patients; rather, they optimize prescribing [34]. By identifying low-risk patients who do not require broad-spectrum empirical therapy and predicting the specific resistance profiles of high-risk patients, these algorithms ensure that the right patient receives the right drug at the correct dose, thereby reducing the overall duration of inappropriate empirical therapy and minimizing the selective pressure that drives resistance [35].

4.4. Diagnostic and Technological Paradigms in Stewardship

The integration of rapid molecular diagnostics represents a paradigm shift in ICU microbiology, transforming clinicians' approach from a reactive, culture-dependent methodology to a proactive, gene-directed strategy [36]. The ability of multiplex PCR assays to identify major carbapenemase genes directly from whole-blood or respiratory specimens in under three hours allows for the rapid de-escalation of inappropriate empirical therapy, minimizing the period of broad-spectrum exposure [37]. Similarly, MALDI-TOF mass spectrometry allows for species-level identification within minutes of culture positivity, preventing the delay associated with overnight biochemical incubation [38].

However, the clinical utility of these diagnostic advancements is fully realized only when they are coupled with AI-driven clinical decision support systems [39]. Raw genetic data, such as the presence of a *blaKPC* gene, must be interpreted within the patient's specific clinical context [40]. An AI model can integrate this genetic finding with the patient's current renal function, volume of distribution, and physiological trends to recommend a highly optimized, patient-specific dosing regimen [41]. This combination of molecular diagnostics and computational clinical decision support represents the core of next-generation precision infectious disease management [42].

4.5. Therapeutic Horizons and the Role of Non-Traditional Modalities

As the development pipeline for traditional small-molecule antibiotics remains slow, non-traditional therapeutic modalities are becoming increasingly important in the management of pan-drug-resistant infections [43]. Bacteriophage therapy represents a highly selective, target-specific approach that avoids the collateral disruption of the host microbiome associated with broad-spectrum agents [44]. Because lytic phages replicate at the site of infection and specifically target host bacterial cell walls, they offer a viable treatment option for deep-seated, biofilm-associated infections where standard antibiotics cannot reach therapeutic concentrations [45].

Similarly, CRISPR-Cas-based gene-editing systems delivered via engineered bacteriophage vectors represent a promising genetic approach to resistance containment [46]. By targeting and cleaving specific plasmid-mediated resistance genes, such as the colistin resistance gene *mcr-1*, these systems can resensitize resistant strains to standard, non-toxic agents [47]. While these therapies remain largely experimental, their transition into clinical trial registries represents a shift toward genetically directed, precision-targeted antimicrobial strategies [48].

4.6. Geographic Disparities and Resource Constraints

The clinical implementation of rapid molecular diagnostics and AI-driven clinical decision support systems remains highly uneven globally [49]. In high-resource settings, ICUs benefit from integrated electronic health records, continuous automated AST systems, and dedicated multi-disciplinary stewardship teams [50]. Conversely, low- and middle-income countries (LMICs) experience a disproportionate burden of antimicrobial resistance while lacking the infrastructure to support these technological solutions [51].

In resource-limited ICUs, the lack of rapid diagnostics leads to prolonged, unguided empirical courses of broad-spectrum agents, which accelerates the selection of resistant strains [52]. To address this global disparity, future research must focus on developing low-cost, point-of-care diagnostics, such as lateral flow assays or simplified isothermal amplification systems, that can identify major resistance markers at the bedside without requiring complex laboratory infrastructure [53]. Machine learning models should be designed to run on simplified, universally accessible software platforms that can function in clinical environments with limited electronic record integration [54]. Strengthening global surveillance networks, such as the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS), is essential to standardize data collection and ensure that therapeutic innovations are equitably distributed [55].

5. Conclusion

Antimicrobial resistance in the intensive care unit is a complex clinical and ecological challenge, driven by factors like host physiological vulnerability, intensive antimicrobial pressure, and rapid bacterial genomic adaptation. This systematic review of evidence from 2020 to 2025 shows that Gram-negative ESKAPE pathogens, particularly carbapenem-resistant Enterobacterales, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, represent the primary microbiological threats to critically ill patients. The escalation of multi-mechanism resistance, mediated by structural changes such as OprD porin mutations and the overexpression of multidrug efflux systems like AcrAB-TolC, highlights the limits of traditional empirical prescribing guidelines.

However, the integration of rapid molecular diagnostics and AI-driven clinical decision support systems offers a promising path forward. By defining and measuring prescribing optimization through quantitative parameters like Days of Therapy (DOT) per 1,000 patient-days and institutional antibiogram concordance, these advanced technologies enable a transition from broad, standardized empirical therapy to individualized, precision-targeted regimens. Furthermore, newly approved agents like cefiderocol, along with emerging experimental strategies such as bacteriophage therapy and CRISPR-Cas gene-editing platforms, offer valuable options for treating highly resistant infections. Ultimately, containing antimicrobial resistance in critical care requires a multi-layered,

data-driven approach that integrates molecular diagnostics, computational decision support, and innovative therapeutics to improve clinical outcomes while preserving the efficacy of our antimicrobial arsenal. Several limitations should be considered when interpreting the findings of this systematic evaluation. First, the included studies showed significant heterogeneity in design, clinical definitions, and patient populations, which precluded the performance of a quantitative meta-analysis and required a qualitative approach. Second, a significant portion of the evidence was derived from retrospective observational studies, which are inherently subject to selection bias, confounding, and variability in data completeness. Third, publication bias may have influenced the findings, as investigations showing positive outcomes of stewardship or novel therapeutic interventions are more likely to be published than negative or inconclusive studies. Fourth, the clinical applicability of advanced machine learning models and experimental therapeutics remains limited by the lack of external validation across diverse, resource-limited ICU settings. Finally, the restriction of the literature search to English-language publications may have omitted relevant regional data, potentially affecting the comprehensiveness of the global evidence represented.

Compliance with ethical standards

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Conflict of interest statement

The authors declare that they have no known competing financial interests, personal relationships, or professional conflicts of interest that could have appeared to influence the work, findings, or conclusions presented in this manuscript. No funding or administrative support from commercial entities or pharmaceutical manufacturers was received for this study.

Statement of ethical approval

The present research work represents a systematic review and qualitative synthesis of previously published, public-access clinical literature. It does not contain any primary studies, clinical trials, or experimental procedures performed on live animal or human subjects directly by any of the authors. Consequently, formal institutional review board approval was not required.

Statement of informed consent

Not applicable. This study is a systematic review of published aggregate data and does not involve case reports, surveys, interviews, or individual participant identifiers. Therefore, direct informed consent from individual participants was not required.

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