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Emerging Antimicrobial Resistance in Gram-Negative Pathogens: Protocol for a Pragmatic Cluster-Randomized Controlled Trial

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ABSTRACT

Introduction: Antimicrobial resistance among Gram-negative pathogens, including extended-spectrum β-lactamase (ESBL)-producing Enterobacterales and carbapenem-resistant Acinetobacter and Pseudomonas, is associated with high mortality and limited therapeutic options. Delayed initiation of effective antimicrobial therapy in bloodstream infections (BSIs) is consistently linked to adverse clinical outcomes. Although rapid diagnostic tests (RDTs) combined with antimicrobial stewardship (AS) improve the timeliness of therapy, high-quality evidence from resource-constrained settings remains limited. This study evaluates a pragmatic strategy integrating rapid diagnostics with stewardship to optimize early targeted therapy.

Methods: This multicenter, parallel-group, pragmatic cluster randomized controlled trial includes 20 hospitals randomized to either an intervention bundle or standard care. The intervention comprises PCR-based pathogen and resistance gene identification, EUCAST rapid antimicrobial susceptibility testing (RAST), and a predefined stewardship algorithm for antibiotic optimization. Standard care includes routine culture, MALDI-TOF identification, and CLSI-guided susceptibility testing. Adult patients with confirmed Gram-negative BSIs are enrolled. The primary outcome is the proportion of patients receiving optimal targeted therapy within 24 hours of culture positivity. Secondary outcomes include time to effective therapy, 30-day mortality, hospital length of stay, adverse events, and antibiotic utilization. Analyses will follow an intention-to-treat approach using mixed-effects regression models.

Results: As this manuscript presents a study protocol, no clinical outcome data are reported. Patient enrollment and trial implementation are ongoing across participating centers.

Conclusion: This rigorously designed pragmatic cluster randomized trial will generate high-quality evidence on whether integrating rapid diagnostics with antimicrobial stewardship improves timely targeted therapy in Gram-negative BSIs, with direct implications for optimizing antimicrobial use and addressing global antimicrobial resistance.

Keywords

Antimicrobial Resistance, Gram-Negative Bacteria, Bloodstream Infection, Rapid Diagnostics, Antimicrobial Stewardship, Cluster Randomized Trial

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INTRODUCTION

Antimicrobial resistance (AMR) has emerged as one of the most pressing global health challenges, with an estimated 4.95 million deaths associated with bacterial resistance in 2019, the majority attributable to Gram-negative pathogens [1]. The World Health Organization continues to classify carbapenem-resistant Acinetobacter baumannii, carbapenem-resistant Enterobacterales, and multidrug-resistant Pseudomonas

aeruginosa as critical-priority pathogens due to their rapid global dissemination and limited therapeutic options [2]. These organisms are major causes of severe infections, including sepsis and hospital-acquired pneumonia, and are consistently associated with high morbidity and mortality [3]. Timely initiation of effective antimicrobial therapy is a key determinant of survival in patients with bloodstream infections (BSIs) and sepsis. Delays in appropriate therapy, even within the first 12 hours following culture positivity, have been associated with a substantial increase in mortality [4]. However, conventional microbiological workflows based on culture and standard antimicrobial susceptibility testing typically require 48–72 hours to yield actionable results [5]. During this critical window, patients are often treated with broad-spectrum empiric antibiotics, which may be suboptimal, contribute to antimicrobial resistance, and increase the risk of adverse drug events [6].

Rapid diagnostic tests (RDTs), particularly multiplex polymerase chain reaction (PCR) platforms applied to positive blood cultures, enable early identification of pathogens and key resistance determinants such as extended-spectrum β-lactamases (ESBLs) and carbapenemases within a significantly shortened timeframe [7]. In parallel, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has introduced Rapid Antimicrobial Susceptibility Testing (RAST), which provides early phenotypic susceptibility results within 4–8 hours [8]. Despite these advances, the clinical impact of RDTs alone remains limited if results are not promptly translated into optimized antimicrobial therapy. Evidence from interventional studies and meta-analyses indicates that meaningful improvements in clinical outcomes, including mortality reduction, are achieved only when RDTs are integrated with structured antimicrobial stewardship (AS) interventions [9]. Accordingly, the Infectious Diseases Society of America strongly recommends the combined implementation of rapid diagnostics and stewardship programs to improve antimicrobial use and patient outcomes [10].

Despite growing evidence, important gaps remain. Most existing studies are conducted in single-center settings or high-resource healthcare systems, limiting generalizability to low- and middle-income countries (LMICs), where the burden of antimicrobial resistance is often higher and healthcare resources are constrained [11]. Furthermore, there is limited high-quality evidence from pragmatic, multicenter randomized trials evaluating scalable diagnostic–stewardship interventions in real-world hospital settings. To address these gaps, we propose a pragmatic, multicenter, cluster-randomized controlled trial evaluating a standardized bundle combining rapid diagnostic testing and antimicrobial stewardship. Cluster randomization at the hospital level is employed to ensure consistent implementation of the intervention and to minimize contamination between treatment arms, in accordance with CONSORT guidelines for cluster trials [12]. This manuscript presents the full study protocol, developed in line with CONSORT 2025 recommendations, with detailed methodological and microbiological procedures to ensure reproducibility. To determine whether a standardized rapid diagnostic and antimicrobial stewardship bundle increases the proportion of adult patients with Gram-negative bloodstream infections receiving optimal targeted antimicrobial therapy within 24 hours of culture positivity, compared with standard care.

METHOD

This study is designed as a multicenter, parallel-group, pragmatic cluster-randomized controlled trial. Participating hospitals serve as the unit of randomization and are allocated in a 1:1 ratio to either the intervention or control arm. A cluster design is selected to accommodate a workflow-level intervention, thereby minimizing contamination across individual patients and reflecting real-world clinical practice. The trial will be conducted and reported in accordance with CONSORT 2025 guidelines, including the extension for cluster randomized trials.

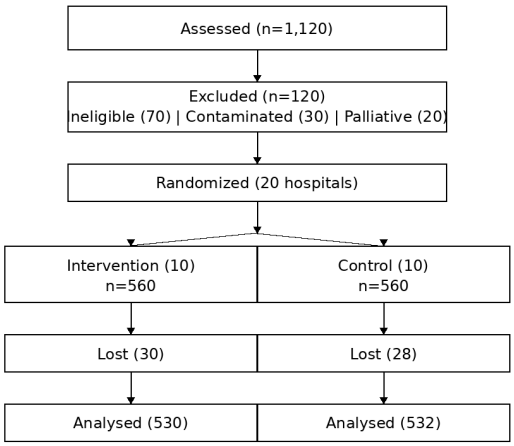

Figure 1. Study Flow Diagram of the Cluster-Randomized Controlled Trial

The study will be conducted across 20 tertiary-care hospitals equipped with on-site microbiology laboratories and continuous blood culture capabilities. These centers represent institutions with moderate-to-high rates of Gram-negative bloodstream infections and established baseline antimicrobial stewardship practices. Eligible participants are adult inpatients (⩾18 years) with a first episode of monomicrobial Gram-negative bacteremia, defined by a positive blood culture yielding Enterobacterales, Pseudomonas aeruginosa, or Acinetobacter baumannii complex.

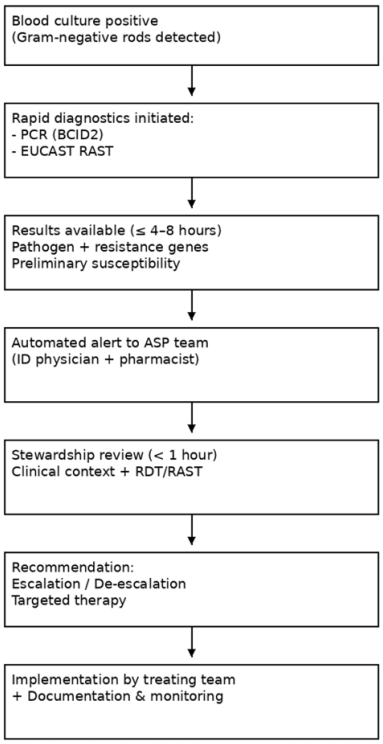

Figure 2. Workflow of the Rapid Diagnostic–Stewardship Intervention

Exclusion criteria include polymicrobial bloodstream infections, likely contaminants, patients receiving palliative care, anticipated survival of less than 48 hours, and cases with incomplete clinical data. All eligible episodes will be consecutively included. Given the pragmatic implementation nature of the trial, a waiver of informed consent is anticipated, subject to institutional ethics approval. The intervention comprises a standardized rapid diagnostic–stewardship bundle integrating three coordinated components designed to accelerate pathogen identification, enable early susceptibility profiling, and facilitate timely optimization of antimicrobial therapy. Upon blood culture positivity indicating Gram-negative organisms, multiplex

polymerase chain reaction (PCR) testing (BioFire FilmArray BCID2 panel) is performed directly on the positive culture broth. This platform enables rapid identification of clinically relevant Gram-negative pathogens alongside key resistance determinants, including extended-spectrum β-lactamases and carbapenemase genes, within approximately one hour. Results are immediately communicated to the antimicrobial stewardship team and simultaneously documented in the electronic medical record to ensure real-time clinical accessibility.

In parallel, rapid phenotypic antimicrobial susceptibility testing is conducted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) RAST methodology. Mueller–Hinton agar plates are directly inoculated from positive blood culture bottles, followed by application of relevant antimicrobial disks. Inhibition zones are interpreted at 4, 6, and 8 hours using current EUCAST RAST breakpoints. Preliminary susceptibility categorizations are released in real time, with appropriate interpretative considerations for early readings. A dedicated multidisciplinary antimicrobial stewardship team, comprising an infectious diseases physician and a clinical pharmacist, receives automated alerts upon availability of rapid diagnostic outputs. Within one hour, the team performs a structured clinical review incorporating patient-specific factors, infection source, and rapid microbiological data. A predefined stewardship algorithm is applied to guide antimicrobial optimization, including escalation, de-escalation, or targeted therapy selection. Recommendations are communicated directly to the treating clinicians and formally documented in the medical record.

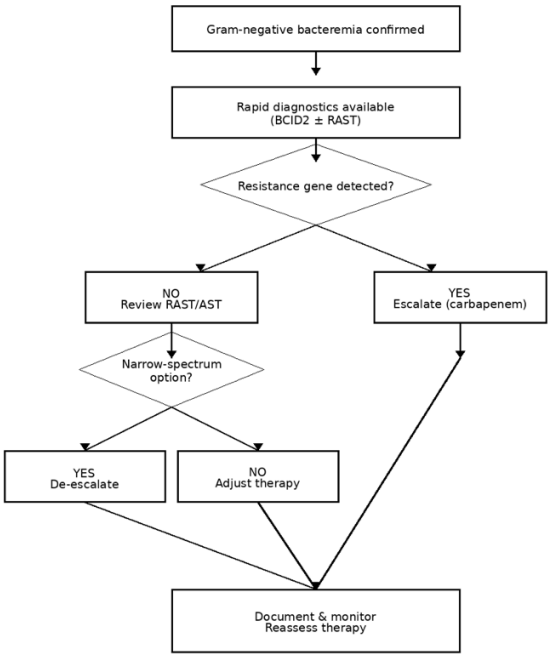

Figure 3. Antimicrobial Stewardship Decision Algorithm

Adherence to recommendations, as well as documented reasons for non-adherence, are systematically recorded for evaluation. Implementation fidelity will be assessed using predefined process indicators, including time from culture positivity to diagnostic reporting, time to stewardship intervention, proportion of eligible cases receiving the complete intervention bundle, and acceptance rates of stewardship recommendations. Hospitals assigned to the control arm will continue standard microbiological and clinical workflows. Blood cultures undergo routine processing, including subculture, organism identification using MALDI-TOF mass spectrometry, and antimicrobial susceptibility testing via automated or manual methods interpreted according to CLSI guidelines. Stewardship activities follow existing institutional practices without mandatory rapid diagnostics or structured intervention algorithms.

The primary outcome is the proportion of patients receiving optimal targeted antimicrobial therapy within 24 hours of blood culture positivity. Optimal therapy is defined using a prespecified adjudication

framework requiring microbiological activity against the identified pathogen, avoidance of unnecessary broad-spectrum agents, and appropriate dosing. Outcome assessment will be performed by an independent adjudication committee blinded to study allocation. Secondary outcomes include time to effective therapy, time to de-escalation, 30-day all-cause mortality, in-hospital mortality, hospital and intensive care unit length of stay, incidence of organ dysfunction, antibiotic utilization metrics, adverse drug events including acute kidney injury and Clostridioides difficile infection, and emergence of antimicrobial resistance within 30 days. The sample size is calculated based on the primary outcome, assuming an increase in optimal targeted therapy from 45% in the control group to 60% in the intervention group. With a two-sided α of 0.05 and 90% power, and accounting for a cluster design with an intracluster correlation coefficient of 0.01, a total sample of approximately 1,000 patients across 20 clusters is required. This design provides adequate statistical power while accommodating potential attrition.

Clusters will be randomized in a 1:1 ratio using a computer-generated sequence with stratification by geographic region and baseline infection rates. Allocation concealment will be maintained until study initiation. Due to the nature of the intervention, blinding of clinicians and patients is not feasible; however, outcome adjudicators and data analysts will remain blinded to treatment allocation. Analyses will follow the intention-to-treat principle. The primary outcome will be analyzed using mixed-effects logistic regression, incorporating cluster as a random effect. Secondary outcomes will be analyzed using appropriate mixed-effects or survival models depending on data type. Missing data will be addressed using multiple imputation under the assumption of missing at random. Prespecified subgroup analyses will explore effect modification by pathogen type, resistance profile, and clinical setting. Blood cultures will be processed using automated systems with standard Gram staining procedures. Organism identification will be performed using MALDI-TOF mass spectrometry, while susceptibility testing in the control arm will follow CLSI standards. The intervention arm will utilize EUCAST RAST protocols for rapid susceptibility assessment. Quality control procedures will adhere to international laboratory standards.

The study protocol will be approved by institutional ethics committees at all participating sites. Given the pragmatic and system-level nature of the intervention, a waiver of individual informed consent is anticipated. The trial will be prospectively registered in a recognized clinical trial registry. Reporting will adhere to CONSORT 2025 guidelines.

RESULTS

As this manuscript presents a study protocol, no actual trial data are reported. The following tables illustrate the planned structure for baseline characteristics and outcome reporting to ensure transparency and reproducibility of the final analysis. Baseline demographic and clinical characteristics will be summarized using appropriate descriptive statistics and presented by study arm. An example of the planned table structure is shown below.

Table 1. Baseline Demographic and Clinical Characteristics (Illustrative Format)

Characteristic	Intervention (n = X)	Control (n = Y)
Age, median (IQR), years	58 (45–70)	59 (46–71)
Male sex, n (%)	300 (50%)	310 (52%)
ICU at onset, n (%)	200 (33%)	210 (35%)
SOFA score, median (IQR)	7 (4–10)	7 (4–10)
Infection source, n (%)		
Urinary tract	180 (30%)	170 (28%)
Pathogen distribution, n (%)		
Escherichia coli	150 (25%)	145 (24%)
Klebsiella spp.	120 (20%)	130 (22%)
Pseudomonas aeruginosa	80 (13%)	85 (14%)
Acinetobacter baumannii	40 (7%)	45 (8%)
ESBL-producing organisms, n (%)	120 (20%)	110 (19%)
Carbapenem-resistant organisms, n (%)	50 (8%)	45 (7%)

Primary and secondary outcomes will be analyzed according to the prespecified statistical analysis plan and reported with effect estimates, 95% confidence intervals, and corresponding p-values.

Table 2. Primary and Key Secondary Outcomes (Illustrative Format)

Outcome	Intervention	Control	Effect (95% CI)	p-value
Optimal therapy ≤24 h, n/N (%)	—	—	—	—
Time to active therapy, h (median, IQR)	8 (6–14)	18 (12–24)	HR 2.10 (1.70–2.60)	<0.001
30-day mortality, n/N (%)	10.9%	12.5%	OR 0.86 (0.59–1.24)	0.40
Length of stay, days (median, IQR)	12 (8–18)	15 (10–22)	—	—
Acute kidney injury, n/N (%)	9.1%	10.6%	OR 0.85 (0.56–1.28)	0.41

Adverse events, including acute kidney injury and Clostridioides difficile infection, will be systematically recorded and compared between study groups. No safety signals are presented in this protocol.

DISCUSSION

This pragmatic cluster-randomized controlled trial was designed to evaluate whether integrating rapid diagnostic technologies with antimicrobial stewardship improves the timeliness of optimal targeted therapy in Gram-negative bloodstream infections (GN-BSIs). By design, the intervention is expected to increase the proportion of patients receiving appropriate therapy within 24 h of blood culture positivity. While improvements in process outcomes are anticipated, the extent to which these translate into patient-centered outcomes, including mortality reduction, will depend on baseline severity, pathogen distribution, and the healthcare context. The protocol incorporates rigorous methodological safeguards to ensure internal validity and reproducibility.

The proposed intervention is supported by a substantial and evolving body of evidence demonstrating that rapid diagnostic technologies alone are insufficient unless coupled with structured antimicrobial stewardship interventions. Large-scale global analyses have highlighted the significant burden of antimicrobial resistance and its contribution to mortality, reinforcing the urgency of optimizing early antimicrobial therapy in severe infections [13]. Randomized clinical trials have demonstrated that the integration of rapid diagnostic testing with stewardship programs significantly reduces the time to effective therapy and improves antimicrobial optimization in patients with gram-negative bacteremia [14]. Furthermore, recent network meta-analyses have confirmed that clinically meaningful benefits, including reductions in mortality, are primarily observed when rapid diagnostics are embedded within active stewardship frameworks rather than implemented in isolation [15]. Importantly, observational data consistently demonstrated a strong association between delays in appropriate antimicrobial therapy and increased mortality in bloodstream infections, emphasizing the critical need to shorten the diagnostic-to-treatment interval [16]. Additionally, evidence from randomized trials evaluating novel antimicrobial strategies in severe gram-negative infections underscores the complexity of treatment selection in the context of evolving resistance patterns [17-20]. Despite these advances, most studies have been conducted in high-resource or single-center settings, which limits their generalizability. The present trial addresses this gap by evaluating a standardized, scalable intervention within a multicenter, pragmatic framework.

This intervention is specifically designed to reduce delays in clinical decision-making by integrating rapid molecular and phenotypic diagnostic tools with real-time stewardship interventions. Multiplex PCR platforms enable the early identification of pathogens and resistance determinants, whereas EUCAST RAST provides timely phenotypic susceptibility data. When combined with structured stewardship decision algorithms, these diagnostic outputs can be translated into immediate and actionable clinical decisions. This approach is consistent with global antimicrobial stewardship strategies, which emphasize the importance of aligning diagnostic information with antibiotic optimization to reduce inappropriate antimicrobial use and selection pressure for resistance [21-23]. The performance of rapid diagnostic platforms, such as the BioFire

BCID2 panel, has been validated in multicenter studies, demonstrating high diagnostic accuracy and clinical utility in bloodstream infections [24,25]. Similarly, EUCAST RAST has demonstrated reliability in providing early susceptibility data, supporting timely therapeutic adjustments [26]. Emerging evidence supports the integration of rapid diagnostics with stewardship interventions to improve clinical outcomes, including mortality reduction and optimization of antimicrobial exposure [27,28]. International guidelines, such as those of the Surviving Sepsis Campaign, emphasize early and appropriate antimicrobial therapy as a cornerstone of sepsis management [28,29]. The incorporation of structured stewardship frameworks, including classification systems such as AWaRe, further enhances rational antibiotic use at both institutional and global levels [30].

This study has several notable strengths. First, the cluster-randomized design minimizes contamination between intervention and control groups and reflects real-world implementation of system-level interventions. Second, the multicenter design enhances external validity and ensures applicability across diverse healthcare settings. Third, the intervention is standardized and reproducible, with clearly defined microbiological and stewardship components aligned with international standards. Fourth, the use of intention-to-treat analysis and blinded outcome adjudication minimizes bias and strengthens the robustness of the findings. Finally, the pragmatic design ensures that the results can be directly translated into routine clinical practice, addressing a critical gap between research and implementation [31]. Several limitations should be acknowledged. The open-label nature of the trial introduces the potential for performance bias; however, the primary outcome is based on objective, time-stamped data, which mitigates this concern. Cluster randomization may result in baseline imbalances; however, stratified randomization and adjusted statistical analyses are planned to address this issue. In addition, rapid diagnostic platforms may not detect all resistance mechanisms, such as certain AmpC β-lactamases or emerging resistance genes, which may limit their diagnostic completeness. Nevertheless, the combination of genotypic and phenotypic methods is expected to reduce diagnostic uncertainty [32-34]. Furthermore, the primary outcome is a process measure, and improvements in this endpoint may not necessarily translate into measurable differences in mortality or other clinical outcomes.

If effective, this intervention has the potential to significantly improve the management of GN-BSIs by enabling earlier and more precise antimicrobial therapy. Timely optimization of antimicrobial treatment may reduce mortality, shorten hospital length of stay, and decrease the emergence of antimicrobial resistance. These findings are particularly relevant in the context of global priority pathogens identified by international health authorities, which continue to pose a major threat to public health [35]. Moreover, the integration of rapid diagnostics with stewardship aligns with global initiatives aimed at strengthening antimicrobial stewardship programs and optimizing antibiotic use across healthcare systems [36-38]. The implementation of structured stewardship bundles has previously demonstrated improvements in clinical outcomes in sepsis, further supporting the potential impact of this approach [39]. Future research should evaluate the cost-effectiveness and sustainability of diagnostic-stewardship interventions across different healthcare settings, particularly in low-and middle-income countries. Expanding this approach to other severe infections, including hospital-acquired pneumonia and intra-abdominal infections, warrants further investigation. Additionally, long-term studies are needed to assess the impact of such interventions on antimicrobial resistance trends and population-level outcomes. Integration with global surveillance systems and real-world data platforms may further enhance the applicability and scalability of these strategies. Ongoing debate regarding the relative importance of timing versus microbiological precision in antimicrobial therapy highlights the need for continued high-quality evidence in this field [40]. This study is positioned to provide pragmatic, implementation-ready evidence bridging the gap between diagnostic innovation and real-world antimicrobial optimization.

CONCLUSION

This CONSORT-compliant cluster randomized controlled trial is designed to provide definitive evidence on the clinical utility of integrating rapid diagnostics with antimicrobial stewardship for Gram-negative bloodstream infections. By enabling early pathogen identification, rapid susceptibility profiling, and protocolized therapeutic optimization, this strategy has the potential to substantially reduce delays in effective antimicrobial therapy. Importantly, the study will move beyond process metrics to evaluate its impact on

clinically meaningful outcomes, including treatment appropriateness and patient prognosis. In the context of escalating antimicrobial resistance and limited therapeutic options, the findings are expected to directly inform clinical practice and strengthen the implementation of diagnostic–stewardship models across diverse healthcare systems.

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None

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COMPETING INTERESTS
All authors have reviewed and approved the final version of the manuscript and agreed to its publication in the Journal of Society Medicine.

AUTHORS' CONTRIBUTIONS
ARK contributed to the conception and design of the study, development of the study protocol, and drafting of the manuscript. MI contributed to the study design, provided critical revision of the manuscript for important intellectual content, and approved the final version for publication. All authors read and approved the final manuscript.

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