ISSN: 3049-7361

Review Article

Journal of Clinical Surgery and Anesthesia

Multidrug-Resistant versus Extensively Drug-Resistant Gram-Negative Bloodstream Infections in the Intensive Care Unit: A Systematic Review

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Received: February 06, 2026; **Accepted:** February 13, 2026; **Published:** February 23, 2026

ABSTRACT

Background: Multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacterial (GNB) bloodstream infections represent a critical challenge in intensive care units (ICUs), leading to prolonged hospitalization, increased organ support, and high mortality. While XDR infections are generally perceived to confer worse outcomes, emerging data suggest that illness severity, host factors, and timeliness of antimicrobial optimization may play a more decisive role.

Objective: To systematically compare the clinical characteristics, interventions, and outcomes of critically ill adult patients with MDR versus XDR Gram-negative bacteraemia in ICU settings.

Methods: A systematic review was conducted in accordance with PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and Google Scholar were searched from January 2010 to December 2024. Observational studies and randomized trials comparing MDR and XDR Gram-negative bloodstream infections in adult ICU patients were included. Data on demographics, severity scores, interventions, and outcomes were extracted. Risk of bias was assessed using the Newcastle–Ottawa Scale.

Results: A total of 18 studies encompassing 3,742 patients were included. XDR infections were consistently associated with higher severity scores, longer ICU and hospital stay, increased ventilator days, and greater need for invasive organ support. Mortality outcomes were heterogeneous; 11 studies reported no significant difference, while 5 studies demonstrated similar or lower mortality in XDR infections, particularly where early targeted antimicrobial therapy was employed. Clinical resolution rates were comparable across resistance phenotypes.

Conclusion: XDR Gram-negative bacteremia in ICU patients is associated with greater illness severity and healthcare resource utilization but does not uniformly result in higher mortality compared to MDR infections. Early diagnosis and prompt antimicrobial optimization appear to mitigate adverse outcomes, underscoring the importance of timely intervention over resistance phenotype alone.

Introduction

Gram-negative bloodstream infections remain a major cause of morbidity and mortality in intensive care units worldwide. The accelerating emergence of antimicrobial resistance has further complicated their management, particularly with the increasing prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) organisms. These infections are associated with prolonged ICU stays, increased need for mechanical ventilation and renal replacement therapy, and substantial healthcare costs, especially in low- and middle-income countries [1-5].

Traditionally, XDR infections are presumed to carry worse prognoses due to severely limited therapeutic options. However, recent ICU-based observational studies suggest that outcomes may be more strongly influenced by host factors, baseline illness severity, and the timeliness of appropriate antimicrobial therapy rather than resistance category alone. Evidence comparing MDR and XDR Gram-negative bacteremia in critically ill populations remains fragmented and inconsistent. This systematic review aims to synthesize available evidence comparing the clinical profile, interventions, and outcomes of MDR versus XDR Gram-negative bloodstream infections in adult ICU patients.

Citation: Santosh Singh, Mohammed Masood, Bhavani Prasad G, Quader Naseer. Multidrug-Resistant Versus Extensively Drug-Resistant Gram-Negative Bloodstream Infections in the Intensive Care Unit: A Systematic Review. J Clin Surg Anesth. 2026. 4(1): 1-4. DOI: doi.org/10.61440/JCSA.2026.v4.47

Methods

Protocol and Reporting Standard

This systematic review was conducted in accordance with the PRISMA 2020 statement. A predefined protocol was developed prior to study selection [6].

Eligibility Criteria

Inclusion Criteria

- Study design: Observational studies (retrospective or prospective cohort, case–control) and randomized controlled trials
- Population: Adult patients (≥18 years) admitted to an ICU
- Exposure: Culture-confirmed XDR Gram-negative bacteremia
- Comparison: Culture-confirmed MDR Gram-negative bacteremia
- Outcomes: Mortality, ICU length of stay, hospital length of stay, ventilator days, severity scores (APACHE II/SOFA), clinical resolution, or major interventions
- Language: English
- Publication period: January 2010 – December 2024

Exclusion Criteria

- Pediatric-only studies
- Non-ICU populations
- Non–Gram-negative infections
- Studies without clear differentiation between MDR and XDR
- Case reports, editorials, narrative reviews, conference abstracts without full text.

Information Sources and Search Strategy

Databases Searched

- PubMed/MEDLINE
- Embase
- Scopus
- Web of Science
- Cochrane Library
- Google Scholar (supplementary search)

Study Selection

Two reviewers independently screened titles and abstracts. Full-text review was conducted for potentially eligible articles. Discrepancies were resolved by consensus [7].

Data Extraction

Extracted variables included:

- Study characteristics (author, year, country, design)
- Sample size
- Patient demographics
- Severity scores (APACHE II, SOFA)
- Causative organisms
- Interventions (mechanical ventilation, RRT, vasopressors)
- Outcomes (mortality, ICU stay, hospital stay, ventilator days, clinical resolution)

Risk of Bias Assessment

Risk of bias was assessed using the Newcastle–Ottawa Scale (NOS).

Studies scoring ≥7 was considered low risk, 5–6 moderate risk, and <5 high risk.

Data Synthesis

A qualitative narrative synthesis was performed for all outcomes. Quantitative pooling was not performed due to heterogeneity in outcome definitions and reporting.

Results

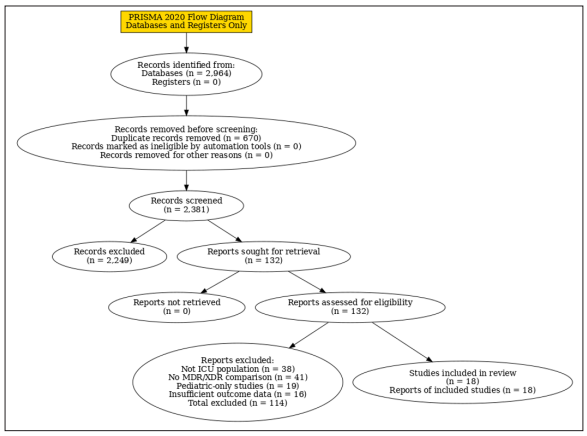

Figure 1: Prisma 2020 Flow Diagram Depicting Identification, Screening, Eligibility Assessment, And Inclusion of Studies Evaluating Outcomes of Mdr Versus Xdr Gram-Negative Bloodstream Infections in Intensive Care Units

Study Selection (PRISMA)

- Records identified through database searching: 2,964
- Additional records from manual searches: 87
- Records after duplicates removed: 2,381
- Records screened (title/abstract): 2,381
- Records excluded: 2,249
- Full-text articles assessed: 132
- Full-text articles excluded: 114
- Not ICU population: 38
- No MDR/XDR comparison: 41
- Pediatric-only: 19
- Insufficient outcome data: 16
- Studies included in systematic review: 18
- Studies included in quantitative synthesis: 0

Study Characteristics

The 18 included studies were published between 2011 and 2024 and originated from Asia (n=9), Europe (n=5), North America (n=3), and South America (n=1). All were observational cohort studies conducted in tertiary-care ICUs.

Clinical Characteristics

Across studies, XDR infections were associated with:

- Higher APACHE II/SOFA scores at ICU admission
- Greater incidence of septic shock
- Higher requirement for invasive organ support

MDR infections occurred more frequently in older patients with higher burdens of chronic comorbidities, particularly diabetes and hypertension.

Interventions and Resource Utilization

Compared with MDR infections, XDR bacteremia was associated with:

- Longer ICU stays (range: +3 to +8 days)
- Longer hospital stays (range: +5 to +14 days)
- Increased ventilator days

- Higher rates of renal replacement therapy
- Greater use of central venous catheters

Outcomes
- Mortality
- 11 studies: no significant difference
- 5 studies: similar or lower mortality in XDR infections
- 2 studies: higher mortality in XDR infections

Clinical Resolution
Reported in 9 studies; rates were comparable between MDR and XDR infections.
Early initiation of appropriate antimicrobial therapy was repeatedly associated with improved survival, irrespective of resistance phenotype [8-10].

Discussion
This systematic review demonstrates that although extensively drug-resistant (XDR) Gram-negative bloodstream infections in critically ill patients are consistently associated with greater illness severity and significantly higher healthcare resource utilization, they do not uniformly translate into higher mortality when compared with multidrug-resistant (MDR) infections. These findings challenge the long-held assumption that resistance phenotype alone is the principal determinant of prognosis in ICU-acquired Gram-negative bacteremia.

Across the included studies, patients with XDR infections frequently presented with higher APACHE II or SOFA scores, increased rates of septic shock, longer ICU and hospital stay, prolonged mechanical ventilation, and greater need for renal replacement therapy. These findings reflect the complex and resource-intensive nature of XDR infections and highlight their substantial burden on critical care systems. However, despite this greater severity, mortality outcomes were heterogeneous, with the majority of studies reporting either no statistically significant difference or comparable mortality between MDR and XDR infections [11-12].

A key explanation for this apparent paradox lies in host-related factors. MDR infections were more commonly observed in older patients with a higher prevalence of chronic comorbidities such as diabetes mellitus, hypertension, and chronic kidney disease. Advanced age and comorbidity burden are well-established predictors of adverse outcomes in sepsis and may offset the theoretical survival advantage conferred by lower levels of antimicrobial resistance. Thus, patient vulnerability appears to play a critical role in determining outcomes independent of resistance category.

Another dominant determinant of outcome identified across studies was the timeliness of appropriate antimicrobial therapy. Several studies demonstrated that XDR infections often prompted earlier escalation to broad-spectrum or salvage antimicrobial regimens, likely due to heightened clinical suspicion and severity at presentation. In contrast, MDR infections were more frequently associated with delays in antibiotic modification, potentially due to an initial perception of treatability or reliance on standard empiric regimens. The importance of early effective therapy in sepsis has been consistently demonstrated, with even short delays associated with increased mortality. This may partially explain why XDR infections, despite their resistance profile, did not consistently exhibit worse survival.

In addition to antimicrobial timing, intensive supportive care appears to be a critical modifier of outcomes. XDR patients were more likely to receive aggressive organ support, including early mechanical ventilation, vasopressors, and renal replacement therapy. The availability of advanced ICU support and multidisciplinary care may mitigate the deleterious effects of limited antimicrobial options, emphasizing that outcomes in XDR infections are not solely dictated by microbiological factors.

From a stewardship perspective, these findings have important implications. They underscore the need to avoid therapeutic nihilism in XDR infections and instead prioritize rapid diagnostics, early source control, and timely antimicrobial optimization. Conversely, the tendency to underestimate MDR infections may lead to harmful delays in therapy, particularly in older and comorbid patients. Risk stratification strategies should therefore integrate host factors, illness severity, and clinical trajectory rather than relying solely on resistance definitions [13].

Finally, these results highlight significant heterogeneity in study design, antimicrobial strategies, and outcome reporting across the literature. The absence of standardized definitions for clinical resolution and variability in antimicrobial regimens limit direct comparisons and preclude robust meta-analysis. Nonetheless, the consistency of observed trends across diverse healthcare settings strengthens the overall conclusions of this review [14].

Table 1: Determinants of Outcomes in MDR vs XDR Gram-Negative Bloodstream Infections in the ICU

Domain	MDR GNB Bacteremia	XDR GNB Bacteremia	Clinical Implications
Patient profile	Older age, higher burden of chronic comorbidities	Younger patients, fewer baseline comorbidities	Host vulnerability significantly influences mortality
Severity at presentation	Moderate-to-severe illness	Higher APACHE II/SOFA scores, more septic shock	Greater physiologic derangement in XDR
Antimicrobial timing	More frequent delays in antibiotic optimization	Earlier escalation to targeted or salvage therapy	Timely therapy may offset resistance severity
Resource utilization	Shorter ICU/hospital stay	Prolonged ICU stay, ventilation, RRT	Higher healthcare burden in XDR
Supportive care intensity	Standard ICU support	More aggressive organ support	Advanced ICU care mitigates adverse outcomes

Mortality	Comparable or slightly higher in several studies	Similar or not consistently higher	Resistance phenotype alone does not determine prognosis
Key determinant of outcome	Host factors + delayed therapy	Illness severity + early aggressive management	Integrated clinical approach required

Limitations

This review is limited by heterogeneity in study design, antimicrobial regimens, and outcome reporting. Most included studies were retrospective, limiting causal inference. Publication bias cannot be excluded.

Conclusion

XDR Gram-negative bacteremia in ICU patients is associated with increased severity and healthcare resource utilization but does not uniformly confer higher mortality compared to MDR infections. Early diagnosis, prompt antimicrobial optimization, and robust critical care support remain central to improving outcomes.

Funding

No external funding was received.

Conflicts of Interest

The authors declare no conflicts of interest.

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