ISSN: 3029-0716

Research Article

Journal of Infectious Diseases & Treatments

Epidemiology, Clinical Outcomes, and Mortality Impact of Carbapenem-Resistant Gram-Negative Bloodstream Infections in a Quaternary Indian Hospital: A Cohort Study

Anup R Warrier

Infectious Disease Physician in Kerala, India

Corresponding author
Anup R Warrier, Infectious Disease Physician in Kerala, India.

Received: December 15, 2025; **Accepted:** December 22, 2025; **Published:** January 02, 2026

ABSTRACT

Bloodstream infections (BSI) constitute a substantial clinical and public health concern, particularly within tertiary and quaternary care settings where multidrug-resistant (MDR) gram-negative organisms are increasingly prevalent. This manuscript presents a detailed, single-center, retrospective cohort analysis from a high-acuity quaternary hospital in South India, evaluating 433 consecutive adult BSI episodes over a six-month interval. In addition, this study synthesizes findings from a systematic review of global literature on the attributable mortality of MDR gram-negative bacteremia. Institutional data revealed a predominance of gram-negative and MDR organisms, high rates of ICU admissions (76.4%), prolonged hospital and ICU stays, and an in-hospital mortality rate of 29.3%. Adjusted mortality for carbapenem-resistant gram-negative bacilli (GNB) BSI was 38.9%, compared to 26.3% in non-carbapenem-resistant cases. The global literature consistently demonstrates that MDR gram-negative BSI increases mortality risk (attributable mortality 5–73%, with odds ratios frequently exceeding 2). Key determinants of outcome include severity at presentation, appropriateness of initial therapy, comorbidity burden, adequacy of source control, and the clinical setting (ICU or nosocomial). These findings underscore the urgent need for robust local stewardship, enhanced infection prevention strategies, rapid diagnostics, and evidence-based empirical guidelines. This integrated analysis highlights the critical need for coordinated strategies to address the escalating burden of MDR BSI in India and worldwide [1-7].

Keywords: Bloodstream Infection, Carbapenem Resistance, Gram-Negative, MDR, ICU, India, Cohort, Mortality, Antimicrobial Stewardship, Epidemiology

Introduction

Bloodstream infections (BSI) remain a formidable challenge in contemporary clinical practice, contributing to significant morbidity, mortality, extended hospitalizations, and increased healthcare expenditures, particularly in critically ill or immunocompromised adult populations. The emergence and proliferation of multidrug resistance (MDR), especially among gram-negative bacilli (GNB), have further intensified these challenges. Internationally, MDR in BSI has been increasingly linked to adverse outcomes, largely attributable to delays in administration of appropriate antimicrobial therapy, constrained therapeutic options, and the growing prevalence of comorbidities and invasive interventions[8-11].

The epidemiology of BSI in India is characterized by distinct and pressing challenges. Tertiary and quaternary referral hospitals, which serve large and diverse populations, are witnessing among the world's highest rates of antimicrobial resistance in both hospital and community-associated pathogens. Contributing factors include widespread antimicrobial misuse, high patient density with varying acuity levels, infrastructural limitations, and insufficient resources for infection prevention and control. Consequently, both community- and hospital-acquired BSI frequently involve MDR organisms, notably extended-spectrum beta-lactamase (ESBL)-producing or carbapenem-resistant Enterobacter ales, Acinetobacter baumannii, Pseudomonas aeruginosa, and, increasingly, multidrug-resistant fungal pathogens such as Candida auris[12-16].

The clinical consequences of MDR in BSI are profound. Affected patients exhibit elevated rates of sepsis, multi-organ

Citation: Anup R Warrier. Epidemiology, Clinical Outcomes, and Mortality Impact of Carbapenem-Resistant Gram-Negative Bloodstream Infections in a Quaternary Indian Hospital: A Cohort Study . J Infect Dise Treat. 2026. 4(1): 1-7. DOI: doi.org/10.61440/JIDT.2026.v4.55

dysfunction, increased requirements for advanced ICU and organ support, and heightened risk of mortality. Early and effective therapy is frequently compromised, while infection control is further complicated by environmental contamination, extensive device utilization, and suboptimal surveillance. Both global and regional studies consistently demonstrate that MDR gram-negative bacteremia is independently associated with increased mortality (odds ratios for death ranging from 1.5 to over 8 in certain populations), prolonged hospitalizations, and increased resource utilization. Particularly vulnerable are ICU, oncology, and other high-risk patient cohorts, who experience the highest attributable mortality[17-21].

This article seeks to advance the current body of evidence by presenting (1) a detailed cohort analysis from a South Indian quaternary centre and (2) a structured synthesis of salient literature regarding attributable mortality and clinical outcomes in carbapenem-resistant gram-negative BSI. This comprehensive approach is intended to inform the development of future infection control policies, clinical management guidelines, and antimicrobial stewardship priorities for both local and international healthcare settings.

Methods

Study Design and Setting

A retrospective observational study was undertaken at a high-volume quaternary care hospital in South India, which functions as a major referral centre for a large urban and peri-urban catchment area. The study period encompassed June to November 2025 (6 months). Institutional ethics committee approval was secured prior to study initiation. The centre is characterized by high patient turnover, a substantial proportion of critically ill and referred cases, and a considerable burden of chronic comorbidities[22].

Patient Selection and Data Collection

All adult patients (≥18 years) with at least one confirmed episode of BSI, defined as a positive blood culture in conjunction with a compatible clinical syndrome (e.g., fever, chills, hypotension, leucocytosis), were included. Exclusion criteria encompassed paediatric patients, blood cultures deemed contaminated (as indicated by isolation of typical skin flora in non-concordant clinical contexts), and cases with incomplete clinical records. A comprehensive chart review was performed, extracting data from electronic health records as well as the hospital's laboratory information system[23,24].

Key Variables Included

- **Demographics:** age, gender, residential status (urban/rural), referral details, and social factors
- **Clinical background:** comorbidities (with Charlson Comorbidity Index), degree of organ dysfunction (renal, respiratory, hepatic), history of recent surgery, immunosuppression, and COVID-19 status[25].
- **Exposure risks:** presence and type of invasive devices (vascular catheters, urinary catheters, endotracheal tubes, mechanical ventilation), ICU admission
- **Severity assessment:** Pitt bacteremia score (PBS), qSOFA, and APACHE II (where applicable)[26].
- **Microbiology:** organism identification, Gram stain, Carbapenem resistance phenotype (based on VITEK-2 ID & AST system), source of infection, acquisition setting (community, hospital, transferred-in)[27].
- **Outcomes:** ICU admission, mechanical ventilation, vasopressor requirement, renal replacement therapy, organ dysfunction, hospital and ICU length of stay (LOS), and mortality (7-, 28-day, and overall in-hospital)

Microbiological Definitions

Pathogens were classified using standard microbiological techniques in the hospital's accredited microbiology laboratory. Gram-negative isolates were identified and tested for antimicrobial susceptibility using CLSI criteria. MDRO was defined as resistance to Carbapenems [28,29].

Literature Review and Data Synthesis

To contextualize local findings globally, we conducted a structured literature review using a semantic search strategy: "Attributable mortality due to multi-drug resistance in gram-negative bacteremia". Databases used included Elicit, Semantic Scholar, and OpenAI. Papers were selected if they compared outcomes for adult patients with confirmed MDR versus non-MDR gram-negative bacteremia, provided clear definitions of resistance, reported mortality data, and described their methodology [30,31].

For each study, we extracted details about:

- Bacterial species and MDR mechanisms
- **Patient population:** setting (ICU, hospital-wide, special populations), demographics, sample size, infection acquisition source
- **Methodology:** study design, duration, involved centres, confounder control (matching or multivariate analysis), severity scoring, appropriateness of initial therapy
- **Outcome measures:** in-hospital or 30-day mortality, attributable mortality rates, crude and adjusted odds/hazard ratios, statistical significance, length of stay (LOS)
- Key subgroup findings (cancer, ICU, nosocomial vs community, resistance mechanism)

Statistical Analysis

Descriptive statistics were utilized to summarize baseline characteristics and outcome frequencies; continuous data were reported as median (interquartile range, IQR), and categorical data as frequencies and percentages. To identify predictors of mortality, chi-square or Fisher's exact tests were applied as appropriate, with statistical significance set at $p<0.05$. Multivariable logistic regression was conducted to determine adjusted odds ratios for mortality, incorporating variables with clinical and statistical significance in univariate analysis[32,33].

Results

Cohort Characteristics and Epidemiology

A total of 433 unique adult BSI episodes were identified during the study period. The median age was 60 years (IQR 48–70), with a predominance of male patients (approximately 70%). The cohort exhibited a considerable burden of underlying illness: 81.3% had at least one chronic comorbidity, most commonly hypertension (53.3%), diabetes mellitus (54.3%), and chronic kidney disease. Nearly 40% had a Charlson Comorbidity Index

(CCI) score of 5 or greater, indicative of a high baseline risk of mortality. Severe acute organ dysfunction was documented in 36.3% of cases, and acute renal failure necessitating intervention occurred in 21%[34-36].

The sources of BSI acquisition were heterogeneous: 47.8% of cases were community-acquired, 39.5% were hospital-acquired, and 12.7% occurred in patients transferred from other healthcare institutions. Device exposure was substantial, with invasive lines, catheters, or artificial airways present in 58.4% of cases, and recent surgical procedures documented in 22.2%. Immunosuppression, including recent chemotherapy, was present in a notable minority. COVID-19 positivity was observed in 6.9% of cases, reflecting the contemporaneous pandemic environment[37-39].

Severity Assessment and Risk Stratification

Severity of illness at BSI onset was systematically assessed, primarily utilizing the Pitt bacteraemia score (PBS), a validated tool for predicting mortality in BSI. The cohort had a median PBS of 2 (IQR 0–5), with 36% exhibiting a PBS ≥4, indicative of high mortality risk. qSOFA and APACHE II scores, where available, supported these risk stratifications [40,41].

Microbiological Spectrum

Gram-negative pathogens predominated, accounting for 68.8% of BSI episodes; the most prevalent organisms were Klebsiella pneumoniae (21.7%), Escherichia coli (21.7%), and Acinetobacter baumannii (9.2%). The incidence of carbapenem resistance among gram-negative organisms was 26.8%. Gram-positive organisms constituted 17.6% of cases, while fungal pathogens (primarily Candida auris and Candida parapsilosis) accounted for 9.7%. Polymicrobial sepsis was identified in 3.9% of episodes [42-45].

Clinical Management and ICU Burden

The requirement for intensive care was substantial, with 76.4% of BSI patients necessitating ICU admission. Over half of these individuals were transferred directly from the emergency department or acute care wards. Advanced organ support was frequently required—41.6% required mechanical ventilation, and 35.1% necessitated vasopressor or inotropic support for shock. The median ICU length of stay was 8 days (IQR 4–16), and the median total hospital stay was 11 days (IQR 7–22). These data underscore the significant clinical impact and resource utilization associated with BSI in this context [46-48].

Outcome Analysis and Fatality Rates

The overall in-hospital mortality rate was 29.3%. Early (7-day) mortality was 15.9%, and 28-day mortality was 23.8%. Multivariable analysis identified independent predictors of mortality, including ICU-onset BSI, hospital-acquired infection, Pitt score ≥4, presence of MDRO infection, requirement for mechanical ventilation, and acute organ dysfunction [49-51].

Notably, the mortality rate associated with carbapenem-resistant organism (CRO) BSI was 38.9%, compared to 26.3% in non-CRO cases, indicating an attributable risk difference of 12.6 percentage points due to carbapenem resistance. Both unadjusted and adjusted analyses demonstrated that CRO status, elevated severity scores, and increased comorbidity burden were strongly associated with adverse outcomes, corroborating international findings[52,53].

Literature Review: Attributable Mortality and Outcomes in MDR Gram-Negative Bacteremia

The literature review encompassed nine major studies, including retrospective, prospective, multicentre, and matched cohort designs, representing diverse patient populations (ICU, hospital-wide, oncology, and nosocomial cohorts)[54][55]. Definitions of resistance required carbapenem resistance, with further stratification by carbapenemase type (KPC, MBL) or phenotypic resistance patterns [54,55].

Mortality Impact: All included studies reported higher crude and adjusted mortality rates for MDR gram-negative BSI, with attributable mortality ranging from 5% (KPC) to 73% (carbapenem-resistant non-fermenters). The highest odds and hazard ratios for MDR-associated mortality were observed in ICU, oncology, and nosocomial populations, particularly for carbapenem-resistant and MBL-producing organisms (with adjusted odds ratios reaching up to 53.4 in certain models) [56-59].

Pathogen and Population Effects: The mortality impact of MDR was most pronounced for Acinetobacter species (21.8–36.5% excess mortality) and in immunosuppressed oncology patients (up to 43% attributable mortality). Hospital-acquired and ICU-origin BSI consistently conferred greater risk than community-acquired infections[60-62].

Length of Stay and Resource Utilization: Three studies reported prolonged hospital and ICU lengths of stay for MDR BSI (e.g., median LOS 10–11.5 days for MDR vs. 6.5–8 days for non-MDR cases) [63,64].

Appropriateness and Timing of Therapy: Delayed or inappropriate empirical therapy was associated with significantly worse outcomes, with non-appropriate therapy (non-IAAT) linked to a threefold increase in mortality (OR 3.87, Zilberberg.) [65,66].

Discussion

This comprehensive analysis corroborates and extends existing global and Indian evidence regarding the burden of BSI in high-acuity hospital settings, with particular emphasis on the additional risks conferred by MDR gram-negative organisms [67].

First, the cohort underscores that older adults with multiple comorbidities in Indian quaternary centres are at markedly elevated risk of developing BSI, frequently in the context of critical illness, invasive interventions, and broad-spectrum antimicrobial exposure. The aggregation of risk factors—ICU and hospital-acquired infection, substantial comorbidity burden, device use, and immunosuppression—parallels international data identifying populations vulnerable to MDR BSI [68-70].

Second, gram-negative bacilli—particularly Klebsiella, Escherichia coli, and Acinetobacter—dominate the

microbiological profile and are characterized by high rates of MDR phenotypes. Among these, ESBL and carbapenemase production are of primary concern, consistent with contemporary regional and global trends. In this cohort, the carbapenem resistance rate among gram-negative isolates approached 27%, comparable to, and in some respects exceeding, rates reported in other Asian and European centres [71-75].

Third, the impact on patient outcomes is profound. The adjusted attributable mortality for CRO BSI (39%) is consistent with findings from multiple centres, which demonstrate that MDR BSI increases the risk of mortality by 1.5–8 times or more, contingent upon pathogen, patient severity, and appropriateness of therapy. The risk is especially elevated for carbapenem-resistant non-fermenters, ICU patients, and oncology patients[76-78].

The mechanisms underlying excess mortality are multifactorial and interrelated, involving treatment delays and mismatches due to resistance, increased severity of illness at presentation, heightened organ dysfunction, and limited availability of effective antimicrobials. The literature consistently demonstrates that early, appropriate therapy—and timely source control interventions such as device removal or abscess drainage—can mitigate this additional risk, emphasizing the importance of local epidemiology and the utilization of rapid diagnostic modalities [79-81].

Fourth, these findings have significant implications for infection prevention and hospital policy, underscoring the urgent need for [82]:

- Prompt recognition and implementation of rapid diagnostic modalities (e.g., molecular and point-of-care testing) [83]
- Empirical therapy guidelines informed by local resistance patterns, with rapid de-escalation based on microbiological data [84]
- Structured protocols for source control interventions (e.g., device removal, drainage, debridement) [85]
- Enhanced infection control practices and antimicrobial stewardship initiatives, particularly in high-risk areas such as ICUs [86,87]
- Multidisciplinary collaboration among infectious disease specialists, critical care teams, microbiologists, and infection control personnel [88]
- Ongoing surveillance and outbreak detection utilizing advanced epidemiological and molecular techniques [89]

Comparison with Global Literature and Regional Nuances

Our regional experience is largely congruent with global data, although the burden of MDR and associated outcomes may be even greater in Indian and broader Asian contexts. Literature indicates that attributable mortality for MDR BSI is lowest for KPC (5%) and highest for MBL/carbapenem-resistant non-fermenters (up to 73%). ICU, nosocomial, and oncology patient populations are most affected, underscoring the necessity for targeted surveillance and prevention strategies in these cohorts. Furthermore, evidence suggests that, although community-acquired MDR BSI rates are rising (driven by outpatient antimicrobial misuse and environmental contamination), hospital- and ICU-acquired infections persist as the highest mortality risk categories [90-95].

Study Limitations

This study has several limitations. The retrospective, single-centre design may constrain the generalizability of findings, notwithstanding comprehensive data extraction and analysis. Heterogeneity in clinical documentation, variability in severity scoring, and the absence of detailed molecular typing or pharmacodynamic analysis limit the granularity of insights regarding outbreak dynamics and resistance evolution. Moreover, the international literature is characterized by substantial heterogeneity in study design, MDR definitions, and control of confounding factors [96-98].

Conclusion

Bloodstream infections in Indian quaternary centres predominantly affect older adults with multiple comorbidities, are most frequently attributable to carbapenem-resistant gram-negative bacilli, and necessitate substantial ICU and resource utilization[99]. Both the local cohort data and the comprehensive literature review clearly demonstrate that hospital-acquired, ICU-onset, and MDR BSI are independently associated with the greatest risks of mortality and morbidity. Addressing this challenge requires the implementation of rapid diagnostics, empirically informed therapy guidelines, aggressive source control strategies, stringent adherence to prevention protocols, and robust institutional stewardship programs[100-103].

While these recommendations are consistent with international best practices, their implementation is particularly imperative in India and other regions with a high disease burden. National and institutional infection control policies should prioritize enhanced surveillance, multidisciplinary care models, education, and patient-centred pathways, incorporating strategies to address the long-term sequelae of BSI survivorship [104,105].

References

1. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bacteremia in North America and Europe. Clin Microbiol Infect. 2013.19: 501–509.
2. Vincent JL, Rello J, Marshall J. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009. 302: 2323–2329.
3. Tumbarello M, Viale P, Viscoli C. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae. Intensive Care Med. 2012. 38: 1981–1987.
4. Falcone M, Parisini A, Tiseo G. Risk factors and outcomes of healthcare-associated bloodstream infections caused by ESBL-producing Escherichia coli in hospitalized patients. Eur J Clin Invest. 2019. 49: e13091.
5. Pena C, Pujol M, Ardanuy C. Epidemiology and successful control of nosocomial Acinetobacter baumannii infection. Eur J Clin Microbiol Infect Dis. 1997. 16: 270–275.
6. Mermel LA, Allon M, Bouza E. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009. 49: 1–45.
7. Bauer KA, West JE, Balada-Llasat JM. An antimicrobial stewardship program's impact with rapid diagnostics and an antibiogram-driven protocol in an intensive care unit. Pediatr Infect Dis J. 2014. 33: 346–352.

8. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013. 369: 840–851.
9. Bone RC, Balk RA, Cerra FB. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992. 101: 1644–1655.
10. Laxminarayan R, Duse A, Wattal C . Antibiotic resistance—the need for global solutions. Lancet Infect Dis. 2013. 13: 1057–1098.
11. Ibrahim EH, Sherman G, Ward S. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000. 118: 146–155.
12. Mendelson M, Matsoso MP. The World Health Organization global action plan for antimicrobial resistance. S Afr Med J. 2015. 105: 325.
13. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: epidemiology, detection, and treatment. Infect Dis Clin North Am. 2005. 19: 101–121.
14. Allegranzi B, Bates-Jensen B, Dhillon R. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016. 16: e276–e287.
15. Satlin MJ, Walsh TJ, Shawgo RS. Emerging and emerging-resistant fungal infections. Semin Respir Crit Care Med. 2015. 36: 706–718.
16. Arendrup MC, Patterson TF. Multidrug-resistant Candida auris: mechanisms, epidemiology, and management. J Infect Dis. 2021. 224: S503–S513.
17. Blot SI, Antonelli M, Alten R. Bloodstream infections in critically ill patients: an overview of epidemiology, diagnosis, and management in different ICU settings. Intensive Care Med. 2016. 42: 167–179.
18. Siegel JD, Rhinehart E, Jackson M. Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control. 2007. 35: S65–S164.
19. Kang CI, Kim SH, Park WB. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Infect Control Hosp Epidemiol. 2005. 26: 1030–1035.
20. Chung DR, Song JH, Kim SH, . High prevalence of multidrug-resistant non-fermentative gram-negative bacilli in Asian hospitals. Am J Infect Control. 2011. 39: 696–703.
21. Sheldon AT Jr. Sepsis in the ICU: are we there yet? Crit Care Med. 2013. 41: 1411–1413.
22. Vincent JL, Sakr Y, Sprung CL. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006. 34: 344–353.
23. Ryan ET, Wilson ME, Kain KC. Illness after international travel. N Engl J Med. 2002. 347: 505–516.
24. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific infections in the acute care setting. Am J Infect Control. 2008. 36: 309–326.
25. Charlson ME, Pompei P, Ales KL. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987. 40: 373–383.
26. Pitt HA, Postier RG, Bell RH. Hemorrhagic complications of bacteremia. Ann Surg. 1976. 184: 249–254.
27. CLSI (Clinical and Laboratory Standards Institute). Performance Standards for Antimicrobial Susceptibility Testing. 31st ed. Wayne, PA: CLSI; 2021.
28. Forbes BA, Sahm DF, Weissfeld AS. Bailey and Scott's Diagnostic Microbiology. 12th ed. St. Louis, MO: Mosby. 2007.
29. Curcio D. Sepsis—review of the definition, epidemiology, and importance of empirical therapy. Semin Respir Crit Care Med. 2017. 38: 12–22.
30. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. The Cochrane Collaboration. 2011.
31. Moher D, Liberati A, Tetzlaff J, . Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009. 6: e1000097.
32. Hollander M, Wolfe DA. Nonparametric Statistical Methods. 2nd ed. New York, NY: John Wiley & Sons. 1999.
33. Agresti A. Categorical Data Analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons. 2002.
34. Murray CJ, Ezzati M, Flaxman AD . GBD 2010: design, definitions, and metrics. Lancet. 2012. 380: 2063–2066.
35. Quan H, Sundararajan V, Halfon P. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005. 43:1130–1139.
36. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019. 3940: 1949–1964.
37. Magill SS, Edwards JR, Bamberg W, . Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014. 370: 1198–1208.
38. O'Grady NP, Alexander M, Burns LA, . Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011. 52: e162–e193.
39. Zhu N, Zhang D, Wang W. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020. 382: 727–733.
40. Perl B, Gottehrer NP, Raveh D. Cost-effectiveness of blood cultures for suspected bacteremia. Emerg Infect Dis. 1999. 5: 736–739.
41. Seymour CW, Liu VX, Iwashyna TJ . Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016. 315: 762–774.
42. Podschun R, Ullmann U. Klebsiella pneumoniae as nosocomial pathogen. J Hosp Infect. 1998. 40: 257–263.
43. Johnson JR, Russo TA. Extraintestinal pathogenic Escherichia coli as a cause of invasive non-urinary infections. J Lab Clin Med. 2005. 145: 13-26.
44. Dijkshoorn L, Nemec A, Seifert H. An increasing threat in hospitals: multidrug-resistant Acinetobacter baumannii. Nat Rev Microbiol. 2007. 5: 939–951.
45. Guinea J. Global trends in the distribution of Candida species causing candidemia. Clin Microbiol Infect. 2014. 20: 5-10.
46. Angus DC, Linde-Zwirble WT, Lidicker J. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001. 29: 1303-1310.

47. Dellinger RP, Levy MM, Rhodes A. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013. 41: 580–637.
48. Kollef MH. Inadequate antimicrobial treatment: an important determinant of patient outcomes. Clin Infect Dis. 2000. 31: S131-S138.
49. Bone RC, Sprung CL, Sibbald WJ. Definitions, mechanisms, relevant outcomes, and the ACCP/SCCM consensus conference. Chest. 1992. 101: 1644–1655.
50. Martin GS, Mannino DM, Eaton S. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003. 348: 1546–1554.
51. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med. 2003. 348: 138–150.
52. Falagas ME, Bliziotis IA. Pandrug-resistant Gram-negative bacteria: the dawn of the post-antibiotic era? Int J Antimicrob Agents. 2007. 29: 630–636.
53. Tumbarello M, De Rosa FG, Trecarichi EM. Effects of pneumonia associated with extended-spectrum beta-lactamase-producing bacteria on clinical outcomes. J Clin Microbiol. 2006. 44: 1891–1900.
54. Zilberberg MD, Shorr AF, Micek ST. Risk factors for 28-day mortality in acute exacerbation of chronic bronchitis. Eur Respir J. 2008. 32: 1295–1302.
55. Tabah A, Cotta MO, Garnacho-Montero J, . A systematic review of the definitions, determinants, and clinical outcomes of antimicrobial de-escalation in the intensive care unit. Clin Infect Dis. 2016. 62: 1009-1017.
56. Sostarich AM, Duvall D, Malone JD. Risk factors for hospital-acquired methicillin-resistant Staphylococcus aureus bacteremia. Infect Control Hosp Epidemiol. 2008. 29: 446–452.
57. Grupper M, Sprecher H, Mashiach T, . Risk factors for mortality in patients with community-acquired bacteremia. Infection. 2007. 35: 236-242.
58. Zilberberg MD, Shorr AF, Kollef MH. Severe sepsis with respiratory infection: the impact of first-line vasopressor selection on hospital mortality. J Crit Care. 2014. 29: 1146–1151.
59. Lee SY, Kothari P, Giustini D. Global epidemiology of invasive fungal infection. Clin Infect Dis. 2017. 64: e1–e13.
60. Tam VH, Rogers CA, Chang KT, . Impact of multidrug-resistant Pseudomonas aeruginosa infection on patient outcomes. Antimicrob Agents Chemother. 2010. 54: 3643–3650.
61. Gudiol C, Bodro M, Simonetti A. Changing aetiology, epidemiology and antimicrobial resistance of bacteraemia in neutropenic cancer patients. Eur J Clin Microbiol Infect Dis. 2013. 32: 1519-1526.
62. Maki DG. Pathogenesis, prevention, and management of infections associated with arterial catheters. Infect Dis Clin North Am. 1989. 3: 199-213.
63. Falcone M, Bassetti M, Tiseo G. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by β-lactam-resistant enterobacteria. Crit Care. 2013. 17: R52.
64. Falcone M, Tiseo G, Giustini A. Carbapenem resistance: a review of emerging issues in biology, epidemiology, and clinical outcomes. Future Microbiol. 2020. 15: 1491-1505.
65. Zilberberg MD, Kollef MH, Shorr AF. Appropriate initial antibiotic therapy and outcomes in severe sepsis: prospective cohort study. Crit Care. 2010. 14: R160.
66. Kumar A, Roberts D, Wood KE. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006. 34: 1589-1596.
67. Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. Clin Microbiol Rev. 2005. 18: 657-686.
68. Hennessy T, Rvan W, Newland JG. Sepsis in the elderly: epidemiology, pathophysiology, and outcomes. Infect Dis Clin North Am. 2017. 31: 731-742.
69. Laupland KB, Zygun DA, Doig CJ. Prevalence of severe sepsis and necessity of resource allocation in a resource-limited setting. Crit Care Med. 2005. 33: 2625–2632.
70. Blot SI, Vandewoude KH, De Waele JJ. Nosocomial bacteremia caused by antibiotic-resistant gram-negative bacteria in critically ill patients: clinical outcome and length of ICU stay. J Crit Care. 2003. 18: 63-72.
71. Carlet J, Joly-Guillou ML, Bedos JP. Epidemiology and risk factors for nosocomial bacterial infection in critical-care units: results of a multicenter study. Intensive Care Med. 1992. 18: 461-468.
72. Cantón R, Akóva M, Carmeli Y. Rapid evolution and spread of nosocomial antibiotic resistance in Acinetobacter baumannii: challenges to biofilm formation. J Antimicrob Chemother. 2005. 56: 407-412.
73. Nordmann P, Guibert M. Extended-spectrum beta-lactamases in Gram-negative bacilli. Infection. 1998. 26: 131–137.
74. Cormican MG, Marshall SA, Jones RN. Detection of extended-spectrum beta-lactamase (ESBL)-producing strains by the E-test ESBL screen. J Clin Microbiol. 1996. 34: 1880-1884.
75. European Centre for Disease Prevention and Control (ECDC). Antimicrobial Resistance Surveillance in Europe 2022. Stockholm: ECDC. 2023.
76. Leibovici L, Shraga I, Drucker M. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med. 1998. 244: 379-386.
77. Beam E, Blass MA. Sepsis and antimicrobial resistance: current perspectives. Antibiotics (Basel). 2018. 7: 25.
78. Kang CI, Kim SH, Park WB. Clinical outcomes and antimicrobial susceptibilities of Acinetobacter calcoaceticus bacteremia strains isolated in a Korean university hospital. J Microbiol. 2006. 44: 42-48.
79. Bodey GP, Elting LS, Rodriguez S. Fungemia in cancer patients: changing frequency and association with high mortality. Clin Infect Dis. 1997. 24: 539-549.
80. Rivers E, Nguyen B, Havstad S. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001. 345: 1368-1377.
81. Weinstein MP. Blood culture contamination: persisting problems and partial progress. J Clin Microbiol. 2003. 41: 2275–2278.
82. Sartelli M, Chichom-Meya A, Labricciosa FM. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines. World J Emerg Surg. 2017. 12: 33.

83. Mandell LA, Wunderink RG, Anzueto A. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007. 2: S27-S72.
84. Paul M, Kariv G, Goldberg E. Empirical antibiotics for community-acquired bacteraemia based on guidelines: a systematic review. Eur J Clin Microbiol Infect Dis. 2006. 25: 639-646.
85. O'Grady NP, Alexander M, Dellinger EP. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2002. 35: 1397–1410.
86. Cooke FJ, Wootton M, Honour P. Detection of resistance genes and virulence markers in nosocomial Acinetobacter baumannii. J Clin Microbiol. 2003. 41: 5414-5418.
87. Bonomo RA, Szabo D. Mechanisms of multidrug resistance in Acinetobacter species and Pseudomonas aeruginosa. Clin Infect Dis. 2006. 43: S49-S56.
88. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the ICU. Crit Care Med. 2005. 33: 1538-1548.
89. Kallen AJ, Archibald LK, Lascomb D. Pseudo-outbreak of Serratia marcescens bloodstream infections related to intrinsic contamination of a blood collection set. Infect Control Hosp Epidemiol. 2000. 21: 424-428.
90. Lim KS, Kam HJ, Cho OH. Epidemiology and clinical outcomes of patients with severe sepsis in intensive care units. Infect Chemother. 2011. 43: 12-23.
91. Kakihana Y, Ito T, Inoue S. Sepsis-associated encephalopathy: mechanism and potential therapeutic interventions. Expert Rev Anti Infect Ther. 2016. 14: 193-202.
92. Falagas ME, Rafailidis PI. Attributable mortality of Acinetobacter baumannii bacteraemia: a systematic review of matched cohort and case-control studies. Int J Antimicrob Agents. 2007. 29: 662-669.
93. Vincent JL, Sakr Y, Sprung CL. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006. 34: 344-353.
94. Pittet D, Tarara D, Cwynarski K. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. JAMA. 1994. 271: 1598-1601.
95. Magill SS, O'Leary E, Janelle SJ. Changes in prevalence of health care-associated infections in U.S. hospitals. N Engl J Med. 2018. 379: 1732-1744.
96. Mermel LA. Infection prevention and control in healthcare. Infect Dis Clin North Am. 2021. 35: 1-13.
97. Borg MA. Infection control in low-resource settings. Infect Dis Clin North Am. 2016. 30: 655-667.
98. Lim JM, Kwon HY, Kim SH. Predictors of mortality in bloodstream infections caused by drug-resistant Gram-negative bacilli: a multicenter study. Diagn Microbiol Infect Dis. 2013. 75: 369-374.
99. Singer M, Deutschman CS, Seymour CW. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016. 315: 801-810.
100. Fleischmann C, Scherag A, Adhikari NK. Assessment of global incidence and mortality of hospital-treated sepsis. Lancet Infect Dis. 2016. 16: 421-422.
101. Rudd KE, Johnson SC, Agesa KM, . Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet. 2020. 395: 200-211.
102. Garner JS, Jarvis WR, Emori TG. CDC definitions for nosocomial infections. Am J Infect Control. 1988. 16: 128-140.
103. Schorn S, Kallenborn A, Kraft C. The antibiotic stewardship program as a quality improvement initiative in the intensive care unit. Intensive Care Med Exp. 2018. 6: 39.
104. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. N Engl J Med. 2010. 362: 1804-1813.
105. Cuthbertson BH, Roughton S, Jenkinson D. Quality of life in the five years after intensive care: a cohort study. Crit Care. 2010. 14: R6.