The Rising Challenge of Multidrug-Resistant Gram-Negative Infections in the Outcome of Hematological Oncology: A review

Abstract

Bloodstream infections (BSIs) caused by Gram-negative bacteria (GNB) are a significant concern in patients with hematological malignancies (HM), particularly when multidrug-resistant (MDR) strains are involved. This review synthesizes key findings from studies investigating the epidemiology, clinical implications, and management strategies for GNB BSIs in HM patients. The reviewed studies shows the heightened mortality risk associated with GNB BSIs, especially in the context of immunocompromised HM patients. Studies highlight the prevalence of MDR GNB, including ESBL, AmpC β-lactamase, and carbapenemase-producing strains, which pose challenges to standard antibacterial therapies. Importantly, the review identifies the need for routine blood culture monitoring, personalized risk assessment, and tailored antimicrobial policies to optimize patient outcomes. Most important MDR groups identified were *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species, Stenotrophomonas maltophilia, Proteus* species. Future research directions include enhancing surveillance systems, developing innovative therapeutic approaches, personalized medicine strategies, strengthening infection control measures, optimizing antimicrobial prophylaxis, and investigating antibiotic-resistant strains and gene identification.

Keywords: Gram-negative bacteria, hematological malignancies, multidrug resistance, mortality risk, antimicrobial therapy, infection control, treatment strategy.

1. INTRODUCTION

Bloodstream infections (BSIs) caused by Gram-negative bacteria (GNB) in patients with hematological malignancies (HM) are particularly concerning due to their association with high mortality rates [1]. This risk is exacerbated when the infections involve antibiotic-resistant strains, making treatment more challenging and less effective. Patients with HM are already immunocompromised, which makes them more susceptible to severe infections, and the presence of resistant GNB further complicates their clinical management and outcomes [2].

The emergence of multidrug-resistant (MDR) Gram-negative bacteria presents a critical concern in hematologic oncology, amplifying the complexity of patient management. These resilient pathogens, including ESBL, AmpC β-lactamase-, and carbapenemase-producing *Enterobacteriaceae*, alongside *Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia,* challenge the efficacy of standard antibacterial therapies [3, 22-23]. Patients with hematologic malignancies, already immunocompromised due to their condition and repeated chemotherapy, are especially vulnerable to such infections. The implications are profound, potentially leading to treatment failure, prolonged hospital stays, escalated healthcare costs, and heightened mortality rates. Thus, understanding the epidemiology, treatment options, and mitigation strategies for MDR Gram-negative bacteria in hematology-oncology is paramount to safeguarding patient outcomes and advancing clinical practice [4].

2. Prevalence and incidence rates of Gram-negative infections

The study of Dhanaraj & Foppiano highlighted the importance of obtaining follow-up blood cultures (FUBC) in patients with hematologic malignancies who develop gram-negative bacterial bloodstream infections

(GNBSI) amidst febrile neutropenia. Conducted at a large urban academic medical center from 2018 to 2021, the retrospective chart review analyzed 47 episodes of GNBSI among 43 patients, predominantly characterized by acute myeloid leukemia (47%) and treated commonly with the R-CHOP chemotherapy regimen (19%). The analysis revealed a significant association between the collection of FUBC and reduced mortality rates at discharge, 30 days, and 90 days. Despite the low incidence of positive FUBC (5%) and uncommon ESBL resistance profiles (6%), the study underscores that patients who had repeat blood cultures exhibited notably lower mortality rates compared to those who did not. These findings advocate for the routine collection of FUBC in managing neutropenic fever due to GNRB, emphasizing its role in improving clinical outcomes for immunocompromised patients [5].

A retrospective study conducted at King Khalid University Hospital in Riyadh, Saudi Arabia, examined 61 episodes of Gram-negative bacteremia (GNB) among 56 cancer patients between January 2013 and October 2015. This study aimed to evaluate the epidemiology, risk factors, and antibiotic resistance patterns of GNB in patients with hematologic or solid organ malignancies. Among the patients, 54% had hematological malignancies, predominantly leukemia (77%) and lymphoma (20%), while the remaining 46% had solid tumors, with colorectal (34.6%) and breast cancer (23%) being the most common. *Escherichia coli* (29.5%) and *Acinetobacter baumannii* (18%) were the predominant pathogens identified. The study found that 34.6% of *E. coli* and *Klebsiella pneumoniae* isolates were extended-spectrum beta-lactamase producers, and imipenem resistance among *Pseudomonas aeruginosa* and *A. baumannii* was notably high at 52.4%. Multi-resistant organisms accounted for 43.5% of cases. Significant risk factors for bacteremia included ICU admission (32.1%), post-surgery status (23.2%), and central line placement (21.4%). The 30-day mortality rate was 32.1%, underscoring the critical need for careful antimicrobial selection based on susceptibility testing to manage infections in malignancy patients effectively [6].

A prospective observational study was conducted to investigate the incidence, clinical and laboratory profiles, microbiological characteristics, treatment, and outcomes of infections during induction chemotherapy in children with acute lymphoblastic leukemia (ALL). The study included children aged 1–14 years newly diagnosed with ALL, treated according to a modified Berlin-Frankfurt-Münster protocol, from January 2014 to June 2015. Out of 227 patients, 150 infection episodes were recorded among 117 patients. The major infection sites were the lungs (35 cases) and the gastrointestinal tract (30 cases). Blood cultures were positive in 45 episodes (30.6%), with Gram-negative organisms, predominantly *Pseudomonas aeruginosa* and *Klebsiella spp*., being the most common isolates. The response to antibiotics was favorable, with only 18% of infection episodes requiring a third-line antibiotic. A significant 90.6% of the infection episodes resolved without sequelae. The overall mortality during induction chemotherapy was 5.3% (12 out of 227 patients), primarily due to infections. The study concluded that infections are the leading cause of morbidity and mortality in patients with ALL undergoing induction chemotherapy, but the majority of patients can achieve good outcomes with prompt and adequate antibiotic treatment [7].

A retrospective observational study conducted at RGCIRC in Delhi analyzed culture reports from cancer patients undergoing treatment over the course of 2013. Out of 13,329 cultures obtained, 23.6% were positive, with a significant predominance of gram-negative isolates (67.9%). *Escherichia coli* emerged as the most common gram-negative bacterium (49.4%), followed by *Klebsiella spp*. (29.7%). Among gram-positive isolates, *Staphylococcus aureus* was the most prevalent. The study revealed a high incidence of extended-spectrum beta-lactamase (ESBL) production in blood and urine samples (87.2% and 88.5%, respectively), as well as beta-lactamase inhibitor (BLBLI) resistance (78% and 83.9%). However, carbapenem resistance was relatively low (10%), and colistin sensitivity remained high (>95%). The study concluded that while the prevalence of MRSA and VRE was low, the high rates of ESBL and BLBLI resistance among gram-negative infections necessitate careful consideration in antibiotic treatment strategies. Gram-negative isolates showed poor sensitivity to cephalosporins and fluoroquinolones, highlighting the challenge of managing bacterial infections in this patient population [8].

A retrospective study conducted at the Cancer Institute in Chennai examined the prevalence and antibiotic resistance profile of bloodstream bacterial infections in pediatric cancer patients in 2013. Out of 1,045 blood

culture samples, 82 (7.5%) were positive, with Gram-negative organisms comprising 61% of these infections. The most frequently isolated Gram-negative bacterium was *Klebsiella pneumoniae* (32%), while *Staphylococcus aureus* (93.5%) dominated among Gram-positive isolates. Notably, there was significant resistance to aminoglycosides and beta-lactam/beta-lactamase inhibitor antibiotics. This study highlights the predominance of Gram-negative bacteria in these infections and underscores the challenges posed by high resistance rates to commonly used empiric antibiotics in the treatment of febrile neutropenia [9].

A study conducted at a tertiary care cancer hospital investigated bloodstream infections in febrile neutropenic cancer patients, focusing on multidrug-resistant (MDR) Gram-negative bacteria (GNB). Of the 529 blood specimens collected, 195 showed bacterial growth, with 102 (52.3%) being Gram-negative and 93 (47.7%) Gram-positive. Among the Gram-negative isolates, a significant 68.6% were identified as MDR, predominantly including *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. These MDR GNB demonstrated high resistance to ampicillin, cefepime, ceftriaxone, and cephradine but retained good susceptibility to colistin. The most prevalent extended-spectrum β-lactamase (ESBL) genes were ctx-m, shv, and tem, while the most common aminoglycoside-resistant gene was aac(6')-Ib. Additionally, plasmid-mediated quinolone resistance genes such as qnrA, qnrB, and qnrS were detected. ESBL determinants were significantly linked with resistance to ciprofloxacin, levofloxacin, amikacin, and carbapenems. Synergistic effects were observed with combinations like ampicillin/sulbactam plus ceftriaxone and amikacin plus levofloxacin against several MDR GNB isolates, underscoring the need for strategic antibiotic use in these high-risk patients [10].

A retrospective study conducted over 43 months at a pediatric oncology unit in Eastern India analyzed bloodstream infections (BSIs) among children with cancer. The primary focus was on mucosal barrier injury-associated laboratory-confirmed bloodstream infections (MBI-LCBI-1), with a secondary objective to assess central line-associated bloodstream infection (CLABSI) rates and compare these to the device utilization ratio (DUR). Of the 47 positive blood cultures obtained, 70% were MBI-LCBI-1 cases and 6.3% were CLABSI cases, resulting in a CLABSI rate of 0.60 per 1,000 central line days. The majority of isolates were Gram-negative bacilli (90%), with *Klebsiella pneumoniae* being the most common. High rates of multi-drug resistant organisms, particularly carbapenem-resistant Enterobacterales, were observed. Notably, all six patients who died within 30 days of BSI had infections with multi-drug resistant organisms. The study underscores the importance of stringent infection control measures to reduce BSI incidence, while the low CLABSI rate indicates effective infection control practices in the unit [11].

This study conducted at a tertiary care cancer center in North-East India aimed to analyze the microbial flora, susceptibility patterns, and clinical variables associated with bloodstream infections in pediatric patients with febrile neutropenia undergoing treatment for solid tumors and hematological malignancies. Over the study period from January 2020 to December 2021, 378 blood culture samples were collected, revealing febrile neutropenia in 252 patients (66.7%). Out of these, 45 blood cultures (17.8%) were positive, with gram-negative organisms constituting 62% and gram-positive organisms 38% of the infections. *Escherichia coli* was the most prevalent gram-negative isolate, followed by *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Coagulase-negative *Staphylococci* (CoNS) were the most common gram-positive isolates. Notably, *Pseudomonas* isolates showed 60% sensitivity to beta-lactam/beta-lactamase inhibitors, and high colistin sensitivity was observed in *Klebsiella* and *E. coli* isolates. The study also reported a 50% incidence of methicillin-resistant *Staphylococcus aureus* (MRSA). These findings underscore the necessity for tailored antimicrobial policies based on specific microbiological profiles and resistance patterns in pediatric cancer patients with febrile neutropenia [12].

A study conducted at the Uganda Cancer Institute explored the impact of bloodstream infections (BSI) on hematologic cancer patients experiencing febrile neutropenic episodes (FNE). The research highlighted the significant mortality associated with BSIs, particularly in cases involving multidrug-resistant (MDR) organisms and polymicrobial infections. Among 629 participants, 181 blood cultures were completed, revealing a 36% positivity rate for pathogenic organisms. Gram-negative bacteria were predominant, with *Escherichia coli* being the most frequently isolated pathogen. Polymicrobial bloodstream infections (PBSI)

accounted for 26% of the cases and were notably associated with higher mortality rates compared to monomicrobial infections (MBSI) and negative cultures. Specifically, patients with PBSI exhibited a 44% mortality rate at 7 days and 63% within 30 days of FNE onset, underscoring the critical need for effective antimicrobial strategies in managing these high-risk infections [13].

3. Prevention & Management of Infections

Infection management in patients with hematological malignancies involves a crucial balance between infection control measures and antimicrobial chemoprophylaxis. While infection control measures are generally safe, their effectiveness can be inconsistent. On the other hand, antimicrobial prophylaxis tends to be effective but carries the risks of increasing resistance rates, toxicity, and additional costs. Therefore, it is essential to carefully evaluate each patient's specific risk for infection, identify the predominant pathogens in the particular clinical setting, and determine the critical periods when patients are most at risk. This comprehensive approach ensures the most appropriate prophylactic strategy is employed. The chapter systematically reviews the key parameters for individual risk assessment and discusses the evidence and recommendations for infection control and antimicrobial prophylaxis targeting bacteria, fungi, viruses, and parasites, providing a robust framework for managing infections in this vulnerable patient population [14].

Cancer-related infections significantly contribute to increased mortality, antibiotic use, and extended hospital stays, with further adverse impacts such as treatment dose delays and reductions, ultimately leading to suboptimal treatment outcomes. To reduce these issues, it is crucial to implement effective risk assessment and evidence-based interventions. The Oncology Nursing Society (ONS) has developed and continually updated the Putting Evidence into Practice (PEP) resource to provide the best available scientific evidence for infection prevention and treatment in cancer patients receiving immunosuppressive therapy. The PEP resource evaluates both pharmacologic and nonpharmacologic interventions, recommending practices such as catheter care bundles, antimicrobial prophylaxis, specific population vaccinations, and contact precautions for resistant organisms. These measures are essential for improving patient care and reducing the costs associated with cancer-related infections [15].

Children are the most prevalent age group affecting blood cancers. While empiric therapy for suspected infections and the treatment of confirmed infections are well-established practices, the routine use of prophylactic strategies in pediatric oncology is less common [16]. Both antimicrobial prophylaxis and non-pharmacological methods for infection prevention. Antimicrobial prophylaxis, although beneficial, carries risks such as increased resistance, toxicity, and cost. Non-pharmacological strategies, including stringent infection control measures, are essential but may not always be effective. Further research is needed to optimize these preventive approaches and to develop tailored strategies that balance efficacy and safety in managing infections among pediatric cancer patients [17].

Bloodstream infections (BSIs) are a significant complication in neutropenic cancer patients, particularly those caused by Gram-negative rods, which are linked to high mortality rates. Prompt empirical antibiotic therapy is crucial in these cases to cover the most common Gram-negative pathogens [18]. However, the rise of multidrug-resistant (MDR) strains over the past decade has rendered traditional antibiotics, such as ceftazidime, cefepime, piperacillin-tazobactam, and even carbapenems, increasingly ineffective. In response, a novel de-escalation approach has been suggested, where broad-spectrum antibiotics are initially used and then narrowed down after 72 hours if no MDR pathogen is identified. The efficacy of fluoroquinolone prophylaxis during prolonged neutropenia is also under scrutiny due to rising resistance. To combat these challenges, robust antibiotic stewardship and infection control programs are essential in cancer centers, ensuring appropriate antibiotic use and reducing the spread of resistant bacteria [19].

4. CONCLUSION

The management of infections in patients with hematological malignancies remains a critical challenge due to the high mortality associated with Gram-negative bacteria (GNB) and the increasing prevalence of

multidrug-resistant (MDR) strains. The need for prompt empirical antibiotic therapy is urgently required, yet the efficacy of traditional antibiotics is diminishing due to rising resistance. Comprehensive infection control measures and judicious use of antimicrobial prophylaxis are essential strategies for reducing infection rates and improving clinical outcomes.

The reviewed studies underscore the importance of routine blood culture monitoring, personalized risk assessment, and tailored antimicrobial policies based on local microbial flora and resistance patterns. Non-pharmacological strategies, such as stringent infection control measures, also play a vital role in preventing infections in immunocompromised patients. The integration of antibiotic stewardship programs within cancer centers is crucial to mitigate the spread of MDR organisms and ensure the effective use of antibiotics.

5. Future Aspects

5.1. Enhanced Surveillance and Monitoring:

Future research should focus on developing more surveillance systems to track infection trends and resistance patterns in real time. This will enable healthcare providers to promptly adjust treatment protocols and prophylactic strategies.

5.2. Innovative Therapeutic Approaches:

The development and clinical evaluation of new antibiotics and alternative therapies, such as bacteriophage therapy or immunotherapies, are critical to addressing MDR infections [20].

5.3. Personalized Medicine:

Advances in genomics and personalized medicine should be leveraged to tailor antimicrobial therapies based on individual patient profiles and specific pathogen characteristics.

5.4. Strengthening Infection Control:

Ongoing education and training programs for healthcare workers on infection control practices, coupled with robust infection prevention infrastructure, are necessary to reduce the incidence of hospital-acquired infections.

5.5. Optimizing Antimicrobial Prophylaxis:

Further research is needed to determine the optimal use of prophylactic antibiotics, balancing efficacy with the risk of resistance, toxicity, and cost. This includes evaluating the role of fluoroquinolone prophylaxis in light of increasing resistance.

5.6. Research on Antibiotic-Resistant Strains and Gene Identification:

Apply functional genomics approaches to understand the role of specific genes in conferring antibiotic resistance, elucidating mechanisms of resistance development and potential targets for intervention.

By addressing these future aspects, the medical community can better manage and prevent BSIs in patients with hematological malignancies, ultimately improving patient outcomes and reducing healthcare costs [21].

AUTHORS' CONTRIBUTIONS

Justy Babu designed the study and wrote the first draft of the manuscript. Dr. S. Sivamalar and Justy Babu managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript."

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