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MANAGEMENT OF INFECTIOUS COMPLICATIONS IN PATIENTS WITH ACUTE LEUKAEMIA

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Abstract. Infectious complications are among the most frequent and life-threatening challenges in the treatment of acute leukaemia, particularly during periods of chemotherapy-induced neutropenia. This study aimed to evaluate the incidence, spectrum, and outcomes of infections in patients with acute leukaemia treated at the Samarkand Regional Multidisciplinary Medical Centre between 2019 and 2023. A total of 108 patients with acute myeloid or lymphoblastic leukaemia were analysed. Febrile episodes occurred in nearly 90% of patients, with 61% of infections microbiologically confirmed. Gram-negative bacteria were the predominant pathogens, with *E. coli*, *K. pneumoniae*, and *P. aeruginosa* being the most common; a significant proportion exhibited multidrug resistance. Fungal infections and viral reactivations were also observed, particularly in those with prolonged neutropenia. The infection-related mortality rate was 17.6%, largely due to sepsis caused by resistant Gram-negative organisms. Early initiation of empirical antibiotic therapy and G-CSF support were associated with improved survival. The findings underscore the urgent need for improved diagnostics, targeted antimicrobial therapy, and local infection control strategies to reduce mortality in acute leukaemia patients in resource-limited settings.

Keywords: Acute leukaemia, infectious complications, febrile neutropenia, multidrug resistance, Gram-negative bacteria, fungal infections, sepsis, chemotherapy, Uzbekistan.

Introduction

Acute leukaemia, encompassing both acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), is a rapidly progressing malignancy of the bone marrow and blood, characterised by the uncontrolled proliferation of immature myeloid or lymphoid

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cells. Intensive induction and consolidation chemotherapy are essential to achieve remission and long-term disease control; however, these regimens result in profound myelosuppression, leading to significant immunosuppression and, consequently, a high vulnerability to infectious complications.

Infectious complications represent one of the most frequent and life-threatening challenges in the management of acute leukaemia. Despite advancements in supportive care and the availability of broad-spectrum antimicrobial agents, infections remain a leading cause of morbidity and mortality in this patient population. This is especially true during periods of chemotherapy-induced neutropenia, when innate immune defences are critically impaired. Even brief delays in initiating appropriate antimicrobial therapy in febrile neutropenic patients can lead to rapid clinical deterioration, septic shock, and death.

The immunocompromised state in acute leukaemia is further aggravated by mucosal barrier injury due to cytotoxic agents, central venous catheter use, prolonged hospitalisation, parenteral nutrition, and frequent transfusions. These factors contribute to the translocation of endogenous flora and facilitate colonisation and invasion by nosocomial and multidrug-resistant (MDR) pathogens. In many centres, including those in developing countries, infections are increasingly caused by organisms resistant to conventional antibiotics, such as extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, methicillin-resistant Staphylococcus aureus (MRSA), and carbapenem-resistant Gram-negative bacilli.

Invasive fungal infections (IFIs) constitute another major complication, particularly in patients with prolonged neutropenia, corticosteroid use, or relapsed/refractory disease. Aspergillus spp., Candida spp., and Mucorales are among the most common fungal pathogens. These infections are often difficult to diagnose early due to non-specific symptoms and limited access to advanced diagnostics such as galactomannan and β-D-glucan assays or high-resolution CT imaging. As a result, empirical antifungal therapy is often initiated based on clinical suspicion, but this approach may delay targeted therapy or lead to overtreatment.

Viral infections, especially reactivation of latent herpesviruses such as HSV and CMV, are also of concern in acute leukaemia patients undergoing immunosuppressive therapy or haematopoietic stem cell transplantation. These infections may manifest as mucositis, pneumonitis, or retinitis and can further complicate the already complex clinical picture.

Effective management of these infectious complications requires a multifaceted approach: risk stratification, timely empirical antibiotic administration, de-escalation based on microbiological data, prophylactic antimicrobial strategies, and stringent infection control measures. Moreover, regular surveillance of local resistance patterns and infection trends is essential to guide empirical therapy and inform antimicrobial stewardship programs.

In Uzbekistan, while access to chemotherapy and basic supportive care for haematologic malignancies has improved, there remains a significant gap in infection prevention and management infrastructure. Regional data on pathogen prevalence, resistance profiles, clinical outcomes, and post-infectious complications are sparse. Without such information, local protocols remain heavily reliant on international guidelines, which may not fully reflect regional microbial ecology, healthcare resources, or patient populations.

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Therefore, the present study aims to investigate the clinical characteristics, microbiological spectrum, antimicrobial resistance patterns, treatment responses, and outcomes of infectious complications in patients with acute leukaemia treated at the Samarkand Regional Multidisciplinary Medical Centre. By identifying key risk factors and evaluating the effectiveness of current management strategies, the study seeks to contribute to the development of evidence-based, locally relevant infection control protocols. Ultimately, the goal is to reduce infection-related mortality and optimise the clinical management of acute leukaemia in resource-constrained environments.

Results

This study analysed 108 patients diagnosed with acute leukaemia who developed infectious complications during chemotherapy between 2019 and 2023. The cohort included 68 patients with acute myeloid leukaemia (AML) and 40 with acute lymphoblastic leukaemia (ALL), with a median age of 39 years (range 15–72), and a male-to-female ratio of 1.4:1. All patients received intensive induction or consolidation chemotherapy, resulting in significant and prolonged neutropenia, with the median absolute neutrophil count (ANC) dropping below 500 cells/mm³ for an average duration of 10.4 ± 3.7 days. During this neutropenic period, 97 patients (89.8%) experienced at least one febrile episode, and 112 infectious episodes in total were recorded among them, as some had multiple infections during their treatment course.

Microbiologically documented infections accounted for 61% of cases, while 29% were clinically diagnosed without culture confirmation, and 10% remained febrile neutropenia of unknown origin despite empirical treatment. Among microbiologically confirmed infections, Gram-negative bacteria were the predominant pathogens, accounting for 55.8% of isolates. The most common organisms included *Escherichia coli* (21.5%), *Klebsiella pneumoniae* (18.7%), and *Pseudomonas aeruginosa* (12.4%). Notably, 39.4% of Gram-negative isolates were extended-spectrum beta-lactamase (ESBL)-producing, and 16.9% exhibited carbapenem resistance. Gram-positive bacteria accounted for 24.1% of isolates, with *Staphylococcus epidermidis* and *Enterococcus faecalis* being the most frequently identified. Fungal infections were diagnosed in 14 patients (13%), mostly invasive pulmonary aspergillosis and disseminated candidiasis. Viral reactivations, primarily HSV and CMV, were observed in 8 cases, confirmed by PCR assays or clinical presentation.

Empirical antibiotic therapy was initiated in all febrile neutropenic patients, most commonly with piperacillin-tazobactam or cefepime. Escalation to carbapenems was required in 38.6% of cases, especially in patients with MDR organism risk factors or hemodynamic instability. Vancomycin was added in 29 patients due to suspected Gram-positive infections. Antifungal therapy was introduced empirically in 42 patients and targeted in 14, using voriconazole, fluconazole, or amphotericin B depending on clinical suspicion and drug availability. G-CSF was administered to 63.8% of patients to support neutrophil recovery. The median time to defervescence was 4.3 ± 2.1 days. Targeted therapy based on culture and sensitivity improved outcomes in 82.6% of cases with confirmed pathogens.

The infection-related mortality rate was 17.6% (19 patients), with sepsis due to MDR Gram-negative infections being the leading cause of death. These cases were often associated with delayed culture results, resistance to multiple antibiotics, and the absence of early intensive

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care support. Among patients who survived, the average hospital stay was 21.8 ± 6.4 days. A statistically significant association was found between infection-related mortality and prolonged neutropenia (>10 days), presence of MDR pathogens, and delayed initiation of empirical therapy ($p < 0.05$ for all). Conversely, early initiation of empirical antibiotics within 1 hour of fever onset, combined with G-CSF support and appropriate escalation, was associated with a higher survival rate.

These findings underscore the high burden of infectious complications in patients with acute leukaemia, particularly from multidrug-resistant Gram-negative pathogens. Despite established empirical treatment protocols, infection-related mortality remains significant, especially in patients with severe neutropenia and delayed microbiological guidance. The data highlight the urgent need for enhanced diagnostic capabilities, access to rapid pathogen identification tools, and regional antimicrobial stewardship efforts to improve outcomes in this high-risk patient population.

Discussion

The results of this study highlight the persistent and severe threat posed by infectious complications in patients undergoing treatment for acute leukaemia. Despite advances in chemotherapy and supportive care, infections remain a leading cause of morbidity and mortality, particularly during prolonged periods of neutropenia induced by intensive induction or consolidation regimens. The high frequency of febrile episodes (89.8%) and documented infections in over half of the patients underscores the vulnerability of this population and the central role infection management plays in determining treatment outcomes.

Gram-negative bacteria emerged as the dominant group of pathogens, consistent with global epidemiological trends. The predominance of *E. coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* aligns with findings from international haematology centres, but the high proportion of multidrug-resistant (MDR) strains—particularly ESBL-producing and carbapenem-resistant isolates—is concerning. These resistant organisms significantly reduce the efficacy of first-line empirical regimens and necessitate early escalation to carbapenems or combination therapies. The association between MDR infections and higher mortality in this cohort reflects the urgent need for proactive infection surveillance and the rational use of broad-spectrum antibiotics to prevent further resistance development.

Fungal infections, although less frequent, were associated with increased length of hospital stay and higher treatment complexity. Most were due to *Aspergillus* species or disseminated *Candida*, occurring in patients with prolonged neutropenia and previous antibiotic use. The limited availability of fungal biomarkers and imaging studies in our setting may have resulted in underdiagnosis or delayed detection. Nonetheless, empirical antifungal therapy in persistent febrile neutropenia was a life-saving measure in many cases, emphasising the importance of early clinical suspicion and access to antifungal drugs like voriconazole and amphotericin B.

Viral reactivations, particularly of HSV and CMV, though relatively infrequent, added another layer of complexity to patient management. These findings suggest the need for enhanced virological monitoring, especially in patients receiving immunosuppressive therapy or presenting with mucocutaneous lesions, and the routine availability of PCR-based assays for early detection and preemptive treatment.

The infection-related mortality rate of 17.6% is in line with data from comparable centres in middle-income countries. Most deaths were attributable to sepsis caused by resistant Gram-

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negative organisms, typically in patients who experienced prolonged neutropenia, delayed empirical antibiotic administration, or lacked early access to intensive care. Importantly, timely initiation of empirical therapy within the first hour of fever onset, along with granulocyte-colony stimulating factor (G-CSF) support and close clinical monitoring, was associated with improved survival. These observations reinforce global recommendations on the "golden hour" principle in febrile neutropenia and support the inclusion of rapid-response pathways in institutional protocols.

Our findings underscore the need to develop and implement comprehensive infection prevention and control strategies tailored to the local microbial environment. These should include regular antibiogram updates, standardised empirical therapy guidelines, rigorous hand hygiene and catheter care protocols, and educational programs for healthcare providers. Additionally, building diagnostic capacity—particularly for rapid microbial detection, resistance profiling, and fungal biomarkers—is essential to optimise antimicrobial stewardship and reduce unnecessary drug exposure.

This study also reveals several resource limitations that constrain infection management in our setting. Delays in microbiological diagnosis, limited access to newer antimicrobial agents, and inconsistent availability of diagnostic imaging hinder timely intervention. Moreover, many patients lacked consistent prophylaxis due to supply interruptions or financial barriers. Addressing these systemic gaps requires not only medical interventions but also institutional investment and health policy support.

In conclusion, infectious complications in acute leukaemia remain a significant threat to patient survival, especially in resource-constrained settings. Multidrug-resistant Gram-negative infections and delayed intervention are the principal drivers of infection-related mortality. Strengthening early diagnostic capabilities, ensuring timely empirical treatment, enhancing infection control practices, and updating local treatment protocols are critical to improving outcomes. The insights from this study can serve as a foundation for regional and national policy development aimed at reducing infection-related mortality in haematological malignancies.

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