BACTEREMIA IN ACUTE LEUKEMIA PATIENTS: A MULTI-CENTER STUDY OF THE JORDANIAN ROYAL MEDICAL SERVICES

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ABSTRACT

Background: Patients with acute leukemia are at an increased risk of infectious complications due to immunity defects caused by the disease itself and exacerbated by the adverse effects of prolonged chemotherapy regimens.

Aim: To determine the epidemiological characteristics and prognosis of bacteremia in patients with acute leukemia, which will facilitate tailoring the best management protocols.

Methods: A retrospective analysis was done using the computerized patient record system on the Hakeem platform between February 2016 and February 2023 to collect patients' demographics, diagnoses, clinical histories, neutrophil counts, blood cultures, and prognoses.

Results: We obtained 162 blood cultures from 139 acute leukemia patients, among which 133 (82.1%) had bacterial growth, 45.1% Gram-negative bacteria, and 37% Gram-positive bacteria . The most isolated organisms were Escherichia coli (22.2%), Staphylococcus epidermidis (16%), and Staphylococcus aureus (6.8%). Age of >18 years (P < .001), severe neutropenia (P=.034), and drug resistance were associated with mortality (P =.010). Non- significant variables were gender, Gram stain and the diagnosis.

Conclusion: Gram-negative bacteria is the most common cause of bacteremia. Age of >18 years, severe neutropenia, and drug resistant bacteremia were significantly less likely tosurvive.

Key words: Acute leukemia, bacteremia, ESBL, neutropenia, mortality.

Vol. 35 (1) April 2026
DOI: 10.12816/0062521

Introduction

Acute leukemia (AL) is an aggressive hematological malignancy characterized by clonal proliferation of blasts in the blood or bone marrow. In terms of morphology, clinical presentation, and genetic makeup, it is a heterogeneous disease that arises in the lymphoid or myeloid lineages. The treatment involves intensive chemotherapy (1-4).

Morbidity and mortality are attributed in a significant part to infectious complications. Qualitative and quantitative defects in granulocytes and lymphocytes occur in AL, which predisposes patients to various infections. Chemotherapeutic regimens often exacerbate these I deficits by prolonging neutropenia and damaging mucosal membranes The use of indwelling catheters is yet another risk factor for infections in such patients (5, 6).

Bacteremia is the presence of viable bacteria in the bloodstream. It can be cleared by the immune system or progress into sepsis and life-threatening organ failure (7).

A dysregulated response to infection in patients with AL increases their vulnerability to a variety

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of infectious consequences, ranging from milder opportunistic infections to more serious and often fatal sepsis (8). Over the past decades, the spectrum of bloodstream infections shifted towards Gram-positive bacteria (GPB). Recently, some studies are reporting a reversal of this shift, especially with the emergence of drug-resistant Gram-negative bacteria (GNB).In this study, we analyzed the spectrum of bacterial bloodstream infections in these patients and their prognosis in the hospitals of the Jordanian Royal Medical Services.

Methods

This study was conducted retrospectively. The approval of the Royal Medical Services Ethics Committee was acquired. The computerized patient record system on the Hakeem platform was utilized to collect data, including patients' demographics (age and gender), type of leukemia, clinical histories, blood culture dates and results, neutrophil counts, and prognoses. Inclusion criteria were cases of acute myeloid and lymphoid leukemia that were confirmed by immunophenotyping and treated by by chemotherapy in the Royal Jordanian Medical Services hospitals between February 2016 and February 2023. We included both male and female patients of all ages. They presented to the emergency department with a fever of ≥38°C . Once patients were admitted, blood cultures were obtained before starting antibiotic treatment. Other inclusion criteria included the availability of patients' blood culture results and neutrophil counts on the same date of the blood cultures on their electronic records.

Blood culture standard procedure:

Blood culture standard procedure involves obtaining aerobic and anaerobic blood culture bottles from two separate venipuncture sites under the aseptic technique, which required using chlorhexidine for 30 seconds to avoid contamination. Samples reach the microbiology department within 2 hours, where they are incubated for 5 days in the BACTEC instrumented blood culture system. Flagged cultures were identified using the VITEK 2 (bioMérieux)automated system, which also provided the antibiotic susceptibility profiles. Underfilled blood culture bottles (less than 5 mL of blood per bottle) are rejected at the microbiology department,because,of delayed bacterial growth and false negative results. Overfilled bottles (more than 10 mL) are also rejected because they might be incorrectly flagged as positive due to the high production of CO 2 by white blood cells. Mortality that occurred within 30 days of the blood culture date was documented. Patients with incomplete data and those who transferred to other hospitals were excluded from this study.wo age categories were defined: patients <18 years old and patients ≥18 years of age. We divided our patients into two groups according to neutrophil counts: The first group had neutrophil counts of <500/µL, and the second group had counts of ≥500/µL The acquired data was analyzed using Microsoft Excel spreadsheet software. The chi-square test was used to calculate the P-value in the categorical univariant analysis. A binary logistic regression was carried out using (IBM SPSS statistics for windows, version 26. Armonk, NY, IBM Corp). A P-value of <.05 was considered significant.

Results

We obtained 162 blood cultures from 139 AL patients. Twenty-three patients presented with fever on two separate occasions, for which blood cultures were obtained again. Their ages ranged from 1-80 years (median = 21.9 years, SD = 19.8 years). Males comprised 55.4% (N = 77) and females 44.6% (N = 62). Acute lymphoblastic leukemia was more frequent than acute myeloid leukemia (65.5% and 34.5%, respectively).Table 1 details the patients' demographics Bacterial growth was detected in

133 cultures (82.1%). GNB were more frequent than GPB (45.1%, N = 73 and 37.0%, N = 60, respectively). Escherichia coli was the most frequent pathogen (22.2% of all bloodstream organisms, 27.1% of bacteremia episodes, and 49.3% of GNB), followed by Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterobacter cloacae (4.3%, 3.7%, and 3.7%, respectively). Sixteen out of 36 E. coli isolates were extended-spectrum beta-lactamase-producing (ESBL) or multi-drug-resistant (MDR), and 1 of 9 Klebsiella isolates was ESBL-producing, amounting to 44.4% and 11.1% of their respective species. An MDR isolate is resistant to at least one agent in three or more relevant antimicrobial categories (9).Staphylococcus epidermidis was the most reported GPB, followed by Staphylococcus aureus and Streptococcus viridans (16%, 6.8%, and 4.9%, respectively). Methicillin resistance was detected in 54.5% of S. aureus isolates. Two enterococcus isolates were found, and both were sensitive to vancomycin. Sixteen blood cultures (9.9%) for patients with febrile neutropenia were reported to have no growth. Details of all the isolates are shown in Table 2. Seventy-seven of 133 bacteremia episodes occurred in the context of severe neutropenia (57.9%). A thirty-day mortality was assessed. Thirty-two out of 133 bacteremia episodes had poor outcomes, and the patients did not survive them (24.1%). Twenty-three episodes of GNB (31.5%) and nine episodes of GPB (15%) had fatal outcomes. The overall mortality of all 139 AL patients, regardless of the time or cause of death, was 28.1%. Table 3 details the bacteremia outcomes among the different study groups. Age above 18 years was associated with mortality, $\chi^2(1, N = 133) = 25.90$, P <.001. Two other variables with a significant association with mortality were severe neutropenia <500/µL and ESBL-producing and MDR bacteremia , $\chi^2(1, N = 133) = 9.43$, P =.002, and $\chi^2(1, N = 73) = 4.72$, P =.030, respectively. The P-values for patients' gender and AL lineage were >0.05 and not significant. Table 4 summarizes categorical variables and their influence on bacteremia outcomes. A logestic regression was done and the overall mortality model was statistically significant when compared to the null model ($\chi^2(5)=39.724$ P<0.001). The value of Nagelkerke R^2, which reflects the proportion of variance in the outcome, was 0.39. Significant factors were age > 18 years (P<0.001), ESBL and MDR bacteria (P =0.010), and severe neutropenia (P =.034). Whereas the other factors were insignificant. Table 5.

Discussion

AL patients with disease- and treatment-related immunosuppression are at risk of serious infectious complications, especially with drug-resistant organisms. This constitutes a major cause of morbidity and mortality. We studied blood culture isolates in AL patients to shine a light on the spectrum of pathogens involved and the outcomes of their treatment in Jordan. Febrile neutropenia is observed in 80% of patients with hematological malignancies, with bacteremia ranking highest among infectious complications in such cases (10). Bacteremia is documented in approximately 15-20% of AL patients with neutropenia (11). In contrast to Western countries, where the spectrum of bloodstream infections shifted towards GPB, our data showed that GNB are more frequent in Jordan (45.1% GNB vs. 37% GPB) (12). Some countries are reporting a similar reversal of this shift, especially with the emergence of MDR GNB (11, 13). Studies from India and China have also reported GNB predominance (14, 15). Cattaneo et al. reported GNB as the predominant relapsing bloodstream infection in AL, with E. coli as the most common pathogen (16). Bacteremia often arises from organisms that colonize the gastrointestinal tract and enter the bloodstream when immunity and the integrity of protective mucosal membranes are compromised by chemotherapy. These organisms are typically GNB species, including Escherichia, Klebsiella, Pseudomonas, Enterobacter, and Stenotrophomonas (17, 18).We have identified E. coli as the most common pathogen causing bacteremia, with 44.4% being ESBL and MDR. The mortality rate was significantly higher in cases of GNB compared to GPB and in cases of drug-resistant organisms among this group compared to sensitive species. Recent studies from Italy and Norway have reported imilar findings (10, 19, 20). Pseudomonas spp. is one of the GNB which constitutes 5-10% of blood stream infections in hematological patients (21, 22). In the GNB group, it followed E. coli in frequency, along with Klebsiella spp. with a prevalence of 5.4%. Staphylococcus epidermidis was the most common agent in the GPB group in our study. It is a part of the normal skin flora and may cause skin and soft tissue infections (23). However, When isolated in blood cultures, S epidermidis is considered a contamination. Such frequency in encountering this organism in our study sheds a light on the importance of aseptic technique in obtaining blood cultures as previously mentioned .A cohort study by Trecarichi et al. in Italy and a survey by Mikulska et al., which compared bacteremia episodes that occurred in adult cancer patients from 18 different countries, had similar distributions to our study in that E. coli was the most common species (27.9% and 30% vs. 27.1%), followed by coagulase-negative staphylococci (24.8% and 24% vs. 19.5%). They reported enterococci as the third isolated pathogen. Our study differs, however, by more frequent streptococci and S. aureus (19,21). Alpha hemolytic streptococci, including S. viridans, which constituted 4.9% of blood isolates in our study, are a major group of the oral flora, and they gain entry to the blood after chemotherapy due to weakening mucosal membranes (11). Neutropenia, the breakdown of mucosal membranes, and indwelling catheters make cancer patients particularly susceptible to GPB. A common cause of such infections is S. aureus, but it tends to be underestimated when studying bacteremia alone. Skin and soft tissue infections, as well as pneumonia, are more frequent sites of infection. Methicillin-resistant species are often encountered in AL patients due to frequent antimicrobial prophylaxis administration and healthcare exposure (24). In this study, S. aureus comprised 6.8% of the isolates, of which 54.5% were methicillin-resistant. Our statistical analysis showed that patients without severe neutropenia are 3.2 times more likely to survive than those with neutrophil counts <500/ μL .According to Zimmer et al., the risk of developing more serious infections is linked to the degree and duration of neutropenia (25). We did not examine the duration of neutropenia, but we shared a similar result: the presence of severe neutropenia was predictive of mortality. Approximately 30% of our patients who succumbed to GNB infections had fatal outcomes,as opposed to 15% of the GPB infections. This is supported by Gustinetti et al., who reported lower mortality in patients with Gram-positive bacteremia than in patients with Gram-negative bacteremia (10).Patients with multidrug resistant bacteremia in the study were less likely to survive. According to Caniza et al., low- and middle-income countries had 10-times higher rates of infection-associated mortality than high-income countries due to the risk of multiple drug-resistant organisms among other factors (26). Sixteen blood cultures (9.9%) had no bacterial growth despite the presence of febrile neutropenia. These patients may have

Table 1: Patients' demographics

Patients' characteristics		**Number (%)** **N = 139**
Gender	Male Female	77 (55.4) 62 (64.6)
Age	Mean (SD) 1-18 years 19-80 years	21.9 (19.8) 86 (61.9) 53 (38.1)
Diagnosis	Acute Lymphoid leukemia Acute Myeloid leukemia	91 (65.5) 48 (35.5)

Table 2: Bloodstream microorganisms' frequencies and characteristics

Organism	**Number (%)** **N = 162**
Gram-negative bacteria	73 (45.1%)
Escherichia coli	36 (22.2%)
ESBL and MDR	16 (9.9%)
Pseudomonas spp.	9 (5.6%)
P. aeruginosa	7 (4.3%)
Klebsiella spp.	9 (5.6%)
ESBL	1 (0.6%)
Enterobacter spp.	8 (4.9%)
E. cloacae	6 (3.7%)
Acinetobacter spp.	6 (3.7%)
A. baumannii	4 (2.5%)
Sphingomonas paucimobilis	2 (1.2%)
Morganella morganii	1 (0.6%)
Stenotrophomonas maltophilia	1 (0.6%)
Pantoea spp.	1 (0.6%)
Achromobacter xylosoxidans	1 (0.6%)
Aeromonas spp.	1 (0.6%)

Gram-positive bacteria	**60 (37%)**
Staphylococcus epidermidis	26 (16%)
Staphylococcus aureus	11 (6.8%)
Methicillin-resistant	6 (3.7%)
Streptococcus spp.	18 (11.1%)
S. viridans	8 (4.9%)
Alpha-hemolytic	7 (4.3%)
S. pneumoniae	1 (0.6%)
S. faecium	1 (0.6%)
Bacillus spp.	3 (1.9%)
Enterococcus spp.	2 (1.2%)
***Candida* spp.**	13 (8%)

Table 3: Distribution of the mortalities and survivors among the studied groups.

Gender		
Male	20 (62.5%)	56 (55.4%)
Female	12 (37.5%)	45 (44.6%)
Age		
≤ 18 years	9 (25%)	78 (77.2%)
>18 years	23 (71.9%)	23 (22.8%)
Neutrophil count		
< 500/µL	26 (81.3%)	51 (50.5%)
≥ 500/ µL	6 (18.7%)	50 (49.5%)
Diagnosis		
AML	14 (43.8%)	30 (29.7%)
ALL	18 (56.2%)	71 (71.3%)
Gram stain		
Gram-negative	23 (71.9%)	50 (49.5%)
Gram-positive	9 (28.1%)	51 (50.5%)
Antibiotic sensitivity		
ESBL, MDR	9 (28.1%)	7 (6.9%)
Sensitive	23 (71.9%)	94 (93.1%)

* Refers to mortality which occurred within 30 days following the date of the blood culture. ESBL = extended spectrum beta lactamase, AML = acute myeloid leukemia, ALL= acute lymphoblastic leukemia, MDR = multi-drug-resistant.

Table 4: Statistical significance of the studied variables in association with mortality in patients with acute leukemia and bacteremia using chi square test.

Categorical variable	Mortalities* N = 32 (%)	Survivors N = 101 (%)	P-value
Male gender	20 (62.5%)	56 (55.4%)	0.482
Age >18 years	24 (75%)	23 (22.8%)	< .001
Severe neutropenia <500/µL	26 (81.3%)	51 (50.5%)	0.002
Acute myeloid leukemia	14 (43.8%)	30 (29.7%)	0.141
GNB	23 (71.9%)	50 (49.5%)	0.027
ESBL and MDR GNB	9 (28.1%)	7 (6.9%)	0.03

* Refers to mortality which occurred within 30 days following the date of the blood culture. ESBL = extended spectrum beta lactamase, GNB = Gram-negative bacteria, MDR = multi-drug-resistant.

Table 5: Logistic regression analysis to predict mortality in acute leukemia patients with bacteremia (N=133).

Characteristic	P-value	Odds ratio	95% CI	
			Lower	Upper
Age>18 years	0	8.92	2.994	26.671
Diagnosis	0.285	1.889	0.589	6.059
Severe neutropenia	0.034	3.316	1.095	10.042
Gram stain	0.539	1.385	0.49	3.918
Drug resistance	0.01	6.328	1.542	25.977
Constant	0.005	0.097		

had respiratory, urinary, or gastrointestinal tract infections. Such infections commonly have a viral etiology. Besides infection, the differential diagnosis of fever in patients with AL includes disease relapse, thrombosis, and drug-induced nephritis and hepatitis (20). The limitations of this study included its retrospective design, which prohibited the authors from acquiring certain information. For example, patients may have received prophylactic antibiotic therapy prior to the date of the blood culture. We also did not look at the duration of the neutropenia episodes or other sites of infection besides bacteremia. The limited number of certain isolated microorganisms prevented the assessment of their influence on the prognosis of bacteremia.

Conclusion

As the spectrum of bacteremia differs from one region to another, knowledge of our local epidemiology, resistance profiles, and prognostic variables is crucial in targeting the diagnostic workup and early treatment to optimize the management and improve the outcome of bacteremia in AL patients. Our findings are consistent with the recently reported trend reversal from GPB to GNB as the causative agents of bacteremia among patients with AL, with a worrisome frequency of drug-resistant organisms.

Abbreviations

AL: Acute leukemia
ESBL: Extended-spectrum beta-lactamase
GNB: Gram-negative bacteria
GPB: Gram-positive bacteria
MDR: Multi-drug resistant

Acknowledgments

The authors of this paper are grateful for the professional editing provided by Luke Palder, the founder and CEO of ProofreadingServices.com

We have no conflict of interest to declare.

References

1.Swerdlow SH, Campo E, Harris NL, et al, editors. WHO classification of tumours of hematopoietic and lymphoid tissues. Rev 4th ed. Lyon, France: IARC; 2017.

2.Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. 2015;373(12):1136-52.1

3.Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J. 2017;7(6):e577.

4. Khan M, Siddiqi R, Naqvi K. An update on classification, genetics, and clinical approach to mixed phenotype acute leukemia (MPAL). Ann Hematol. 2018;97(6):945-53.

5. Logan C, Koura D, Taplitz R. Updates in infection risk and management in acute leukemia. Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):135-9.

6.Taplitz RA, Kennedy EB, Flowers CR. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update summary. J Oncol Pract. 2018;14(11):692-5.

7. Huerta LE, Rice TW. Pathologic difference between sepsis and bloodstream infections. J Appl Lab Med. 2019;3(4):654-63.

8. Hoag JB, editor. Oncology critical care [Internet]. InTech; 2016 [cited 2023 Nov 24]. doi: http://dx.doi.org/10.5772/61590.

9. Magiorakos A, Srinivasan A, Carey R, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81.

10. Gustinetti G, Mikulska M. Bloodstream infections in neutropenic cancer patients: A practical update. Virulence. 2016;7(3):280-97

11. Rolston KVI. Infections in patients with acute leukemia. Infect Hematol. 2014 Nov; 27:3-23..

12. Lech-Maranda E, Seweryn M, Giebel S, et al. Infectious complications in patients with acute myeloid leukemia treated according to the protocol with daunorubicin and cytarabine with or without addition of cladribine: A multicenter study by the Polish Adult Leukemia Group (PALG). Int J Infect Dis. 2010;14(2):e132-40.

13. Carvalho AS, Lagana D, Catford J, et al. Bloodstream infections in neutropenic patients with haematological malignancies. Infect Dis Health. 2020;25(1):22-9.

14. Lakshmaiah KC, Malabagi AS, Govindbabu, et al. Febrile neutropenia in hematological malignancies: clinical and microbiological profile and outcome in high-risk patients. J Lab Physicians. 2015;7(2):116-20.

15. Wang E, Zhang C, Tang Y, et al. Antibiotic susceptibility and prognostic analysis of Gram-negative bacterial bloodstream infection in patients with acute leukemia. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2020;45(9):1068-73.

16. Cattaneo C, Antoniazzi F, Tumbarello M, et al. Relapsing bloodstream infections during treatment of acute leukemia. Ann Hematol. 2014; 93(5):785-90.

17. McMahon S, Sahasrabhojane P, Kim J, et al.Contribution of the oral and gastrointestinal microbiomes to bloodstream infections in leukemia patients. Microbiol Spectr. 2023;11(3):e0041523.

18. Stoma I, Littmann E, Peled J, et al. Compositional flux within the intestinal microbiota and risk for bloodstream infection with Gram-negative bacteria. Clin Infect Dis. 2021;73(11):e4627-35.

19. Trecarichi EM, Pagano L, Candoni A, et al; HeMABIS Registry—SEIFEM Group, Italy. Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: an Italian multicentre prospective survey. Clin Microbiol Infect. 2015;21(4):337-43.

20. Hansen BA, Wendelbo O, Bruserud O, et al. Febrile neutropenia in acute leukemia: epidemiology, etiology, pathophysiology and treatment. Mediterr J Hematol Infect Dis. 2020;12(1):e2020009.

21. Mikulska M, Viscoli C, Orasch C, et al; Fourth European Conference on Infections in Leukemia Group (ECIL-4), a joint venture of EBMT, EORTC, ICHS, ELN and ESGICH/ESCMID. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients. J Infect. 2014;68(4):321-31.

22. Zhao Y, Lin Q, Liu L, et al. Risk factors and outcomes of antibiotic-resistant Pseudomonas aeruginosa bloodstream infection in adult patients with acute leukemia. Clin Infect Dis. 2020;71(Suppl 4):S386-93.

23. Natsis NE, Cohen PR. Coagulase-Negative Staphylococcus Skin and Soft Tissue Infections. Am J Clin Dermatol. 2018 Oct;19(5):671-677.

24. Holland T, Fowler VG Jr, Shelburne SA III. Invasive gram-positive bacterial infection in cancer patients. Clin Infect Dis. 2014;59(Suppl 5):S331-4.

25.Zimmer AJ, Freifeld AG. Optimal management of neutropenic fever in patients with cancer. J Oncol Pract. 2019;15(1):19-24.

26. Caniza MA, Odio C, Mukkada S, Gonzalez M, Ceppi F, Chaisavaneeyakorn S, Apiwattanakul N, Howard SC, Conter V, Bonilla M. Infectious complications in children with acute lymphoblastic leukemia treated in low-middle-income countries. Expert Rev Hematol. 2015;8(5):627–645.