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Original Article

Evaluating the Effects of Colonization with Multidrug-Resistant Bacteria on the Outcomes of Induction Chemotherapy in Patients with Acute Leukemia: A Prospective Analysis

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Abstract

Introduction The presence of multi-drug resistant (MDR) bacteria has been linked to higher rates of morbidity and mortality in patients with acute leukemia.

Objective This prospective study aimed to evaluate the prevalence of MDR bacteria in stool samples of patients undergoing induction chemotherapy for acute leukemia and to explore its association with clinical outcomes.

Materials and Methods The study recruited 200 patients, aged 1-60 years, with newly diagnosed acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) who were scheduled to receive intensive induction chemotherapy. Stool samples were obtained on days 1 and 15 of the induction phase, and standard bacterial culture methods were used to determine culture and sensitivity.

Results Two hundred patients were enrolled from January 2018 to March 2020. On day 1, 35.7% of the stool cultures were positive, with all identified bacteria being MDR. On day 15, 36.7% of the samples were positive for MDR bacteria. MDR E. coli and MDR Enterococcus faecium were the most common organisms isolated in the stool culture. The detection of MDR bacteria in day 15 stool cultures was significantly associated with an increased risk of infections, admissions to the intensive care unit, mortality, and failure to achieve remission.

Conclusion These findings indicate that monitoring stool colonization with MDR bacteria during induction chemotherapy could be crucial for identifying patients at elevated risk of adverse outcomes and optimizing antimicrobial strategies.

Keywords
- infection
- acute leukemia
- multidrug resistant
- chemotherapy
- stool culture

Introduction

Acute leukemias are aggressive hematological malignancies with high morbidity and mortality rates.[1–3] Infections during induction chemotherapy significantly contribute to these outcomes.[3–5] Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) patients exhibit immune dysfunction, making them susceptible to infections. Gram-negative

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bacteria are the primary pathogens in neutropenic patients in low- and middle-income countries (LMICs). The gastrointestinal microbiome plays a crucial role in infection development.[6] Chemotherapy-induced gastrointestinal mucosal damage leads to an increased translocation of commensal pathogens across the gut barrier, heightening the risk of bloodstream infections and febrile neutropenia.[7,8] Prolonged and inappropriate antibiotic use has resulted in the emergence of multidrug-resistant (MDR) bacteria in LMICs.[9–11]

Studies, including from our center, have shown a high prevalence of gram-negative MDR bacteria in stool at diagnosis in patients with acute leukemia.[12,13] Most of these studies have demonstrated a positive correlation between stool colonization at diagnosis and an increased risk of sepsis and mortality.[12,13] However, most are retrospective, have a small sample size, and focus on stool culture at diagnosis rather than during treatment. We, therefore, conducted the Stool Culture Correlation with Acute Leukemia Outcome (SCALO) study, which is a prospective study on bacterial stool colonization in patients with cancer, and assessed the stool culture positivity at diagnosis and during treatment.

Materials and Methods

The SCALO study constituted a secondary objective of the randomized controlled trial (RCT) on neutropenic versus regular diet for acute leukemia induction chemotherapy.[14] The trial was an open-label, superiority-design study conducted at a single center.

Patients were enrolled in the study after obtaining written informed consent from patients aged $\geq$18 years and parents/caregivers for those under 18 years. Patients between 8 and 18 years provided assent. Two hundred patients were randomly assigned in a 1:1 ratio to either a regular diet or a neutropenic diet. The primary aim of the RCT was to evaluate the incidence of significant infections between the two dietary groups. In the neutropenic diet group, raw fruit and vegetable consumption was not allowed, whereas the regular diet group was permitted to consume these foods. Patients in both arms were advised to follow food safety guidelines. Further details on the RCT can be found in the study of Radhakrishnan et al.[14]

Objectives and Outcomes

The SCALO study aimed to evaluate the prevalence of MDR bacterial colonization in stool on days 1 and 15 during the induction phase of acute leukemia. Additionally, the study sought to examine the relationship between stool MDR colonization and blood culture positivity and its association with infections and mortality.

Inclusion and Exclusion Criteria

The principal inclusion criteria comprised patients aged 1 to 60 years who had been diagnosed with AML or ALL and were scheduled for induction chemotherapy. Additionally, these individuals were required to exhibit no clinical, radiological, or microbiological signs of infection at the time of diagnosis. On the other hand, patients receiving palliative therapy or hematopoietic stem cell transplantation were excluded from participating in the study. We attempted to collect stool samples on both day 1 (before starting induction chemotherapy) and day 15 of the induction period. Nonetheless, a few patients could not provide stool samples on the precise days. We extended the collection window to 72 hours, following day 15, for these specific cases to secure the samples. However, these instances were included and treated as if they were collected on either day 1 or 15 for analytical purposes.

Treatment Details

Children (<18 years) diagnosed with ALL were subjected to treatment as per the risk-adjusted approach outlined in the Indian Collaborative Childhood Leukemia (ICICLE) group protocol.[15] For children (<18 years) with AML, treatment involved the use of the "3 + 7" regimen (consisting of daunorubicin and cytarabine) or the cytarabine, daunorubicin, and etoposide (ADE) regimen.[3] Patients between 18 and 40 years with ALL were managed using the Berlin, Frankfurt, and Munster-95 (BFM-95) regimen, while those older than 40 years followed the German protocol.[16,17] Patients older than 18 years diagnosed with AML were treated with the "3 + 7" regimen.[18] Every participant in the study received oral voriconazole as a prophylaxis against fungal infections. Antibiotic prophylaxis and growth factors were not administered.

Assessment and Management of Infections

Individuals displaying signs of potential infection underwent a clinical assessment. The decision of the attending doctor determined the need for blood cultures, as well as cultures of tissues and fluids, imaging tests, and specialized screenings for identifying viral infections such as dengue or influenza. Hemogram and biochemical tests were conducted based on the clinical context. *Clostridium difficile* testing in the stool in patients with diarrhea was done based on the physician's decision. The assessment of infections was conducted from the point of randomization until the conclusion of the induction phase or hospital discharge or day 40 of induction, whichever occurred earlier.

In our study, we identified infections based on clinical or radiological signs. We defined a "major infection" as conditions like pneumonia, urinary tract infections, bacteremia, fungemia, meningitis, cellulitis, diarrhea, peritonitis, empyema, sinusitis, abscesses, and other infections that can lead to severe outcomes.[14] Only infective diarrheas diagnosed clinically or on stool culture were included in major infection.[14] Any other infections were categorized as minor. Febrile neutropenia, often seen in acute leukemia patients undergoing induction chemotherapy, was not categorized as major or minor if no clear source of infection was evident according to our previous definition. For our reporting, we treated febrile neutropenia as a separate occurrence.[14] If another major infection, minor infection, or febrile neutropenia arose at least 48 hours after the previous episode was fully resolved, we regarded it as a new episode.[14]

The medical team followed the hospital's established procedure for managing infections. Initial treatment for febrile neutropenia involved using cefoperazone–sulbactam with teicoplanin as the first-line empiric antibiotic. When necessary, the second-line antibiotic options were imipenem and meropenem, and the third line option consisted of colistin and/or tigecycline. Patients with shock or those requiring invasive ventilation were started on meropenem, colistin, and/or tigecycline, and adjustments were made to blood culture results and the patient's condition. Amphotericin B or caspofungin was employed for fungal infections. The duration of antibiotic and antifungal treatment was determined by the judgment of the attending physician. Antibiotics were escalated for patients with MDR bacteria in stool based on the stool culture sensitivity and the physician's assessment of the patient's clinical status.

Stool specimens were procured from all patients on the initial and 15th day of induction chemotherapy. A minimum of 5 mL of stool sample was collected within sterile containers. Within a 2-hour time frame, the containers holding the stool samples were transferred to the microbiology department at our center. Stool cultures were then cultivated on 5% sheep blood agar and McConkey agar supplemented with selenite F broth, following the guidelines set by the Clinical and Laboratory Standards Institute for antimicrobial testing. In terms of interpretation, a stool culture was categorized as "negative" when it demonstrated no growth, polymicrobial growth, or the presence of typical intestinal bacteria. Conversely, a stool culture was considered "positive" if it exhibited the growth of a pathogenic bacterium (MDR or non-MDR). Positive stool cultures underwent further evaluation for antibiotic sensitivity. Typical intestinal bacterium in the study was defined as bacteria commonly found in the intestinal flora, which is not associated with disease or infection and is not likely to be harmful. We performed the Carba NP test to detect carbapenemase production for identifying MDR bacteria. Resistance genotyping was not performed using molecular tests like polymerase chain reaction (PCR) or next-generation sequencing (NGS).

Blood cultures were collected as clinically indicated by the attending clinician during the induction chemotherapy phase. The BacT/Alert automated system was used for blood cultures.[19] The VITEK 2 system was used for antibiotic susceptibility testing.[20] Whenever deemed necessary, samples of urine, sputum, and other body fluids were submitted as components of the infection workup.

MDR bacteria were characterized as those exhibiting resistance or intermediate susceptibility to at least one antimicrobial drug in three out of five groups defined by the Centers for Disease Control and Prevention National Healthcare Safety Network (CDC-NHSN) criteria.[21] These categories include cephalosporins, fluoroquinolones, β-lactam/β-lactamase inhibitor combinations, and carbapenems. MDR *Enterococcus faecalis* was defined by nonsusceptibility to at least one agent in three or more of the following antimicrobial categories: penicillins, carbapenems, streptogramins, glycopeptides, aminoglycosides, oxazolidinones, fluoroquinolones, lipopeptides, glycylcyclines, and tetracycline.[22]

All patients were treated for febrile neutropenia and major and minor infections according to the hospital's antibiotic policy and culture reports. Patients were hospitalized until the completion of induction chemotherapy. Patients were monitored daily throughout the study period, with a study team member updating their clinical information daily.

Statistical Plan

A sample size of 200 was determined based on the primary aim of the RCT on the neutropenic diet. Descriptive statistics were used to summarize the demographic and clinical data. Categorical variables were compared using the χ^2 or Fisher's exact test. Outcomes were independently analyzed for day 1 and 15 stool cultures. Patients with missing stool culture data were excluded from the analysis. To assess the impact of covariates on MDR stool culture positivity on days 1 and 15, a multivariate logistic regression model was applied. A two-tailed significance threshold of 0.05 was set, and statistical analyses were conducted using SPSS version 17 (IBM).

Ethics

The trial received approval from the Cancer Institute Ethics Committee (reference: IEC/2017/17, dated December 21, 2017) and was prospectively registered with the Clinical Trials Registry of India (registration number: 2018–01–011418). All procedures conducted in the study involving human participants adhered to the ethical guidelines established by the institutional and/or national research committee, in line with the 1964 Helsinki Declaration and its subsequent revisions or equivalent ethical principles.

Results

A total of 200 patients were enrolled between January 2018 and March 2020. On day 1, stool samples were collected from 193 patients; on day 15, samples were obtained from 185 patients. The patient demographic features and clinical and laboratory data are provided in ►**Table 1**. ►**Table 2** presents the organisms isolated from stool and blood cultures on days 1 and 15, while ►**Table 3** provides the antibiotic sensitivity patterns of these isolated organisms.

Day 1 Stool Cultures

Among the 193 patients who gave stool culture samples on day 1, 69 (35.7%) patients had a positive stool culture, all of which were MDR, and 124 (64.2%) patients had a negative stool culture (►**Table 1**). Major infections were reported in 21 patients (30.4%) with positive stool cultures and in 33 (26.6%) patients with negative stool cultures ($p = 0.57$). Seven patients with positive stool cultures (10.1%) and seven (5.6%) patients with negative stool cultures on day 1 died during the study period ($p = 0.24$). Out of the seven deaths in the stool culture–positive patients, five were due to sepsis, while the rest of the deaths were attributed to progressive disease. Similarly, out of the seven deaths in the stool culture–negative patients, six were due to sepsis, and the

Table 1 Demographic features

Characteristic	$N = 200$ (%)
Median age, y (range)	13 (1–60)
Sex	
Male	122 (61)
Female	78 (39)
Age	
Pediatric (<18 y)	131 (66)
Adult	69 (34)
Diagnosis	
ALL	162 (81)
Pediatric	112 (69)
Adult	50 (31)
AML	38 (19)
Pediatric	19 (50)
Adult	19 (50)
Diet	
Regular	98 (49)
Neutropenic	102 (51)
Central venous catheter	38 (19)
Day 1 stool culture, $n = 193$	
MDR positive total	69 (36)
Gram positive	34 (49)
Gram negative	34 (49)
Gram positive + negative	1 (1.5)
Non-MDR-positive total	0
Gram positive	0
Gram negative	0
Negative	124 (64)
Day 15 stool culture, $n = 185$	
MDR-positive total	67 (36)
Gram positive	24 (36)
Gram negative	40 (60)
Gram positive + negative	3 (4.5)
Non-MDR-positive total	1 (1.5)
Gram positive	0
Gram negative	1
Negative	117 (64)
Blood culture	
MDR-positive total	3
Gram positive	0
Gram negative	3 (100)
Non-MDR-positive total	11
Gram positive	3 (27)
Gram negative	8 (73)
Fungal positive	1
Fungal negative	185

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDR, multidrug resistant.

remaining one was due to progressive disease. Blood cultures during the study period were positive in 5 patients (7.2%) with stool culture–positive results and 10 patients (8%) with negative stool cultures ($p = 0.83$). Among the five positive blood cultures in the stool culture–positive group, only one patient had similar organisms in both stool and blood (MDR *Escherichia coli*).

Day 1 stool culture positivity for MDR bacteria correlated significantly with the use of third-line antibiotics ($p = 0.03$) and not achieving remission at the end of induction ($p < 0.001$) (►**Table 4**). On multivariate logistic regression, only the use of third-line antibiotics ($p = 0.003$) significantly correlated with a positive day 1 stool culture.

Day 15 Stool Cultures

Among the 185 patients who gave stool culture samples on day 15, 68 (36.7%) patients had positive stool cultures, 67 (36.2%) of them were positive for MDR bacteria, and 117 (63.2%) patients had a negative stool culture. Major infections were reported in 33 patients (48.5%) with positive stool cultures and 20 (17.1%) patients with negative stool cultures ($p = 0.00001$). Seven (10.2%) patients, each with positive stool cultures, and one (0.8%) patient with negative stool cultures on day 15 died during the study period ($p = 0.0006$). Six out of seven deaths in stool culture–positive patients and one death in stool culture–negative patients were due to sepsis. Blood cultures during the study period were positive in 10 patients (14.7%) in stool culture–positive patients and in 4 patients (2.5%) with negative stool cultures ($p = 0.01$). Two patients with positive stool cultures also had positive blood cultures with a similar organism, which was MDR *E. coli*.

Thirty-five out of the 124 patients with a negative stool culture on day 1 had a positive stool culture on day 15, among whom 17 patients had major infections, 4 had positive blood cultures, and 2 died. Eight patients who had positive stool cultures on day 1 could not be sampled on day 15 as two died, two defaulted treatment, and four could not give samples. Five patients who did not provide stool cultures on day 1 had day 15 stool culture positivity. Thirty-three of the 69 patients with positive stool cultures on day 1 had a negative stool culture on day 15.

Day 15 stool culture positivity for MDR bacteria correlated significantly with increased incidence of febrile neutropenia ($p < 0.001$), mechanical ventilation ($p = 0.021$), inotropic support ($p = 0.001$), use of third-line antibiotics ($p < 0.001$), AML diagnosis ($p < 0.001$), not achieving remission at the end of induction ($p < 0.001$), hypoalbuminemia ($p = 0.024$), and mortality ($p = 0.006$; ►**Table 4**). On multivariate logistic regression, hypoalbuminemia ($p = 0.02$) correlated significantly with a positive day 15 stool culture. None of the patients who underwent stool testing for *C. difficile* had a positive result.

Discussion

The present study aimed to investigate the prevalence of MDR bacteria in stool cultures of patients with acute leukemia undergoing induction chemotherapy and its correlation with patient outcomes. The results of this prospective study reveal important insights into the association between MDR bacterial colonization and clinical outcomes in this high-risk patient population.

The findings of this study demonstrate that a significant proportion of patients with acute leukemia exhibited positive stool cultures for MDR bacteria on both day 1 and day 15 of induction chemotherapy. Notably, the prevalence of MDR bacteria in stool cultures remained consistent at around

Table 2 Organisms isolated from stool cultures and blood cultures

Organisms	Day 1 stool culture	Day 15 stool culture	Blood culture
MDR *Escherichia coli*	21 (30%)	23 (34%)	2
MDR *Enterococcus faecalis*	10 (14%)	5 (7%)	0
MDR *Klebsiella pneumonia*	12 (17%)	17 (25%)	1
MDR *Enterococcus faecium*	22 (32%)	17 (25%)	0
MDR *E. faecium* + MDR *E. coli*	1 (1%)	3 (5%)	0
MDR *Klebsiella* + MDR *E. coli*	1 (1%)	0	0
Vancomycin-resistant *E. faecium*	2 (3%)	2 (3%)	0
E. coli	0	1 (1%)	1
Pseudomonas aeruginosa	0	0	3
Candida albicans	0	0	1
Alcaligenes faecalis	0	0	1
K. pneumonia	0	0	2
E. faecalis	0	0	1
Staphylococcus aureus	0	0	3

Abbreviation: MDR, multidrug resistant.

35.7% on day 1 and 36.7% on day 15, with MDR *E. coli* and MDR *Enterococcus faecium* being the predominant organisms isolated. This high prevalence of MDR colonization underscores the vulnerability of patients with acute leukemia to microbial infections during periods of immunosuppression, which is further compounded by the emergent challenge of antibiotic resistance.

We have chosen, arbitrarily, to collect stool samples on day 15 of induction for the following reasons: patients are midway through induction and are usually in the nadir phase of neutropenia, making them susceptible to infections; the majority would have attained disease remission, at least clearance of blasts in the peripheral blood; the stool microbial flora would have had sufficient time to alter during hospitalization; and most deaths due to progressive disease at our center occur in the first 2 weeks of induction.

The analysis of patient outcomes in relation to stool culture results revealed several significant associations. First, the presence of positive stool cultures on day 15 was strongly correlated with an increased incidence of major infections. This finding highlights the clinical relevance of MDR bacterial colonization in stool cultures as a potential predictor of infection risk. Moreover, positive day 15 stool cultures were significantly associated with other adverse outcomes, including positive blood cultures, mortality, febrile neutropenia, hypoalbuminemia, the need for inotropic support, failure to attain remission, and a diagnosis of AML. These associations substantiate the notion that MDR colonization in the gastrointestinal tract has broader implications beyond localized infections and can contribute to systemic complications and poorer clinical trajectories.

Importantly, the lack of significant correlation between day 1 stool culture results and the outcomes suggests that early colonization might not be as indicative of adverse clinical outcomes as colonization persisting into day 15. This temporal distinction might reflect the dynamics of bacterial colonization during induction chemotherapy and could offer insights into the evolving risk profile of patients over time.

A retrospective study from Tata Memorial Hospital in Mumbai reported a stool MDR colonization (rectal swab) rate of 62.1% among 1,094 patients younger than 15 years with hematolymphoid malignancies at the time of diagnosis.[13] Bloodstream infections were documented in 62.7% of patients with positive MDR bacteria in stool cultures, while only 10.6% of patients with negative stool cultures had a positive blood culture.[13] The rectal swab at baseline demonstrated a sensitivity and specificity of 90.6 and 59.4%, respectively, in predicting bloodstream infections.[13] Patients with MDR-positive stool cultures at baseline exhibited a significantly higher incidence of intensive care unit admissions and mortality.[13]

A retrospective study conducted at our institution, focusing on pediatric patients with acute leukemia, reported a prevalence of 50% for MDR stool culture positivity at the time of diagnosis. MDR stool colonization at baseline was associated with a significantly higher rate of blood culture positivity and mortality.[12]

In contrast to the Mumbai study and our previous retrospective study, we did not observe a significant correlation between stool colonization with MDR bacteria at baseline and blood culture positivity or mortality in the current study. However, positive MDR stool colonization at baseline was significantly associated with not achieving disease remission at the end of the induction period and increased use of third-line antibiotics in the current study.

Gundluru et al from Chandigarh prospectively studied stool culture surveillance at baseline and 2 months into chemotherapy in 79 patients with acute leukemia younger than 12 years.[23] The stool culture colonization with MDR

Table 3 Sensitivity pattern of organisms to antibiotics

Day 1 stool c/s	Cefoperazone/ sulbactam	Amikacin	Piperacillin/ tazobactam	Meropenem	Teicoplanin	Tigecycline	Colistin	Linezolid	Vancomycin
MDR *Escherichia coli*	0	8%	0	0	0	100%	100%	NR	NR
MDR *Enterococcus faecalis*	0	0	0	0	100%	100%	0	100%	100%
MDR *Klebsiella*	0	15%	0	0	0	100%	100%	NR	NR
MDR *E. faecium*	0	0	0	0	100%	100%	NR	100%	100%
VR *E. faecium*	0	0	0	0	0	100%	NR	100%	0
Day 15 stool c/s	**Cefoperazone/ sulbactam**	**Amikacin**	**Piperacillin/ tazobactam**	**Meropenem**	**Teicoplanin**	**Tigecycline**	**Colistin**	**Linezolid**	**Vancomycin**
MDR *E. coli*	0	11%	0	0	0	100%	100%	0	0
MDR *E. faecalis*	0	0	0	0	100%	100%	0	100%	100%
MDR *Klebsiella*	0	16%	0	0	0	100%	100%	0	0
MDR *E. faecium*	0	0	0	0	100%	100%	100%	100%	100%
VR *E. faecium*	0	NR	0	0	0	100%	NR	100%	0

Abbreviations: C/S, culture and sensitivity; MDR, multidrug resistant; NR, not reported in culture sensitivity; VR, vancomycin resistant.
Note: 100% indicates all bacterial cultures were sensitive to the antibiotic and 0% indicates none of the bacterial cultures were sensitive to the antibiotic.

bacteria at baseline and 2 months was 17.5 and 22.5%, respectively.[23] Stool MDR colonization at baseline and 2 months did not predict sepsis, bloodstream infection, or mortality in the study.[23]

The dichotomy in the literature regarding the impact of stool surveillance culture on outcomes could be due to regional differences, different age groups of the population studied (pediatric vs. adults), and the microbial profile at the respective institutions. Environment, diet, nutritional status, socioeconomic status, and the community prevalence of MDR bacteria in food and water sources can also be responsible for the regional variation in gut bacteria colonization.[24]

Thirty-three out of the 69 patients who had positive stool cultures on day 1 were found to have negative stool cultures on day 15. The reasons for this shift in stool culture status during chemotherapy remain unclear. Chemotherapy is known to alter the gut microbiome, and administering antibiotics, which can significantly impact gut flora, may also play a role.[25]

The study results prompt consideration of the potential clinical implications of surveillance for MDR colonization in stool cultures during acute leukemia induction. Detecting early patients at high risk of poor outcomes, as indicated by persistent MDR colonization on day 15, could inform targeted antimicrobial interventions, thereby mitigating the progression of infections and associated complications. Targeted interventions include antibiotic de-escalation strategy, barrier nursing for MDR stool culture colonized patients, and gut decontamination. Whether a de-escalation strategy of initiating third-line antibiotics in patients who develop features of infection or sepsis with a day 15 positive stool culture for MDR bacteria or gut decontamination reduces morbidity and mortality needs to be evaluated.[26,27] Furthermore, these findings underscore the need for vigilant monitoring of infection-related parameters and microbiological data in patients displaying positive stool cultures, particularly at later stages of induction.

This study's limitations include its focus on acute leukemia patients at a single center only during the induction period, which could restrict the generalization of the findings. Additionally, we did not delve into the mechanisms underlying the association between MDR colonization and adverse outcomes, warranting further research to elucidate the causal pathways. Patients with infections at diagnosis were excluded from the neutropenic diet RCT inclusion criteria, which would have led to a bias in our results.

Conclusion

This prospective study highlights the substantial prevalence of MDR bacterial colonization in stool cultures of patients undergoing induction chemotherapy for acute leukemia. Importantly, persistent MDR colonization in stool cultures on day 15 is closely linked to increased risks of infections, mortality, and other adverse clinical outcomes. These findings advocate for the inclusion of stool culture surveillance as a valuable tool in risk stratification and guiding clinical decision-making for this vulnerable patient population.

Table 4 Clinical outcomes based on stool culture on days 1 and 15

	Day 1			Day 15		
Characteristic	**Stool MDR bacteria positive ($N=69$)**	**Stool MDR bacteria negative ($N=124$)**	***p*-value**	**Stool MDR bacteria positive ($N=67$)**	**Stool MDR bacteria negative ($N=118$)**	***p*-value**
Infections (both major and minor)						
Yes No	27 42	45 79	0.69	39 28	32 86	0.00002
Major infections						
Yes No	21 48	33 91	0.57	33 34	20 98	0.00001
Induction mortality						
Yes No	7 62	7 117	0.24	7 60	1 117	0.0067
Blood culture						
Positive Negative	5 64	10 114	0.83	10 57	4 114	0.01
Pneumonia						
Yes No	14 55	17 107	0.23	17 50	12 106	0.006
Febrile neutropenia						
Yes No	25 44	43 81	0.82	40 27	26 92	0.00001
Ventilation						
Yes No	07 62	6 118	0.15	7 60	2 116	0.021
Inotropes						
Yes No	13 56	16 108	0.26	18 49	7 111	0.0006
Use of third-line antibiotics						
Yes No	23 46	24 100	0.03	31 36	14 104	0.00001
Age						
Pediatric Adult	50 19	76 48	0.1181	44 23	79 39	0.8597
Sex						
Male Female	44 25	73 51	0.5045	43 24	72 46	0.669
Diagnosis						
ALL AML	53 16	102 22	0.3617	44 23	106 12	0.00055
Diet						
Regular Neutropenic	40 29	56 68	0.8804	34 33	57 61	0.749
Complete remission						
Yes No	59 10	109 15	0.0001	53 14	113 5	0.00033
Serum albumin (g/dL)						
≤ 3.5 > 3.5	28 41	52 72	0.8546	21 46	57 61	0.0247

(*Continued*)

Table 4 (*Continued*)

	Day 1			Day 15		
Characteristic	Stool MDR bacteria positive ($N = 69$)	Stool MDR bacteria negative ($N = 124$)	*p*-value	Stool MDR bacteria positive ($N = 67$)	Stool MDR bacteria negative ($N = 118$)	*p*-value
Day 15 stool MDR						
Yes No Not sent	28 35 6	35 83 6	0.08			

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDR, multidrug resistant.

Further research is warranted to establish the underlying mechanisms and to explore the potential interventions that can be informed by such surveillance.

Authors' Contributions

Data collection was performed by M.C., V.R., V.V., P.B.B.L., D.G., J.P.K., and P.G. The data analysis was performed by V.R. and S.R. The management of patients in the trial was handled by V.R., D.G., P.B.B.L., J.P.K., and P.G.

Data Availability Statement

The data cannot be shared due to patient privacy and ethical issues.

Presentation

This article was presented as an oral presentation at the SIOP 2023 Annual Meeting and poster presentation at the MASCC 2023 Annual Meeting.

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Conflict of Interest

None declared.

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