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RESEARCH ARTICLE

RISK FACTORS FOR BLOOD STREAM INFECTIONS IN PATIENTS WITH CHILDHOOD LEUKEMIA AT A TERTIARY CARE CENTRE IN SOUTH INDIA.

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Abstract

Objective: To analyze risk factors for Blood Stream Infections (bsis) in children with leukemia and determine if liberalized diets posed a higher risk compared to restrictive neutropenic diets.
Design: Cross-sectional observational study
Setting: Tertiary care hospital in South India. Participants: The study included 169 admissions of 41 children aged 1-18 years with Acute Leukemia (ALL and AML) during 2021-2022.
Results: Among the participants, 35.8% experienced bsis during episod es of febrile neutropenia. Gram-negative bacteria were isolated in 14 cases, and Gram-positive cocci in 5. Notably, all Multi-Drug Resistant (MDR) isolates were found in patients with hospital stays exceeding 15 days. Significant risk factors identified in the study included**:** •Hospital stay exceeding 15 days •Presence of a central venous catheter •Severe neutropenia (absolute neutrophil count <500/ul) •Transfer to the ICU The type of hospital room, dietary choices (including raw fruits, vegeta bles, poultry, fish, meat, curd), constipation, mucositis, and the duration of catheter placement did not significantly affect BSI risk. Furthermore, serum Procalcitonin levels during febrile neutropenia were not correlate d with the occurrence of bsis.
Conclusion: The study concluded that hospital stays exceeding 15 days, the presence of central venous catheters, ICU transfers, and severe neutropenia were independent risk factors for bsis in children with leukemia. Additionally, the risk of MDR bsis increased with prolonged hospitalization. Importantly, the study suggested that liberal diets with safe food handling practices did not appear to increase BSI risk compared to restrictive neutropenic diets. Therefore, the emphasis should be on safe food handling for patients undergoing chemotherapy, rather than imposing strict dietary restrictions

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Introduction:-

Acute leukemia, the most prevalent childhood hematological malignancy, accounts for 35% of pediatric cancers. Despite improved antimicrobial and chemotherapy practices reducing disease severity and enhancing survival rates, bloodstream infections remain a leading cause of severe complications and mortality in hemato-oncology patients.[1-3] In the past, gram-positive microorganisms were the common culprits of bsis in leukemic patients, but recent trends show a rise in gram-negative pathogens in many centers.

Understanding local pathogen prevalence is crucial for effective management. Despite prophylactic measures, bloodstream infections remain a critical threat during chemotherapy and can be fatal.[2,4,5]In the current era marked by MDR-bacterial infections, there is a scarcity of data concerning the epidemiology, outcomes, and mortality risk factors for BSI in this patient category. Such insights are vital for enhancing empirical treatment and potential antibiotic prophylaxis. Understanding this epidemiology is critical for managing febrile neutropenia in acute leukemia patients.[6]

This study aims to enhance care and survival in high-risk leukemia patients by identifying BSI risk factors during chemotherapy. It will investigate clinical manifestations, laboratory data, systemic complications, isolated microorganisms in blood cultures during febrile episodes, antimicrobial susceptibility, and clinical outcomes, focusing on pediatric leukemia patients.

Neutropenic diets, traditionally emphasizing "low-bacteria" well-cooked foods, have been the standard for vulnerable patients due to gut mucosal vulnerability. Yet, there's a lack of clinical trial data assessing their efficacy. This study seeks to determine if these restrictive diets are more effective in infection prevention than liberalized diets.[7-10.]

Materials and Methods:-

Setting:-

Children admitted in Pediatric and Hemato-oncology departments of a tertiary care hospital in Kochi (Amrita Institute of Medical Sciences) during the period January 2021 to June 2022.

Study Design:

Hospital based prospective observational study.

Inclusion criteria:

All Children in the age group of 1year-18 years of age admitted in Pediatric and Hemato-oncology departments with acute leukemia.

Exclusion criteria:

1. Lymphoma and other non hematological malignancies.
2. One positive blood culture with non- pathogenic microorganisms of normal skin flora.

Sample size:

Based on the proportion of blood stream infection among those with absence of neutropenia (13.3%) and relative risk of 3.09 observed from the pilot study result conducted in 32 samples, and with 20% relative precision and 99% confidence the minimum number of sample sizes comes around 39 each group. Totalling to 78 samples.

Methodology:-

After Institutional research board approval, data was collected from children between 1 and 18 years with Acute leukemia treated at our institution from January 2021 to June 2022.

1. Clinical presentations (ECOG score)
2. Laboratory data
3. CBC(ANC) were collected at time of admission for all patients.
4. Within one hour of fever, blood was drawn for culture from peripheral vein, central line (if present), along with CBC and serum procalcitonin.
5. Microorganisms isolated and its antimicrobial susceptibility patterns
6. Length of their stay, whether the stay was in ward or single room,
7. Admission count
8. Presence of central line and its duration, breach in dressing,

9. Other complications increasing susceptibility for infection (constipation Diarrhea and mucositis) were compiled
10. Diet recorded by direct interview of parents.

Methods of statistical analysis:-

Statistical analysis was done using IBM SPSS 20. (SPSS Inc, Chicago, USA). For all the continuous variables, the results are represented as Mean±SD, and for categorical variables as frequency and percentage. To obtain the association of categorical variables, chi square test was applied. To compare the mean difference of numerical variables between groups, Mann Whitney U test was applied. A p value of <0.05 was considered as statistically significant.

Results :-

The study sample consisted of 43 children with Acute Leukemia of age 1-18 years, of which 30(69.7%) were in the age group of </=10 years. There were 27 male patients(62.8%).Twenty six children(60%) had Acute lymphoblastic Leukemia(ALL) and 17(40 %),Acute Myeloid Leukemia (AML).A total of 169 admissions during one year with 53 (31.3%) events of documented febrile neutropenia were present.

BSI was documented in 35.8% of Febrile neutropenia admissions(n=19).Of these, 15 patients had (78.9%) Gram Negative Bacilli(GNB) and 4(21.1%) had Gram Positive Cocci(GPC)isolated.Out of 19(35.8%) documented bsis, 14 were Gram Negative Bacteria and 5 Gram Positive Cocci. All multidrug Resistant isolates were detected in patients with hospital stay more than 15 days (n=4;p:<0.001).

The BSI isolation was comparable in the ward and single room (p=0.96).Intake of raw fruits and vegetables(P:0.97),poultry(P:1.0),fish(P:1.0),meat(0.917),curd(P:0.7)was not a predisposing factor for BSI.Constipation(p=0.925),Mucositis(p=0.48)were not predisposing for bsis. Number of days of Peripherally inserted Central catheter insitu was not significant(P:0.58).Serum Procalcitonin value during febrile neutropenia was not correlating with bsis(p=0.21).

Table 1. Significant Risk factors for BSI in Acute Leukemia.

Risk factors	Number of patients	Number of BSI	P value
Hospital stay > 15 days	42	14	<0.001
Severe neutropenia (ANC< 500)	36	8	0.045
Presence of Central venous catheter(CVC)	17	10	<0.001
ICU Shift	9	4	0.007

Hospital stay lasting more than 15 days, Absolute neutrophil count(ANC)< 500, Presence of Central venous catheters and shift to ICU were identified as independent significant risk factors for blood stream infection in our cohort.

Discussion:-

Our study cohort showed 19(35.8%) documented blood stream infections in 53 febrile neutropenia admissions of a total of 169 admissions in 43 patients aged 1-18 years being treated for acute leukemia from our institution during January 2021 to June2022.

Table 2. Risk Factors

Risk factors	N(%)
1)Comparison of BSI with Total Number of Hospital Days During Admission.(p :<0.001)	
<7days	3(15.8)
7-15 days	2(10.5)
>15 days	14(73.7)
2)Comparison of incidence of BSI with Neutrophil status during BSI isolation. (p :0.045)	
No neutropenia	9(47.4)
Mild neutropenia	1(5.3)
Moderate neutropenia	1(5.3)
Severe neutropenia	8(42.1)
3)Comparison of Incidence of BSI with Number of Days of Severe Neutropenia. (p :0.320)	
0-5 days	15(78.9)
6-10 days	2(10.5)
>11 days	2(10.5)
4)Comparison of BSI with ICU stay. (p :<0.007)	
ICU stay absent	15(78.9)
ICU stay present	4(21.1)
5)Comparison of incidence of BSI in those with PICC line/central line. (p :<0.001)	
PICC line Present	10(52.6)
PICC line absent	9(47.3)
6)Comparison of BSI with number of days of PICC line/central line insitu. (p :0.589)	
0-50 days	3(16.7)
50-150 days	8(44.4)
>150 days	7(38.9)
7)Comparison of BSI Isolation in ward and Single room. (p :0.96)	
Ward	11(57.9)
Single room	8(42.1)
8)Comparison of BSI with Intake raw fruits and Vegetables. (p :0.974)	
Present	5(73.7)
Absent	14(26.3)
9)Comparison of BSI with Intake of cooked Fish. (p :1.000)	
Present	4(21.1)
Absent	15(78.9)

10)Comparison of BSI with Intake of cooked poultry. (p :1.000)	
Present	2(10.5)
Absent	17(89.5)
11)Comparison of BSI with Intake of cooked Meat. (p :0.997)	
Present	3(15.8)
Absent	16(84.2)
12)Comparison of BSI with Intake of curd. (p :0.704)	
Present	9(47.4)
Absent	10(52.6)
13)Comparison of BSI with mucositis. (p :0.481)	
Present	1(5.3)
Absent	18(94.7)
14)Comparison of BSI with Day 1 serum Procalcitonin Levels during febrile neutropenia. (p :0.215)	
Serum Procalcitonin >/= 1	5(31.3)
Serum Procalcitonin <1	11(68.8)
15)Distribution mortality status among those with BSI.	
Alive	18(94.7)
Dead	1(5.2)

The dietary risk factors analysed for blood stream infections in children with acute leukemia , whether they followed a liberalised diet with raw fruits and vegetables , curd, cooked non vegetarian food or a strict neutropenic diet showed no significant difference. Eventhough very severe neutropenia was a significant risk factor for BSI in our cohort (p value: 0.045), the duration was not.

Procalcitonin values at the start of febrile neutropenia were not found to be significant. Presence of mucositis or the duration of PICC line in-situ were found not to be significant.

The commonest isolated gram-negative pathogen was Burkholderia cepacia (n=4;21%) and gram-positive microorganism was Streptococcus Species(n=2;10.5%). Burkholderia was the most common species identified in blood culture (n=5, 26.3%).
Multidrug Resistant Bacteria was isolated in 21%(n=4) out of total 19 BSI isolates.
The antimicrobial susceptibility of Gram negative organisms revealed that 66.6 % (n=2) of Klebsiella species were multidrug resistant.

Ecoli and Enterobacter cloacae Complex species were multidrug resistant in 50%(n=1) isolates respectively.Burkholderia,Acinetobacter, Stenotrophomonas maltophila, Sphingomonas paucimobilis and all 4 (21.1%)Gram positive Organisms being sensitive Isolates.

ORGANISM	Frequency (n ,%) 19,100	Percentage	Sensitive(n)	MDR(n)
Gram Negative	**15**	**78.9**		
Burkholderiacepacia	4	21%	4	0
Burkholderia Gladioli	1	5.2%	1	0
Ecoli	2	10.5%	1	1
Klebsiella Pneumonia	3	15.7%	1	2
Acinetobacter	1	5.2%	1	0
Enterobacter cloacae complex	2	10.5%	1	1
Stenotrophomonous Maltophila	1	5.2%	1	0
Sphingomonas paucimobilis	1	5.2%	0	0
Gram Positive	**4**	**21.1%**		
Coagulase negative staphylococci	1	5.2%		
Streptococcus Species	2	10.5%		
Bacillus	1	5.2%		

Table 3. Distribution of isolated microorganisms from the blood stream.

BSI was documented in 19 febrile neutropenia admissions, of which 15 were Gram negative isolates and 4,Gram positive isolates. All four Multidrug resistant isolates were Gram Negative. The remaining gram negative isolates and all gram positive isolates were antibiotic sensitive.

The hospital stay during each admission among 169 admissions was divided into <7 days,7-15 days and more than 15 days for ease of analysis. While comparing BSI with total number of hospital days during each admission in our study,14 (73.6%) out of 19 patients with BSI had hospital stay more than 15 days which is statistically significant (p = <0.001).

In our study the median (Q1-Q3) total number of hospital days in patients with febrile neutropenia , but no blood stream isolates was 7days (5-11).The median number of days of hospitalisation in patients with Antibiotic sensitive isolate was 33 days (11-45). MDR isolates were detected in patients hospitalised for a median period of 17.5days (25.5-52.5).This finding was found to be statistically significant (p<0.001).All the 4 MDR isolates were only in patients with hospital stay more than 15 days.

Neutropenia is graded as Mild with Absolute neutrophil count (ANC) of <1500, Moderate (ANC <1000), Severe Neutropenia(ANC<500). While comparing the of incidence of BSI with neutropenic status during BSI isolation,8 (42.1%) out of 19 admissions with BSI occurred when the patients had severe neutropenia, which was found to be statistically significant (p = 0.045).

Admissions were subdivided into </=5 days,6-10 days and more than 11 days of severe neutropenia. The comparison of the BSI with total number of days of severe neutropenia was not found to be statistically significant (p = 0.320).

It was found out that 4 (44.4%) out of total 9 admissions with ICU stay had BSI. This was found to be statistically significant (p = 0.007). However, it may be possible that the BSI leading to septic shock may have led to the ICU shift.

While comparing the incidence of BSI in those with PICC line/central line,10(52.6%) out of 19 admissions with BSI occurred when they had PICC line insitu. The comparison of incidence of BSI in those with PICC line/central line was found to be statistically significant (p <0.001). However, prolonged PICC line insitu period did not significantly increase the risk of BSI (p = 0.589).

Association of Breach in PICC line dressing and the incidence of BSI was also studied. Only one child had breach in central line dressing during our study frame and that child did not have BSI. (p value=0.58).

Reported rates of PICC-related bloodstream infection (BSI) have ranged from 0.4 to 0.8 per 1,000 catheter-days[11-16]. However, most of the previously reported studies were retrospective, and nearly all were conducted in the outpatient setting. Thus, the risk of PICC-related BSI in hospitalized patients is unclear [17]. Our study design was prospective and we found 11(61.1%) BSI per 1000 catheter days.

During each admission, the disability score of the child was calculated using ECOG score. Of admissions with BSI 89.5% (n=17) had ECOG score of 1 & 2 not found to be statistically significant (p = 0.474).
The BSI isolation was comparable in the ward and single room. (p = 0.96).

We followed Food and Drug Administration approved food safety guidelines (fsgs) while handling regular diet from 2009.Intake of raw fruits and vegetables(P:0.974), poultry(P:1.0), fish(P:1.0), meat (0.997), curd(P:0.704) with safe food handling practices was not a predisposing factor for BSI.

Trauma to mucosa aiding the bacteria to invade and cause BSI in children with leukemia was also studied. Constipation(p=0.925), Mucositis(p=0.48) were not predisposing for bsis in our study.
Association of BSI with Laboratory markers for infection such as Serum procalcitonin levels studied was not found to be statistically significant (p=0.215). Serum Procalcitonin value during febrile neutropenia was not correlating with bsis.

Among children with documented BSI,one child(5.2%) died due to disease relapse during our study period of one year.
The identification of risk factors for poor outcomes may help in devising protocols for providing targeted therapy based on risk criteria and thus help to reduce the cost of supportive care as well as reduce the adverse effects of antibiotic therapy. Prospective studies of febrile neutropenia among children enrolled in large cooperative trials may be beneficial in evaluating these risk factors further.

Conclusions:-

1)Hospital stay more than 15 days, presence of Central Venous line , transfer to ICU and severe neutropenia were found to be independent risk factors for BSI in our study.
2)Risk of MDR bsis increased with the rise in cumulative days of hospitalisation.
3)Liberalised diets with safe food handling practices did not seem to increase the risk of BSI, hence safe food handling should be prioritized over a restricted neutropenic diet for vulnerable patients.
4)Burkholderia species 26.3% (n=5) was the most common identified in blood culture.
5)Incidence of Multidrug Resistant Bacteremia in children with acute leukemia in our study was 21%(n=4) out of total 19 BSI isolates.

What is Already Known?

Patients with leukemia are at high risk of Blood stream Infections during neutropenia and mucositis.

What this Study Adds?

Longstanding PICC lines/central lines is not a risk factor for BSI if maintained hygienically with proper regular change of dressing.

Liberalised diets with safe food handling practices is not a risk factor for BSI in children with Acute leukemia on chemotherapy.

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