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Sri Ramachandra Journal of Health Sciences

Original Article

Profile of febrile neutropenia in childhood cancer patients and the clinical utility of procalcitonin and C-reactive protein in identifying severe infections

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ABSTRACT

Objectives: Febrile neutropenia (FN) is a medical emergency requiring prompt diagnosis of underlying infection and early administration of antibiotics. Updates about the spectrum and resistance patterns of pathogens isolated are essential for the successful management of FN.

Materials and Methods: The purpose of this study was to describe the clinical profile, outcome, infective pattern and the clinical utility of procalcitonin (PCT) and C-reactive protein (CRP) in febrile neutropenic children, admitted to our center between 2017 and 2019. Children aged <18 years with confirmed malignancy and FN were enrolled in the study.

Results: The study population was 54 patients. A total of 90 episodes of FN were noted. Hematologic malignancies accounted for 74% of the cases. Only 15 (16.6%) of the study population had clinical foci of infection. Overall culture positivity was 20 %. Among the children with central venous catheter, 21.8% had culture positivity. The most common bacterial isolates were Gram-negative bacilli, with *Acinetobacter* being the most common pathogen. The overall mortality rate was 5.5%. Among 18 culture positive cases, CRP was positive in 10 (55.5 %) cases and PCT was positive in 12 (66.6 %) cases.

Conclusion: Gram-negative organisms are the major infective agents in developing countries. Central venous catheter remains the foci of infection in these patients. Raised CRP and PCT are predictors of complications during FN.

Keywords: Febrile neutropenia, Childhood cancer, C-reactive protein, Procalcitonin

INTRODUCTION

Chemotherapy-related neutropenia causing infections is a major concern in pediatric malignancies. Febrile neutropenia (FN) is a medical emergency. The mortality rate among febrile neutropenic children is reported as 0.7–3.9% in developed countries.[1,2] In neutropenic patients, serious infections can manifest with minimal symptoms and fever can be the only sign of infection. In 1970s, Gram-negative agents were more frequently observed followed by Gram-positive organisms in 1990s and recently, there is again an increase in the frequency of Gram-negative organisms being isolated in febrile neutropenic patients.[3-5]

Mortality and morbidity of FN can be significantly reduced by the initiation of appropriate antibiotics at the early stage and hence identifying the causative microorganisms and their antibiotic susceptibility is important. The clinical outcome of a child with FN depends on child's underlying disease, age, duration of the neutropenia, severity of neutropenia, foci of infection, presence of indwelling catheter, duration of indwelling catheter, spectrum of antibiotics usage, and antimicrobial resistance. This study was to describe the clinical profile of FN and to assess the diagnostic utility of C-reactive protein (CRP) and procalcitonin (PCT) in identifying infection.

MATERIAL AND METHODS

Children aged <18 years of age with a malignant condition with an absolute neutrophil count of <1000/mm^3 or expected to decrease to <500 cells/mm^3 during next 48 h admitted between 2017 and 2019 were included in the study. Institutional ethics committee approval was obtained.

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Received: 13 May 2022 **Accepted:** 01 December 2022 **EPub Ahead of Print:** 29 December 2022 **Published:** 03 February 2023 **DOI**: 10.25259/SRJHS_11_2022

Informed consent was obtained from the parents. After relevant history and physical examination, blood samples for complete hemogram, CRP, and serum PCT were collected for everyone. X-ray chest, urine routine, urine culture, and other cultures (e.g., pus and stool) were done when clinically indicated. Blood cultures (two sets of blood culture, 5 mL each one from central line, and the other from peripheral line) were taken and were repeated after 72 h if fever persisted or while stepping up the antibiotics. Computed tomography (CT) scan of paranasal sinuses, CT thorax and abdomen, and serum galactomannan was done for fungal screening in children with prolonged fever after 72 h of appropriate antibiotics or whenever clinically indicated. Invasive fungal infections were classified using the 2002 European Organization for Research and Treatment of Cancer/National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria.

For collecting oropharyngeal swab, the tongue was held down by depressor and with a sweeping motion; the posterior pharyngeal wall and tonsillar pillars were swabbed. For nasopharyngeal swabs, the head was tilted back to 70° and a swab was inserted deep into nostril, rotated, and taken out.

Febrile neutropenic patients were managed as per institutional FN guidelines consistent with IDSA recommendations. For all febrile neutropenic children who were hemodynamically stable after relevant investigations first-line antibiotics Inj. Piperacillin tazobactam and amikacin was started. But in case of severe mucositis, or risk for staphylococcal infection or previous port/PICC infection, Inj Teicoplanin was started. In case of children with hemodynamic instability Inj. Meropenem and Teicoplanin was started as first-line drug. Anti-viral and antifungals were added in those who were expected to have prolonged severe neutropenia, those with severe oral ulcers and those who were febrile after 72 h of appropriate iv antibiotics.

Statistical methods

Results were analyzed using SPSS version 16. Statistical significance was taken as P <0.05. Descriptive data were expressed as mean ± standard deviation. Qualitative data were analyzed using Chi-square test. Quantitative data were analyzed by Mann–Whitney test.

RESULTS

The demographic details of the study population are shown in [Table 1].

Only 15 (16.6%) had identifiable foci at the time of admission. Two of them were identified to have dengue fever after laboratory confirmation. Our culture positivity rate was 20%. Among the 18 culture positive cases, 14 (77.7%) of them had central venous catheter. Among the culture positivity in children with central lines, 8 (57.2%) were Gram-negative organisms and 6 (42.9%) were Gram-positive organisms.

Among the total 18 culture positive cases, 11 were gram negative organisms (61%) and 7 were Gram-positive organisms (38.9%). *Acinetobacter* was the commonest Gram-negative bacilli (4; 22.2%), followed by *Klebsiella* (3; 16.7 %), *Escherichia coli* (3; 16.7%), and *Pseudomonas* (1; 5.6%). Among Gram-positive organisms, *Staphylococcus* (4; 22.2% Staph aureus-3, CONS-1) and *Streptococcus* (3; 16.7%; *Streptococcus pneumoniae*-1, *Streptococcus mitis*-1, Group a Streptococci-1) were commonly reported.

Piperacillin tazobactam had the highest *in vitro* efficacy against *E. coli*, Carbapenem resistance was most prevalent among *Klebsiella* and only 56% of *Klebsiella* and 31% of Pseudomonas was sensitive to aminoglycosides. Piperacillin tazobactam and Amikacin were administered as first line antibiotics in 84 (93.3%) patients. Meropenem and Teicoplanin were administered as first-line antibiotics

Table 1: Demographic details of the study population.

Parameters	*n* (%)
Study population	90
Gender	
Male	58 (64)
Female	32 (36)
Age	
<2 years	14 (16)
3–5 years	38 (42)
6–12 years	26 (29)
>12 years	12 (13)
Diagnosis	
Acute leukemias	67 (74.4)
Acute lymphoblastic leukemias	58 (86.5)
Acute myeloid leukemias	9 (13.4)
Lymphomas	14
Hodgkin lymphoma	2 (2.5)
Non-Hodgkin lymphoma	12 (14.8)
Solid tumors	9 (10)
Neuroblastoma	3 (33.3)
Hepatoblastoma	2 (22.2)
Brain tumors	1 (11.1)
Osteosarcoma	2 (22.2)
Ewings sarcoma	1 (11.1)
Central lines	64 (71)
Infusa port	54 (84%)
PICC line	10 (16)
Absolute neutrophil count	
<100	45 (50)
101–500	35 (39)
501–1000	10 (11)
Foci of infection	15 (16.6)
Ear infection	2
Respiratory	6
GIT	1
Skin and soft-tissue	4
Urinary tract	2
Culture positivity	18 (20)
Central venous catheter	14
Peripheral blood	4

in 6 (6.7%) who presented in shock. *Acinetobacter* was sensitive to amikacin, piperacillin tazobactam, ciprofloxacin, levofloxacin, cefaperazone with sulbactum and resistant to ampicillin and cephalexin.

Out of 84 children who received piperacillin-tazobactam and amikacin, 54 (64.2%) children required meropenem and teicoplanin as second-line antibiotics (did not respond to first-line antibiotics/or based on culture reports). Among 90 children, 37 (41.1%) required antifungals (Voriconazole/ Amphotericin) and 36 (40%) children required anti-viral (Acyclovir/oseltamivir).

Details of the children who presented with shock are shown in [Table 2].

A total of 85 (94%) had uneventful course and overall mortality rate was 5.5%. [Table 3] shows the details of the children who died.

Among 18 culture positive cases, CRP was positive in 10 cases and PCT was positive in 12 cases. Sensitivity, specificity, positive predictive value, and negative predictive value of CRP was 55.5%, 50%, 21.7%, 81.8%, and of PCT was 66.6%, 55.5%, 27.2%, and 86.9%, respectively. [Tables 4 and 5] depict the correlation between CRP and PCT and culture positivity.

DISCUSSION

In neutropenic patients, inflammatory response is suppressed and serious infections can manifest with minimal symptoms and the origin of fever is not being identified in more than 50% of the cases despite advanced laboratory techniques.

A total of 90 episodes of FN were observed during the study. The hematological malignancies were associated with more FN episodes than the solid tumors (74% vs. 10%). Among 90 FN episodes, 18 (20%) microbiologically documented infections were noted. No foci of infection could be identified in 73 (81.1%) at the time of admission. This correlates with study by Kapoor *et al.* who has reported that 78% of his study population had no foci of infection.[6] The most common focus of infection among our study population was lower respiratory tract infection 6 (40%) which is similar to study by Kar *et al.* who has reported mucositis (33.4%) and pneumonia (24.7%) as the common clinical foci.[7] Gurlinka *et al.* have reported 14.4 % culture positivity and only case of identifiable foci during 69 episodes of FN.[8]

Blood culture positivity rates were 20% in our study and urine culture was positive in 2 cases. Ghosh *et al.* have reported 30% culture positivity in his study about high risk FN patients.[9] Das *et al.* have reported 19.8% culture positivity in his study.[10] In our study, 17 (94.4 %) had isolated bacterial infection and 1 (5.55%) had polymicrobial sepsis and one had invasive fungal infection.

The mortality rate of our study was 5.5%. Among the 5 children who died, 2 were relapsed ALL and both of them presented in shock, one acute myeloid leukemia had invasive candida infection, three of them had no documented blood culture positivity though CRP and PCT was positive in all the five cases.

Kar *et al.* have reported 13.2% mortality rate in his study.[7] Das *et al.* have reported a mortality rate of 10%.[10] Paganini *et al.* concluded that presence of advanced stage of malignancy, severe associated comorbidities and bacteremia at presentation can be predictors of mortality in children with FN.[11]

Our study proved that in developing country, Gram-negative bacteremia is still more common. The shift toward greater incidence of Gram-negative infections is attributed to increased use of indwelling intravascular catheters and fluoroquinolone and trimethoprim sulfamethoxazole prophylaxis.

Table 2: Details of the children who presented with shock.

S. No.	Diagnosis	Comorbids	C-reactive protein	Procalcitonin	Culture	Indwelling catheter
1.	ALL	Pneumonia	+ve	+ve	*Streptococcus pneumoniae*	Yes
2.	ALL (Relapse)	Nil	+ve	+ve	No growth	No
3.	ALL (Relapse)	AGE	+ve	+ve	*Escherichia coli*	No
4.	ALL	Nil	-ve	+ve	No growth	No
5.	PNET	Nil	+ve	+ve	No growth	Yes
6.	ALL	Nil	-ve	+ve	*Acinetobacter*	Yes

CRP: C-reactive protein

Table 3: Details of the children who died.

S. No.	Diagnosis	Co-morbidity	C-reactive protein	Procalcitonin	Blood culture
1.	ALL	B/L pneumonia	+ve	+ve	*Streptococcus*
2.	ALL (Relapse)	No foci	+ve	+ve	No growth
3.	ALL (Replase)	AGE	+ve	+ve	*Escherichia coli*
4.	PNET	No foci	+ve	+ve	No growth
5.	Acute myeloid leukemia	Candida infection	+ve	+ve	No growth

Table 4: Correlation between CRP and culture positivity.

	Culture		Total	*P*-value
	Positive	Negative		
CRP				
Positive	10 (21.7)	36 (78.3)	46	0.673
Negative	8 (18.2)	36 (81.8)	44	
Total	18 (20)	72 (80)	90	

CRP: C-reactive protein

Table 5: Correlation between procalcitonin and culture positivity.

	Culture		Total	*P*-value
	Positive	Negative		
Procalcitonin				
Positive	12(27.3)	32 (73.7)	44	0.09
Negative	6 (13)	40 (87)	46	
Total	18 (20)	72 (80)	90 (100)	

We had 61% Gram-negative isolates and the most common Gram-negative isolates of our study were *Acinetobacter* (4; 22.2%), followed by *Klebsiella* (3; 16.7%), *E. coli* (3; 16.7%), and pseudomonas (1; 5.6%). Reddy *et al.* had prevalence as high as 92% for Gram-negative isolates with *Klebsiella* (48%) being the most common organism.[12] Ghosh *et al*. had a prevalence of Gram-negative isolates at 56% with pseudomonas (12%) being most common.[9] Lakshmaiah *et al*. had a 64% prevalence of Gram-negative isolates with *E. coli* (32%) being the most common.[13]

In our study, carbapenems, cephalosporins, cefoperazone sulbactam, fosfomycin, and piperacillin tazobactam showed the highest *in vitro* activity against *E. coli*, whereas in cases with *Klebsiella pneumoniae*, carbapenem, and fosfomycin were effective compared to cephalosporins and aminoglycosides. All pseudomonas species were sensitive to beta lactam/beta lactamase inhibitor which decreased to 66% in *Acinetobacter* and 50% in *E. coli* and 31% in *Klebsiella*. There was high degree of resistance to aminoglycosides with only 56% of *Klebsiella* and 31% of *Pseudomonas* sensitive to aminoglycosides. Among Gram-positive organisms, 85.7% were sensitive to Cefotaxime, and 71.4 % were sensitive to ampicillin. Among our 18 culture positive cases, 17 (94.4%) were sensitive to first-line antibiotics (piperacillin-tazobactam and amikacin) and only 1 (5.6%) was resistant to piperacillin-tazobactam.

In a study by Lakshmaiah *et al*., the antibiotic sensitivity among GNB was highest for imipenem (100%), followed by piperacillin-tazobactam (86.95%), most of the *E. coli* isolates were resistant to cefoperazone-sulbactam, piperacillin-tazobactam. Gram-positive isolates including MRSA were uniformly sensitive to levofloxacin, teicoplanin, linezolid and vancomycin.[14] Similar antibiotic sensitivity pattern of high sensitivity of GNB to cefoperazone/sulbactam, carbapenems, piperacillin/tazobactam, and resistance to third generation cephalosporins has been reported in other studies.[15,16]

PCT has been proposed as a biomarker for discriminating bacterial and viral infections due to the significantly higher increase in its levels in the presence of bacterial stimulus. PCT levels have been shown to be significantly higher in FN especially in Gram-negative infections, but not in to viral illness or elevated in inflammatory conditions or mucositis.[17] Elevated PCT values at presentation correlated with increased risk of severe infections as per Hemming *et al.* and but PCT values did not vary between sepsis or less severe infections at admission but was significant on day 2 as per Santolaya *et al*.[18,19] CRP, an acute phase reactant synthesized during infection and acute inflammation, too has been widely used as in indicator of infection. CRP has been documented to be higher in clinically or microbiologically documented infections when compared to fever of unknown origin. CRP was reported to be more sensitive but not more specific than PCT. As PCT levels are reported to rise within 3–4 h in response to infection as compared to 24–48 h required for CRP, initial levels of CRP at admission might not reflect the true picture and hence needs serial monitoring.

In our study among 18 culture positive cases, CRP was positive in 10 cases and 12 cases had PCT positivity. Sensitivity, specificity of CRP and PCT was 55.5%, 50%, and 66.6%, 55.5%, respectively. Although CRP and PCT were not very useful in prediction of culture positivity, both CRP and PCT were positive in patients with hemodynamic instability and in those who succumbed to death. In our study, the positive predictive value, negative predictive value of CRP was 21.7% and 81.8% and of PCT was 27.2% and 86.9%, respectively.

In a study by Reitman *et al*., serum PCT was higher in positive blood cultures than with sterile blood cultures. In ruling out bacteremia, PCT showed 76% specificity and 93% negative predictive value.[20] In a study by Kim *et al*., PCT was found to have better diagnostic value than CRP to detect bacteremia in FN.[21]

Asturias *et al*. had reported a direct association between elevated CRP, the duration of FN, bacteremia, and mortality.[22] Avabratha *et al*. have quoted that antibiotic response in pediatric FN can be assessed by serial monitoring of CRP.[23] Oberoi *et al*. have proved that CRP is a strong predictor of complications in pediatric FN.[24]

CONCLUSION

Gram-negative organisms are still the predominant causative agents reported during FN, as noticed in other studies from similar background. Raised CRP and PCT are indicators of severe adverse events during FN.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Sneha L, Ramasamy S, Krishna V, Sekar U, Sridharan KS, Iyengar SK, *et al*. Profile of febrile neutropenia in childhood cancer patients and the clinical utility of procalcitonin and C-reactive protein in identifying severe infections. Sri Ramachandra J Health Sci 2022;2:61-5.