ORIGINAL ARTICLE

Frequency of Different Infectious Etiology and its outcome in Pediatric Febrile Neutropenic Patients at Children's Hospital Lahore, Pakistan

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Abstract

Objectives
Febrile Neutropenia is the well-known life-threatening complication of oncological therapy and is an oncologic emergency. Causative organism are different in different areas so it is really important to identify causative organisms its outcome, in local settings and then to establish local guidelines.

Material and Methods
This prospective study was conducted from July 2017 to December 2017 at The Children's Hospital and Institute of Child Health Lahore Pakistan, in the department of pediatric hematology oncology and bone marrow Transplant. All patients with diagnosis of febrile neutropenia and having positive cultures were included. Empirical antibiotics were started as per local guidelines.

Results
Among 390 febrile neutropenic patients 220 samples turned to be positive. Male to female ratio was 1.2:1. Acute lymphoblastic Leukemia was most common disease followed by Non Hodgkin Lymphoma. Among negative organism *Pseudomonas aeruginosa* was the most common (25%) followed by *klebsiella pneumonia* 20%. Among Gram positive organisms *Staphylococcus* species was the mostly found in 36 patients (16.4%) where *streptococcus* species was isolated in 7 patients (3.2%)

125 cultures were sensitive to first line (56.8%), 101 (45.9%) sensitive to second line 119 (54.1%) organism were resistant to second line .115 organisms (52.3%) were sensitive to third line and almost 90% gram positive organisms were sensitive to third line .33 samples were not sensitive to any antibiotic among all these.73 patients (33.2%) discharged within 48 hrs of admission. 47 patients (21.4%) left against medical advice and 30 patients (13.6%) unfortunately expired.

Conclusion
Infectious etiology and its outcome in our center is a bit different from western world so it is suggested to establish local guidelines with respect to sensitivity patterns

Key Words
Infectious etiology, Febrile Neutropenia, Causative organism, oncological therapy

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Introduction

Cancer is one of the leading causes of mortality and morbidity among children. Worldwide, it is estimated that childhood cancer has an incidence of more than 175,000 per year, and a mortality rate of approximately 96,000 per year.[1] In developed countries, childhood cancer has a mortality of approximately 20% of cases. In low resource settings, on the other hand, mortality is approximately 80%, or even 90% in the world's poorest countries.[2,3]

Febrile Neutropenia is the well-known life-threatening complication of oncological therapy and is an oncologic emergency. It is also a leading cause of mortality. Empiric antibiotic therapy upon presentation has dramatically improved outcomes and decreased mortality from febrile neutropenia.[4]

A causative organism is only identified in one third of the time, therefore antibiotics are aimed at treating a broad spectrum of pathogens. However, the outcome is really dependent on causative organisms, empirical therapy, time duration between fever spike and first dose of antibiotics.[4]

In the Children's hospital and ICH Lahore, guidelines advised by American Society of Infectious Diseases (IDSA) with some modifications are being followed. The nutritional status, hygiene and the spectrum of causative organisms may be different from (developed) western world. So, it is really important to analyze the causative organisms, their sensitivity pattern and outcome in local settings as first step to develop and improve the local guidelines.

Objective

To identify different causative organism in febrile neutropenic patients and their outcome to establish local guidelines

Materials and Methods

This prospective study was conducted from July 2017 to

December 2017 at The Children's Hospital and Institute of Child Health Lahore Pakistan, in the department of pediatric hematology oncology and bone marrow transplant. All patients with diagnosis of febrile neutropenia and having positive cultures were included. The history, diagnosis, severity of neutropenia and outcome was noted.

Febrile Neutropenia was defined as single spike of 101 F or two spikes of 100.4 F in one hour with absolute neutrophil count (ANC) of ≤500 cells/microliter, or an ANC ≤1000 cells/microliter with a projected nadir of ≤500 cells/microliter.[4] Bacteremia was defined as organism isolated from blood, urine, wound or CSF after ensuring it was not contaminated. Total of 436 cultures were collected, 5ml of blood and 2 cc of CSF were sent in the department of pathology in same hospital. The patients whom cultures were turned to be negative were excluded from study.

Empirical antibiotic therapy was started just after collecting samples according to local guidelines which included piperacillin-tazobactum and amikacin as first line. After receiving the results of the culture sensitivities, patients were divided into three groups. The patients included in group 1 were sensitive to first line antibiotics, 2nd who were sensitive to second line which included ciprofloxacin & cefaoparazone-salbactum and 3rd who were sensitive to third line which included meropenum and vancomycin. Outcome was labeled as cured, discharged, left against medical advice (LAMA) and died.

The data was collected on the pre-designed proforma. Data was analyzed using SPSS Version.

Results

The data analysis of study revealed that among total 390 febrile neutropenic patients 220 samples turned to be positive. Male to female ratio was 1.2:1. Acute lymphoblastic Leukemia was most common disease n-149 (67.7%) followed by Non Hodgkin Lymphoma i.e. N-17 (7.7%). (Figure 1)

Blood culture was the most common specimen N-103 (46.8%) followed by urine culture N-39 (17.7%) which turned to be positive, least positivity was found in CSF cultures N-8 (3.6%). Gram negative organisms were mostly found among cultures (80.4%) whereas positive organisms were found in 19.6% patients. Among negative organism *Pseudomonas aeruginosa* was on top of list found in 25% specimens followed by *klebsiella pneumonia* 20% and then *Ecoli* 16.8%. *Acinetobacter* was found in 20 patients (9.1%) *Ccitrobactor* in 6 patients (2.7%) *Enterobacter* in 4 patients (1.8) and same frequency of *Enterococcus faecalis*. Among Gram positive organisms *Staphylococcus* species were the most common found in 36 patients (16.4%) where *streptococcus* species was isolated in 7 patients (3.2%). (Figure 2)

When different cultures were analysed with respect of culture sensitivity 125 cultures were sensitive to first line (56.8%) where piperacillin/tazobactum and Amikacin was first line. 101 (45.9%) cultures were sensitive to second line antibiotic which was Ciprofloxacin, sulfaparazone and 119 (54.1%) organism were resistant to second line. With respect to third line which was meropenum and vancomycin 115 organisms (52.3%) were sensitive and almost 90% gram positive organisms were sensitive to third line. 33 samples were not sensitive to any antibiotic among all these. (Figure 3)

73 patients (33.2%) discharged within 48 hrs of admission. 47 patients (21.4%) left against medical advice and 30 patients (13.6%) unfortunately expired. (Figure 4, Table 1)

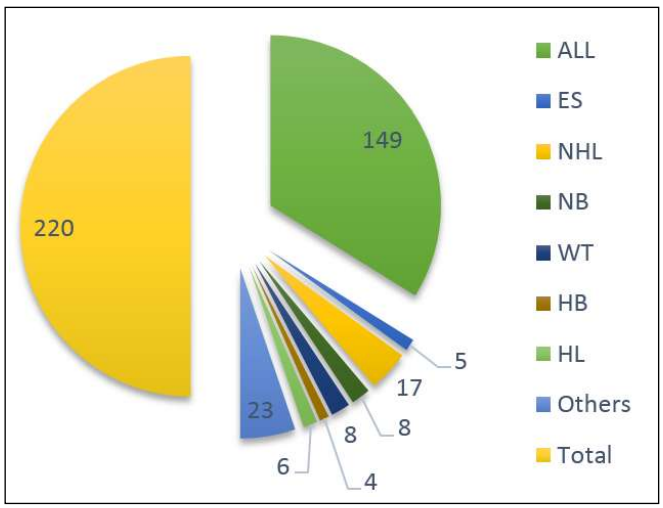

Fig 1. Disease Burden

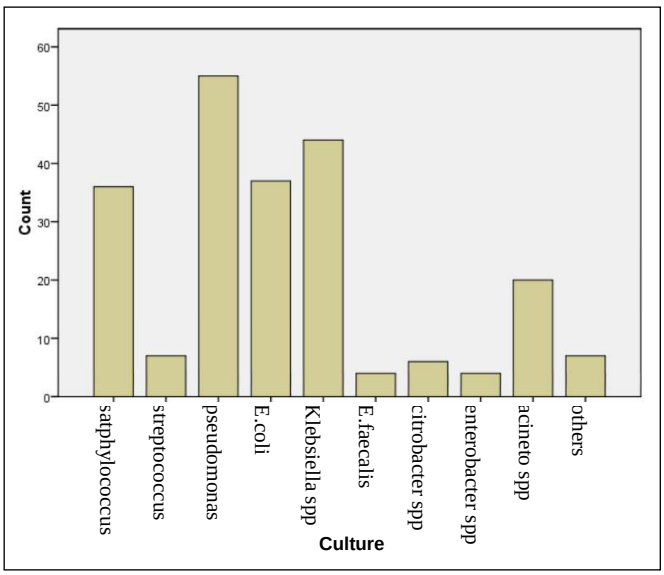

Fig 2. Frequency of different pathogens

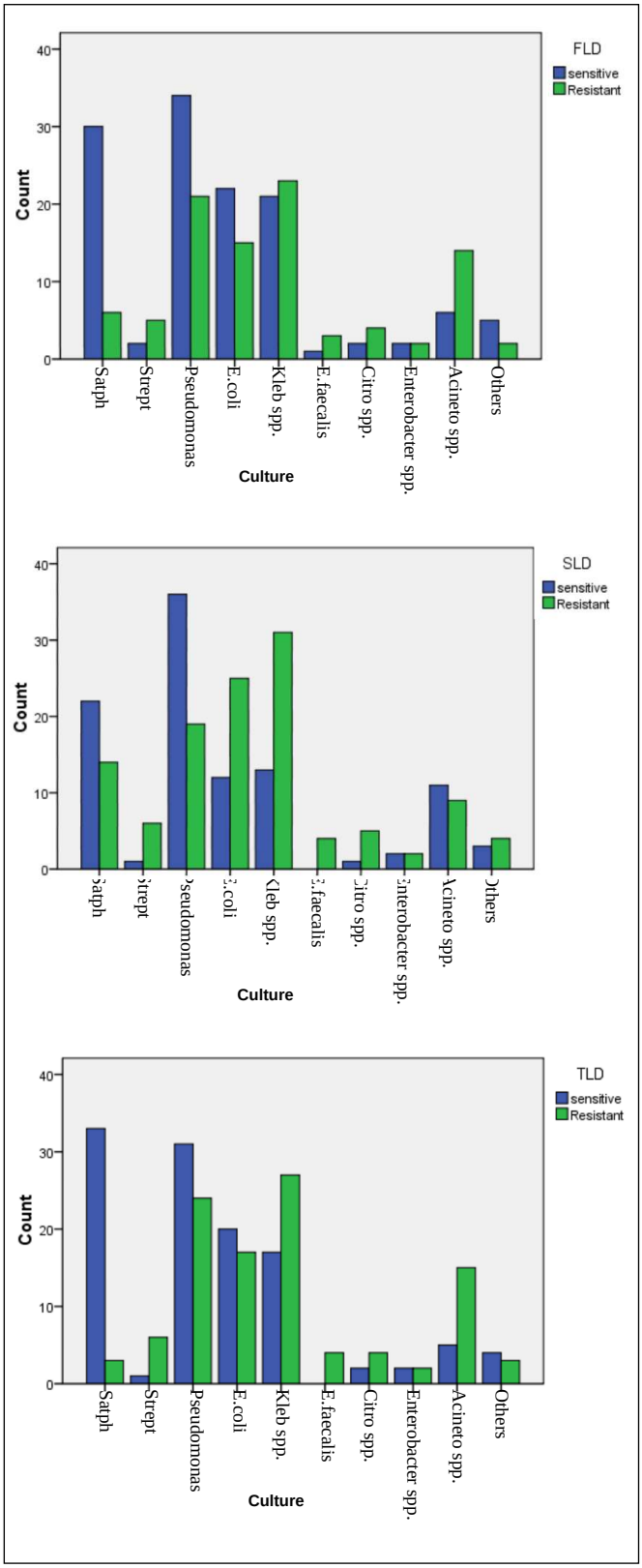

Fig 3. Sensitivity patterns of different pathogens

FSD: First Line Defense, SLD: Second Line Defense, TLD: Third Line Defense

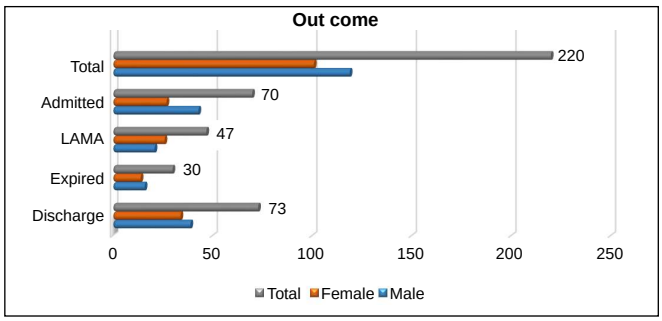

Fig 4. Outcome of febrile neutropenic patients

Table 1: Outcome of different pathogens

Cultures Vs Outcome	Outcome				
Organisms	**Discharge**	**Expired**	**LAMA**	**Admitted**	**Total**
Satphylococcus	11	0	6	19	36
Streptococcus	2	3	1	1	7
Pseudomonas	28	5	5	17	55
E.coli	8	7	13	9	37
Klebsiella spp	9	11	10	14	44
E. faecalis	2	0	1	1	4
Citrobacter spp	2	2	1	1	6
Enterobacter spp	1	1	1	1	4
Acineto spp	6	1	7	6	20
Others	4	0	2	1	7
Total	73	30	47	70	220

Discussion

Over the last three decades a lot of work has been done to evaluate epidemiology and its outcome in febrile neutropenia patients. In our study gram negative organisms are top of list. Similarity is seen in late 70s when gram negative organisms were noted to be main culprits. In late 80s and 1990s gram positive bacteria were isolated in febrile neutropenia individuals[5,6,7,8] there are many factors which can explain this shift like prophylactic use of quinolones,[9,10] the use of in-dwelling intravascular catheters for administration of chemotherapies.[11]

Our study however revealed that gram negatives are the main causative organism in patients suffering with febrile neutropenia. This is not very unusual. There are many studies especially in south Asia and Asia especially where routine of central lines is not very common and gram negatives organism are top on list.[12]

Study published in Indian journal of blood transfusion in 2015[12] also showed gram negative pathogens isolated from blood of febrile neutropenia patients which is in comparison to our results. That study also is in comparison with our results that pseudomonas is number one culprit among gram negative organisms. *Acinobacte*r was second in number but in our study *Klebsiella* is the second most causative organism. But there is one thing common that these both organisms are very resistant to routine antibiotics. In a study[13] from All India Institute of Medical Sciences, where different pathogens and antibiotic resistance was compared showed *Acinetobacter* spp. emerging as common pathogen which is exactly supportive to our results.

Roongpoovapatr P, Suankratay C *et al*. also observed that Gram-negative bacteria were the most frequently isolated pathogens (63.9%), followed by Gram-positive bacteria (29.9%) and fungi (6.2%)

But in contrast of our observation *Escherichia coli* (46.8%) and coagulase-negative *Staphylococcus* (27.6%) were the most common isolates among Gram-negative and Gram-positive bacteria, respectively.[14] In another study Gram-negative bacteria were the most were found in 71% incidents followed by Gram-positive bacteria (35.8%) and *Candida species* (1.9%). Surprisingly, invasive mold infections were noted in eight episodes. The overall mortality was 19.2%.[15]

If we discuss the sensitivity pattern of these organism with respect to our local three antimicrobial lines of defense. It is also matter of concern that about 29% pseudomonas and almost 50 % klebsiella were resistant to all three lines of antimicrobial therapy. Same with *acenobacter* which was only 20% sensitive to all three lines of antimicrobial drugs. *Citrobacter* was 67% resistant to all three defense lines and it comprises 3% of total organism isolated.

It means in almost over all 15 % patients our all three lines are failing to cure the neutropenic patients. Our center is not using ciprofloxacin or any other antibiotic as prophylaxis, our 30% causative organisms are sensitive to second line which include quinolones so prophylactic use of quinolones may make a difference especially in high risk neutropenic patients. Pseudomonas is usually part of hospital acquired infection so it is need of hour to further improve infection control measures.

Reference

1. Ward EM, Thun MJ, Hannan LM, Jemal A (Sep 2006). "Interpreting cancer trends". Annals of the New York Academy of Sciences. 1076:
2. Bengre ML, Prabhu MV, Arun S, *et al*. Evaluation of the multinational association for supportive care in cancer(MASCC) score for identifying low risk febrile neutropenic patients at a south Indian tertiary care centre. *J Clin and Diag Research* 2012;6(5):839-843.
3. Gea-Banacloche JC, Palmore T, Walsh TJ, *et al*. Infections in the cancer patient. In: Devita, Hellmen, Rosenberg, eds. Devita, Hellman & Rosenberg's cancer: principles & practice of oncology. 8th edn. Philadelphia: Lippincott Williams & Wilkins 2008:2579-2611.
4. Sharma A, Lokeshwar N. Febrile neutropenia in haematological malignancies. *J Postgrad Med* 2005;51 (Suppl 1): S42-48.
5. C. Viscoli, O. Varnier, M. Infections in patients with febrile neutropenia: epidemiology, microbiology, and risk stratification *Clin Infect Dis* 40 (Suppl 4) (2005), pp. S240-S245
6. S.H. ZinnerChanging epidemiology of infections in patients with neutropenia and cancer: emphasis on Gram-positive and resistant bacteria *Clin Infect Dis* 29 (1999), pp. 490-494
7. M. Akova Emerging problem pathogens: a review of resistance patterns over time *Int J Infect Dis* 10 (Suppl 2) (2006), pp. S3-S8
8. H. Wisplinghoff, H. Seifert, R.P. Wenzel, M.B. Edmond Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States *Clin Infect Dis* 36 (2003), pp. 1103-111
9. M. Cruciani, R. Rampazzo, M. Malena, L. Lazzarini, G. Todeschini, A. Messori, *et al*. Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis *Clin Infect Dis* 23 (1996), pp. 795-805
10. E.A. Engels, J. Lau, M. Barza Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis *J Clin Oncol* 16 (1998), pp. 1179-1187
11. O.W. Press, P.G. Ramsey, E.B. Larson, A. Fefer, R.O. Hickman Hickman catheter infections in patients with malignancies Medicine (Baltimore), 63 (1984), pp. 189-200
12. Prakas Kumar Mandal, Suman Kumar Maji Micro-organisms Associated with Febrile Neutropenia in Patients with Haematological Malignancies in a Tertiary Care Hospital in Eastern India *Transfus* (Jan-Mar 2015) 31(1):46–50
13. Sood P, Seth T, Kapil A, Sharma V, Dayama A, Sharma SK *et al* (2012) Emergence of multidrug resistant acinetobacter blood stream infections in febrile neutropenia patients with haematological cancers and bone marrow failure syndromes. *J Indian Med Assoc* 110:439–444
14. Roongpoovapatr P1, Suankratay C. Causative pathogens of fever in neutropenic patients at King Chulalongkorn Memorial Hospital. *J Med Assoc Thai* 2010 Jul;93(7):776-83.
15. Kuan-Po Huang a, Tso-Fu Wang b, Sung-Chao Chu b, Yi-Feng Wu b, Rou-Yun Wang b, Ruey-Ho Kao Analysis of pathogens and susceptibility in cancer patients with febrile neutropenia and bacteremia: Experience in a single institution in eastern Taiwan *Tzu Chi Medical Journal* 23 (2011) 115e118