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# Outcome of Intermediate Risk Pediatric Febrile Neutropenia – a Single Center Prospective Study from Pakistan

Muhammad Rahil Khan*, Muhammad Shamvil Ashraf*, Sundus Iftikhar**

*Department of Pediatric hematology/oncology, The Indus Hospital, Korangi Campus, Karachi, 75190, Pakistan
**Head of Department of Statistics and training unit, The Indus Hospital, Korangi Campus, Karachi, 75190, Pakistan

## Abstract

### Purpose
Febrile Neutropenia (FN)is an oncological emergency, which requires early recognition and prompt antibiotics administration for better outcome.We aimed to determine the outcome and association of demographic, clinical and laboratory data of intermediate risk pediatric febrile neutropenia treated with piperacillin / tazobactam and amikacin in a tertiary care hospital of Pakistan.

### Methods
All intermediate risk pediatric febrile neutropenia less than 16 years of ageadmitted in the pediatric oncology ward of The Indus Hospital from May to July 2016 were enrolled prospectively. Relapsed patients, low and high-risk FN were excluded. Outcome defined as success if discharged after completion of antibiotics or as failure if antibiotics changed, antifungal added or need of intensive care due to hemodynamic instability and death.

### Results
Total 141 episodes occurred in 136 children. Success rate was 83 %(n=117) and failure 17%(n=24). Major reason of failure was change in antibiotics (79.2%) due to persistent fever > 72 hrs.Three deaths occurred in the entire cohort due to probable fungal infection. On multivariable analysis, four independent risk factors were found to be significant for failure- ANC< 100 at presentation (aOR (95% CI):11.45 (1.70-77.19), p= 0.012), CRP=20mg/dl (aOR (95% CI):3.94 (1.03-15.12), p=0.045), respiratory rate (aOR (95% CI):1.48 (1.17-1.88), p=0.001) and heart rate (aOR (95% CI):0.96 (0.93-1.00),p=0.048).

### Conclusion
Our approach to treat intermediate risk febrile neutropenia was optimal. Strategy of low and high risk needs investigation. Based on our results, scoring model can be formulated for further refinement of our current management.

**Key Words**
febrile neutropenia, intermediate risk

*Corresponding Author: Muhammad Rahil Khan, Department of Pediatric hematology/oncology, The Indus Hospital, Korangi Campus, Karachi, 75190, Pakistan. Email: rahil.khan@tih.org.pk*

## Introduction
Febrile Neutropenia (FN) in children on chemotherapy is asignificant cause of mortality and morbidity. Itrequires prompt evaluation and early treatment withantibiotics.[1] This becomes more important in low income countries like Pakistan where infections such as diarrhea, pneumonia and malaria are high constituting major causes of mortality in children under five years.[2] Such FN patients presenting in the emergency department (ED) are routinely started on early empirical broad-spectrum antibiotics without waiting for laboratory results. This approach of early empirical therapy has resulted in decreasein infection related mortality in developed countries to 1-3%.[3]

To avoid antibiotic resistance, FN patients are stratified into low and high risk and treated accordingly with risk-adapted antibiotics. This risk stratification is based on the patient's primary diagnosis, treatment and episode related factors such as height of fever and blood counts.[4]

The choice of empirical antibiotics depends on regional and institutional local pathogens and antibiotic sensitivity and resistance pattern.[5] This ranges from multidrug treatment with an additional gram negative regimen to a more recent approach of monotherapy with antipseudomonal beta lactam or carbapenem in uncomplicated FN patients.[1, 4]

In Pakistan, there is scarcity of data on FN, its risk stratification and outcome in pediatric population. To our knowledge there are only two studies on pediatric FN in Pakistan[2, 6] but with limitations. We at The Indus Hospital (TIH), stratify our FN patients into three categories – high, intermediate and low risk based on multiple factors as demonstrated in table 1 and treat accordingly with different regimen. Such stratification has also been used by other groups.[7, 8] Based on antibiotic sensitivity pattern, our intermediate risk FNs (IRFN) are treated with a combination of piperacillin/tazobactam and amikacin. This study intended to determine the outcome of IRFN and explore factors associated with the outcome.

## Material and Methods
### Study design and setting
This was a prospective, observational and non-intervention studyconducted from May – July 2016 in pediatric oncology

unit of TIH after approval from Institutional Review Board (IRB). TIH treats more than 800 new cancer patients peryear with 60 febrile neutropenia admitted in pediatric oncology unit (POU) in a month. POU is 50 bedded including ward with isolation rooms, emergency department (ED), daycare, procedure room, pediatric intensive care unit (PICU) and high dependency unit.

The details of demography (age and gender of the patient, primary cancer diagnosis, chemotherapy phase and last date of chemotherapy administration, use of colony stimulating factor), clinical (presenting complains, time to reach ED after fever at home, height of temperature on presentation, examination details including vital signs, soft tissue infection or degree of mucositis if present, inpatient course, change of antibiotics, reason of change, last date of antibiotics) and laboratory investigations in ED and in ward (CBC including absolute neutrophil count (ANC), blood cultures, C-reactive protein (CRP), Chest X-Ray (CXR), Urine and Stool detailed report (D/R), cultures, repeat cultures, Computed Tomography (CT) scan of chest and ANC at discharge were documented in the predesigned case report form.

**Patients' Selection and FN Management**

All IRFN patients less than 16 years of age admitted from the ED or daycare unit in the ward and received piperacillin / tazobactam and amikacin were included. Informed consent was taken from guardian or patient, if eligible. Relapsed patients, all low and high risk febrile neutropenia**,** febrile patients admitted on antibiotics other than piperacillin / tazobactam and amikacin were not enrolled in the study.

On presentation, detailed history and complete examination was done and relevant hematological(CBC,CRP) radiological (CXR–if respiratory symptoms present)and microbiological investigations(blood cultures and if any focus- stool, urine or skin cultures) were carried out in ED. The first dose of piperacillin / tazobactam and amikacin were given within an hour of arrival to ED after taking cultures. During admission, same antibiotics were continued if remained stable. Amikacin was stopped after 72 hours if cultures were negative. Patients were discharged if remained afebrile for 36-48hrs with no complications or signs of clinicalillness,resolution of initial focus and rising ANC. In case of persistent fever > 72hrs, culture positivity or hemodynamic instability at any point time during admission, cultures were repeated and antibiotics were switched to carbapenem with/ without vancomycin and colomycin or other antibiotic according to sensitivity and shifted to PICU if indicated. If patients remained febrile > 96 hours, CT chest (HRCT) was done for invasive fungal infection (IFI)and empirical antifungal (amphotericin- B) was added.

**Definitions**

**Fever:**Êaxillary temperature >38.5$^0$C or two consecutive readings of >38.0$^0$C for 2 hÊ

**Neutropenia:** ANC <0.5 × 10$^9$/l, or expected to fall below 0.5 × 10$^9$/l.

**Success outcome**– IRFN completed five days course of piperacillin/ tazobactam, amikacin and discharged safely without complication.

**Failure outcome**- change in antibiotics due to either clinical deterioration, prolonged fever for more than 72 hrs or cultured organism resistant to piperacillin-tazobactem, need for antifungal treatment or fluid resuscitation requiring PICU admission and death.

**Risk Stratification** – defined in table.1

**Table 1- Risk Stratification Definition[7,8]**

| Low Risk | Intermediate Risk | High Risk |
|---|---|---|
| Patients of<br>• Acute lymphoblastic leukemia (ALL) on maintenance therapy,<br>• Solid tumor with Post chemo day > 10 ( except B-NHL ) with<br>o possible daily follow up,<br>o contactable on phone,<br>o leaving at one hour distance from hospital,<br>o no appearance of illness (hemodynamically stable),<br>o no obvious focus of infection like pneumonia, diarrhea sinusitis,, abscess and no other significant co-morbidity | Febrile Neutropenia with all ALLs (except low risk), acute myeloid leukemia, B-Non-Hodgkin Lymphoma (BNHL) and solid tumors with post chemo day < 10 and no high risk features | Febrile neutropenia with signs of hemodynamic instability which include<br>• difficulty in breathing,<br>• oxygen saturation < 90 %,<br>• tachycardia,<br>• hypotension,<br>• weak peripheral pulses,<br>• poor capillary refill,<br>• oliguria,<br>• altered consciousness,<br>• convulsions,<br>• fluid resuscitation<br>• need of inotrope |

**Statistical Analysis**

Data were entered and analyzed using SPSS version 21. Mean (SD) were computed as appropriate for all the quantitative variables-age, vital signs, laboratory investigations like Hemoglobin (Hb), White Cell Count (WCC). Frequency and percentage were computed for all the qualitative variables i.e., gender, primary diagnosis, chemotherapy phase. Independent sample t-test were applied as appropriate to assess significant difference in all the aforementioned quantitative variables between the outcomes. Chi-square test/Fisher exact test were applied as appropriate to assess significant association of all the aforementioned quantitative variables with outcome. Univariate and multivariable logistic regression was applied to assess risk factors associated with regimen failure. All the variables with P-value <0.25 were included in multivariable analysis. P-value <0.05 was considered significant.

**Results**

A total 141 admissions of IRFN occurred in 136 children during the study period. Table 2 enumerates the description of demographical, clinical and laboratory features of our cohort. Hundred and four episodes were leukemic patients. Granulocyte

**Table 2- Descriptive analysis of intermediate risk febrile neutropenia**

| Variables | Leukemia n=104 n (%) | Lymphoma and solid organ cancers n=37 n (%) | Overall n=141 n (%) |
|---|---|---|---|
| Age inyears (mean ± SD) | 7.8 ± 4.0 | 9.3 ± 3.9 | 8.2 ± 4.0 |
| Gender | | | |
| *Female* | 38 (36.5) | 19 (51.4) | 57 (40.4) |
| *Male* | 66 (63.5) | 18 (48.6) | 84 (59.6) |
| Phases of chemotherapy | | | |
| *Induction* | 39 (37.5) | 13 (35.1) | 52 (36.9) |
| *Consolidation* | 29 (27.9) | 21 (56.8) | 50 (35.5) |
| *Interim maintenance* | 13 (12.5) | 2 (5.4) | 15 (10.6) |
| *Delayed intensification* | 17 (16.3) | 1 (2.7) | 18 (12.8) |
| *Maintenance* | 6 (5.8) | - | 6 (4.3) |
| Chief compaints at presentation | | | |
| *Fever only* | 46 (44.2) | 13 (35.1) | 59 (41.8) |
| *Fever with other symptoms* | 58 (55.8) | 24 (64.9) | 82 (58.2) |
| Temperature at presentation | | | |
| *37 $^{o}$c* | 45 (43.3) | 14 (37.8) | 59 (41.8) |
| *>37 $^{o}$c and <=38 $^{o}$c* | 41 (39.4) | 18 (48.6) | 59 (41.8) |
| *>38 $^{o}$c* | 18 (17.3) | 5 (13.5) | 23 (16.3) |
| Duration of fever | | | |
| *<24 hours* | 100 (96.2) | 34 (91.9) | 134 (95) |
| *24-48 hours* | 2 (1.9) | 1 (2.7) | 3 (2.1) |
| *>48 hours* | 2 (1.9) | 2 (5.4) | 4 (2.8) |
| Patients with soft tissue infection | 6 (5.8) | 3 (8.1) | 9 (6.4) |
| Heart rate per min (mean ± SD) | 121 ± 21 | 125 ± 16 | 122 ± 20 |
| Respiratory rate per min (mean ± SD) | 25 ± 4 | 25 ± 4 | 25 ± 4 |
| Systolic blood pressure mmHg (mean ± SD) | 101 ± 11 | 100 ± 10 | 101 ± 11 |
| Diastolic blood pressure mmhg (mean ± SD) | 59 ± 11 | 60 ± 10 | 59 ± 11 |
| Absolute Neutrophil Counts (ANC) on admission | | | |
| <100 | 63 (60.6) | 24 (64.9) | 87 (61.7) |
| >=100 | 41 (39.4) | 13 (35.1) | 54 (38.3) |
| C-Reactive Protein mg/dl | | | |
| Below median (<20 mg/dl) | 54 (51.9) | 17 (45.9) | 71 (50.3) |
| Above median (>=20mg/dl) | 50 (48.1) | 20 (54.1) | 70 (49.6) |
| Hemoglobin g/dl (mean ± SD) | 8.2 ± 1.7 | 8.7 ± 1.3 | 8.3 ± 1.6 |
| White Blood Cells 10^9/L | | | |
| <1000 | 62 (59.6) | 24 (64.9) | 86 (61) |
| >=1000 | 42 (40.4) | 13 (35.1) | 55 (39) |
| Platelet 10^9/L (mean ± SD) | 115.5 ± 133.6 | 124.3 ± 99.6 | 117.8 ± 125.3 |
| Chest X-ray (n=94) | | | |
| *Normal* | 64 (61.5) | 21 (56.8) | 85 (90.4) |
| *Infiltrates* | 8 (7.7) | 1 (2.7) | 9 (9.6) |
| Culture Repeated | 19 (18.3) | 6 (16.2) | 25 (17.7) |
| *Type of culture (n=25)* | | | |
| *Blood* | 19 (100) | 5 (83.3) | 24 (96) |
| Reason for repeating culture (n=25) | | | |
| *Persistence of fever* | 16 (84.2) | 6 (100) | 22 (88) |
| *New symptom/ focus of infection* | 1 (5.3) | - | 1 (4) |
| *Other* | 2 (10.5) | - | 2 (8) |
| Absolute Neutrophil Counts at discharge | | | |
| *<100* | 27 (26) | 4 (10.8) | 31 (22) |
| *>=100* | 77 (74) | 33 (89.2) | 110 (78) |
| Outcome | | | |
| *Success* | 85 (81.7) | 32 (86.5) | 117 (83.0) |
| *Failure* | 19 (18.3) | 5 (13.5) | 24 (17.0) |
| Reason for failure (n=24) | | | |
| *Change in Antibiotics* | 15 (78.9) | 4 (80) | 19 (79.2) |
| *Need for fungal Treatment* | 1 (5.3) | - | 1 (4.2) |
| *Need for PICU* | 1 (5.3) | - | 1 (4.2) |
| *Combination* | 2 (10.5) | 1 (20) | 3 (12.5) |

colony stimulating factor (G-CSF) was used as part of the chemotherapy protocol in 17.7% episodes (n=25). Nearly 73 % events occurred in induction and consolidation. Blood cultures were positivein only 3.5% of patients. Overall 117 (83%) events were treated successfully with our regimen and 24 (17%) didn't respond. Major reason of failure was change in antibiotics (n=19, 79.2%) mainly due to prolonged fever of more than 72 hours (n=12, 63.2%) followed by bacterial growth (n=7, 36.8%). Three (2% of events) died due to probable invasive fungal infection (IFI) on CT chest. Four (2.8%) episodes needed PICU either due to hemodynamic instability or IFI requiring mechanical ventilation. Around61.7% had ANC <100/mm3 on admission and 78% had ANC >100/mm3 on discharge.

Table.3 demonstrates univariate and multivariable analysis of factors associated with failuresin leukemia patients. On univariate analysis, variables found to be significant for failure were consolidation phase (OR:7.56( 95% CI 1.56-36.7) p=0.012) , RR (OR:1.22 (95% CI 1.07-1.38)p= 0.002), soft tissue infection (OR:5.12 (95% CI 0.95-27.71) p=0.058), platelet count(OR:0.98 (95% CI 0.97-0.99) p=0.006), WCC< 1000(OR:3.032 (95% CI 0.93-9.9), p=0.066), CRP=20mgl/dl (OR:2.33(95% CI 0.93-

**Table. 3 Univariate and multivariable analysis of leukemia patients**

| Variables | Univariate Analysis | | Multivariable Analysis | |
|---|---|---|---|---|
| | **Odds Ratio (95% CI)** | **P-value** | **Adjusted Odds Ratio (95% CI)** | **P-value** |
| Age in years | 0.98 (0.87-1.11) | 0.793 | 1.10 (0.92-1.31) | 0.313 |
| Gender | | | | |
| *Male* | 0.98 (0.35-2.76) | 0.976 | 0.75 (0.21-2.72) | 0.658 |
| *Female* | Ref | | Ref | |
| Phases of Chemotherapy | | | | |
| *Induction* | 3.54 (0.63-19.8) | 0.15 | | |
| *Consolidation* | 7.56 (1.56-36.7) | 0.012 | | |
| *Interim Maintenance, Delayed intensification and maintenance* | Ref | | | |
| Chief Complaints | | | | |
| *Fever only* | Ref | | | |
| *Fever with other symptoms* | 1.93 (0.67-5.54) | 0.224 | | |
| Temperature at Presentation | | | | |
| *37 °c* | Ref | | | |
| *>37 °cand<=38 °c* | 0.49 (0.15-1.57) | 0.227 | | |
| *>38 °c* | 1 (0.27-3.72) | 1.00 | | |
| Heart rate per min | 0.997 (0.97-1.02) | 0.813 | 0.96 (0.93-1.00) | 0.048 |
| Respiratory rate per min | 1.22 (1.07-1.38) | 0.002 | 1.48 (1.17-1.88) | 0.001 |
| Systolic blood pressure mmhg | 1.01 (0.97-1.06) | 0.635 | | |
| Diastolic blood pressure mmhg | 0.99 (0.95-1.04) | 0.697 | | |
| Hemoglobin g/dl | 0.84 (0.62-1.12) | 0.24 | | |
| Platelet 10^9/L | 0.98 (0.97-0.99) | 0.006 | | |
| Soft tissue infection | | | | |
| *Yes* | 5.12 (0.95-27.71) | 0.058 | | |
| *No* | Ref | | | |
| White blood cell count 10^9/L | 0.54 (0.21-1.42) | 0.213 | | |
| *<1000* | 3.032 (0.93-9.9) | 0.066 | | |
| *>=1000* | Ref | | | |
| C-Reactive Protein mg/dl | | | | |
| *Below Median (<20 mg/dl)* | Ref | | Ref | |
| *Above Median (>=20mg/dl)* | 2.33 (0.93-5.87) | 0.072 | 3.94 (1.03-15.12) | 0.045 |
| Absolute Neutrophil Counts at Admission | | | | |
| *<100* | 7.21 (1.58-33.15) | 0.011 | 11.45 (1.70-77.19) | 0.012 |
| *>=100* | Ref | | Ref | |

5.87), p=0.072) and ANC<100(OR:7.21 (95% CI 1.58-33.15) p=0.011). When these factors were selected for multivariable analysis, ANC< 100 at presentation (aOR:11.45(95% CI 1.70-77.19) p= 0.012), CRP=20mg/dl (aOR:3.94 (95% CI 1.03-15.12) p=0.045), RR (aOR:1.48 (95% CI 1.17-1.88), p=0.001) and HR (aOR:0.96 (95% CI 0.93-1.00)p=0.048) were found to be the risk factors associated with failure.

**Discussion**

Pediatric oncology is one of the success stories in medicine. The survival in developed countries has reached approximately 80%.[9] Unfortunately in many low middle-income countries is still dismal between 5-10%.[10] Multiple factors are related to low survival. The lack of National standard of care policies and protocols is one major reason of poor outcome.[11]

FN is one of the leading cause of mortality in cancer children especially in Pakistan where FN burden is high.[6, 12] Regrettably, in Pakistan, national guidelines for febrile neutropenia doesn't exist. Institutional FN guidelines are being followed but results are not much published regarding the outcome of their strategies. In this study we validated our institutional approach of risk stratification. We have shown that our stratification of FN into low, intermediate and high risk has good results in the intermediate risk category. This success is comparable to other's FN strategy as documented by Timothy *et al* (91.5%).[13] The rate of change of antibiotics (17%) were much lower (61%) than seen by Chamberlain *et al*.[14]

Infection related mortality in our cohort were much lower (n=3, 2.1%) incontrast to 22-27% deaths seen in other regional studies from Pakistan and India.[2, 15] This might be due to inclusion of all low and high risk FNs in their study. The other factor could be poor supportive care and high percentage of bacteremia-25.8% by Mahmud *et al*[2] and 36% by Dubey *et al*.[15] Low bacteremia in our study (3.5%) seems to be true representative rather than being false negative results as patients with positive blood cultures had prolonged fever and needed a change in antibiotics. So it's less likely to be an issue of laboratory yield. Contrary to above published reports with high bacterial culture rate, studies with low rate (8.5- 16%) have documented low mortality in FNs.[13] This confirms that decreased rate of bacterial infection in this study is an important factor for our low mortality.

Immediate antibiotic administration, ideally within an hour, after arriving in emergency department (ED) is now considered an important factor for better outcome.[16] Although exact time was not calculated, but one cause to success could be early institution of antibiotics in our ED. We have a dedicated pediatric oncology ED so there are less chances for patients being missed or delayed in general pediatric ED. Our ED team arewell-trained to prescribe and administer first dose of antibiotics in all neutropenic fevers without waiting for investigation results.

The other reason for our better achievement could be early arrival of patients to hospital once their symptoms appeared at home. Majority (95%) of the patients reached within 24 hours of symptoms. This is in contrast to only 27% FN patients reaching hospital earlier than 24 hours seen by Alia *et al*.[6]

The ANC<100/mm$^3$ at the time of admission was the leading independent failure risk factor in our study. Patients with ANC<100/mm$^3$ had 11.45- fold failure risk on multivariable analysis. Similar relationship of ANC <100/mm$^3$ with FN complications was also identified by others.[17,18] The other important variable for predicting unfavorable outcome in this and various studies was CRP. CRP is an acute phase reactant and a marker for invasive bacterial infection.[3] This study showed that baseline CRP>20mg/dl had 3.45 fold higher chances of failure. Similar significance of CRP was also elaborated by others[17, 19, 20] but their CRP cut off levels were different.

Some factors found significant for high riskin other studies were statistically not substantial in our study. These include peak temperature of more than 38.5°C or 39°C at presentation, <7 days of chemotherapy, female gender and age less than 5 years.[8, 18, 20] Although hemoglobin and platelet level had significance on univariate analysis in our study as documented by Amman *et al* and Rondinelli *et al* but were not statistically significant in the multivariable analysis.[8, 19]

The strength of our study are its prospective nature and comparable sample size to other prospective FN studies done in children.[21, 22] Based on our results, we can propose a scoring model and further document the validation of risk factors identified. Multiple factors based scoring system had been tested earlier by different investigators.[8,18,19,23] This helps in identifying high-risk patients needing aggressive approach on presentation and on the other hand minimizing over treatment of low risk FNs.

Our study was a single center study, one of the major limitation. Absolute monocyte count< 100/mm3[8, 21] and undernutrition[17] have been associated with adverse outcomes in other studies. Our study failed to assess and document significance of these factors.

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