RESEARCH PAPER

# Risk Factors for Microbiologically-documented Infections, Mortality and Prolonged Hospital Stay in Children with Febrile Neutropenia

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**Objective:** To analyze the risk factors for microbiologically documented infection, mortality and hospital stay more than 5 days in children with febrile neutropenia.

**Design:** Cross-sectional study (July 2013-September 2014).

**Setting:** Government-run, tertiary-care, university hospital in Chandigarh, Northern India.

**Participants:** 414 episodes in 264 children aged <12 years, not undergoing stem-cell transplantation.

**Outcome measures:** Predictors for 'high-risk' febrile neutropenia.

**Results:** Microbiologically-documented infections were observed in 82 children (19.8%); bacterial 14.2%, fungal 4.3%, polymicrobial 9.7%. Complications were documented in 109 (26%) children. 43 (10.3%) died: 8 due to fungal and 35 due to bacterial sepsis. Children admitted within 7 days of the last chemotherapy ($P$<0.01) and having a non-upper respiratory focus of infection ($P$<0.02) were at risk of developing microbiologically-documented infections and death. Platelet count <20000/uL ($P$=0.03) was an additional predictor for microbiologically-documented infections, while albumin <2.5 g/dL ($P$=0.04) and C-reactive protein >90 mg/L ($P$=0.02) were risk factors predicting mortality. The median (IQR) duration of hospital stay was 5 (3,8) days. Hospital stay >5 days was seen in 144 (35%) children. Children with acute myeloid leukaemia ($P$<0.01) and admitted within 7 days of chemotherapy ($P$=0.02) were likely to have a prolonged hospital stay >5 days.

**Conclusions:** Febrile neutropenic children admitted within 7 days of completion of chemotherapy, those with a non-upper respiratory focus of infection, CRP >90 mg/dL, platelet <20000/uL and albumin <2.5 g/dL need to be considered as 'high risk' for complications and mortality.

**Keywords:** *Chemotherapy, Mycosis, Neutropenic sepsis, Prognosis*.

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Chemotherapy-related neutropenia leading to infections is a major concern in pediatric oncology. Aggressive management, including prompt hospitalization, early administration of broad-spectrum antibiotics, and close monitoring in a dedicated unit, has reduced mortality from chemotherapy-induced febrile neutropenia (FN) [1]. While most children remain clinically well and do not have a proven infection [2], a microbiologically documented infection (MDI) in a child with FN increases the risk of death, as well as the complications and duration of hospital stay [3-5]. The aim of the current study was to prospectively analyze the risk factors for MDI, mortality and prolonged hospital stay in children with FN.

## METHODS

The study was performed in a 20-bedded pediatric hematology-oncology unit of a government-owned, tertiary-care, university hospital in Northern India. The unit looks after children ≤12 years of age. Children presenting with FN following chemotherapy were prospectively enrolled between July 2013 and September 2014 after an informed consent. Children undergoing stem-cell transplantation, those on palliative care, and those presenting with FN at the time of diagnosis of cancer were excluded. All patients were treated with empirical intravenous broad-spectrum antibiotics (cefoperazone-sulbactum 50 mg/kg 8-hourly, amikacin 15 mg/kg/day), after obtaining venous blood sample for a complete blood count, C-reactive protein (CRP) and blood culture (Bactec method). Cultures were obtained from other sites based on clinical presentation. Patients presenting with hemodynamic compromise were started on a carbapenem (Meropenem: 40 mg/kg/dose 8-hourly) with Vancomycin (15 mg/kg/dose 8-hourly). Antibiotics were administered within one hour of presentation. Voriconazole (9 mg/kg/dose 12-hourly) was used as

antifungal prophylaxis in children with acute myeloid leukemia (AML). Standard protocol was continued for management till the resolution of fever or recovery of counts [6,7]. Repeat cultures were sent in presence of persistence of fever beyond 48 hours. Computed Tomography (CT) of chest was done for all children with prolonged FN (more than 5-7 days) in the intensive phases (induction/consolidation) of therapy for hematological malignancies. In children with FN in the maintenance phase and those with solid tumours, a CT chest was guided by the clinical indications. Imaging of other areas (sinus/abdomen/brain) remained symptom-directed, and histological confirmation was attempted based on accessibility of the lesion. Serum galactomannan was requested for all children with prolonged FN and underlying hematological malignancy. Granulocyte colony stimulating factor (G-CSF) was used as per protocol for solid tumours following chemotherapy. We did not use G-CSF in hematological malignancies or during episodes of FN. Criteria for discharge included absence of fever for at least 24 hours duration, a sterile blood culture in children admitted without a focus of infection or hemodynamic compromise. In presence of a documented positive blood culture, antibiotics were administered for a minimum of 7 days duration beyond the last negative culture. For children with non-upper respiratory focus of infection and presenting with hemodynamic compromise with a negative culture, antibiotics were administered for 7 days. Clinical and laboratory information was entered in a case record form at admission and during hospital stay. Ethical clearance was obtained from the institutional review board.

Microbiologically documented infection (MDI) was defined as a positive bacterial or fungal culture from a normally sterile body fluid or compartment, and detection of an antigen or product of polymerase chain reaction by a validated microbiologic method. Invasive fungal disease (IFD) were classified into possible, probable and proven infections according to the EORTC/MSG-2008 criteria [8]. Non-upper respiratory focus of infection (non-URI) was considered when there was history or clinical examination suggestive of other foci of infection, namely, chest signs suggesting involvement the lower respiratory tract, cutaneous manifestations (rash/nodule/ulcer), sinusitis, diarrhea, with/without pain abdomen, or involvement of the central nervous system. Neutropenic enterocolitis was diagnosed in presence of abdominal pain with febrile neutropenia and increased bowel wall thickness on ultrasound/CT. Presence of definite signs of inflammation of the perianal soft tissue, with or without presence of a fissure, was defined as perianal sepsis. A urinary tract infection was diagnosed in presence of a positive urine culture in a symptomatic child. Complications included events during the episode of FN that required active intervention beyond antimicrobial therapy. Undernutrition was defined as a Z score <–2SD for either weight-for-age (0-10 years), or height-for-age (0-12 years), or weight-for-height (0-5 years), or BMI-for-age (5-12 years) at the time of admission using the WHO standards [9].

Univariate analysis was used to screen for admission parameters potentially associated with high risk for MDI and mortality. Length of stay was used as a dichotomous variable (<5 days and ≥5 days) for the purpose of the initial bivariate analysis. Parameters associated with a high risk ($P$<0.02 by univariate analysis) were selected for logistic regression analysis. For each variable significantly associated with a high risk by logistic regression analysis, the risk ratio was calculated with the corresponding 95% confidence interval (CI). The cut-off points for C-reactive protein (CRP) level and platelet count were determined by constructing a receiver operator characteristic curve. All statistical analyses were performed using SPSS version 20.0.

## RESULTS

We studied 414 episodes of FN in 264 children. The median age was 5 years, with male to female ratio of 3:1. Majority of children were suffering from hematological malignancies (367; 88.6%). The cohort characteristics and the outcomes are detailed in ***Table* I**.

MDI was documented in 82/414 (19.8%) episodes; 59 (14.2%) had isolated bacterial infection and 16 (4.3%) had IFD. Eight (9.7%) had polymicrobial sepsis. Pneumonia was radiologically documented in 44 (10.6%). Commonest bacterial isolates included *Escherichia coli* (12; 17.9%), *Staphylococcus aureus* (9; 13.4%) and *Klebsiella pneumoniae* (7; 10.4%). Predominant isolates were from blood (63; 94%); other sources included urine (2; 3%), pus and ear discharge (1; 1.5% each). All patients with IFD had underlying hematological malignancies (ALL: 13, 81.2%; AML: 3, 18.7%). IFD were 'proven' in 6 (37.5%), 'probable' in 6 (37.5%), and 'possible' in 4 (31.2%). Fungi identified included, Mucor (2), Aspergillus (5), Candida (2) and Pseudallescheria (1).

Twenty-six percent (109/414) of episodes had complications. These included fluid-refractory shock (50; 12%), respiratory failure (50; 12%), neutropenic enterocolitis (22; 5.3%), acute kidney injury (19; 4.5%) and encephalopathy (16; 3.9%) (***Table* I**). Mortality rate was 10.3% (43/414; 8 with IFD, and 35 with bacterial sepsis). IFD resulted in 50% mortality. Median duration of

**TABLE I** BASELINE CHARACTERISTICS AND OUTOME OF CHILDREN WITH FEBRILE NEUTROPENIA (*N*=414)

| *Parameters* | *n* (%) |
|---|---|
| *Demographic characteristics* | |
| Males | 315 (76) |
| Underlying malignancy | |
| Acute lymphoblastic leukemia | 307 (74.2) |
| Acute myeloid leukemia | 38 (9.2) |
| Non-Hodgkin lymphoma | 16 (3.8) |
| Hodgkin lymphoma | 6 (1.4) |
| Solid tumours | 47 (11.4) |
| Chemotherapy interval ≤ 7 days | 141 (34.1) |
| Intensive phase of chemotherapy | 279 (67.4) |
| Temperature ≥39°C | 132 (32) |
| Under-nutrition | 70 (16.9) |
| Clinical focus of infection | 166 (40) |
| Upper respiratory focus | 57 (13.7) |
| Non-upper respiratory focus | 109 (26.3) |
| *Laboratory parameters* | |
| Hemoglobin ≤70 g/L | 56 (13.5) |
| Absolute neutrophil count ≤100/µL | 130 (31.4) |
| Platelet count < 20000/iL | 165 (60.1) |
| C-reactive protein > 90mg/L | 145 (35) |
| Albumin < 2.5 g/dL | 35 (8.5) |
| *Outcome* | |
| Discharged within 5 d of admission | 252 (60.9) |
| Discharged beyond 5 d of admission | 119 (28.7) |
| Died | 43 (10.4) |
| Microbiologically documented infections | 82 (19.8) |
| Bacterial infections | 65 (79.3) |
| Invasive mycoses | 16 (19.5) |
| Combined bacterial and invasive mycosis | 1 (1.2) |
| Complications | 109 (26.3) |
| Fluid refractory shock | 50 (12) |
| Respiratory failure | 50 (12) |
| Encephalopathy (non-metabolic) | 16 (3.9) |
| Miscellaneous metabolic complications | 64 (15.4) |
| Renal failure | 19 (4.5) |
| Neutropenic enterocolitis | 22 (5.3) |
| Congestive cardiac failure | 3 (0.7) |
| Coagulopathy and bleeding | 2 (0.5) |
| Gangrene | 1 (0.2) |
| Pleural effusion | 1 (0.2) |
| Liver abscess | 1 (0.2) |
| Complications needing admission to intensive care | 28 (6.7) |

hospital-stay was 5 days (IQR 3,8) for patients who were discharged, and 7 days (IQR 2,13) for patients who died. Sixty-five percent (270) patients had a hospital stay ≤5 days; 252 (93%) of these were discharged and 18 (7%) died. In those with a stay of >5 days (144; 35%), 119 (83%) were discharged and 25 (17%) died (*P*=0.001). Episodes with MDI (*vs* no MDI) were more likely to have complications (43 *vs* 66; OR 4.44; 95% CI 2.6-7.4), prolonged stay >5 days (67 *vs* 164; OR 4.5; 95% CI 2.5-8.3), and, mortality (26 *vs* 17; OR 8.6; 95% CI 4.3-16.8) (*P*<0.001).

Factors predictive of MDI on univariate analysis included: diagnosis of AML, chemotherapy interval ≤7 days, under-nutrition, presence of central venous line (CVL), presence of non-URI focus of infection, temperature ≥39°C, hemoglobin ≤70 g/L, absolute neutrophil count (ANC) ≤100/uL, platelet ≤20000/uL, CRP >90 mg/L, and albumin <2.5 g/dL. Among them, chemotherapy interval ≤7 days, a clinical focus of infection other than an URI, and platelet count <20000/µL at admission were independent predictors of MDI on multivariate analysis (***Table* II**).

Factors predictive of mortality on univariate analysis included: chemotherapy interval ≤7 days, presence of non-URI focus of infection, temperature ≥39°C, hemoglobin >70 g/L ,ANC ≤100/uL, platelet ≤20000/uL, CRP >90 mg/L, and albumin <2.5 g/dL. Significant predictors for mortality on multivariate analysis included interval from last chemotherapy ≤7 days, clinical focus other than URI, CRP >90 mg/L, and albumin <2.5 g/dL (***Table* II**).

On univariate analysis, risk factors for admission >5 days included: diagnosis of AML, chemotherapy interval ≤7 days, presence of non-URI focus of infection, temperature ≥39ºC, presence of CVL, ANC ≤100/uL, platelet ≤20000/uL, CRP >90 mg/L and albumin <2.5 g/dL. Significant predictors for a hospital-stay >5 days on multivariate analysis included diagnosis of AML and interval from last chemotherapy ≤7 days (***Table* II**).

## DISCUSSION

In the current study on children admitted with FN, 19.8% had microbiologically-documented infections; 26% developed complications, 28.7% were discharged beyond 5 days and 10.3% died. Children admitted within 7 days of the last chemotherapy, and having a non-upper respiratory focus of infection were at risk of developing MDI and dying. Platelet count <20000/uL was an additional predictor for MDI, while albumin <2.5 g/dL and CRP >90 mg/L were risk factors for mortality. Children with AML and those admitted within 7 days of chemotherapy were likely to have a stay beyond 5 days.

**TABLE II** RISK-FACTORS FOR MICROBIOLOGICALLY DOCUMENTED INFECTIONS, MORTALITY AND HOSPITAL STAY BEYOND 5 DAYS IN CHILDREN WITH FEBRILE NEUTROPENIA (*N*=414)

| *Risk factors* | *OR (95% CI)* | *P value* |
|---|---|---|
| *Risk factors for microbiologically documented infections* | | |
| Diagnosis of AML | 1.71 (0.67-4.29) | 0.25 |
| Chemotherapy interval ≤7 d | 3.60 (1.69-7.64) | 0.001 |
| Non-URI focus of infection | 1.96 (1.12-3.41) | 0.015 |
| Temperature ≥39°C | 1.67 (0.51-5.43) | 0.39 |
| Under-nutrition | 1.25 (0.63-2.49) | 0.51 |
| Central venous line | 0.81 (0.36-1.81) | 0.60 |
| Hemoglobin ≤70 g/L | 0.76 (0.44-1.32) | 0.33 |
| Platelet ≤20000/uL | 2.18 (1.04-4.54) | 0.03 |
| ANC ≤100/uL | 0.85 (0.40-1.79) | 0.67 |
| CRP >90 mg/L | 1.71 (0.85-3.44) | 0.13 |
| Albumin <2.5 g/dL | 1.16 (0.48-2.84) | 0.73 |
| *Risk factors for mortality* | | |
| Chemotherapy interval ≤7 d | 18.91 (2.34-152.52) | 0.006 |
| Non-URI focus of infection | 6.10 (2.5-15.0) | <0.001 |
| Temperature ≥39ºC | 1.24 (0.28-5.53) | 0.77 |
| Hemoglobin >70 g/L | 0.45 (0.15-1.35) | 0.15 |
| Platelet ≤20000/uL | 2.18 (1.04-4.54) | 0.03 |
| ANC ≤100/uL | 2.69 (0.71-10.21) | 0.14 |
| CRP >90 mg/L | 8.17 (2.21-30.24) | 0.02 |
| Albumin < 2.5 g/L | 3.03 (1.07-8.609) | 0.04 |
| *Risk factors for hospital stay >5 d* | | |
| Diagnosis of AML | 3.40 (1.41-8.34) | 0.007 |
| Chemotherapy interval ≤7 d | 1.77 (1.10-2.85) | 0.02 |
| Non-URI focus of infection | 1.38 (0.88-2.17) | 0.16 |
| Temperature ≥39ºC | 1.65 (0.62-4.38) | 0.31 |
| Central venous line | 1.46 (0.76-2.8) | 0.25 |
| Platelet ≤20000/uL | 1.81 (0.98-3.35) | 0.057 |
| ANC ≤100/uL | 1.63 (0.97-2.71) | 0.06 |
| CRP > 90 mg/L | 2.21 (0.79-6.17) | 0.13 |
| Albumin < 2.5 g/dL | 1.87 (0.82-4.30) | 0.14 |

*AML: Acute myeloid leukemia; ANC: Absolute neutrophil count.*

The study was performed prospectively and included 414 episodes of FN treated uniformly, as in-patients, following a strict protocol. The limitation of this study was that it was restricted to a single center. The results are more likely to be relevant in low- and middle-income countries as a higher number of episodes are likely to have a definite focus of infection at admission in these settings [10-15]. The microbiological spectrum is also different from high-income countries.

Predictors of prolonged hospital stay among adults with cancer-associated FN have included a diagnosis of a hematological malignancy, high-dose chemotherapy, prolonged neutropenia, and bloodstream infection with gram-negative, multi-drug-resistant bacteria [16]. In a pediatric study, the diagnosis of AML had predicted stay beyond 5-days [17]. Patients with Hodgkin lymphoma, soft tissue sarcoma, and ovarian/testicular tumours had shorter stays [5]. On the other hand, time since the last chemotherapy of ≤7 days has been reported to predict the risk of invasive bacterial sepsis in a study of 447 pediatric FN episodes from Chile [3]. A study from Argentina has shown an overt clinical site of infection to be associated with mortality [15]. A clinically identified focus, barring those with an upper respiratory focus, has predicted the risk of serious complications in a study from Brazil [15]. Mueller, *et al.* [5] reported that upper respiratory infection (6%) and acute otitis media (3.7%) were associated with a shorter hospital stay. The absence of clinical signs of a viral infection has also been shown to be a risk-factor for bacterial sepsis [18]. Thrombocytopenia at different cut-offs has been associated with MDI [3,16,19]. In particular, Badiei, *et al*. [20] demonstrated a significant association between a platelet count <20000/mm$^3$, and life-threatening infections. Thrombocytopenia acts as a surrogate marker for marrow suppression and increased consumption in sepsis. A low albumin has predicted inferior outcomes in many disease states including FN. Hypoalbuminemia reflects a complex interplay of an inflammatory state with hepatic function and glomerular filtration, and is not simply a marker for undernutrition [21]. CRP, a relatively inexpensive biomarker, has been well studied in FN [3,18]. A direct association between elevated CRP, and the duration of FN, bacteremia, and mortality, has been previously reported [22]. A study from India reported CRP to be a good tool for diagnosing infections, and suggested that serial monitoring to be useful in assessing response to antibiotic therapy in pediatric FN [23]. A previous study in the unit has demonstrated that CRP was the strongest predictor of complications in pediatric FN [24].

In the current study, we have attempted to identify risk factors present at admission, which would help predict MDIs, mortality and prolonged hospital stay in pediatric FN. Identifying such patients at 'high risk' can optimize management by timely and rational use of antibiotic regimens, heightened anticipation and monitoring for complications, and resource allocation for finances and logistics. This may have implications in resource-limited settings, where treatment-related mortality and morbidity are higher as compared to the developed nations.

**WHAT IS ALREADY KNOWN?**

- Children with febrile neutropenia have a heterogeneous outcome, and all do not need equally aggressive antimicrobial therapy or prolonged admission.

**WHAT THIS STUDY ADDS?**

- Risk factors for microbiologically-documented infection, mortality, and hospital stay beyond five days are provided.

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