Febrile Neutropenia Syndromes in Children: Should Management Differ for Primary, Persistent, Recurrent or Engraftment Fever?

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Febrile neutropenia (FN) is a common condition in children receiving chemotherapy and can be life-threatening.

Four FN syndromes have been described: Primary, Prolonged, Recurrent and Engraftment fever.

Whether the diagnostic and therapeutic approach should differ for these FN syndromes remains uncertain and has been named a research gap in the recent International Pediatric Fever and Neutropenia Guideline 2017.2

There is no consensus approach or good quality evidence regarding the management of recurrent FN, resulting in varied clinical practice. Most experts group persistent and recurrent FN together as one entity.

To characterize FN syndromes which may inform the clinical approach to the diagnosis and treatment of FN in pediatric cancer.

Retropective medical record review was performed in all pediatric cancer patients with a diagnosis of FN in the pediatric oncology unit at University of Chicago Medicine Comer Children’s Hospital from July 2009 to July 2016.

Each episode of FN (by IDSA definition)3 was further characterized as one of the four following syndromes: 

1. Primary: Responsive to empiric antibiotic therapy
2. Prolonged: Fails to defervesce after at least 5 days of broad spectrum antibacterial therapy
3. Recurrent: The new onset fever or clinical worsening occurs within 4 days of neutrophil recovery

Exclusion criteria: All episodes of fever in patients with ANC<500/L and/or without drop to <500/L, within 48 hours.

For patients with more than one admission for FN, each admission was counted as a separate episode.

Patient demographics and clinical outcomes were compared by syndrome using chi-square and t-test where appropriate to evaluate for differences in presentation, etiologies of fever and clinical outcomes.

A total of 562 FN episodes (FNEs) were identified in 189 patients.

63% of FNEs occurred in patients with hematologic malignancy, 24.4% occurred s/p SCT (Table 1)

FNEs were categorized as primary (67.3%), prolonged (18.5%), recurrent (9.6%), and engraftment fever (4.6%) (Figure 2)

Bacteremia was documented in 23.4% of FNEs. Fungal infection was documented in 9.4% FNEs (Table 2).

Comparison of recurrent and prolonged FNEs reveals that proven fungal infections occurred more often (11% vs 1%) (P<0.015) and mortality was increased 13% vs 3.8% (P=0.07) in patients with recurrent fever (Table 3).

Recurrent FNE has higher mortality than prolonged and primary FN possibly attributed to higher rates of fungal infection. Engraftment fever is associated sometimes with poor outcomes (Figure 3).


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FN is not one entity. FN syndromes should be recognized separately to define the most likely etiologies of FN and to optimize the diagnostic and therapeutic approach to each patient.

When compared to patients with prolonged fever, patients with recurrent FN are more likely to have invasive fungal infections and increased mortality.

Evaluation for fungal infection and the addition of empiric antifungal therapy should be strongly considered in patients presenting with empiric fever.

Prospective studies are needed to inform approaches in medical management depending on the presenting FN syndrome and patient risk factors.

References


