Management of Febrile Neutropenia in Children: Current Approach and Challenges

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Abstract

Neutropenia can result from failure, infiltration, or suppression of the bone marrow due to nonmalignant disorders, cancers, chemotherapy, radiation, or a combination of these. Febrile neutropenia (FN) is a hemato-oncological emergency and is an important cause of death in immunocompromised children. Prompt and stepwise management of FN helps to minimize the morbidity and mortality considerably. In resource-constraint countries, additional challenges can be encountered during the treatment of fever in neutropenic patients. In India, many children with FN are initially treated at regional centers and later referred to tertiary units if needed. Pediatricians should hence be familiar with the treatment algorithm and specific issues related to the management of FN.

Keywords: Antibiotic resistance, Febrile neutropenia, Risk, Supportive care.

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Introduction

Low neutrophil count is an important cause for septicemic deaths in children globally. In hemato-oncological practice, febrile neutropenia (FN) is the most commonly encountered medical emergency. In India and many resource-poor countries, there is a relatively high incidence of bacterial, fungal, and opportunistic infections. The emergence of antimicrobial drug resistance further compounds this problem. Thus, the management of FN can be particularly challenging in the Indian scenario. Most of the published literature on treatment has been on children following cancer chemotherapy. However, other nonmalignant neutropenic disorders can also be associated with high morbidity and mortality. This review is to provide a stepwise approach and to highlight the challenges faced by clinicians in the management of febrile episodes in children with neutropenia.

Definition and Problem Statement

Neutropenia is a decrease in circulating neutrophils in the nonmarginal pool. It is classified into mild, moderate, severe, and profound, with absolute neutrophil counts (ANC) of 1,000–1,500, 500–1,000, 100–500, and <100 cells/mm^3, respectively.[1,2] The Infectious Diseases Society of America (IDSA) defines clinically severe neutropenia as ANC <500 cells/mm^3 or <1,000 cells/mm^3 with an anticipated decline to less than 500 within 48 hours.[3] In neutropenic children, fever may be the only sign of a serious systemic infection, as they are often unable to mount an appropriate inflammatory response. FN is the presence of a single oral or tympanic temperature ≥101°F (38.3°C) or two persistent temperatures ≥100.4°F (38°C) at least 1 hour apart in a neutropenic patient.[4]

The incidence of FN varies according to the underlying disease and intensity of treatment. It is frequently encountered in children with bone marrow failure syndromes, marrow infiltrative disorders, following chemotherapy, after hematopoietic stem cell transplantation (HSCT), primary immunodeficiency states, and hemophagocytic lymphohistiocytosis. Other causes such as viral infections, drugs, autoimmunity, and cyclical neutropenia rarely

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result in life-threatening complications, as these children typically do not have profound and prolonged neutropenia.

Prior to the 1970s, febrile neutropenia in pediatric patients used to be highly fatal. With dedicated hemato-oncology nursing, early interventions, improved supportive care, and availability of newer antimicrobial agents, the outcome is now much better. In developed countries, 0.7–3.9% of all FN episodes currently result in death.[5,6] For middle- and low-income countries, mortality rates are considerably higher at 4–13.2%.[7–10]

Patient Characteristics and Risk Stratification

Many variables can have an impact on the outcome of infective episodes in children with FN (Table 1). These include the severity of neutropenia, functional capacity of neutrophils, anticipated recovery of neutrophil count, absolute monocyte count (AMC), mucocutaneous breach or other foci for entry of pathogens (mucositis, impetigo, pressure sores), presence of a central venous catheter (CVC), and the exposure to other immunosuppressive medications. Malnutrition is known to play an important adverse prognostic role.[7]

Based on some of these parameters, FN has been risk stratified, particularly in children who have received cytotoxic chemotherapy (Table 2).[11–20] High-risk group is associated with increased probability of having a microbiologically documented infection and/or clinical

complications, especially intensive care unit admissions and mortality. Earlier studies were simplistic and had merely taken into account peak temperature, AMC, and ANC.[11–13] More recent analyzes have focused on additional parameters, including the underlying diagnosis, intensity of myelosuppressive treatment, duration of neutropenia, presence of bacteremia, hemodynamic variables, mucositis, and radiographic lung changes.[14–20]

Risk stratification of FN serves multiple purposes such as the choice of initial antibiotics, decision to admit in hospital, duration of therapy, anticipation of unusual infections, need for intensive care monitoring, de-escalation of antimicrobial regimen, estimation of cost of treatment, and even predicting the probability of mortality. Risk based approach to children with FN has been incorporated into clinical practice in Western countries since many years.[21,22] Its applicability and safety in the Indian scenario is yet to be established. A recent study by Kumar et al. has demonstrated that children with

low-risk FN can be treated with empirical intravenous antibiotics in an outpatient setting.[23] The study also showed that treatment can safely be discontinued after a 24-hour afebrile period.[23] However, it must be noted that outpatient-based management is not yet the standard of care in resource-poor countries.

DIAGNOSTIC TESTS IN FEBRILE NEUTROPENIA

FN is typically a clinical diagnosis, with well-established definition criteria, as described above. Management of these children is generally protocol based and similar, at least during the initiation of therapy. However, it is not uncommon to have persistence of fever spikes even after escalation of treatment up to third- or fourth-line antimicrobial combinations. In such situations, accessory diagnostic tests may be informative in clinical practice.

Blood culture is by far the most contributory test in any child with FN, albeit its low yield of 20–30%.[8,10] Identification of bacteremia and delineation of its antibiotic sensitivity pattern guide the clinicians. Biomarkers are of debatable value in severely neutropenic patients, but some studies have shown good discriminatory power for serum procalcitonin level compared to C-reactive protein.[24,25] A simple laboratory test such as a peripheral smear is useful in children with profound neutropenia following myeloablative conditioning for HSCT. In such patients, appearance of even 3–4 neutrophils in a previously empty smear is reassuring and is a reliable predictor of engraftment. Ongoing pyrexia despite negative blood cultures and escalation of antibiotics raises the concern of invasive fungal infections and *Pneumocystis carinii*. Selected patients may thus benefit from bronchoalveolar lavage, serial galactomannan levels, urine culture, high-resolution computed tomography (CT) scan of thorax, transesophageal echocardiogram, and rarely, tissue diagnosis.

Table 1: Factors affecting the outcome of febrile neutropenia

Pretreatment variables	Parameters during treatment
Severity of neutropenia	Time to first dose of antibiotics
Duration of neutropenia	Hemodynamic instability
Protein energy malnutrition	Microbiologically documented infection
Severe mucositis	Persistence of fever beyond 72 hours
Absolute monocyte count	Persistence of neutropenia beyond 5 days
Presence of central venous catheter	Multidrug-resistant organisms
Prior exposure to immunosuppressants	Organ impairment

Table 2: Studies on risk stratification of febrile neutropenia in pediatric oncology[11–20]

Study	Year	Sample size and risk parameters	High risk
Rackoff et al.[11]	1996	Peak temperature, AMC	AMC <100 cells/mm^3, Temperature >39°C
Klaassen et al.[12]	2000	AMC	AMC <100 cells/mm^3
Baorto et al.[13]	2001	AMC, ANC	AMC <100 cells/mm^3, ANC <500 cells/mm^3
Alexander et al.[14]	2002	AML, Burkitt lymphoma, ALL in induction, progressive or relapsed disease, hypotension, tachypnea, hypoxia 94%; new CXR changes, altered mental status, severe mucositis, vomiting, abdominal pain, focus of infection	Presence of ANY of these
Ammann et al.[15]	2004	Temperature >39°C, comorbidity requiring in-patient care, WBC <1,000 cells/mm^3, disease not in remission	Presence of ANY of these
Paganini et al.[16]	2007	714 FN episodes. Advanced stage malignancy (3), Co-morbidity (2), Bacteremia (1)	Risk of mortality 5.8%, 15.4% and 40% for scores of 4, 5 and 6 respectively.
SPOG-AE[17]	2008	Preceding chemotherapy more intensive than ALL maintenance (4), hemoglobin <9 g/dL (5); WBC <300 cells/mm^3 (3), platelet <50,000/mm^3 (3)	Total score ≥9 identifies children at risk for ICU admission or death.
Hakim et al.[18]	2010	332 FN episodes. Type of malignancy: AML (20), ALL/lymphoma (7), solid tumor (0); Seriously unwell (14); Temperature ≥39°C (11); ANC <100 cells/mm^3 (10)	Total score ≥24 for invasive bacterial disease. Total score ≥19 for clinical complications.
SOPG-Bacteremia[19]	2011	423 FN episodes. Shaking or chills (5); Hb ≥9 g/dL (3); platelet <50,000/mm^3 (3); Other need for in patient care (3)	Identifies children at risk for bacteremia.
PICNICC[20]	2016	Peak temperature, clinically unwell, malignancy type, total WBC count, hemoglobin level, AMC	Developed from meta-analysis of 22 studies. Predicts high risk for MDI.

Scores are provided in brackets. AMC, absolute monocyte count; ANC, absolute neutrophil count; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; ICU, intensive care unit; CXR, chest x-ray; WBC, total white blood cell count; FN, febrile neutropenia; AE, adverse event; MDI, microbiologically detected infection

CHOICE OF ANTIMICROBIAL AGENTS

The time duration from onset of fever to administration of the first dose of intravenous antibiotics is an important predictor of early mortality in children with FN.[26] This dose is ideally to be commenced within 60 minutes of arrival to the hospital. If the child has a CVC, blood culture should be drawn from all its lumens and labeled appropriately. In other situations, peripheral venous samples must be drawn in aerobic and anaerobic culture media. Institutional susceptibility patterns based on blood culture results should be given due consideration when selecting the intravenous antibiotic regimen.

The current guidelines recommend an antipseudomonal β-lactam drug as the first-line antibiotic.[3,4] It is often combined with an aminoglycoside in high-risk and/or unstable children. The combination provides coverage against most gram-negative bacilli responsible for immediate mortality and has reasonable activity against gram positive organisms. In clinical practice, piptazobactam 90 mg/kg Q6H is usually combined with amikacin 15 mg/kg Q24H. Serum creatinine needs to be closely monitored, as aminoglycoside drug level estimation is not easily available in India. If clinically and hemodynamically stable, this first-line regimen can be continued for up to 48 hours even if the child remains febrile. Blood culture and sensitivity reports should guide the subsequent management.

Escalation of antibiotics will be required if the child has persistent fever and is especially important in the presence of a CVC. This second-line regimen must provide wider coverage against drug-resistant gram-negative pathogens and should possess bactericidal action against gram-positive organisms, including *Streptococci* and *Staphylococci*.[3,4] The recommended choice is a carbapenem with a glycopeptide antibiotic, such as meropenem at neutropenic dose of 20 mg/kg Q8H and teicoplanin 10 mg/kg Q12H for three doses, then Q24H. It is prudent to discontinue the initial antibiotics and draw a fresh set of blood cultures before changing to second-line treatment. Alternative choices are imipenem–cilastatin with vancomycin. Linezolid is generally avoided in neutropenic patients due to the risk of further bone marrow suppression.

At 96 hours, persistent fever especially if blood cultures are sterile requires the addition of empirical treatment against invasive fungal infections.[3,4] In children who have already been on a prophylactic antifungal medication as part of their hemato-oncology treatment regimen, another class of antifungal drug should be chosen for empirical therapy. Often, this involves changing from an oral azole to intravenous liposomal amphotericin or an echinocandin. HRCT thorax and ultrasonogram of abdomen are useful screening investigations to identify foci of invasive fungal infection.

Emerging carbapenem-resistant, gram-negative bacilli is an increasingly common cause of mortality in India. Colistin, polymyxin-B, and fosfomycin are available options in such situations. In practice, early addition of intravenous colistin may be warranted in an unstable child with septic shock, even if blood cultures do not demonstrate carbapenem-resistant gram-negative bacilli. More recent drugs such as ceftazidime–avibactam combination must be used restrictively and ideally only if the sensitivity pattern shows pan-resistance to all other antibiotics.

Vigorous supportive care, including fluid and electrolyte management, inotropes, ventilation, use of granulocyte colony-stimulating factors in selected cases, blood product transfusions, enteral or parenteral nutrition, and removal of CVC, is equally important in sick children with profound and prolonged neutropenia.

DE-ESCALATION AND DURATION OF TREATMENT

Antibiotics can be discontinued in a clinically stable child if blood culture is sterile, with an afebrile period of at least 24 hours and absence of profound neutropenia, ie., ANC $\geq200/mm^3$. If the child is expected to remain severely neutropenic, de-escalation of antibiotics to third-generation cephalosporins may be considered. In children who had an initial positive blood culture, it is recommended to repeat the culture 48 hours later and continue antibiotics for 7 days from the first negative culture. This is especially important in those with CVCs. Empirical antifungal therapy is usually discontinued as soon as the episode of FN resolves. In probable or proven fungal infections, systemic antifungal therapy is required for a minimum of 2 weeks and can be changed to an oral prophylactic drug once the neutrophil count has recovered $>1,500/mm^3$.

CHALLENGES IN THE MANAGEMENT

Delay in Commencement of Treatment

The ability to commence antibiotics early remains the single biggest challenge in clinical practice.[26,27] In India, especially in non-urban centers, delays are encountered both in getting the child to the hospital and in the prompt initiation of antibiotics in the emergency department.[27] Parental education about the high mortality of FN and the need for immediate action needs to be reinforced at every visit. Emergency department should have strict protocols in place to prioritize and fast-track the care of FN patients.[26]

High Prevalence of Malnutrition

Poor nutritional status is an adverse prognostic factor both due to reduced tolerance to chemotherapy as well as high mortality from infections. Prasad et al. analyzed 250 episodes of FN in Indian children, of which as many as 110 (44%) were found to be associated with grades 2–4 protein energy malnutrition (PEM).[7] Often, the underlying disease process such as acute leukemia or aplastic anemia is aggressive and warrants immediate treatment. Usually, the pediatrician does not get the opportunity to fully address the nutritional status when treating these patients. As a result, FN can be associated with higher death rates, and this poses an additional challenge in resource poor countries. Every effort must be taken to ensure that PEM is corrected alongside the definitive treatment of the underlying hemato-oncological disorder.

Applicability of Risk Stratification

The main objective of risk stratification is to identify a subset of children in who FN can be managed on an outpatient basis, thereby reducing the cost and workload on the hospital.[22] In India, this approach has been proposed by centers of excellence with high patient load.[7] However, it should be noted that this is a potential double-edged weapon. An essential prerequisite is that the child should be closely monitored at home, and the parents should be to get the patient back to hospital promptly in case of any deterioration. Established tools such as the MASCC risk index (multinational association for supportive care in cancer) used in adult patients are not to be applied to children.[28]

Antimicrobial Resistance

Multidrug-resistant microorganisms with high fatality is a growing concern worldwide and especially so in India. Various working groups have highlighted the ongoing issue of antibiotic misuse in the community.[29,30] In the absence of regulations by health authorities, it is difficult to restrict the use of antibiotics in general practice. Concern has also been raised about the rampant antibiotic usage on poultry and farm animals.[31,32] In addition, many children with FN have a prior history of repeated admissions, and thus a higher chance for contracting drug-resistant nosocomial infections. The past two decades have witnessed an increase in extended spectrum beta-lactamase (ESBL) producing gram-negative bacteria, vancomycin-resistant *Enterococci* (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[4] The recent reports of *Klebsiella pneumoniae* strains resistant to colistin and polymyxin B are particularly worrying.[33,34]

Newer Fungal Infections

With bone marrow suppressive intensive chemotherapy protocols and wider use of HSCT, there is increased incidence of opportunistic fungal infections. Mucor, non-*Candida albicans* strains, and resistant aspergillosis are increasingly being encountered. Fluconazole-resistant yeast, such as *C glabrata and C krusei*, are frequently reported in neutropenic patients.[4] Previously unidentified fungi are getting established as human pathogens.[35,36] Thus, over the past decade, drug-resistant human fungal infection has been emerging as a serious concern.[37]

Community Transmission of Covid-19, H1N1, SARS

FN is typically associated with a higher incidence of bacterial and fungal infections. Cell-mediated immunity is relatively intact, and hence viral infection is not usually a common problem, except for disseminated *Varicella*. However, during pandemics such as the recent COVID-19, neutropenic children have been at particularly high risk, both for contracting the infection and for mortality.[38] Outbreaks are sudden and unexpected and clinicians are required to adapt quickly. Healthcare teams are often left with insufficient time and resources to prepare against these adversities.

High Cost of Supportive Care

Although supportive care has improved significantly, many families are still unable to afford the formidable cost. This cost can be higher than the expenditure for definitive treatment for the underlying disease. Daily use of systemic antifungals and higher end antibiotics are beyond the reach of many self-funding parents. Upfront clear and dedicated counseling sessions must form an integral part of treatment of every hemato-oncological disorder. This will enable parents to take informed decisions and make necessary logistic arrangements. In addition to support from health authorities, there is a role for NGOs and crowd-funding organizations in making supportive care affordable.

Concurrent Immunosuppressants

A small but significant subset of children are likely to be receiving immunosuppressive therapy during an episode of FN. Children with aplastic anemia may be on treatment with cyclosporine or antithymocyte globulin. Children post-HSCT are likely to be on steroids or tacrolimus as graft vs host disease prophylaxis. Prolonged prior exposure to immunosuppressive drugs increases the risk for opportunistic infections such as tuberculosis,

aspergillosis, mucor, cytomegalovirus, adenovirus, herpes simplex, and disseminated varicella. These children should be managed at tertiary care centers as far as possible.

Conclusion

FN is a leading cause of death in children following chemotherapy and in those with bone marrow failure syndromes. Although newer antimicrobials are entering the market regularly, the emergence of multidrug-resistant gram-negative bacilli and fungal infections are major concerns. The cost of medications and supportive care are often prohibitive for low-income families. Clinicians should be aware of the direct correlation between the time to initiation of antibiotics and early mortality in children with FN. A stepwise approach to treatment will avoid over treatment and achieve the best possible outcome. Pediatricians must give sufficient attention to the additional challenges encountered in neutropenic children in resource-poor countries.

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