Chapter 78

Indian Guidelines for Febrile Neutropenia

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INTRODUCTION

The Indian Society of Medical and Pediatric Oncology (ISMPO) released guidelines for fever with neutropenia in 2002. Febrile neutropenia (FN) is fever associated with abnormally low neutrophil count signifying an immunocompromised state secondary to malignancy or its treatment and is a common and often critical condition that adversely impacts the prognosis of patients. It is a medical emergency.1

The guidelines are aimed at standardizing patient care and bringing in uniform practices across the country. Emphasis was particularly given on the concept of prompt empirical antibiotic therapy to maximize efficacy. It was reiterated that these guidelines need to be dissipated amongst medical colleges and primary healthcare centers, private practitioners and primary care physicians, who maybe the first point of contact for these patients. This may serve as reference to standardize patient care throughout the country. The guidelines are at par with Guidelines of International Organizations, e.g. American Society of Clinical Oncology (ASCO), Infectious Disease Society of America (IDSA) and the National Cancer Comprehensive Network (NCCN).

The mortality rate of FN has diminished steadily but remains significant. Overall mortality rates are 5% in patients with solid tumor (1% in low-risk patients) and as high as 11% in some hematological malignancies. Though there have been major advances in prevention and treatment of FN, this still remains one of the most feared complications of cancer chemotherapy. Prognosis is worst in patients with proven bacteraemia, with mortality rates of 18% in Gram-negative and 5% in Gram-positive bacteraemia.2

DEFINITION

Febrile neutropenia is defined as single oral temperature of 38.3°C (101.4°F) or 38.0°C (100.4°F) over 1 hour with less than 500 neutrophils/mm³ or less than 1,000 neutrophils/mm³ with a predicted decline to 500/mm³ over the next 48 hours. In some situations, where fever may not be there but obvious infection is present and absolute neutrophil count (ANC) is low, it may be treated as FN.3 The single most important determinant of neutropenic fever is the ANC less than 100 and the duration of neutropenia (> 14 days).

WHY IS FEBRILE NEUTROPENIA IMPORTANT?

It is considered an Oncological Emergency and any delay in treatment actually leads to significant morbidity and mortality. The socioeconomic impact of such episodes and their management along with the potential delays in effective anticancer treatment compels us to give high priority to prevention of neutropenic fever.4

Pathogenesis

In addition to neutropenia, disruption of mucociliary barriers, extensive use of invasive devices and shifts in inherent microbial flora due to prolonged antimicrobial usage predispose these patients to infection. Besides these, qualitative defects in neutrophil function described in hematological malignancies also contribute to FN.5 With impaired immunity, opportunistic organisms in the host or environment such as Pneumocystis jiroveci and molds become potential pathogens. Additionally, in immunocompromised host, polymicrobial infections are not unusual and nosocomial, multidrug resistant microbes are often observed. Patients may become colonized with resistant strains of organisms, e.g. extended spectrum beta lactamase (ESBL) producing strains of Gram-negative organisms (E. coli, Klebsiella, Pseudomonas), methicillin-resistant strain of Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE). Though Gram-negative infections still predominate in most of the centers in India, the incidence of Gram-positive infections are on the rise. Incidentally, Western literatures report a dominance of Gram-positive organisms in FN.

Amongst fungal infections, Candida spp. and Aspergillus sp. are common in the neutropenic host. The increase in incidence of Candida non-albicans and invasive aspergillosis in many institutions and in certain patient populations such as transplant recipients is of great concern. Aggressive chemotherapy with prolonged periods of neutropenia, improved culture techniques and increasing use of antifungal agents for prophylaxis are some of the factors that could be related to the changing trend of fungal pathogens.

Parasites and viral infections are other important causes of primary infections or cause secondary complications. Pneumocystis jiroveci is an important cause of pneumonia, especially in patients receiving corticosteroids. Herpes simplex virus (HSV), varicella-zoster virus (VZV) and cytomegalovirus (CMV) are the most prevalent among viral pathogens.6

The role of empirical antibiotics to reduce morbidity and mortality in FN has long been recognized. In 1966, Bodey and colleagues demonstrated that the risk of infection clearly increased when ANC dropped below 1,000/mm³ with a marked increase when the ANC was below 500/mm³.7 Schimpff et al. demonstrated a better outcome in patients with neutropenic fever who were treated with empiric antimicrobial therapy.8 Following this there were two studies from the National Cancer Institute showing that continuation
of antibiotics even after resolution of fever in patients who remain neutropenic and empiric addition of antifungals in patients with persistent neutropenic fever were associated with better outcome.

**Risk Stratification**

The Multinational Association for Supportive Care in Cancer (MASCC) Index Score for identifying low-risk febrile neutropenic cancer patients is shown in Table 1.

The maximum value in this system is 26, and a score of less than or equal to 21 predicts a less than 5% risk for severe complications and a very low mortality (< 1%) in FN patients. According to the MASCC prognostic index (detailed further down): as low as 3% if the MASCC score is more than 21, but as high as 36% if the MASCC score is less than 15.  

Apart from these risks, poor nutritional status, impaired renal and hepatic function, diabetes and prolonged steroid therapy are some of the other risk factors which a clinician needs to consider in FN.

Major sites of infection are the alimentary tract (i.e. mouth, pharynx, esophagus, intestine, and rectum), sinuses, lungs, genitourinary tract, skin. Neutropenic enterocolitis is a life-threatening condition caused by mixed aerobic and anaerobic Gram-negative bacilli (including *Pseudomonas* and *Clostridium* species).  

**Management Strategies**

Local doctors must consider FN as medical emergency and manage instantly based on infrastructure, use empiric antibiotics and should refer the patient to a higher center if there is high-risk. The other recommendations from the panel for Indian Guidelines for FN are:

- Utilize data from Indian Journal of Microbiology for prevalence of organisms and sensitivity patterns
- Collect data from public and private tertiary cancer and multispecialty hospitals
- Consider using clinical pharmacist and/or infectious disease specialist as and when needed
- Curb over the counter availability of antibiotics
- Profile of infection data between solid and hematological malignancies need to be distinguished.

**Lab Investigations**

- A complete hematological and biochemistry profile should be done. The latter is done to assess comorbidities, any end-organ effects of sepsis and to determine if any antibiotic dose modifications or contraindications apply
- *Blood culture*: Initial blood cultures should be collected as soon as possible. Follow-up cultures should preferably be collected during the phase of mounting fever. Samples should be taken both for aerobic and anaerobic cultures from peripheral/central and from any indwelling IV lines. Urinalysis and urine culture (caution: absence of pus cells on urinalysis does not rule out urinary tract infection (UTI) in the setting of neutropenia), sputum Gram stain and culture if productive cough. Lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis should not be done routinely. Cultures from catheter tips also need to be sent in specific circumstances.

- **Imaging investigations**: Chest X-ray should be obtained even in the absence of pulmonary symptoms or signs. Pulmonary infiltrates may not develop until the neutropenia begins to recover. Thoracic computed tomography (CT) has not been shown to improve outcomes in the absence of clinical pulmonary abnormalities but can be considered in the setting of clinical abnormalities and a normal chest X-ray. Specially, in the index of suspicion for invasive pulmonary aspergillosis. Other imaging tests should be guided by the clinical picture (e.g. CT scan abdomen for hepatosplenic candidiasis). Piperacillin tazobactam may interfere with galactomannan assay (required for the diagnosis of invasive aspergillosis).

**Approach**

The first approach is to quickly initiate empiric intravenous monotherapy after sending necessary samples for culture sensitivity.

A study was performed in a tertiary care cancer hospital in India with the objective to describe the profile of infections in FN in acute leukemia and hematopoietic stem cell transplant (HSCT) recipients with emphasis on response to therapy and outcome. Of the 200 episodes enrolled, acute leukemia induction comprised 40.5%, consolidation with high-dose cytarabine 22.5%, HSCT 29% (auto-HSCT 84%) and others 8%. Microbiologically documented infections comprised only 30% of episodes, while bacteremia was documented in 26% episodes. Gram-negative isolates were more common (55.7%). Cefoperazone-sulbactam had the highest *in vitro* efficacy against Gram-negative rods. Carbapenem resistance was most prevalent among *Acinetobacter* spp. (80%) and *Pseudomonas aeruginosa* (50%). Among high-risk FN patients, in spite of a high level of resistance to antibiotics, a frontline regime containing cefoperazone-sulbactam could restrict the use of imipenem, resulting in an acceptable mortality of 8%, thus increasing cost effectiveness.

Panelists for Indian Guidelines stress on intravenous dual therapy with an aminoglycoside plus an antipseudomonal penicillin (with or without a beta-lactamase inhibitor) or an extended spectrum antipseudomonal cephalosporin. Aminoglycoside use carries the inherent risk of renal toxicity. These toxicities require careful monitoring and necessitate frequent reassessment, but once-daily aminoglycoside dosing may diminish such renal toxicity. Linezolid or teicoplanin can be administered to patients harboring VRE.

Consider vancomycin if no remission of fever in next 48 hours. Vancomycin should not be considered as an empiric routine component of initial therapy for fever and neutropenia because of the risk of emergence of vancomycin-resistant organisms. Initial vancomycin therapy should be considered for serious infections associated with the following clinical situations:

- Clinically apparent, serious catheter-related infection
- Substantial mucosal damage and high-risk for infection with penicillin-resistant viridans streptococci [especially patients receiving prophylaxis with quinolone antibiotics or trimethoprim/sulfamethoxazole (TMP/SMX)]
- Blood culture positive for Gram-positive bacterium prior to final identification and susceptibility testing
- Known colonization with penicillin/cephalosporin resistant pneumococci or methicillin-resistant *Staphylococcus aureus*
- Hypotension or septic shock without an identified pathogen.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>The Multinational Association for Supportive Care in Cancer Index Score</th>
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<tbody>
<tr>
<td><strong>Characteristic</strong></td>
<td><strong>Point score</strong></td>
</tr>
<tr>
<td>Burden of illness:</td>
<td></td>
</tr>
<tr>
<td>No or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or no previous fungal infection in hematologic tumor</td>
<td>4</td>
</tr>
<tr>
<td>outpatient status</td>
<td>3</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Aged &lt; 60 years</td>
<td>2</td>
</tr>
</tbody>
</table>
Hematology

Vancomycin should be discontinued in 2–3 days if a resistant Gram-positive infection is identified and if clinically appropriate (see above). If fever persists beyond 5 days then add empiric antifungals.

For interstitial infiltrates, consider fluoroquinolone, macrolide or doxycycline to cover mycoplasma and legionella, empiric TMP/SMX or pentamidine (for sulfurredic patients) for patients at high-risk from Pneumocystis jirovecii pneumonia and antivirals like rimantadine, amantadine during influenza season.

Fungal infections are very common in neutropenic patients. Candida albicans have recently been surpassed by non-albicans species in neutropenic patients and these bugs are resistant to fluconazole. With the widespread use of fluconazole in the 1990s as prophyaxis in high-risk patients with acute leukemia and transplant recipients, empiric antifungal therapy for neutropenic fever principally involved switching from fluconazole to amphotericin B, to broaden the antifungal spectrum to include molds, but at the expense of greater toxicity. The newer lipid formulations of amphotericin B are significantly less toxic. Voriconazole or echinocandins can also be used in candidemia with acceptable toxicity. Voriconazole is approved for use in invasive aspergillosis. The availability of lipid formulations of amphotericin B, newer azoles and echinocandins have prompted many centers to use these agents prophylactically in hematological malignancies and transplant recipients.6

Duration of Antimicrobial Therapy

Depends on clinical course, neutropenia recovery, antimicrobial toxicity, results of cultures and opinions of infectious disease specialists. The study by Pizzo et al. was the first to highlight the importance of continuing antibiotics in neutropenic patients who became afebrile after a prolonged fever.7

If a definite focus of infection is identified by investigations such as a UTI or pneumonia, the treatment duration should be appropriate for that specific infection. If a pathogen is identified in the blood cultures, especially Gram-negative bacilli, generally a 10–14 day course of antibiotics is recommended. If no source is identified either clinically or from blood cultures, antibiotics can be stopped if the patient is afebrile and the ANC has recovered to 0.5 × 109 cells/L although some recommend a minimum of 7 days of therapy. If the fever resolves but the ANC is still low then there is no consensus on duration of antibiotics but a reasonable strategy would be to continue the antibiotics for another 5–10 days depending on the clinical picture. If still the neutropenic patient is unstable or has significant mucositis, antibiotics should be continued for at least 14 days even if afebrile.8

Step-Down to Oral Antibiotics

Patients who have rapidly improved on IV antibiotics and who are afebrile, hemodynamically stable and no longer neutropenic, can be switched to an appropriate oral regimen for the balance of the chosen antibiotic duration. If these patients are stable, have controlled comorbidities and a safe home environment with good backup by caregivers then they can further pursue domiciliary treatment. If the patient has been on a prophylactic quinolone prior to the FN episode, these should be avoided on discharge. Ciprofloxacin plus amoxicillin-clavulanate or levofloxacin 500 mg OD are reasonable step-down regimens. Culture and sensitivity results can also guide domiciliary therapy and the results must be reviewed prior to discharge. For pediatric population cefixime is a reasonable option. However, clinicians should note that quinolone prophylaxis is not routinely recommended in FN.

Antimicrobial Prophylaxis

Patients on alemtuzumab therapy should be under TMP-SMX combination as prophyaxis. Patients suffering from hematological malignancies with high-risk of developing infections can receive prophyaxis with fluoroquinolone or TMP-SMX.

For autologous and allogeneic hematopoietic stem cell transplant antifungal prophyaxis should be maintained with fluconazole or micafungin (Category 1). For patients with significant graft versus host disease (GVHD) consider posaconazole (Category 1).

Secondary prophyaxis in patients with prior aspergillosis includes voriconazole.

Acyclovir (antiviral prophyaxis) is given to patients with fluconazole/clarithromycin, bortezomib and alemtuzumab based on treatment of patients undergoing allogeneic or autologous HSCT.9

Colony Stimulating Factors

Granulocyte colony-stimulating factor (G-CSF) can decrease the duration of neutropenia, fever and hospitalization but these benefits are modest and mortality is unaffected. They can be considered in the hospitalized patient with pneumonia, hypotension, sepsis, organ dysfunction or for patients on regimens that are known to cause prolonged neutropenia. Growth factors may be used for prophyaxis (primary or secondary) or for therapeutic purposes. G-CSFs should not be used to treat afebrile neutropenia or in cases of uncomplicated FN and should be avoided in those receiving concomitant chemotherapy and radiation. Ideally, primary prophyaxis is indicated for chemotherapy regimens where the propensity for FN occurrence is more than 20%.

If a patient has already experienced chemotherapy induced neutropenia during previous cycle, then G-CSF can be used for secondary prophyaxis if there is a proven benefit in maintaining the dose (curative purpose) and schedule. However, dose reduction or dose delay can be considered rather than G-CSF prophyaxis in those with FN or prolonged neutropenia where intention of treatment is not curative. Ideally, G-CSF is administered 24–72 after chemotherapy and not on the day of chemotherapy. It should be continued till postnadir ANC recovery to normal or near normal.

The various types of growth factors in usage are:
- Filgrastim
- Sargramostim
- Pegfilgrastim: The pegylation causes reduced renal clearance and prolonged action so that single dose is sufficient for one chemotherapy cycle having a minimum interval of 2 weeks between cycles.

The doses of G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) are 5 mcg/kg/day, 250 mcg/m²/day and 6 mg once respectively. Pegfilgrastim is convenient as it is used once and should be given exclusively as primary prophyaxis for 2 weekly regimens and not for treatment of FN. Mode of administration is preferably subcutaneous. Safety data is similar between filgrastim and pegfilgrastim.10

Scenario in India

Practice has changed dramatically in India of late. Growth factor usage has increased exponentially and is becoming cheaper day-by-day. Due to the substantial reduction in the cost of growth factors
there has been extensive use even with chemotherapy regimens having lower risk of neutropenia (< 20%). Initially, ASCO guidelines recommended its prophylactic use only if the chemotherapy schedule had the potential to result in significant neutropenia (grade 3 and 4), i.e. more than 40%. Subsequently, this cut-off was reduced to 20%. Further, the cost of hospitalization is dramatically different between developed and developing countries and health care is cheaper in the latter. As of now, the cost of antibiotics in India is becoming quickly become the most expensive component of the treatment—even higher than the cost of chemotherapy and growth factors. Lastly, unique to our country, due to challenging logistics, e.g. difficult terrain, inaccessible medical facilities and inability to reach hospital within 24 hours of onset of fever many International guidelines are flouted and India centric innovative measures are needed.\textsuperscript{15} This clearly shows that prophylactic use of G-CSF was, is and shall remain “standard” of care in India (and many developing countries) for majority of patients receiving aggressive chemotherapy, beyond the scope of the revised International guidelines like ASCO or ESMO (European Society of Medical Oncology) or NCCN.

The present article aims to improve education, awareness and trend in practice in FN amongst primary care physicians, who are the first point of contact for these patients prior to their arrival in tertiary referral cancer units.

REFERENCES