Management of febrile neutropenia in childern

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Introduction

Febrile neutropenia is fever in a patient with neutropenia. It is a clinical emergency that is associated with high morbidity and mortality. Fever is defined as a single recording of an oral temperature of 38.3° C (101°F) or a rectal temperature of 39°C[1] or an oral temperature of at least 38.0°C (100.4°F) or a rectal temperature of 38.6°C on two occasions within a 24 hour period[2]. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 cells/mm³ or a count less than 1000 cells/ mm³ with a predicted decrease to less than 500 cells/mm³ within 48 hours after the onset of fever[5]. It should be documented by a *manual differential count* preferably by a haematologist, as the management is more intense and costly based on this finding alone. Susceptibility to infection is greater when neutrophil counts are lower, rate of decline is fast and in protracted neutropenia (i.e. neutropenia lasting more than 10 days)[5]. *Neutropenia with syndromes such as chronic benign neutropenia, chronic granulomatous disease, are however, excluded from the above definition*[4]. The clinical judgement need not wait until the absolute neutrophil count drops below a threshold level to intervene. Better patient outcomes can be achieved by anticipation and early appropriate as well as aggressive intervention.

As neutropenic patients mount minimal inflammatory response *even with a severe infection, symptoms and signs may be minimal or absent*. Matters are made worse by normal or near normal laboratory results in the presence of sepsis. Cellulitis may occur with minimal pain, pneumonia without discernible infiltrate on chest x-ray, meningitis without pleocytosis and urinary tract infection without pyuria[5].

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Aetiology of neutropenia

Causes of neutropenia are shown in table 1.

Table 1
Causes of neutropenia [6]

- ***Drug induced neutropenia***
    - *Cancer chemotherapeutic agents* (cyclophosphamide, methotrexate)
    - *Antimicrobials* (penicillins, chloramphenicol, trimethoprim)
    - *Anti-inflammatory drugs* (indomethacin, ibuprofen)
    - *Anti-psychotics & antidepressants* (phenothiazines, imipramine,)
    - *Antithyroid drugs* (thiouracil, propylthiouracil, carbimazole)
    - *Anticonvulsants* (valproic acid, phenytoin, carbamazepine)
    - *Cardiovascular drugs* (captopril, propranolol, hydralzine)
    - *Antihistamines* (cimetidine, ranitidine,)
    - *Miscellaneous drugs* (IV immunoglobulin, penicillamine)
- ***Infection associated neutropenia***
    - *Viral infections* (HIV, hepatitis B, infectious mononucleosis, dengue)
    - *Bacterial infections* (Gram negative sepsis, typhoid fever,)
    - *Fungal infections* (histoplasmosis)
    - *Parasitic infections* (malaria)
- ***Bone marrow infiltration with malignancy***
    - Leukaemia, Lymphoma and other neoplasia
- ***Neutropenia associated with collagen vascular disease***
    - SLE
- ***Nutritional deficiencies***
    - Vitamin B_{12}, folic acid and copper deficiency
- ***Miscellaneous immunological causes***
    - Following bone marrow transplant and blood transfusions

Causes of fever in neutropenic patients are diverse. Fifty percent are due to occult or established infections. Other causes include line-associated fever, drug fever, graft versus host disease and underlying malignancy.

Sixty to seventy percent of infections are caused by Gram positive organisms, 30% by Gram negative organisms and 10% are non-bacterial. Fungi commonly cause secondary infections but can also cause primary infections [5]. Even with infection, a positive microbiological diagnosis is reached only in 40-75% even in the best of centres with state-of-the-art laboratory facilities[2]. Thus, *no organisms isolated from specimens do not mean no infections and antimicrobial agents should not be abruptly discontinued based on negative culture reports.* Common infective causes of fever in neutropenia are shown in table 2.

Table 2
Common infective causes of fever in neutropenia [2,5]

Bacterial infections
- *Gram-positive (60%)* Staphylococcus Epidermis, other coagulase negative Staphlylococci, Viridans Streptococci, Enterococcus faecalis
- *Gram-negative (30 %)* Escherichia coli, Klebsiella spp, Pseudomonas aeruginosa
- *Others (10%)* Staphylococcus Aureus, Corynebacterium JK, Acinetorbacter spp
- Mixed infections
- Anaerobes

Fungal infections Candida spp, Aspergillus fumigatus

Viral infections (CMV, VZV)

Pneumocystis carinii

Clinical evaluation

Since signs and symptoms of inflammation are minimal in the severely neutropenic patient, especially if accompanied by anaemia[7], a thorough history taking and examination is essential to elicit subtle clinical features. It is important to elicit a history of administration of blood products within the previous 24 hours and rigors associated with flushing the central venous line in situ. Common sites of infection are the alimentary tract and skin. Thus, special attention should be paid to periodontium (teeth and gum), pharynx, lower oesophagus, lungs, perineum including anus, eyes including fundi and bone marrow aspiration sites, vascular access sites and tissues surrounding the nails[5].

Laboratory evaluation

The place of properly performed full blood count (FBC) and blood picture in management cannot be overemphasised. The markers of inflammation such as levels of circulating C-reactive protein, IL-6, IL-8, and procalcitonin may be affected by bacteraemia in a febrile neutropenic patient. C-reactive protein is a useful investigation in these patients, as normal values virtually excludes bacterial or fungal sepsis[2], but therapeutic decisions should not be taken *based only on CRP values*, as severe fungal infections have been reported with normal CRP levels[8].

Bacterial and fungal cultures should be sent in *appropriate media immediately and whenever changing or adding anti-microbial agents*. If a central venous line is in place, more than one set of blood samples should be drawn for culture from the device lumen *and* from a peripheral vein[9]. The yield of bacterial and fungal isolates depend on *culture systems* used[10] and the *volume of blood* sample[11]. If a catheter entry site is inflamed or draining, a specimen should be taken for Gram staining and culture. If such lesions are chronic, then a specimen should also be sent for non-tuberculous mycobacteria isolation [12]. It is also important to ensure that the microbiology services are equipped to cater to the unique needs of neutropenic patients.

No routine cultures from anterior nares, oropharynx, urine and rectum are recommended unless such results are used for infection control purposes[5]. Urine cultures should be considered when there are symptoms and signs of urinary tract infection, where there is an indwelling urinary catheter or when urine analysis reports are abnormal[5]. *Cerebrospinal fluid analysis is also not recommended routinely* but should be performed if infection in the central nervous system is suspected in the absence of, or manageable thrombocytopenia (above 60,000/ mm^3). Aspiration or biopsy of suspicious skin lesions for cytological testing, Gram staining, and culture[13] are also advocated.

Chest x-ray (CXR) is indicated if respiratory symptoms or signs are present. A baseline CXR may help but is not cost effective. A study revealed that high-resolution CT scan of chest showed evidence of pneumonia in more than half of febrile neutropenic patients with normal CXRs[14].

For follow up, daily FBC is advocated along with blood urea (BU), serum electrolytes (SE), serum creatinine, liver function tests (LFT), coagulation profile and CXR. Other routine ICU investigations are recommended at regular intervals.

Table 3
Initial investigations in a febrile neutropenic patient

o   FBC with manual differential white cell count & blood picture
o   CRP
o   Blood cultures (peripheral and through central venous catheter lumen)
o   Fungal blood cultures
o   Respiratory secretions for rapid detection of viral antigen
o   Stool microscopy & culture (if indicated)
o   Urine full report and culture & ABST(if indicated)
o   Analysis & culture of CSF   (if indicated)
o   Aspiration or biopsy of suspicious skin lesions for Gram staining and culture & ABST
o   Chest X-ray (consider CT/ Thorax)
o   BU , SE & serum creatinine
o   Liver function tests
o   Coagulation screen

Management of Febrile Neutropenia

This could be considered under 3 main headings.

•   Stabilization of patient.
•   Antimicrobial regime.
•   Other therapeutic options.

Stabilization

This is similar to any other patient with severe sepsis. Oxygen therapy, including ventilation, intravenous crystalloids, colloids and inotropes are indicated as appropriate and volume status is monitored by CVP to stabilize patient. It is important to anticipate and take appropriate steps to prevent and manage organ dysfunctions such as renal, central nervous system, liver, DIC, coagulopathy and ARDS.

Antimicrobial Therapy

This has been shown to reduce the incidence of sepsis, septic shock, ARDS, organ dysfunction and mortality in febrile neutropenia[1,5]. As progression of sepsis is rapid and clinical diagnosis of bacterial sepsis difficult in febrile neutropenia, empirical intravenous antibiotic therapy should be administered promptly to all neutropenic patients at onset of fever. Afebrile neutropenic patients with suspected infection (e.g. unexplained tachycardia, hypotension, lethargy) should also be started on empirical antibacterial therapy as for febrile neutropenic patients[1]. Following guidelines are based on the document released by Infectious Disease Society of America (IDSA)[5].

Management of Low Risk Patients

At present, there are no established criteria for risk stratification in children with neutropenia for severe infection. Recently Klasseen et al have prospectively derived and validated a clinical prediction rule for paediatric febrile neutropenia. Children with an initial absolute monocyte count of more than $100/mm^3$, with no co-morbidity and with normal CXR findings are at the lowest risk for significant bacterial infections[15]. Nevertheless, all children with febrile neutropenia are currently managed as at high risk for severe infection with initial intensive intravenous (IV) antibiotic therapy[1].

Treatment with Intravenous antibiotics

Three antibiotic regimens with similar efficacy are recommended for initial IV therapy All 3 regimes include a drug with anti-pseudomonal activity. Recommended initial antibiotic guidelines are: monotherapy, two-drug therapy without vancomycin or vancomycin plus one or two antibiotics.

Monotherapy

A third or fourth generation cephalosporin (ceftazidime or cefepime) or a carbapenem (imipenem-cilastatin or meropenem) are recommended monotherapies. Except ceftazidime, all 3 antibiotics mentioned above have excellent activity against viridans streptococci and pneumococci. Ceftazidime or cefepime can be a useful choice in mild to moderate renal failure but clinicians should be aware that extended spectrum of β lactamases (ESBL) and type 1 β lactamases have reduced the utility of ceftazidime for monotherapy[16].

Two-Drug Regime without Vancomycin

In this category an aminoglycoside is combined with an anti-pseudomonal agent. The 3 most commonly used combinations are:

•   An aminoglycoside with an anti-pseudomonal cephalosporin (ceftazidime or cefepime)

- An aminoglycoside with a carbapenem (imipenem-cilastatin or meropenem).

- An aminoglycoside with an anti-pseudomonal carboxypenicillin or ureidopenicillin. (Ticarcillin-clavulanic acid or piperacillin-tazobactam)

Such combination therapies have synergistic effects against some gram negative bacilli and minimize emergence of resistance[5]. Disadvantages of antibiotic combinations such as ceftazidime and an aminiglycoside are lack of adequate coverage for gram-positive organisms, nephrotoxicity, ototoxicity and hypokalaemia associated with aminoglycosides. A recent trial shows that, ciprofloxacin plus piperacillin-tazobactam is as effective as tobramycin and piperacillin-tazobactam[17].

Vancomycin with One or Two drugs

Use of vancomycin should be limited to specific indications as excessive use in hospital is associated with the emergence of vancomycin resistant organisms, especially enterococci. Although vancomycin has not been shown to influence overall mortality due to gram-positive organisms, mortality due to viridans streptococci may be reduced by using vancomycin[5]. Ticarcillin, piperacillin, cefepime (but not ceftazidime), and carbapenems all have excellent activity against most strains of viridans streptococci. Indications for inclusion of vancomycin into the initial empirical therapy are[5]:

- Hypotension or other evidence of cardiovascular impairment associated with sepsis.

- Serious catheter-related infections such as bacteraemia and cellulites.

- Blood culture positive for gram-positive bacteria before final identification and sensitivity results.

- Colonization with penicillin and cephalosporin-resistant pneumococci or methicillin-resistant S. aureus.

- Substantial mucosal damage due to intense chemotherapy, infection with viridans streptococcus & prophylaxis with quinolones are also considered as indications for using vancomycin in some centres[18].

Although, vancomycin was most commonly combined with ceftazidime in the past, some centres justify the combination of vancomycin with cefepime or a carbapenem due to emergence of ceftazidime resistance.

Guidelines for Initial Antibacterial Therapy

- First, decide whether vancomycin is indicated.

- If so, then begin treatment with vancomycin and a cephalosporin (cefepime or ceftazidime) or a carbapenem with or without an aminoglycoside.

- If vancomycin is not indicated, then start monotherapy with a cephalosporin (cefepime or ceftazidime) or a carbapenem (meropenem or imipenem-cilastatin).

- Two antibiotics in combination are indicated for complicated cases or if resistance is a problem.

- A knowledge of the local pattern of microbes and antibiotic susceptibility will be very useful in selection of antimicrobials.

Antibiotic Therapy during the First Week

At least 3-5 days of antibiotic therapy are needed to assess efficacy of treatment. Hence it is recommended that the initial antibiotic regimen could be continued for 5 days, despite fever spikes, unless a change is needed either due to clinical deterioration of patient or culture reports indicating otherwise. A study involving 488 febrile neutropenic patients has revealed that *median time for clinical response was 5 (2-7) days*[19].

Management of patients who become afebrile

If organism is isolated, antibiotics may be changed, if necessary, according to the sensitivity pattern while maintaining broad-spectrum coverage. If organism is not isolated, the same antibiotics should be continued as for high-risk patients. Minimum duration of therapy should be 7 days or until cultures become negative and patient is free of significant signs and symptoms It would be desirable to wait until neutropenia resolves, before stopping antibiotics but this may not be applicable for prolonged neutropenic patients.

In children without signs of sepsis (chills, hypotension etc.) and severe mucositis *at any time in the current febrile episode,* and children who are afebrile for more than 48 hours with absolute neutrophil count of more than 100 cells/mm^3 and who

are at low risk for complications can be switched on to *oral cefixime* from IV antibiotics. Studies show that, changing over to oral cefixime after 48 to 72 hours of IV antibiotics in such patients is as effective and safe as continued IV therapy *while managed as an in-patient*[5]. Antibiotics may suppress but not eradicate an infection in a neutropenic patient. Hence, whilst following above guidelines, one should be vigilant and treat each patient on his or her own merit.

Management of persistent fever during empirical therapy

If fever persists for more than 3 days after initiation of empirical treatment, begin a diagnostic reassessment work up. If by day 5 reassessment is unrevealing and fever is persisting, proceed with one of the following management strategies.

- Continue same treatment if patient is clinically stable and resolution of neutropenia is imminent.

- Change antibiotic(s), if there is progression of disease or drug toxicity. (Particularly look for indications to add / omit vancomycin and isolation of organisms from the specimens).

- Add an antifungal agent (amphotericin B) with or without changing antibiotics if neutropenia is expected to persist for more than 5 to 7 days.

Studies suggest that up to *one-third of neutropenic patients with fever who are not responding to a one week course of empirical antibiotic(s) have systemic fungal infection* most commonly due to Candida or Aspergillus species[20,21]. In other words, fever not responding to empirical antibiotic therapy for more than 5 days in a profoundly neutropenic patient, can be considered as an indication for anti-fungal therapy. Every effort should be made however, to determine whether fungal infection is present before initiating antifungal therapy.

Whilst on empirical antibiotic therapy, persistent fever with a negative clinical and laboratory infection screen suggests that the patient may have a non bacterial infection, resistant organisms, a slow responder, emergence of a second infection, inadequate dosage, drug fever, infection at avascular site like venous catheter or "abscess", cell-wall deficient bacteraemia or even inadequate laboratory facilities for isolation of particular organism[2,5].

Duration of Antimicrobial Therapy

The most important factor that determines the successful discontinuation of antibiotics is the resolution of neutropenia. Antibiotics may be stopped if neutrophil count is $>500/mm^3$, patient is afebrile for 2 consecutive days and no infection is diagnosed after 3 days of treatment. Duration of treatment is not well defined in patients who become afebrile but remain neutropenic[5]

Other Therapeutic Options

94

Antiviral Therapy

Antiviral drugs are not *routinely* included in empirical treatment of febrile neutropenia[5]. They are indicated only if there is clinical or laboratory evidence of viral infections. However, *even in the absence of fever, acyclovir is indicated*, if there is evidence of herpes simplex or varicella-zoster infection[5]. Cytomegalovirus infection, not uncommon in patients who have undergone bone marrow transplantation, is usually treated with ganciclovir or foscarnet. Viral respiratory tract infections are managed with suitable antiviral agents.

Therapy with Colony-Stimulating Factor

Although, the use of recombinant human granulocyte-colony stimulating factors and granulocyte-macrophage colony stimulating factor have been *consistently shown to reduce the duration of neutropenia* and time spent in hospital[5,22], this does not seem to improve infection related morbidity and mortality[5]. Thus routine use of colony stimulating factors in *uncomplicated cases* of febrile neutropenia should be avoided.

Colony Stimulating Factor may be considered in following circumstances[5]: pneumonia, septic shock, severe cellulites or sinusitis, systemic fungal infections, multi-organ dysfunction in sepsis and infections that do not respond to appropriate antibiotics. Expected worsening of the course of illness and long delay in recovery of neutropenia are other indications.

Granulocyte Transfusion

The routine use of granulocyte transfusion is not indicated as this carries the risk of transmission of cytomegalovirus, alloimmunization associated fever, graft versus-host reactions and progressive platelet refractoriness. However, in following special

circumstances, granulocyte transfusions can be considered[5]:

- When bacterial infection cannot be controlled with optimal antibiotics and G-CSF.

- In severe uncontrolled fungal infections.

Antibiotic prophylaxis

The prophylactic use of antibiotics in early *afebrile period of neutropenia* seems beneficial[5]. Prospective, randomized trials suggest that trimethoprim-sulfamethoxazole (TMP-SMZ) and quinolones are most effective and for this purpose[5]. TMP-SMZ is highly effective in prevention of Pneumocystis carinii pneumonia in both neutropenic as well as non-neutropenic patients[5]. *TMP-SMZ or quinolones however, are not recommended for routine use.*

Anti-fungal therapy

For prophylaxis against fungal infections, *routine use* of fluconazole or itraconazole is not advocated even though certain antifungals have been shown to reduce systemic and superficial infections. However, there are special circumstances in which fluconazole or itraconazole may be used for prophylaxis[5].

Cost of Management

Reducing the costs of therapy has been the focus in many studies[23, 24]. Using the most appropriate therapy/therapies in the most effective doses for the optimum duration is one such strategy. *Avoidance of indiscriminate use of any treatment modalities* including intra venous fluids, antibiotics, colony stimulating factors, antivirals, anti-fungals and blood or blood products will also help to reduce cost.

Early changeover to oral treatment and restriction of antimicrobial prophylaxis to shorter periods and fewer patients will facilitate in reducing expenses. Avoidance of unnecessary investigations also substantially cut down the costs.

Regular audits of cost-effectiveness are also a must, to keep unnecessary and unproductive expenditures to a minimum. Measures to reduce the cost of care do not mean omitting or delaying costly interventions inappropriately.

Conclusions

Febrile neutropenia is a life threatening illness where early intervention is essential to improve prognosis. Better understanding of pathophysiology with simplified, structured treatment approach will facilitate early diagnosis and employment of appropriate treatment. Initial *empirical intravenous broad spectrum antibiotic* therapy reduces the mortality and morbidity. Being acquainted with local infections and antibiotics sensitivity pattern is vital. Management in the long-term is complex and best handled by specialist centres. Expert opinion must be sought whenever necessary, particularly in units where febrile neutropenia is not frequently managed.

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