Febrile neutropenia in childhood cancer

Improved outcomes in childhood cancer have been achieved largely through more intensive and toxic treatment regimens.

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There have been major advances in the treatment of and outcomes in childhood cancer. Improved outcomes have largely been achieved by more intensive and toxic treatment regimens, including cytotoxic chemotherapy,[1] radiotherapy and/or surgery. Chemotherapy-induced immunosuppression renders children who receive treatment for cancer extremely vulnerable to life-threatening infections, which are a major cause of morbidity and mortality. Prompt and aggressive intervention with empiric antibiotics has reduced mortality in this group of patients.

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Pathophysiology

Host immune defence is dependent on an intact and healthy innate and adaptive immune system. Innate defence includes physical barriers such as intact mucosal surfaces, phagocytic cells and cytokine response networks. Adaptive immunity refers to the pathogen-specific response generated by T-lymphocyte cell-mediated immunity.[2,3]

The nature of the treatment offered to children receiving chemotherapy undermines both the innate and adaptive defences, leaving the young patient vulnerable to opportunistic infections.[3]

The innate immune system may be compromised as result of mucositis after chemotherapy and the disruption of epithelial barriers during central venous access, tumour infiltration, and surgery.[2]

The adaptive immune system may become dysfunctional because of the effect of chemotherapeutic agents and radiotherapy on the proliferation and maturation of lymphocytes.[2]

Definitions

To classify and treat patients with febrile neutropenia adequately, one has to have a clear understanding of specific terms and their relevance to oncology patients. Fever in febrile neutropenia is defined as a single oral temperature above 38.3˚C, observed once, or a sustained temperature of greater than 38.0˚C for at least 1 hour or on more than one occasion in a 24-hour period. Neutropenia is defined as an absolute neutrophil count of less than $0.5x10^9$/l or $1.0x10^9$/l, which is expected to decrease in the next 48 hours.[2,4,5]

Approach

A child with possible febrile neutropenia should be viewed as a medical emergency and needs immediate attention. Information on all children receiving chemotherapy should include the most recent treatment received and contact details of the treating oncology centre and physician.[2] It is appropriate to contact the treating centre for information on the child's treatment if the family do not have a summary of his/her treatment details.

History

A detailed history should include recent chemotherapy or other treatment, such as antimicrobial therapy, as well as the nature and duration of symptoms. Specific questions should address the possible exposure to opportunistic infections, e.g. tuberculosis. The duration of fever, presence of rigors and dizziness, and intake and output are important. Any indication of a focus of infection should be sought, which could include one of the following: mucocitis, earache, headache, cough, local swelling, possible cellulitis, irritation or itching at the site of the indwelling intravenous catheter, dysuria, frequency and pain on passing stools.[2-4] A positive history may indicate the causative organism, but very often there will be no clear source of infection as the child with neutropenia is unable to produce an adequate inflammatory response and therefore has no localising signs.

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Physical examination

The severity of the child's illness should be determined quickly and management should be tailored accordingly. The initial assessment must include vital data such as blood pressure, pulse rate, temperature, respiratory rate and capillary refill time. If the child is stable, a meticulous clinical assessment should be done.[3]

Particular care must be taken to examine the respiratory tract, insertion site of the central venous catheter or any previous sites of intravenous catheterisation. The perianal region is seldom examined, but it is essential that it be done as it may provide clues to possible *Pseudomonas* infection. The gastrointestinal system must also be carefully examined as typhlitis or neutropenic enterocolitis is a common cause of severe infection. Typhlitis is derived from the Greek *typhlon* for caecum. Typhlitis is an acute, life-threatening condition characterised by inflammation and infection of the bowel in the region of the caecum.[5] It occurs mainly in immunocompromised patients. Gram-negative organisms penetrate the mucosa frequently at the ileocaecal junction, causing pain and extreme tenderness in the right ileac fossa. Clinically, patients with typhlitis are indistinguishable from those with an acute surgical abdomen.

Management

All children suspected of having febrile neutropenia should be assessed immediately.[2,4] A seemingly well child can progress to irrevocable septic shock in a very short period. One should carefully examine the child and look for signs of early septic shock. Corrective measures should be initiated to prevent multi-organ failure, which leads to a high mortality rate. Definitions of sepsis-related terminology are given in Table I.

In the case of sepsis or sepsis-related illness, the child should be admitted to a high-care or an intensive care facility,[2] where he/she must urgently receive aggressive fluid resuscitation and inotropic support. It is therefore important to immediately refer the child to the nearest centre that can offer these services.

The gastrointestinal system must also be carefully examined as typhlitis or neutropenic enterocolitis is a common cause of severe infection.

Special investigations

Information obtained from special investigations may be useful in guiding further management, but should in no way delay resuscitation or definitive antimicrobial therapy. Tests should include a full blood count, including platelet and differential counts, electrolytes and blood culture (an adequate blood culture from a central line is sufficient). Tests may also be done on wound swab, lumbar puncture and urine samples.[1-4] A chest radiograph should be considered if there are respiratory symptoms such as tachypnoea or respiratory distress, but one would expect to see only very subtle changes on a radiograph.

Table I. Sepsis-related terminology[11]

Systemic inflammatory response syndrome (SIRS)	Temp. >38.5°C, <36°C Tachycardia >SD for age Respiratory rate >SD for age White cell count above or below age norms
Sepsis	SIRS in presence of proven or suspected infection
Severe sepsis	Sepsis with cardiovascular dysfunction, respiratory distress syndrome, or organ dysfunction (>2) (including neurological, renal, hepatic, haematological)
Septic shock	Sepsis with cardiovascular dysfunction, including hypotension, vasopressor dependence acidosis, elevated lactate oliguria, delayed capillary refill rate, core to peripheral temperature gap >3°C

Empiric antibiotics

Since the 1970s when empiric antibiotic therapy was first introduced there has been a dramatic improvement in the survival of oncology patients.[6] Prior to this there was a tendency to observe the patient until a source of infection became apparent.[7] This approach in a child with febrile neutropenia may have catastrophic consequences and should be avoided. Most units have individualised empiric antibiotic policies based on the most prevalent organism.

Gram-positive bacteria may cause a variety of infections in children with cancer, including infection of the bloodstream, skin and soft tissue, and upper and lower respiratory tract. Bacteraemia or bloodstream infections are the most common infections caused by this group of bacteria. The most common organisms in this group are the coagulase staphylococci (*Staphylococcus aureus*) and the viridans group of streptococci. The viridans group of streptococcal infections may lead to the so-called viridans streptococcal sepsis syndrome (VSSS).[6] Patients present with fever, rash and hypotension and the mortality ranges from 10% to 100%. *S. aureus* is another common Gram-positive organism that causes infection in patients with neutropenia and is often associated with indwelling central venous catheters.[4]

Gram-negative organisms constitute a major infection problem in neutropenic patients. Gram-negative pathogens, e.g. *Pseudomonas aeruginosa, Escherichia coli* and *Klebsiella pneumoniae,* often lead to severe sepsis and shock. Other organisms include *Enterobacter* and *Serratia* spp. Gram-negative organisms, such as *Acinetobacter* spp. and *Stenotrophomonas maltophilia*, are difficult to eradicate and may colonise a patient or a ward.[6]

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The most serious form of sepsis originates from the Gram-negative group of bacteria. Most empiric antibiotic regimens offer good control over this group of organisms. A typical choice would be an anti-pseudomonal beta-lactam antibiotic and an aminoglycoside, e.g. piperacillin/tazobactam plus amikacin. Other monotherapy regimens of 3rd- or 4th-generation cephalosporins with anti-pseudomonal activity, e.g. ceftazidime or cefepime, may also be used provided cognisance is taken of the presence of beta-lactamase-producing bacteria.[2,4]

The decision to add Gram-positive cover is based largely on signs of infection in cases of indwelling catheters and the duration of fever.[1,6] Usually, if there is no defervescence within 48 hours, or if there are signs of a line infection such as itching at the insertion site, erythema or discharge, vancomycin therapy should be initiated if renal function is adequate.

Antifungal therapy is seldom started as empiric therapy unless there is documented evidence of an invasive fungal infection.[4] The introduction of antifungal treatment is mostly based on the duration of the neutropenia and the fever. Amphotericin B

Table II. Organisms commonly implicated in febrile neutropenia[2,9]

Gram positive
- *Staphylococcus* spp. (*S. epidermidis*)
- *Streptococcus* spp. (alpha-haemolytic)
- *Enterococcus* spp. (*E. faecium*)
- *Bacillus* spp. (*B. cereus*)
- *Clostridium* spp. (*C. difficile*)

Gram negative
- Enterobacteriaceae (*E. coli, Klebsiella* spp., *Enterobacter* spp., *Serratia* spp.)
- *Pseudomonas aeruginosa*
- *Stenotrophomonas maltophilia*
- Anaerobes

Fungi
- *Candida* spp.
- *Aspergillus* spp.
- Zygomycetes

Viruses
- Herpes simplex virus
- Varicella zoster virus
- Cytomegalovirus
- Epstein-Barr virus
- Adenovirus
- Influenza virus
- Para-influenza virus

may be started after 5 days of unresponsive fever in the absence of a definitive source.

Additional considerations

Granulocyte-colony stimulating factor

The use of granulocyte-colony stimulating factor (G-CSF) remains controversial. If the risk of febrile neutropenia is high after intensive chemotherapy it is recommended that G-CSF be used prophylactically. However, even if the duration of neutropenia is reduced, there is little evidence to indicate that G-CSF will decrease the mortality rate. It therefore does not appear to have a positive impact on survival.[8,9]

Adrenal gland suppression

Most leukaemia protocols suggest using very high doses of corticosteroids therapeutically, which often lead to panhypopituitary dysfunction. As a result, the body cannot respond to stress adequately, which may lead to the exacerbation of septic shock. All patients with a possible panhypopituitary dysfunction should diagnostically be given a stress dose of steroids (hydrocortisone).[2]

Risk assessment

The approach to febrile neutropenia, as discussed above, is aggressive and will adequately treat the majority of patients.[3] There is a move to stratify patients into high-risk and low-risk groups even if they are neutropenic and have a fever.[3] Not all patients are at equal risk of significant morbidity and mortality. Risk factors such as age, temperature, absence of positive blood cultures, hydration, outpatient and remission status, and nature of the cancer have been identified as possible predictive factors that may differentiate between high- and low-risk patients.[3] Low-risk children may be managed as outpatients and offered oral antibiotics or no antibiotics. This approach, if applied correctly and under strict guidelines, may potentially prevent admission and limit antibiotic exposure. However, the danger and consequences of undertreating a child with febrile neutropenia may be catastrophic. This approach is best reserved for specialised centres where the patients are well known to the clinicians and very clear policies and access to care are in place.[3]

A seemingly well child can progress to irrevocable septic shock in a very short period.

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In a nutshell

- Febrile neutropenia, secondary to the malignancy, is the most significant factor contributing to the mortality rate of children diagnosed with cancer.
- There have been major advances in supportive care, and the mortality rate related to complications has fallen to 1 - 5% in most centres.
- With the decentralisation of care and because most patients return to their communities after and between chemotherapy cycles, children with febrile neutropenia may present to peripheral centres.
- Emergency departments and clinicians should have written policies or standard operating procedures regarding the management of febrile neutropenia.
- Each case should be viewed as a medical emergency. Prompt aggressive management may save many lives.