Empiric antibiotic therapy in a child with cancer and suspected septicemia

Desiree Caselli, Olivia Paolicchi
Department Pediatric Hematology Oncology, Azienda Ospedaliera Universitaria Meyer Children Hospital, Firenze, Italy

Abstract

Improved outcome in the treatment of childhood cancer results not only from more aggressive and tailored cancer-directed therapy, but also from improved supportive therapy and treatment of life-threatening infectious complications. Prompt and aggressive intervention with empiric antibiotics has reduced mortality in this group of patients. The role of anti-infective therapy is now considered an important element of the application of current chemotherapy regimens.

Although much attention has been paid to the role of invasive fungal infections in the immune compromised host, it is important to remember that 85% of febrile episodes still have bacterial origin and, therefore, identification and treatment of septicemia in the child with cancer remains a very important issue for the specialist physician.

Throughout the 1960s and 1970s, gram-negative organisms were most frequently isolated from patients with nosocomial blood stream infections. Since then, infections due to gram-positive organisms have become increasingly frequent, from 62% in 1995 to 76% in 2000. In addition, over the past two decades, antibiotic resistance rates rose for all predominant organisms, including Staphylococcus aureus, coagulase-negative staphylococci, enterococci, and gram-negative pathogens. Thus, antimicrobial prophylaxis and treatment have become increasingly difficult, and timely and accurate epidemiological information is needed to guide appropriate empirical therapy.

Definitions

Fever
Increased central body temperature above normal values. Word Health Organization fever definition was used: body temperature above 38°C (standard readings 36.5-37°C). Fever of unknown origin (FUO) is defined as fever without a known cause. According to Italian Society of Pediatrics guidelines, body temperature was measured in tympanic membrane with an infrared radiation thermometer.

Neutropenia
Total neutrophil count of less than 1x10^9/L in children below one year of age and less than 1.5x10^9/L in patients older than one year. Slight neutropenia is defined as 1-1.5x10^9/L neutrophils, moderate between 0.5-1x10^9/L, deep for neutrophils less than 0.5x10^9/L.

Sepsis
Sepsis-related terminology.

Systemic inflammatory response syndrome
Body temperature more than 38.5°C, less than 36°C, tachycardia above SD for age, respiratory rate above SD for age, white cell count above or below age-related normal values (Table 1).

Sepsis with cardiovascular dysfunction, respiratory distress syndrome, or organ dysfunction (>2) (including neurological, renal, hepatic, hematologic).

Monomicrobial sepsis
One pathogenic (bacteria or fungus) isolated from hemoculture. In cases of staphylococci coagulase-negative, corynebacteria (except for C. jeikeium) or other cutaneous skin contaminant: two different positive hemocultures in 24 h are needed or the same pathogen must be isolated from hemoculture and another site of infection (cellulitis/abscess).

Polimicrobial sepsis
Two or more different pathogens from the same hemoculture, or from different ones taken within 24 h.

Central venous catheter related sepsis
Fever (>38°C) with shivering within 2 h of CVC handling associated with positive hemoculture and/or: relevant pathogen isolated from CVC but not from peripheral blood sample; same pathogen isolated from CVC tip/sleeve (after CVC removal) and from blood sample collected through catheter; positivity for a pathogen from CVC tip/sleeve (after CVC removal) and from blood sample taken from CVC site.

Key words: antibiotic therapy, child, cancer.

Received for publication: 13 October 2011.
Revision received: 7 November 2011.
Accepted for publication: 18 November 2011.
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Pediatric Reports 2012; 4:e2
doi:10.4081/pr.2012.e2
removal), but not from peripheral blood sample; pathogen isolated from blood culture and from CVC emergency secretion or from CVC subcutaneous tunnel.

**Initial patient evaluation and risk assessment**

All children with cancer undergoing chemotherapy, and thus at risk for severe neutropenia, should be assessed immediately when fever appears.\(^2\)\(^,\)\(^6\) A seemingly well child can progress to irrevocable septic shock in a very short period of time. It is important to remember that concurrent steroid therapy, especially with high-dose dexamethasone, can increase the risk that fever is falsely low or absent at the onset of septicemia. Thus, during these kinds of therapies, parents should be appropriately trained to recognize that, when the child’s clinical picture appears to change with (but even without) fever, they must inform the medical team if the child is being treated as an outpatient. Fever in neutropenic patients represents an emergency, and it is mandatory to start an empiric antibiotic therapy immediately.\(^1\)\(^1\) Since this practice found a common consensus, the mortality rate in children has decreased from 1% to 0.4%.\(^1\)\(^2\)

Children with febrile neutropenia should be evaluated as soon as they get to the hospital. Initial physical inspection, including vital signs, should be performed as soon as possible. In the case of clinical signs of septicemia, aggressive fluid resuscitation and inotropic support is mandatory. In an apparently stable child, detailed history should include recent chemotherapy or other treatment to assess the likelihood of severe neutropenia even before performing a blood count. Specific questions should address the possible exposure to opportunistic infections (e.g. tuberculosis) and the previous history of clinically relevant infection or colonization. The duration of fever, presence of rigors and dizziness, and fluid intake and output are important. Any indication of a

**Table 1. Systemic inflammatory response syndrome.\(^9\)**

| Age (yr) | Respiratory rate (breaths/min) | Heart rate (beats/min) |
|---------|-------------------------------|-----------------------|
| <1      | 30-60                         | 100-160               |
| 1-2     | 24-40                         | 90-150                |
| 2-5     | 22-34                         | 80-140                |
| 6-12    | 18-30                         | 70-120                |
| >12     | 12-16                         | 60-100                |

**Table 2. Patient evaluation (modified from NCCN guidelines).\(^1\)\(^3\)**

| Initial clinical presentation | Findings | Evaluation | Addition to initial empiric regimen |
|-------------------------------|----------|------------|-----------------------------------|
| Mouth/mucosal membrane        | • Necrotizing ulceration | • Culture and gram stains (HSV, fungal, leukemic infiltrate) | o Adequate anaerobic activity? |
|                               | • Thrush | • Biopsy suspicious lesions | o Anti-HSV therapy? |
|                               | • Vesicular lesions | • Viral cultures/PCR + direct fluorescent ab tests for HSV/VZV | o Systemic antifungal therapy? |
| Esophagus                     | 1. Retrosternal burning | • Cultures suspicious oral lesions (HSV, fungal) | o Antifungal therapy (fluconazole) |
|                               | 2. Dysphagia/odynophagia | • Endoscopy if no response to therapy | o Anti HSV therapy |
|                               |          | • CMV esophagitis in pt at high risk | |
| Abdominal pain                |          | • Abdominal CT/ultrasound | o Initial therapy guided by clinical findings |
|                               |          | • Alkaline phosphatase, transaminases, bilirubine, amilase, lipase | o Antifungal therapy for thrush |
| Perirectal pain               |          | • Perirectal inspection | o Acyclovir for possible HSV |
|                               |          | • Consider abdominal/pelvic CT | |
| Vascular access devices (VAD) | 1. Entry or exit inflammation | • Swab exit site drainage for culture | o Metronidazole if C. difficile |
|                               | 2. Tunnel infection/port pocket infection, septic phlebitis | • Blood culture from each VAD port | o Adequate anaerobic therapy? |
| Lung infiltrates              | 1. Low risk | • Blood and sputum cultures | o Vancomycin initially or add it if site not responding after 48 h empiric therapy |
|                               |          | • Nasal wash for respiratory viruses, rapid tests | o Remove catheter and culture surgical wound |
|                               |          | • Legionella urine Ag test | o Add vancomycin |
|                               |          | • Consider BAL, particulary if no response to initial therapy or if diffuse infiltrates present | |
|                               |          | • Blood and sputum cultures | |
|                               |          | • See low risk | |
|                               |          | • CT chest to better define infiltrates | |
|                               | 2. Intermediate to high risk | | o Azithromycin/fluoroquinolone |
|                               |          | o Antiviral? | o Vancomycin/linezolid? |
|                               |          | o Mold active antifungal agent? | |
|                               |          | o Antiviral? | |
|                               |          | o TMP_SMX? | |
|                               |          | o Vancomycin/linezolid? | |
focus of infection should be sought. This could include one of the following: mucositis, headache, cough, local swelling, cellulitis, irritation or itching at the site of the indwelling intravenous catheter, dysuria, frequency and pain on passing stools.2,4,6 The gastrointestinal system must also be carefully examined as typhilitis or neutropenic enterocolitis is a common cause of severe infections (Table 2). Although a positive history may indicate the causative organism, 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 localizing signs.

On the basis of the initial evaluation, the physician may be asked to decide on several issues which are clinically relevant: selection of initial choice of empiric antibiotic therapy, including type and route of administration, and the need for patient admission.14 To address this issue, attempts have been made to build and validate methods to define the individual patient risk for early complication. An example of the scoring system adopted by the American Society of Hematology (ASH) in 2001 is summarized in Table 3. Only patients at risk for septicemia fall within the scope of this review.

**Diagnostic studies**

According to the guidelines developed by the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) for the management of febrile neutropenia, at least two separate blood culture sets have to be collected and inoculated into an aerobic bottle; if abdominal signs are present an anaerobic bottle must be added.15 Initial, and then daily, tests should include full blood examination (FBE) with differential white cell count, urea, electrolytes and serum creatinine, liver function, CRP, procalcitonin. Cultures from other sites should be taken according to clinical indication. A chest X-ray is indicated for patients with respiratory symptoms or signs.4,8,14,15 Other specific diagnostic tools are suggested in Table 2.

### Antibiotic therapy

Despite the relevance of the topic, consensus is still lacking on initial treatment of children with suspected septicemia during febrile neutropenia.16 Although data on patient’s history, allergies, symptoms, signs, recent antibiotic use and culture data, as well as local flora and infection patterns, are relevant, they may be insufficiently informative to direct individual treatment. Meta-analyses of randomized controlled trials in sepsis have shown that monotherapy with an antipseudomonal beta-lactam (e.g. piperacillin-tazobactam, ceftazidine, meropenem) is as efficacious as combination therapy.15-17 Piperacillin-tazobactam or ceftazidine appear to be a very reasonable choice for first-line monotherapy.17-18 Analysis of local epidemiology must support this choice, by ruling out clusters of multi-resistant strains of Gram-negative bacteria (Table 4). Patients with impaired renal function (glomerular filtration rate less than 50 mL/min) will require adjustments to the suggested doses based on calculated creatinine clearance.17-18

There is also no evidence that combination regimens prevent the emergence of resistant organisms. The potential risk of nephrotoxicity with betalactam/aminoglycoside combination therapy may outweigh any potential benefit.17-18

Overall, individual institutions treating children with cancer should design and implement a careful, ongoing data-collection allowing monitoring of the local epidemiology of bacterial infection. This will form the basis for a definition of the institutional protocol for empiric antibiotic therapy for febrile neutropenia, especially in high-risk patients.16

### Use of glycopeptides

With the increasing rate of gram positive infections in neutropenic patients (in particular those caused by methicillin-resistant staphylococci and enterococci) the use of glycopeptides as part of initial empirical treatment has become controversial.15,17,18

At present, despite the high incidence of these kind of infections, the only indications for the use of this class of antibiotics are in cases of severe sepsis or septic shock, strong suspicion of cutaneous, soft tissues, CVC related infection or in the centers with a very high rate of gram-positive infections.15,17,18

In patients with vancomycin-resistant staphylococci infection, linezolid proved to be effective and safe in pediatric patients.20

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**Table 3. Risk Assessment: ASH 2001 Guidelines.**

| Risk Level | Criteria |
|------------|----------|
| High risk | Deep and prolonged neutropenia (ANC<100cell/mm³) |
| Medium risk | Hematologic malignancy, Allogeneic BMT, Significant comorbidities, Shock signs or symptoms/complicated infection |
| Low risk | Solid tumor / standard CT, Neutropenia <7 days, No comorbidities, Clinical and hemodynamic stability |

**Table 4. Organisms implicated in febrile neutropenia.**

| Gram positive | Gram negative | Fungi | Viruses |
|---------------|---------------|-------|--------|
| *Staphylococcus* spp. (β *epidermidis S. aureus*) | *Enterobacteriaceae* (E. coli, Klebsiella spp., Enterobacter spp., Serratia spp.) | *Candida* spp. | Herpes simplex virus |
| Coagulase-negative staphylococci | *Pseudomonas aeruginosa* | *Aspergillus* spp. | Varicella zoster virus |
| *Streptococcus* spp. (alpha-haemolytic) and pyogenes, pneumoniae | *Stenotrophomonas maltophilia* | *Zygomycetes* | Cytomegalovirus |
| *Viridans* group | *Anaerobes* | *Pusuarium* spp. | Epstein-Barr virus |
| *Enterococcus* spp. (E. faecium) including vancomycin-resistant strains | |
| *Bacillus* spp. (B. cereus) | |
| *Clostridium* spp. (C. difficile) | |
| *Listeria monocytogenes* | |

Modified from Pazou and Poplack.19
Modification of empiric therapy

The median time of defervescence in patients successfully treated with frontline antibiotic is 3-5 days. Therefore, escalation of antibiotic coverage should not occur prior to this period in the absence of clinical instability, isolation of resistant microorganism or emergence of new infection loci (Table 5). 15,17,18

Duration of therapy

Length of therapy is basically guided by neutrophil pattern and by the bacterial isolate, when proven. 12,14-18,20 If defervescence occurs in 3-5 days of treatment, neutrophils count is more than 500/mm³ and the patient remains afebrile for more than 48 h, antibiotic therapy can be stopped. 14,21 If the neutrophil count remains low, the approach is controversial, although it is generally accepted that: if patient’s clinical conditions are good and stable, the treatment can be interrupted after 5-7 days of apyrexia; in case of profound neutropenia and unstable condition, treatment should not be stopped; if neutrophil count is more than 500/mm³, but the patient is still febrile despite a wide-spectrum antibiotic therapy, fungal, mycobacterial or viral infection should be suspected 15,17,18 (Table 6).

Table 5. Modification of empiric antibiotic therapy during the course of neutropenic fever.

| Time/condition | Reason for acting and action |
|----------------|------------------------------|
| Modify initial antibiotic regimen within 3-5 days only for reasons specified | • clinical instability  
• isolation of a resistant organism  
• persistent positive blood cultures  
• emergence of new infective loci  
• severe intolerance to antibiotic therapy  
• clinical suspicion for uncovered microorganisms:  
  1. CVC related infection → Gram positive cocci  
  2. Perianal cellulitis/titlitis → enterococci, anaerobi, Gram negative enterobacteria  
  3. Pneumonia → fungi, mycoplasma, legionelia, PCP |
| After 5-7 days of persistent fever despite a broad spectrum antibacterial regimen and no identified fever source | Addition of antifungal therapy? Only in high-risk patients on a preemptive approach with evaluation of possible infection (TC - Galactomannan antigen) |

Table 6. Dose range of principals antibiotics used in pediatric neutropenic patients.

| Drug              | Dose                           | Comments |
|-------------------|--------------------------------|----------|
| Vancomicina       | 10 mg/kg q6h                   | Vancomycin is active against virtually all strains of community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) and should be used for all life-threatening and severe infections. |
| Linezolid         | <12yo: 10 mg/kg/dose q8h       |          |
|                   | > 12yo: 10 mg/kg/dose q12h     |          |
| Daptomycin        | 4 mg/kg/ ev/die                | See also Abdel-Rahman SM, et al. 22 |
| Dalfopristin/quinoapristin | VRE 7.5 mg/kg/dose q8h | Only in central venous line |
| Imipemen          | 10-15 mg/kg, 6h ( max 4 gr/die) |          |
| Meropenem         | 20-30 mg/kg/dose q8h           |          |
| Piperacillin/Tazobactam | 75-100 mg/kg/dose q8h |          |
| Cefepime          | 50 mg/kg/dose q8h              |          |
| Cefotaxime        | 50 mg/kg/dose q6-8h            |          |
| Ceftriazone       | 80-100 mg/kg/d once daily      |          |
| Ciprofloxacin     | IV: 15 mg/kg/dose q8h          |          |
| Levofloxacin      | <1yo10 mg/kg/dose q12h         |          |
|                   | > 1yo10 mg/kg/dose q24h        |          |
| Gentamicin        | 2.5 mg/kg/dose q8h             |          |
| Amikacin          | 18-20 mg/kg/die                | Charnas R, Luthi AR, Ruch W. 23 |
| Tobramycin        | 2.5 mg/kg/dose q8h             | EORTC. 24 |
| TMP/SMX           | 20 mg TMP/100 mg SMX/kg div. 6 hrly | For therapy |
| Metronidazole     | 7.5-10 mg/kg/dose q6-8h        |          |

Modified from NCCN guidelines 2011-11-02, JMH Guidelines for Antimicrobial Use, Philip A. Pizzo, MD David G. Poplack Principles and Practice of Pediatric Oncology, 6th edition 2011.

Conclusions

Physical examination, blood tests (in particular: full blood count, electrolytes, creatinine, CRP, procalcitonin), and blood cultures should be performed, and wide range antibiotic therapy be administered as soon as possible. Beta-lactam monotherapy, such as piperacillin-tazobactam or cefepime, is the empiric therapy of choice for all clinically stable patients with neutropenic fever. Combination therapy with an antipseudomonal beta-lactam antibiotic plus aminoglycoside is recommended for...
patients with systemic compromise. Vancomycin is not recommended as initial empiric therapy unless there is systemic compromise or an approved indication for its use. Patients who have been assessed as low-risk for medical complications may be switched to oral antibiotics and considered for early discharge. The choice of institutional initial empiric antibiotic therapy should always also consider the local epidemiology based on information available from periodic surveys.

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