Empiric antibiotic therapy in a child with cancer and suspected septicemia

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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. Physical examination, blood tests, and blood cultures must be performed, and antibiotic therapy must be administered as soon as possible. Beta-lactam monotherapy, such as piperacillin-tazobactam or cefepime, may be an appropriate empiric therapy of choice for all clinically stable patients with neutropenic fever. An anti-pseudomonal beta-lactam antibiotic plus gentamicin is recommended for patients with systemic compromise.

Introduction

The recent advances and improved outcome in the treatment of childhood cancer observed over the last decades result not only from more aggressive and better tailored cancer-directed therapy, but also from improved supportive therapy.[1] In solid tumors, more aggressive surgery, supported by more effective anesthesia techniques and refined radiotherapy, has made a significant contribution to improved outcome. In leukemia, improved outcome is mainly due to more effective chemotherapy. This is achieved with repeated use of multiagent courses, also resulting in repeated episodes of deep and extended cytopenia, and in particular neutropenia. Eighty percent of post-chemotherapy neutropenic episodes which last more than one week are complicated by fever, and about 60% of them have an infectious etiology.[2] In selected situations, such as children with high burden of acute lymphoblastic leukemia, the risk of failure to achieve first complete remission by the end of the first month of induction therapy can be comparable or even higher, at least in some chemotherapy programs, to that of life-threatening infectious complications.[3-6] Thus, since prompt and aggressive intervention with empiric antibiotics has reduced mortality in this group of patients,[2-4] 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.[6]

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.[7] 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.[8]

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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 1×10^9/L in children below one year of age and less than 1.5×10^9/L in patients older than one year. Slight neutropenia is defined as $1\text{-}1.5\times10^9$/L neutrophils, moderate between $0.5\text{-}1\times10^9$/L, deep for neutrophils less than 0.5×10^9/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

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, hematologic).

Septic shock

Sepsis with cardiovascular dysfunction, including hypotension, vasopressor dependence acidosis, elevated lactate oliguria, delayed capillary refill rate, core to peripheral temperature gap of more than 3°C.[10]

Monomicrobial sepsis

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

Polimicrobial sepsis

Two or more different pathogens from the same hemocolture, 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 hemocolture 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), 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.[2,4,6] 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.[11] Since this practice found a common consensus, the mortality rate in children has decreased from 1% to 0.4%.[12]

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).[13]

Initial clinical presentation	Findings	Evaluation	Addition to initial empiric regimen
Mouth/mucosal membrane	• Necrotizing ulceration	• Culture and gram stains (HSV, fungal, leukemic infiltrate) • Biopsy suspicious lesions	o Adequate anaerobic activity? o Anti-HSV therapy? o Systemic antifungal therapy?
	• Thrush		o Antifungal therapy (fluconazole)
	• Vescicular lesions	• Viral cultures/PCR + direct fluorescent ab tests for HSV/VZV	o Anti HSV therapy
Esophagus	1. Retrosternal burning 2. Dysphagia/odynophagia	• Cultures suspicious oral lesions (HSV, fungal) • Endoscopy if no response to therapy • CMV esophagitis in pt at high risk	o Initial therapy guided by clinical findings o Antifungal therapy for thrush o Acyclovir for possible HSV
Abdominal pain		• Abdominal CT/ultrasound • Alkaline phosphatase, transaminases, bilirubine, amilase, lipase	o Metronidazole if C. difficile o Adequate anaerobic therapy?
Perirectal pain		• Perirectal inspection • Consider abdominal/pelvic CT	o Ensure adequate anaerobic therapy o Consider enterococcal coverage o Consider local care
Vascular access devices (VAD)	1. Entry or exit inflammation	• Swab exit site drainage for culture • Blood culture from each VAD port	o Vancomycin initially or add it if site not responding after 48 h empiric therapy
	2. Tunnel infection/port pocket infection, septic phlebitis	• Blood culture from each VAD port	o Remove catheter and culture surgical wound o Add vancomycin
Lung infiltrates	1. Low risk	• Blood and sputum cultures • Nasal wash for respiratory viruses, rapid tests • Legionella urine Ag test • Consider BAL, particulary if no response to initial therapy or if diffuse infiltrates present	o Azitromyci/fluoroquinolone o Antiviral? o Vancomycin/linezolid?
	2. Intermediate to high risk	• Blood and sputum cultures • See low risk • CT chest to better define infiltrates	o Azithromycin/fluoroquinolone 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 typhlitis 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.[4,6,14,15] 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 betalactam (*e.g.* piperacillin-tazobactam, cefepime, ceftazadime, meropenem) is as efficacious as combination therapy.[15-17] Piperacillin-tazobactam or cefepime 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 controversal.[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 vancomicin-resistant staphylococci infection, linezolid proved to be effective and safe in pediatric patients.[20]

Table 3. Risk Assessment: ASH 2001 Guidelines.[11]

High risk	- Deep and prolonged neutropenia (ANCA<100cell/mm^3) - Hematologic malignancy - Allogeneic MBT - Significant comorbidities - Shock signs or symptoms/complicated infection
Medium risk	- Solid tumor / high-dose CT / autologous BMT - Neutropenia between 7-14 days - Irrelevant comorbidities - Clinical and hemodynamic stability
Low risk	- Solid tumor / standard CT - Neutropenia <7 days - No comorbidities - Clinical and hemodynamic stability - FUO/non-complicated infection

Table 4. Organisms implicated in febrile neutropenia.

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

Modified from Pizzo 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/mm^3 and the patient remains apiretic 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/mm^3, 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).

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* aminoglicoside is recommended for

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 foci • severe intolerance to antibiotic therapy • clinical suspicion for uncovered microorganisms: 1. CVC related infection → Gram positive cocchi 2. Perianal cellulitis/tiflitis → enterococci, anaerobi, Gram negative enterobacteria 3. Pneumonia → fungi, mycoplasma, legionella, 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 > 12 yo: 10 mg/kg/dose q12h	
Daptomycina	4 mg/kg / ev /die	See also Abdel-Rahman SM, *et al.*[22]
Dalfopristin/quinopristin	VRE 7.5 mg/kg/dose q8h Skin infection 7.5 mg/kg/dose q12h	Only in central venous line
Imipemen	10-15 mg/kg .6h (max 4 gr/die)	
Meropemen	20-30 mg/kg/dose q8h	
Piperacillin/Tazobactam	75-100 mg/kg/dose q6h	
Cefepime	50 mg/kg/dose q8h	
Cefotaxime	50 mg/kg/dose q6-8h	
Ceftazidime	50 mg/kg/dose q8h	
Ceftriaxone	80-100 mg/kg/d once daily	
Ciprofloxacine	IV: 15 mg/kg/dose q8h	
Levofloxacine	</= 5 yo10 mg/kg/dose q12h > 5 yo10 mg/kg/dose q24h	
Gentamicin	2.5 mg/kg/dose q8h	
Amikacin	18-20 mg/kg/die	Charnas R, Luthi AR, Ruch W.[23] EORTC.[24]
Tobramycin	2.5 mg/kg/dose q8h	
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 ,UMHS Guidelines for Antimicrobial Use, Philip A. Pizzo, MD David G. Poplack Principles and Practice of Pediatric Oncology, 6th edition 2011.

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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