Infections in Acute Lymphoblastic Leukaemia

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Abstract

We did a retrospective study of all acute lymphoblastic leukaemia (ALL) patients on United Kingdom ALL protocol who were admitted for febrile neutropenia. The aim of the study was to document the types of infections and aetiological agents associated with febrile neutropenia and to document the factors affecting mortality. Over the $8^1/_2$-year period from 1986 to June 1995, there were 77 episodes in 32 children with a mean of 2.4 episodes. Morbidity due to infection was 61%; unknown causes of fever contributed 39%. Of the microbiologically documented infections, majority were Gram-negative bacteraemia. There were 7 deaths (22%) during the study period, 3 (9%) of which were due to overwhelming sepsis, with 4 contributed by the relapse status of the leukaemia. Mortality was increased by prolonged neutropenia, relapse of the leukaemia and invasive fungal infection.

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Introduction

Children undergoing chemotherapy for cancer are especially vulnerable to infection because of immunosuppression related to their underlying illness, the effects of chemotherapy and radiotherapy. Empiric antimicrobial chemotherapy is the mainstay of therapy for febrile neutropenic episodes pending the culture results. Here we document the organisms causing febrile neutropenia and the risk factors for mortality in our acute lymphoblastic leukaemia (ALL) patients.

Patients and Methods

A retrospective survey of all febrile neutropenia episodes in paediatric ALL patients on United Kingdom ALL protocol Tan Tock Seng Hospital was carried out. The protocol consist of induction chemotherapy using 3 to 4 drugs, followed by intensification chemotherapy of 6 drugs after achieving remission on day 28 of chemotherapy. During the $8^1/_2$-year period between 1986 and June 1995, there were 77 episodes in 32 children with a mean of 2.4 episodes (range 1 to 6 episodes). Medical records were examined in an assessment of the demographic characteristics of patients, the status of their underlying cancer, the presence of microbiologically documented infections, clinical infections, the pertinent laboratory findings, the antibiotic therapy administered, reasons for changes in antibiotics and the clinical outcome.

A febrile episode was defined (Table I) as the presence of fever >38°C (axillary) with neutropenia of <1000 polymorphs per mm^3 and the absence of non-infectious causes such as blood transfusions. All patients were examined to look for possible sources of infections and had 2 sets of blood cultures taken for aerobic, anaerobic and fungal organisms, urine microscopy and 2 sets of urine cultures. Patients who had intravascular central lines also had blood cultures taken from the central lines as well as the peripheral lines. Only patients with diarrhoea or vomiting had stool or anal swab cultures sent. A chest X-ray was done only if the patient had respiratory symptoms. In such patients, sputum cultures were also taken. Patients who had other symptoms such as sinusitis, otitis media and mouth ulcers had the relevant cultures done.

Patients were then started on empiric antibiotics while awaiting the culture results. Table I gives the plan for antibiotic therapy. Empiric amphotericin B was added if the fever persisted. As this was a retrospective study, some patients had different empiric antibiotics used, such as amoxycillin / clavulanate, ampicillin / sulbactam. For the same reason, some patients had empiric amphotencin B started later than day 5 to 7.

Febrile neutropenic episodes were classified into 1 of 3 categories according to clinical findings, course of the illness and microbiologic data. The 3 categories were:

(1) Episodes with definite clinical signs and symptoms of infection with microbiological confirmation: Microbiologically-documented infections.

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TABLE I: PROTOCOL FOR FEBRILE NEUTROPENIA

Fever >38°C (axillary) + neutropenia <1000 polymorphs/mm^3
Absence of non-infectious causes
↓
Clinical evaluation
Cultures: blood, urine, ± stool/rectal, sputum
Chest X-ray if pulmonary symptoms
↓
Start empiric antibiotics
Community-acquired: IV amoxycillin + gentamicin
↓
Toxic-looking/hospital-acquired: IV third-generation cephalosporin + aminoglycosides
e.g. ceftriaxone/ceftazidime + gentamicin/amikacin
↓
Persistent fever
Neutropenia resolving → Continue same antibiotics
OR
Clinical deterioration or persistent neutropenia
↓
Re-evaluate, re-culture
± Change antibiotics
Add on empiric Amphotericin B by day 5 to 7

(2) Episodes with definite clinical signs and symptoms of infection but lacking specific microbiological confirmation: Clinical infections.
(3) Other episodes were categorised as fevers of unknown origin.

A single positive blood culture was considered to be significant evidence of bacteraemia except for coagulase-negative *Staphylococcus*, in which blood cultures from 2 separate sites or at 2 different times were positive, or if the patient was at high risk due to the presence of a central intravascular catheter. Fungaemia was diagnosed with a positive fungal blood culture.

Statistical Analysis

Mann-Whitney U test used to assess factors such as duration of fever, duration of neutropenia and severity of neutropenia associated with poor outcome i.e. death. Fisher's exact test was used to analyse phase of chemotherapy (induction, intensification, relapse), relapse and fungaemia. Statistical significance was defined as $P<0.05$.

Results

During the $8^1/_2$-year period from 1986 to June 1995, there were a total of 77 episodes in 32 patients, averaging 2.4 episodes per patient (range 1 to 6 episodes). Characteristics of patients are shown in Table II. 71% of the patients were in the 2 to 10 years age group. Almost two-thirds of the patients were male.

Twenty-four episodes occurred during the post-induction and 28 post-intensification phases of chemotherapy. Mortality rates between the 2 groups were not statistically significant (Table III). Of the 77 febrile neutropenic episodes, 18 (22.3%) occurred in patients who had relapsed. Mortality during relapse (4 out of 18) was significantly higher compared to patients not in relapse (3 out of 59, $P = 0.047$). The outcome was worse if the patient had longer duration of neutropenia. The median duration of neutropenia was 7 days compared to a median of 21 days in those who died ($P = 0.0096$). The outcome did not depend on the duration of fever. The median duration of fever was 3 days in those who recovered versus 7 days in those who died ($P = 0.07$). Neither did the severity of neutropenia on admission affect the mortality. The median neutrophil count in those who recovered was 210 / mm^3 versus 100 / mm^3 in those who died ($P = 0.366$).

TABLE II: PATIENTS' PROFILE

Characteristic	Number of patients (%)
Age (years)	
1 to 2	4 (12.5)
2.1 to 5	11 (34.4)
5.1 to 10	12 (37.5)
>10	5 (15.6)
Sex	
Male	20 (62.5)
Female	12 (37.5)
Type of chemotherapy induction	30
Intensification	28

There were 31 (47.7%) microbiologically-confirmed infections, 21 (32.3%) unknown causes of fever and 13 (20%) clinical infections on admission. Of the microbiologically-proven infections, there were 23 primary bacteraemias (Table IV); the majority of them were mixed Gram-negative and Gram-positive infections (41%), followed by single Gram-negative bacteraemias (27%) and Gram-positive bacteraemias (22%). There were 11 urinary tract infections, all of which were Gram-negative except one *Enterococcus sp*. There were 10 pneumonias, all of which were diagnosed clinically and by chest X-ray; none of the patients had positive sputum cultures. Details of the rest of the infections are given in Table V.

Among the microbiologically-documented infections, Gram-negative isolates (total 48) exceeded the Gram-positive infections (total 8) by 6 times. *Escherichia coli* (E. coli) was the most frequently isolated Gram-negative organism (16), followed by *Klebsiella* species (12), *Acinetobacter* species (8) and *Pseudomonas aeruginosa* (*P. aeruginosa*) (5). Other Gram-negative infections included 2 *Pseudomonas* species, 2 *Enterobacter sp.*, and 1 *Proteus sp.* in the urine. Of the Gram-positive infections, there were 3 streptococcal bacteraemias (all were alpha haemolytic-streptococci) and 1 Group D *Streptococcus* gastroenteritis, 1 methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from a leg abscess, 2 *Staphylococcus aureus* bacter-

TABLE III: CLINICAL CHARACTERISTIC OF FEBRILE NEUTROPENIA EPISODES AND EFFECTS ON OUTCOME

Characteristic		Recovery	Mortality	*P* value
Median duration of fever (days)		3*	7*	0.07
Median duration of neutropenia (days)		7*	21*	0.0096
Median neutropenia count (absolute neutrophil count/mm^3)		210*	100*	0.366
Type of chemotherapy#				
n = 77	Induction (episodes)	22	2	0.441
	Intensification (episodes)	27	1	
Relapse #				
n = 77	Yes (episodes)	14	4	0.0479
	No (episodes)	56	3	
Fungal infections documented #				
n = 77	Yes (episodes)	2	2	0.0194
	No (episodes)	70	3	

* Median using Mann-Whitney U test
\# No. of febrile episodes using Fisher's test
n Total number of febrile episodes

TABLE IV: BACTERAEMIAS

Type of organisms	Numbers (%)
Gram-negative infections	6 (27)
E. coli	2
Acinetobacter	2
Pseudomonas sp.	1
X. maltophilia	1
Gram-positive infections	5 (22)
S. aureus	2
Streptococcus	2
Enterococcus	1
Mixed Gram-negative and Gram-positive	9 (41)
Acinetobacter + P. aeruginosa	2
Acinetobacter + E. coli	1
Klebsiella + E. coli	1
Klebsiella + E. coli + Plesiomonas	1
E. coli + coagulase-negative Staphylococcus	1
Enterobacter + Streptococcus group D	1
E. coli + Klebsiella + Streptococcus	1
Pseudomonas sp. + Streptococcus	1
Mixed bacterial and fungal	3(13.6)
Acinetobacter + P. aeruginosa + C. tropicalis	1
Acinetobacter + Klebsiella + Aspergillus + Rhodotorula	1
P. aeruginosa + Candida sp.	1

TABLE V: TYPES OF INFECTIONS

Site	Numbers
Bacteraemia	23
Urinary tract infections	11
Pneumonia	10
Mouth ulcers/gingivitis	6
Skin infections	5
Herpes zoster	2
Malignant otitis media + mastoiditis	1
Necrotising fasciitis	1
Osteomyelitis	1
Peritonsillar abscess	1

aemia including 1 from a patient with osteomyelitis of the right femur neck, 1 *Enterococcus* urinary tract infection and 1 *Enterococcus* bacteraemia. There were 2 patients with central venous catheters (Port-a-Cath); 1 had *Xanthomonas maltophilia* and another patient had coagulase-negative *Staphylococcus* with *E. coli* bacteraemia.

There were 4 documented fungaemias, contributing 12.9% of all microbiologically documented infections. One patient had *Aspergillus flavus* and *Rhodotorula* species isolated 16 days from the start of the febrile neutropenia episode. He was treated successfully with Amphotericin B. prior to the documented fungaemia, he had been on multiple courses of antibiotics for necrotising fasciitis involving the right flank extending to the left thigh, from which *Acinetobacter baumanii*, *P. aeruginosa* and *Klebsiella* species were isolated. Of the 3 remaining fungaemias, 2 patients had *Candida tropicalis* in the blood and both died; 1 of the *Candida* species was unidentified. Mortality was higher if there was a documented fungal infection ($P = 0.019$).

Regarding the empiric antibiotics used, 27 patients were on empiric ampicillin + gentamicin and 24 patients were on ceftriaxone / ceftazidime + gentamicin / amikacin. The numbers of those given other empiric antibiotics e.g. amoxycillin / clavulanate were small. Those who were given ampicillin and gentamicin were well-looking and from the community whereas those who were given third-generation cephalosporins and aminoglycosides were toxic-looking or had a suspected nosocomial infection. A change in antibiotics was equally

necessary no matter what combination of empiric antibiotics was used. These changes included additions or modifications of the initial regime or the addition of antiviral therapy. These antibiotic changes should be considered as adjuncts to the overall management of the patient and not as a failure of the initial regime. There were 43 febrile neutropenic episodes requiring a change of antibiotics (55.8%). Reasons for changes in the empiric antibiotic regime included: poor clinical response (37%), resistance of organisms (23.2%), new infections (11.6%) and other reasons e.g. the addition of other antibiotics (9%). A combination of 2 or more reasons were seen in 8 patients (18.6%). A poor clinical response was defined as the lack of improvement of the fever or neutropenia or clinical well-being after 48 to 72 hours. New infections were clinical infections which were not initially present but developed during the course of the illness such as necrotising fasciitis.

There were 7 deaths (22%) during the febrile neutropenic episodes with 3 (9%) out of the 7 due to overwhelming sepsis (Table VI). The other 4 deaths were contributed by the poor leukaemia status as they were in relapse. Three of the patients died during / post-induction phase: 2 patients had *Candida tropicalis* in the blood, with 1 of the two also having a peritonsillar abscess with *P. aeruginosa*; 1 patient died from multi-resistant *Klebsiella* species. The 4 patients who were in relapse included 1 patient who had malignant otitis media and mastoiditis from which *P. aeruginosa* was grown; 1 patient had gingivitis with *Enterobacter* species, *E. coli* in the blood and *Proteus* species in the urine; 1 patient had *Klebsiella* species and *E. coli* in the blood who later developed a flank abscess, left pneumonia and a sacral sore and 1 patient had no source of fever but had metastases along the spinal cord.

TABLE VI: TYPES OF INFECTIONS AND LEUKAEMIC STATUS OF PATIENTS WHO DIED

Name	Leukaemia status	Infections
MR	1st relapse	No source. Died from spinal metastases
NH	Induction	Blood, urine: *Candida tropicalis*
ZWN	Induction	Blood: *Candida tropicalis, Acinetobacter, P. aeruginosa*
TCC	2nd relapse	Blood: *Klebsiella sp., E. coli* Flank abscess, Left pneumonia Sacral sore, Sympathetic knee effusion
YKO	1st relapse	Blood: *E. coli* Urine: *Proteus sp.* Gingivitis: *Enterobacter*
NSF	1st relapse	Malignant otitis media Mastoiditis: *P. aeruginosa*
SD	Intensification	Blood: multi-resistant *Klebsiella*

Discussion

Patients with febrile neutropenia are treated empirically with antibiotics as they have a 60% likelihood of being infected.[1] Empiric therapy should be used after careful evaluation for the source of infection and after proper collection of appropriate specimens. The clinician should continue to evaluate the patient for new infections because as the duration of neutropenia increases, patients are more vulnerable to second or even multiple infections, notably fungal infections.[2] We must not, however, allow the use of empiric antibiotic therapy to replace thorough clinical evaluation and must keep in mind the possibility of suprainfections and simultaneous multiple infections.

In this retrospective study of febrile neutropenia in acute lymphoblastic leukaemia paediatric patients, the morbidity due to infection was 61%; unknown causes of fever contributed 39%. Forty-eight per cent of the infections were microbiologically confirmed of which the majority were primary bacteraemias (74%).

Among the infections, the majority were Gram-negative organisms: *E. coli*, *Klebsiella* species, *Acinetobacter* species and *P. aeruginosa*. The possible sources of these infections were the gut, urinary tract and respiratory tract. At other cancer centres, *E. coli* and *Klebsiella sp.* remain the most common Gram-negative organisms.[2,3] Gram-positive infections in our study contributed only 18.6% of the total bacterial infections. There was only 1 documented methicillin-resistant *Staphylococcus aureus* infection. Therefore there do not appear to be any need to start empiric vancomycin before culture results are ready. This is in keeping with the recommendation that at institutions where methicillin resistance is uncommon, vancomycin should not be included in empiric antibiotic regimens.[4] The predominance of Gram-negative isolates could be due to the low utility of central venous catheters. These devices have contributed, at various other cancer centres, to the widespread change in the epidemiology of aetiological agents of bacteraemias with a upsurge in gram-positive organism and fungaemias.[2,3]

Invasive fungaemias contributed 12.9% and were associated with a high mortality. Candidiasis was the most frequently encountered fungal infection, similar to other cancer centres.[3] Our sole patient with *Aspergillus flavus* was admitted at a time when the hospital was undergoing extensive renovation. Construction work in hospitals has been associated with infection due to *Aspergillus* species in neutropenic patients.[5] Amphotericin B should be started by day 5 if no clinical improvement occurs, as fungal infections are associated with a high mortality.

There was a higher mortality in patients with longer duration of neutropenia; however, the severity of the neutropenia did not influence the outcome although

patients with counts <100 / mm^3 are at the highest risk for infection. There were 7 deaths in our series (22%). Three out of 7 were due to overwhelming sepsis. The other 4 deaths were contributed by the relapse of leukaemia. The mortality was higher in those patients in relapse. Excess mortality in relapsed patients is multifactorial; it is related to progressive neoplastic disease and to persistent neutropenia. Patients in relapse have diminished marrow reserves related to more intensive chemotherapy which contributes to the duration of neutropenia and hence risk of infection.[1]

To reduce the morbidity due to infection, we have to be vigilant about preventive measures including vigorous hygiene, well-cooked food, handwashing, proper asepsis when handling central intravascular lines. To reduce mortality due to infection, we must be more aggressive about modifications to our antibiotic regimes and the early commencement of antifungal therapy.

REFERENCES

1. Walsh T J. Editorial response: Evolving risk factors for invasive fungal infections—All neutropenic patients are not the same. Clin Infect Dis 1994; 18:793-8.
2. Pizzo P. Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 1993; 328:1323-32.
3. Koll B S, Brown A K. The changing epidemiology of infections at cancer hospitals. Clin Infect Dis 1993; 17(Suppl 2):S322-8.
4. Bodey G. Empirical antibiotic therapy for fever in neutropenic patients. Clin Infect Dis 1993; 17(Suppl 2):S378-84.
5. Armstrong D. Empiric therapy for the immunocompromised host. Rev Infect Dis 1991; 13(Suppl 9):S763-9.