

Febrile Neutropenia in Haematological Disorders: a Single Centre review of Antibiotic Policy and the Outcome

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Abstract

Aims: To review the current management of febrile neutropenia based on current in-vitro sensitivity data.

Setting: A tertiary care haematology centre.

Study Design: This is a single centre retrospective analysis of the outcome of febrile neutropenia treated with broad-spectrum combination antibiotics.

Patients and Methods: A total of 120 episodes of fever occurred in 78 patients. There were 61 males and 17 females. All patients were suffering from various haematological disorders on conventional treatment or receiving peripheral blood stem cell transplantation. Each episode of febrile neutropenia was treated with IV Ceftriaxone and Amikacin as first line therapy. If there is no response in 48 hours or if patients deteriorated clinically, subsequent changes are made until fever settled or neutrophils recovered.

Results: Out of 78 patients, 61 were male and 17 female. Age range was 2 to 69 years with a median of 22 years. Response to empiric therapy was seen in 50%. In the remaining 50%, second line and third line therapy was continued without any further change in 9 and 3 patients respectively. Imipenem was used in combination with Amikacin as salvage therapy as a last resort in 40 patients who failed to respond to various combinations of antibacterial antibiotics. Out of these 40 patients, 10 developed fungal infection and could not survive while the remaining 30 defervesced within 72 hours of starting this combination. In 120 episodes of febrile neutropenia, 78 patients were on chemotherapy or pre or post bone marrow transplantation and E-coli, S. aureus, Klebsiella, Candida, and P. aeruginosa, were the most common organisms isolated.

Conclusion: Current empiric therapy could be continued for the treatment of febrile neutropenia. When modification is needed, second line combination should incorporate Imipenem, Cefepime or Piperacillin-tazobactam. If fever does not settle after 96 hours of antibiotic treatment, anti-fungal therapy should be added (JPMA 53:190;2003).

Introduction

Life threatening complications due to bacterial infections have been reported in 10-20% of febrile episodes in neutropenic patients. Standard management of febrile neutropenia involves hospitalisation; work up to find out the cause of febrile episode, prompt use of empirical antibiotics and barrier nursing.¹ To prevent this, broad-spectrum antibiotic therapy is initiated empirically in these patients at the onset of fever. The combination of b-lactam antibiotics plus an aminoglycoside or glycopeptides was considered to be the gold standard of empiric therapy in febrile neutropenic patients.¹⁻³ Recently, monotherapy using carbapenems and third and fourth generation cephalosporins as initial therapy in febrile neutropenia have shown that this approach is safe and effective.^{4,5} Bacterial organisms that are frequently isolated when fever is present include aerobic gram-positive cocci and bacilli such as coagulase positive and negative Staphylococci, Viridans species of Streptococci, Enterococcus faecalis faecium and

gram-negative bacilli such as Escherichia coli, Klebsiella spp., Pseudomonas aeruginosa and Diphtheroides.⁶⁻⁸ Currently, the initial selection of an antibiotic regimen is based on the types of organisms causing infection in each institution; their susceptibility to antibiotics and the individual characteristics of each patient. The risk of infection rises with a fall of neutrophil count.⁷ One of the first signs of infection in neutropenic patients is fever. In fact up to 60% neutropenic patients who develop fever have an established or occult infection and up to 20% with neutrophil count of less than 100/cmm have bacteraemia.^{1,2} Therefore, with this high risk of bacterial infection, which is coupled with the insensitivity of diagnostic tests and delays in the identification of pathogens, immediate empiric administration of broad-spectrum antibiotics is suggested.

The objectives of this study are to review the current management of febrile neutropenia in our institution based on current in-vitro sensitivity data and clinical response to existing first line combination of antibiotics, changes made in the antibiotics if no response was obtained with empiric therapy and revise the antibiotic policy.

Patients and Methods

This is a retrospective analysis of data on febrile neutropenic patients who were treated at Bismillah Taque Blood Diseases Centre (BTBDC), Karachi, from September 1999 to January 2002 with conventional chemotherapy, patients with idiopathic aplastic anaemia and those who received allogeneic peripheral blood stem cell transplantation. Eligible patients were those with fever defined as an elevation of temperature to 100.5°F over at least 4 hours period or a single spike of 102°F. Neutropenia was defined as an absolute neutrophil count (ANC) $<0.5 \times 10^9/l$ and with presumptive infection. Patients who had repeated febrile neutropenic episode during consecutive chemotherapy treatment were enrolled more than once. Exclusion criteria was the use of IV or oral antibiotics other than antifungal prophylaxis during last 48 hours, a history of allergic reaction to any of the antibiotics used in the study, or evidence of hepatic or renal failure. All patients received Itraconazole 100 mg orally as antifungal prophylaxis.

After a detailed history and a thorough physical examination at the time of fever in neutropenic patients, a complete blood count, renal and hepatic function tests, electrolytes, chest X-ray, urinalysis with culture and blood cultures were sent. Patients who had diarrhoea or sore throat, stool and throat swab/sputum were also sent. All patients received Inj. Ceftriaxone 50mg/kg/day in two divided doses along with Inj. Amikacin 15 mg/kg/day in two divided doses. Details of subsequent changes are given in Table 1. General guidelines for the management of febrile neutropenia such as clean diet, proper hand washing, cleanliness and avoidance of individuals with fever or suspected infections were followed.

Each febrile episode was classified as either due to clinically or microbiologically documented infection or of undetermined origin. Criteria for microbiologically documented infection were similar to Pizzo et al.¹ Each patient was physically examined daily. Blood counts were done daily and blood cultures repeated in those with persistent fever of above 102°F. Other tests were repeated as needed.

Clinical and microbiological outcomes were evaluated at 72 hours, 7 days after the start of antibiotic treatment and at resolution of neutropenia. Treatment outcome was classified as a success without modification when patient recovered from fever and neutropenia on initial empirical therapy. Success with modification involved ultimate recovery from fever and neutropenia but requiring alteration different antibiotic, antifungal or antiviral agent. The treatment was considered as failure if fever persisted for longer than 7 days without any response leading to patients' death or the patient showed clinical deterioration with or without persistence of primary isolated microorganism or detection of a new organism.

Febrile episodes were classified according to the kind of infection (i) fever of unknown origin (FUO) (ii) microbiologically documented infection (MDI) (iii) clinically documented infection (CDI) and according to the suspected source or site of infection (unknown, bacteraemia, fungaemia, viraemia, lower respiratory tract infection, upper respiratory tract infection, gastro-intestinal tract infection, soft tissue infection and line related infection).³ FUO was defined as both the absence of any clinical or radiological sign of infection other than fever and no isolation of causative organism. The diagnosis of microbiologically documented infections was based on both isolation of causative organism from body fluids and accompanied by clinical symptoms adopted from the case definitions of the Centres for Disease Control (CDC) surveillance system for nosocomial infection.³ Bacteraemia or fungaemia was defined as fever with positive blood cultures for bacteria or fungi with or without septic symptoms or signs of localized infection. Viral infection was defined as fever both typical exanthema. Fever arising from a clinically evident source of infection including radiological findings without detection of any pathogen was classified as clinically documented infection.^{2,3} Bacterial isolates were identified and tested according to standard

Table 1. Response to antibiotic regimen

	Empiric therapy (ceftriaxone amikacin)	Second line (Pip-Tazo amikacin)	Third line (vancomycin ceftazidime)	Fourth line (imipenem amikacin)
Success (intention to treat)	60/120	3/60	7/57	30/40
Median time to defervescence	3 days	3 days	3 days	2 days
Mortality	10			
Mortality from infection	6			

identification techniques and antibiotic susceptibility tests as suggested in NCCLS document M-100-S58.⁹

Results

Between November 1999 to January 2002, a total of 120 episodes of febrile episodes were documented in 78 patients. There were 61 males and 17 females whose age ranged from 2 to 69 years.(median 22 years). Clinical characteristics of these patients are given in Table 2. After 48 hours of treatment with empiric therapy line antibiotics, 50% patients continued with un-modified therapy; in the remaining 50%, second line and third line therapy was continued without any further change in 9 and 3 patients respectively. Imipenem was used in combination with Amikacin as salvage therapy as a last resort in 40 patients who failed to respond to various combinations of antibacterial antibiotics. Out of these 40 patients, 10 by this time developed fungal infection and could not survive while the remaining 30 defervesced within 72 hours of starting this combination. Response to antibiotic regimen is shown in Table 2.

Table 2. Comparison of underlying condition and disease status

Patients	Numbers	Episodes of Febrile Neutropenia
Diagnosis		
AML	9	18
ALL	19	37
AA	27	36
b-Thalassaemia major	9	10
Fanconi's Anaemia	1	2
NHL	4	8
HD	1	1
CML	4	4
MM	3	3
MF	1	1
Disease Status		
Induction / Intensification	76	
BMT	27	
Maintenance	5	
Other		

ALL; acute lymphoblastic leukaemia, AML; acute myeloid leukaemia, AA; aplastic anaemia, NHL; non-Hodgkin's lymphoma, HD; Hodgkin's disease, CML; chronic myeloid leukaemia, MM; multiple myeloma, MF; myelofibrosis, BMT; bone marrow transplantation.

In 120 episodes of febrile neutropenia, 78 patients were on chemotherapy or pre or post bone marrow transplantation. E-coli, S. aureus, Klebsiella, Candida and P. aeruginosa, were most commonly encountered organisms (Table 3). The antibiotic policy of BTBDC was developed to cover most of these organisms i.e. gram positive and negative both. FUO was defined as both the absence of any clinical or radiological sign of infection other than fever and no isolation of causative organism. It occurred in 18 episodes. The diagnosis of microbiologically documented infections was based on both isolation of causative organism from body fluids and accompanied by clinical symptoms adopted from the case definitions of the Centres for Disease Control (CDC) surveillance system for nosocomial infection. MDI occurred in 60 episodes of fever. Fever arising from a clinically evident source of infection including radiological findings without detection of any pathogen was classified as clinically documented infection. The CDI occurred in 42 episodes. Fungal isolates were obtained in 11 episodes from 16 different samples i.e. throat swab, mouth swab, sputum or blood. Viral exanthema was seen in three patients. Table 3 shows results of documentation of infection.

Table 3. Documentation of infection.

Organisms	Numbers
Total sepsis	120
Gram Negative Isolates (all sample types)	34
E. coli	13
Pseudomonas spp.	6
Klebsiella spp.	14
Gram Positive Isolates (all sample types)	26
S. aureus	19
CNS	3
Streptococci	2
Fungal infection	11
MDI with isolation of bacteria from any clinical material	60
Viral MDI	3
Fungal MDI	11
Mixed infection	19
CDI	42
FUO	18

MDI; microbiologically documented infection

CDI; clinically documented infection

FUO; fever of unknown origin

CNS; coagulase negative Staphylococcus

A total of 502 samples were sent for culture during 120 febrile neutropenic episodes; 117 (23.3%) cultures yielded an organism. The yield of blood culture was 12% i.e. 32/265, for urine was 12.5% i.e. 9/72, for stool 31% i.e. 10/34, sputum 50% i.e. 9/18 while for throat swab showed 23% i.e. 3/23 yield. Three gram negative organisms isolated from specimens were *E. coli*, *Klebsiella* spp and *P. aeruginosa*. Four drugs consistently showing sensitivity against these organisms were Imipenem, Cefepime, Piperacillin-tazobactam and Amikacin. While other 3rd generation cephalosporins, aminoglycosides and quinolones were highly resistant.

Discussion

Traditionally broad-spectrum antibiotic combination is used as empirical therapy in febrile neutropenia, 44% febrile episodes require a modification. Modification of antibacterial therapy is a reality in clinical practice in the treatment of febrile neutropenia. Many studies have reported various response rates to empirical therapy from 50-70%.^{1,4,5,7} Our study has included a large group of profoundly neutropenic patients (absolute neutrophil count of <100/cmm). In an analysis comparing febrile episodes in children and adults, bacteraemia occurred in 22%, clinically documented infection in 19% and PUO in 49% patients. In our study, documented bacteraemia and infections were comparable to those reported in the literature. First line antibiotics achieved a success rate of 50%, the remaining require modification.

The results of empiric therapy used were comparable to other published reports.^{8,10,11} Practice of repeated changes of combination of broad-spectrum antibiotics was not an effective strategy. Rather, a suspicion of fungal infection should direct the physician to start parenteral antifungal therapy if temperature does not settle in 96 hours after starting empiric therapy. Antibiogram showed a very high rate of multidrug resistant organisms in this cohort of nosocomial infections in neutropenic patients. Like other studies, severity and duration of neutropenia were the two most important indicators of the outcome. Treatment failure in 10 patients was found to be related to a delay in starting parenteral antifungal therapy, severe persistent neutropenia and progressive underlying disease.

E. coli, *Klebsiella* spp and *P. aeruginosa* were the most common gram negative isolate while *S. aureus* was the most common gram positive organism isolated. *Candida* spp. were grown in a significant proportion. Four drugs showing sensitivity against these organisms were Imipenem, Cefepime, Piperacillin-tazobactam and Amikacin. While other 3rd generation cephalosporins, aminoglycosides and quinolones were highly resistant. A close surveillance of antibiogram will guide us in any change in the pattern of infection and sensitivity to existing profile. In conclusion, based on current antibiogram of nosocomial isolates in our centre, existing first line combination could be continued. When modification is needed, second line combination should incorporate Imipenem, Cefepime or Piperacillin-tazobactam. Alternatively, monotherapy with either

of three could become empiric therapy while in non-responders addition of Amikacin or a glycopeptide would be a logical approach.

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