

Usefulness of Bacteriologic Cultures in Choice of Antibiotics in Patients with Chemotherapy-induced Neutropenic Sepsis

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Abstract

Neutropenic sepsis is a potential problem in cancer patients undergoing cytotoxic chemotherapy. Septic work-up including cultures from various sites is routinely done for these patients. To assess the usefulness of these cultures, a retrospective review of all patients admitted for neutropenic sepsis in the period from June 1994 to August 1995 was conducted. All patients included in the study had solid tumours which were being treated at our institution during the study period. All had fever and documented neutrophil count of $<1 \times 10^9/l$ on at least one occasion. There was a total of 41 patients with 52 episodes of neutropenic sepsis. Of the 52 episodes, there were positive cultures in 14 (27%) episodes, including 7 from blood, 2 from urine and 5 from skin. In the bacteriologic cultures, gram-negative bacteria were isolated in 11 episodes and gram-positive bacteria in 5 episodes (2 episodes had both gram-negative and gram-positive bacteria isolated, and 1 episode had two gram-negative bacteria). Majority of the patients (96%) were treated with a third generation cephalosporin with/without an aminoglycoside. This empirical treatment was effective with resolution of fever in 39 (75%). Thirteen (25%) had change of antibiotics because of deteriorating clinical state or drug resistance. Nine patients with unabated sepsis had bacteriological cultures which grew organisms resistant to the empirical antibiotics. Eight responded to the change of antibiotics. One patient with pseudomonas bacteraemia failed to respond to empirical treatment with ceftriaxone and died before antibiotics could be changed. Of the patients with positive cultures, the results of drug sensitivity made a difference to treatment. None of the patients with negative cultures died from sepsis. It appears that even though the rate of positive culture is low (27%), it is still useful as a guide when change of antibiotics is required.

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Introduction

Marrow suppression is a common problem associated with the use of chemotherapeutic agents in the treatment of cancer patients. As many as one-third of patients treated with chemotherapy develop neutropenic fever, of which the majority will be due to sepsis.¹ For patients with solid tumours, the numbers are much smaller but it has also contributed significantly to morbidity and mortality associated with chemotherapy.

Various studies have demonstrated isolation of pathogens in approximately 30% to 40% of patients with neutropenic fever,¹⁻³ of which half have associated bacteraemia.³⁻⁵ Mortality for patients with untreated neutropenic sepsis is high especially if associated with bacteraemia. However, the use of empirical antibiotics has resulted in a marked decrease in the mortality rate.⁶ While many different antibiotic regimes have been proposed, with varying results,^{2,3,7-11} effective empirical antibiotic therapy can reduce overall mortality to about 10%.^{2,6,8}

We conducted a retrospective review to document our experience with neutropenic sepsis and to look at the usefulness of bacteriologic cultures, in particular with regards to the choice of empirical antibiotic therapy.

Materials and Methods

Patients treated with chemotherapy in our department and admitted with neutropenic sepsis from June 1994 to August 1995 were reviewed. As fever is often the only early sign of infection, patients with neutropenia and a febrile state unaccountable by underlying disease or treatment were entered in the review. An absolute neutrophil count of less than $1 \times 10^9/l$ on at least one blood count reading was required^{4,12} and an oral temperature of 38°C or more for at least one hour was accepted as febrile state.¹²

Prophylactic antibiotics before onset of fever are not routinely given to our patients treated with chemotherapy. Patients who had fever but no documented neutropenia, and those with a non-infective cause for

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fever for example transfusion reaction and fever during infusion of medication were excluded. Patients with fever from tumour necrosis or inflammation were also excluded from the review.

All patients were evaluated for potential source of infection from the urinary tract, lungs, skin and blood (from central lines as well as from peripheral veins). A detailed clinical history and physical examination was done at presentation. Investigations included daily full blood counts, chest radiograph, urinalysis, blood and urine cultures. Sputum, stools as well as swabs from skin lesions and sores were cultured when indicated. Daily physical examinations were performed throughout the period of hospitalization.

Chest infection was diagnosed when the chest radiograph showed infiltrates or consolidation not attributed to pulmonary metastasis or malignancy. Positive urine culture was defined as bacterial colonies of more than 10⁵ per ml. Bacteraemia was defined as positive blood cultures and skin infection was diagnosed when there was clinically evident cutaneous lesions with positive bacteriologic cultures from the lesions.

All patients were started on empirical antibiotics decided on by the managing physicians. In 50 out of 52 neutropenic sepsis episodes, a third generation cephalosporin with/without aminoglycoside was used. One patient had cefuroxime with an aminoglycoside and one had vancomycin alone. Eight patients had in addition, cloxacillin, metronidazole or erythromycin (Table I). Antibiotic choice was reassessed at 72 hours and modification to the antibiotic regimes was made when patients failed to respond or when culture results showed organisms resistant to the empirical antibiotics given. Patients were considered to have responded when there was resolution of fever or when there was a downward trend of temperature.

TABLE I: EMPIRICAL ANTIBIOTICS USED

No. of episodes	Ceftriaxone	Ceftazidime	Gentamicin	Metronidazole	Cloxacillin	Vancomycin	Cefuroxime	Erythromycin
35	+		+					
2	+		+	+				
3	+		+		+			
1	+		+					+
1		+	+					
6	+							
1	+			+				
1	+				+			
1			+				+	
1						+		

Results

A total of 2247 patients with solid tumours were treated with chemotherapy in the period from June 1994 to August 1995. There were 52 admissions for neutropenic fever in 41 patients (of which 14 were males and 27 were females). Thirty-two patients had 1 episode of neutropenic fever, seven had 2 episodes and two had 3 episodes. The median age was 55 years, with a range of 16 to 78 years. The primary malignant disease is highlighted in Table II.

Fever occurred, on the average, 10 days post day 1 of chemotherapy (range 3 to 20 days). This coincided with the period of neutropenia post-treatment. Average duration of neutropenia was 4 days. In 34 episodes, patients came to hospital on the day or the day after onset of fever. None of the patients were started on antibiotics by the general practitioners.

Bacteria were isolated from 14/52 (27%) episodes of neutropenic sepsis. Seven positive cultures were from the blood, 2 from the urine and 5 from the skin. Gram-negative bacteria were isolated in 11 episodes and gram-positive bacteria were isolated in 5 episodes (2 episodes had both gram-negative and gram-positive bacteria). Pseudomonas was cultured in 4 episodes, being the most frequent organism isolated (Table III). Of the 14 episodes with positive cultures, 5 had organisms sensitive to empirical treatment given. The organisms included *Escherichia coli*, *Proteus mirabilis* and *Klebsiella pneumoniae*.

TABLE II: PRIMARY MALIGNANT DISEASE IN THE 41 PATIENTS

Lymphoma	14
Breast cancer	11
Gastrointestinal tract cancer	7
Lung cancer	4
Genitourinary tract cancer	3
Sarcoma	2

TABLE III: ORGANISMS ISOLATED FROM THE 17 POSITIVE CULTURES

Gram-negative	12/17 (71%)
<i>Pseudomonas aeruginosa</i>	4
<i>Klebsiella</i>	3
<i>Escherichia coli</i>	2
<i>Acinetobacter</i>	2
<i>Proteus</i>	1
Gram-positive	5/17 (29%)
<i>Coagulase-negative staphylococcus</i>	2
<i>Staphylococcus aureus</i>	2
<i>Enterococcus</i>	

The remaining 9 had resistant organisms including *Pseudomonas aeruginosa*, *Enterococcus* and *Coagulase-negative Staphylococcus* which required a change of antibiotics.

Empirical treatment was effective with resolution of neutropenic sepsis in 39/52 (75%) episodes. In 13/52 (25%) episodes, a change of antibiotics was required because of persistent fever alone (4 episodes) or culture isolation of a bacteria resistant to empirical therapy (9 episodes). In all 9 episodes where a resistant organism was cultured, fever was a consistent finding. Resolution of fever was achieved with a change of antibiotics in all patients except one who died from pseudomonas bacteraemia before antibiotics could be changed (Fig. 1). Overall mortality for our series was 2%, with an average hospital stay of 9 days.

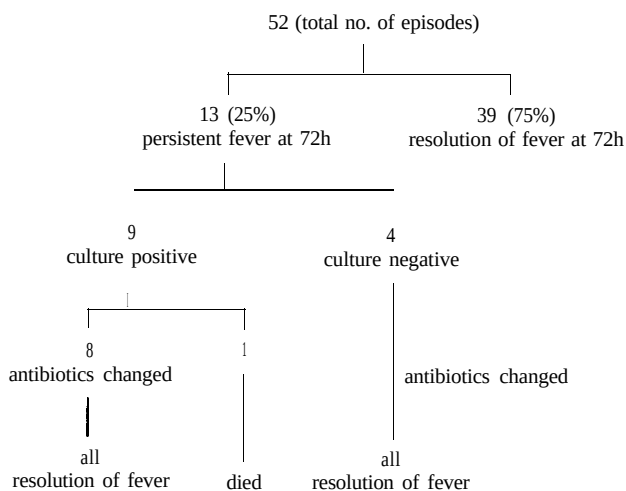


Fig. 1. Response to empirical antibiotics.

Discussion

With the increasing use of aggressive chemotherapy in the treatment of solid tumours, neutropenic sepsis is becoming a significant source of morbidity and mortality. In patients with neutropenia, initial physical findings are usually unrevealing and fever is often the only early sign of infection. Hence, there has been

tremendous interest in monitoring the type of pathogens predominantly cultured from these patients and in formulating the best form of empirical treatment.

In the 52 episodes of neutropenic sepsis from June 1994 to August 1995, there were positive cultures in 14 (27%) episodes of which 7 were from blood cultures. The rate was consistent with that from previous studies, where 30% to 40% of patients with neutropenic sepsis have positive cultures, of which about half was due to bacteraemia.¹⁻⁵

In our series, the predominant group of organisms cultured was the gram-negative bacilli, accounting for 71% of positive cultures, of which the commonest was *pseudomonas*. The pattern has not changed in our centre since 1990.^{2,11} This is very interesting because there appears to be a trend towards a greater proportion of gram-positive organisms in the last two decades, mainly *coagulase-negative staphylococci* and *streptococci*, in some of the larger series. It was postulated to be due to increasing use of central venous catheters as well as an increased incidence of chemotherapy-induced mucosal injury. In the first International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) trial in the 1970s, gram-negative pathogens were responsible for bacteraemia in 71% of cases versus 29% with gram-positive organisms.¹³ In 1991, the ratio has become 31% gram-negative organisms to 69% gram-positive organisms.¹⁴ The reason for the lag in the changing bacterial spectrum in our centre was not clear. One postulation was possibly a lower incidence of mucosal injury in our patients from treatment, but the data were not available for further discussion. None of our patients had fungal infection and this was not unexpected, as most of them did not have prolonged period of neutropenia, the period being an average of 4 days in our review. Fungal infection is known to occur in a small proportion of patients with neutropenic sepsis, mainly those predisposed by high dose corticosteroids, prolonged antibiotics and prolonged or profound neutropenia.¹³

Mortality for patients with neutropenic sepsis was high in the days when treatment was delayed until patients had definite clinical signs or isolation of pathogens, and was as high as 91% for neutropenic cancer patients with gram-negative bacteraemia.¹⁵ This has changed since the era of empirical antibiotic treatment. There were many studies in the literature which attempted to ascertain the most effective empirical antibiotic regime based on previous bacteriologic data. They were targeted at the commoner organisms cultured, which used to be the gram-negative bacilli. The most effective regimes had been combination therapies with combined use of a β -lactam with an aminoglycoside,^{2,3,7,8,13} or two β -lactams.^{7,13} Most studies reported an initial response rate of 70% to 80%. With the changing pattern

of infective organisms in patients with neutropenic sepsis, the adequacy of previously proposed regimes is questioned. However, mortality rate from the gram-positive cocci infections is low and delayed treatment with vancomycin has not significantly affected the outcome.^{14,16}

The empirical antibiotics choice in the majority of our patients which comprised mainly of a cephalosporin with/without gentamicin was based on previous world literature^{8,10} and also on our own local experience.^{2,11} This proved to be effective in 75% of our patients. In the instances where patients failed to respond or had resistant organisms cultured, mainly *pseudomonas* or a gram-positive coccus, all except one responded to a change of antibiotics. However, the fact that 9 out of 14 episodes with positive cultures had organisms resistant to our empirical antibiotics suggest that we can improve the results of our empirical treatment by extending the coverage to ensure anti-pseudomonas therapy. Since morbidity and mortality associated with gram-positive organisms are not high, it is reasonable to add on cloxacillin or vancomycin only when suspicion of gram-positive infection is strong, when there is culture-proven gram-positive infection or when patients fail to respond to empirical treatment. For patients with profound neutropenia and sepsis not responding to antibacterial regimes, there may be a role for anti-fungal treatment with empirical amphotericin B. Haematopoietic growth factors may be used when indicated.¹⁷

In summary, the rate of positive cultures in patients with neutropenic sepsis from our centre is similar to that found elsewhere but in contrast to other reports, gram-negative bacilli remain the predominant organisms cultured. The antibiotics (a third generation cephalosporin with/without gentamicin) used as empirical therapy are effective in the majority of our patients, but when patients fail to respond to first line antibiotics, culture results are important, serving as a useful guide in antibiotics modifications. A review of the types of organisms common in this subgroup of patients and their sensitivity patterns also help formulate more effective empirical and second line therapy for use in the future. Hence, aggressive investigations and relevant cultures remain an important part of management of neutropenic sepsis.

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