

Emerging Bacterial Resistance Patterns in Febrile Neutropenic Patients: experience at a tertiary care hospital in Pakistan

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Introduction

Major advances have been achieved in the management of patients with cancers, such that patients with previously untreatable illness may now receive therapy and survive. However, this has been obtained with aggressive use of chemotherapy and antimicrobial therapy. This has necessitated more and more use of invasive procedures, like placement of porta-catheters, which may also contribute to increased susceptibility to infections. The net result is that patients surviving severe underlying diseases may succumb to bacterial, fungal, viral or protozoan infections.¹ This is particularly true for cancer patients, especially those with haematological and lymphoid malignancies², in whom infectious complications represent an important cause of morbidity and mortality, as chemotherapy results in neutropenia in a vast majority of the patients.³

A febrile neutropenic patient needs immediate empirical antibiotics⁴, failure of which may lead to septicaemia and mortality.⁵ The composition of the empiric therapy continues to remain somewhat controversial. Over the past decade there has been a considerable change in the pattern of pathogens causing infections in cancer patients. The classic beta-lactam and/or an aminoglycoside combination has long been considered the best therapeutic approach for febrile neutropenia⁶ because of its broader spectrum, potential synergistic activity against gram-negative rods, and its potential ability to reduce the

emergence of resistant strains.⁷ With time the resistance to beta-lactam antibiotics has been on the rise and warrants close monitoring of the sensitivity patterns of different organisms.⁸ Previous studies in this institute have shown a

changing trend in the spectrum and sensitivities of various bacterial isolates in neutropenic patients.⁹⁻¹¹ The aim of our study is to look at the clinical presentation of neutropenic patients, the spectrum and site of isolation of bacterial organisms and their sensitivity patterns. In addition the common antibiotic used in the management of febrile neutropenic patients at our institution is also reviewed.

Material and Method

The data were collected retrospectively from the records of all neutropenic patients with an absolute neutrophil count (ANC) of less than 500/ml admitted during the period of 3 years from August 1999 to July 2002 at AKUH. The patients had either haematological or non-haematological underlying malignancy. The organisms were isolated using standard techniques. Antimicrobial sensitivity testing of all isolates was performed on Diagnostic Sensitivity Test plates by Kerby - Bauer method. The clinical information, culture/ sensitivity data and the antibiotic management of febrile neutropenic patients were recorded and data was analyzed using SPSS 10.0..

Results

A total of 404 patients were admitted, with haematological or non-haematological malignancies and an absolute neutrophil count (ANC) of less than 500/ml during the period of 3 years, from August 1999 to July 2002 at AKUH. About half of the patients were below 20 years of age. Of the total 55% were males and 45% were females; 65% of the patients had haematological malignancies and around half were suffering from leukaemia. The distribution of various malignancies is shown in Figure.

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The most common presenting symptom was fever (86%). Other common symptoms and examination findings included cough (14%), chest signs (14%), Vomiting (14%), oral mucositis (10%), sore throat (8%) and diarrhoea (7%). Positive X ray findings were found in 18 % of the patients. A total of 124 bacterial isolates were obtained from 96 patients and a focus of infection was identified in 23% of the patients. Of the 124 isolates 47% were gram positive and 53% were gram negative. Sixty-five (16.1%) patients had septicaemia at the time of admission. CoNS were the most common gram positive organism isolated, followed by *Staphylococcus aureus* and *Enterococcus* spp. Majority of the gram positive organisms were isolated from blood (67%), while remaining were isolated from porta-catheters, wound infections, urine, respiratory tract and pus.

A variety of gram negative organisms were isolated in patients with febrile neutropenia. *E. coli* being the most common isolated gram negative rod, followed by *Pseudomonas* and *Klebsiella* spp. Gram negative organisms were isolated from more diverse sites with a nearly equal isolation from blood and urine in majority of the cases. The other sites of isolation for gram negative organisms included respiratory tract, stool, pus and wound. Unlike gram positive bacteria, gram negative isolates were rarely obtained from porta- catheters and only one isolate of *Pseudomonas aeruginosa* was cultured from the port.

The resistance patterns of various gram positive and gram negative organisms were noted. Methicillin resistance was very high among *Staphylococcus epidermidis* and other CoNS (88%) and only 8% of the *Staphylococcus aureus* were found to be MRSA among this group of patients. Vancomycin resistance among CoNS was found in 4% of the isolates and 25% of the *Enterococcus* spp. were found to be resistant to vancomycin (VRE).

Among gram negative organisms, an emerging resistance pattern to all commonly used antibiotics was noted. There was a high level of resistance among isolates of the *E. coli* to fluoroquinolones (62%), aminoglycosides (48%) and cefixime (31%). About 31% of *Pseudomonas* spp. was resistant to fluoroquinolones and 15% of the isolates were also resistant to aminoglycosides, ceftazidime and aztreonam. Similarly 67% of *Klebsiella* spp. was found resistant to cefixime and 57% were resistant to aminoglycosides. Resistance to piperacillin-tazobactam was also found in 7-14% of the isolates and around 8% of the *Pseudomonas* spp. was also

resistant to imipenem.

The most common initial antibiotics used for the treatment of neutropenic fever were combination of amikacin, and piperacillin-tazobactam (53%) followed by amikacin and ceftazidime (33%). Success without modification of initial antibiotic regimen was documented in 63% of the cases. In the remaining 37% of the patients, initial antibiotic regimen required modification for clinical and microbiological reasons. The most frequent antibiotics used in modified regimens included imipenem (38%), metronidazole (32%) and cloxacillin (22%). Granulocyte Colony Stimulating Factor (G-CSF) was used in 21% of the patients and systemic antifungal treatment was required in 23% of the patients; 46% of the patients required supportive blood transfusion and platelet transfusion was given to 31%. The average duration of neutropenia following chemotherapy was 6.4 days and the overall mortality rate was 6% among febrile neutropenic patients.

Discussion

Haematological and lymphoid malignancies were predominant among neutropenic febrile patients with acute leukemia comprising nearly half of our studied patients. This pattern of distribution is similar to previously documented studies.⁹ Similarly fever was the most common symptom at presentation (85%) in our patients and a similar percentage of fever is well documented in previous studies.¹² The presence of chest signs in 14% and positive X-ray findings in nearly one fifth of the patients is consistent with other studies.¹³ Presence of diarrhoea and oral mucositis is a strong predictor of oral viridans streptococci (OVS) bacteraemia; simultaneous CoNS bacteremia may also be associated with mucositis.¹⁴

In earlier trials during 1970s, gram-negative rods were predominant. In the mid-1980s, however, the epidemiological situation changed completely¹ and gram-positive bacteria became far more prevalent. The reason for this may be more frequent use of indwelling catheters¹⁵, broad spectrum antibiotics with increased selective pressure on micro-organisms¹ and possible use of H₂-blockers and other antacids, are considered to be some of the factors associated with this transition.¹⁶

Similar transition from predominantly gram negative to gram positive organisms was also noticed in the two previous studies published in Pakistan. In 1991 among the gram-negative organisms *Pseudomonas aeruginosa* was the most common organism. Gram positive organisms comprised almost one fourth of the total isolates, and about 15% were

Staphylococcus aureus. *Staphylococcus epidermidis* (CoNS) was not isolated in that series.⁹ In 1998 54% organisms isolated in febrile neutropenic patients from our institution were gram-negative while the remaining 46% were gram positive.¹¹

Our series show a similar spectrum of organisms, however CoNS was found to be the predominant gram positive organism in contrast to *Staphylococcus aureus*. Among gram-positive organisms CoNS, *Staphylococcus aureus*, *Enterococcus* spp. and oral viridans streptococci (OVS) were the most common bloodstream isolates in febrile neutropenic patients at our institution. Although in general these gram positive organisms are quite indolent, *Streptococcus mitis* is reported to be associated with serious complications such as sepsis and adult respiratory distress syndrome (ARDS).^{17,18}

The plateau that has been reached in the transition to gram positive bacterial organisms from gram negative organisms is also evident from other international studies. In a study published by Haupt and co-workers¹⁹, an increase in the incidence of gram-negative bacteraemia of 3.4% per year was reported in children treated for solid tumours in the period 1985-1996. In another study by Aksu and coworkers²⁰ almost 50% of late-onset bacteraemia following bone marrow transplantation was due to gram-negative rods. Gaytan-Martinez and coworkers²¹ in their study found *Escherichia coli* to be the most frequently isolated pathogen during febrile neutropenia in cancer patients.

Among gram positive isolates in our study, CoNS showed a very high resistance, with 50% of the strains resistant to cloxacillin as compared to 10% in the previous studies. Similarly there is an emergence of vancomycin resistance to *Enterococcus* and CoNS, which was not reported in previous studies from this institution. An alarming 25% of *Enterococcus* and 4% of CoNS isolates were resistant to vancomycin. The isolation of vancomycin resistant *Enterococcus* (VRE) and CoNS, especially from blood and urine cultures in immuno-compromised patients poses serious therapeutic limitations in the eradication of these infections. This pattern of emerging bacterial resistance among gram positive organisms was not seen in previous studies from Pakistan. Similarly resistance among other gram negative organisms has also increased when compared to previous studies.⁹⁻¹¹ The finding of markedly increased resistance of *E. coli* (62%) and *Pseudomonas aeruginosa* (31%) to fluoroquinolones in our study is of real concern, especially with frequent use of

this antibiotic for infection prophylaxis in neutropenic patients. The emergence of fluoroquinolones resistance in *E. coli* had been well documented in cancer patients from the West, especially among neutropenic patients who had received prophylactic norfloxacin.^{22,23} This high degree of *E. coli* resistance among our patients implies indiscriminate use of antibiotics by local practitioners in the community and also in the hospitals throughout the country. Similarly finding of higher resistance of gram negative organisms to aminoglycosides, third generation cephalosporin and emergence of bacterial resistance to newer ultra-broad spectrum antibiotic like piperacillin- tazobactam and imipenem also appears to be on the rise. Similar trends have also been observed internationally in other published studies.²⁴

The classic beta-lactam and an aminoglycoside combination had long been considered the best therapeutic approach for febrile neutropenia.²⁵ The choice of antibiotics in our institute was also an aminoglycoside in combination with anti-pseudomonas cephalosporin; however frequent modifications were required in treatment, once the culture results became available. Antibiotic resistance among gram negative bacilli may limit the efficacy of some beta- lactam antibiotics, and this may be a cause of concern for institutions using monotherapy.²⁶ Single-agent therapy became a possibility when broad-spectrum antibiotics, such as third and fourth generation cephalosporin with anti-pseudomonas activity (ceftazidime and cefepime), ureidopenicillins with beta-lactamase inhibitors (e.g. piperacillin/ tazobactam) and carbapenems (e.g. imipenem) became available.^{27,28} Vancomycin may be used empirically in febrile patients with prolonged and profound neutropenia and as initial empiric therapy in febrile neutropenic leukaemia/lymphoma patients with indwelling venous access devices.²⁹ With the use of early and aggressive antibiotics in febrile neutropenic patients, the overall mortality rate from 1978 to 1994 has decreased from 21% to 7%.¹ Our study also shows a similar low mortality rate of 6.1% among febrile neutropenic patients at our institution.

It can thus be concluded that the trend of conversion from gram negative to gram positive bacterial isolates in febrile neutropenic patients, seen in 1980s and early 1990s, has halted and there is now a static proportion of gram positive and gram negative organisms isolated from neutropenic patients. Local antibiotic policies, bacteriological resistance patterns, antibiotic toxicity, and a number of patient-related factors should be taken into account before deciding the best choice of

antibiotics for the treatment of neutropenic fever. An increasing trend of resistance to commonly used antibiotics is emerging especially among gram negative organisms like *E. coli*, *Pseudomonas*, and *Klebsiella* spp. In addition there is evidence of emerging vancomycin resistance among isolates of *Enterococcus* spp. and CoNS, which was not seen before in our patient population. There is an urgent need for active surveillance of local bacterial resistance patterns and development of guidelines for the rationale use of antibiotics in the hospitals. Similar studies need to be conducted more frequently in all major hospitals throughout the country so the right choice of empiric antibiotics could be defined for febrile neutropenic patients.

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Abstract

Objective: To look at the clinical presentations, spectrum and site of isolation of the organisms, sensitivity patterns of the organisms and the antibiotic prescribing practices for the treatment of febrile neutropenic patients at our hospital.

Methods: The data were collected retrospectively

from the records of all neutropenic patients with an absolute neutrophil count (ANC) of less than 500/ml admitted during the period of 3 years from August 1999 to July 2002 at AKUH.

Results: Out of the total of 404 patients, 65% had hematological malignancies and around half of them had leukaemia, 86% of the patients presented with fever. A total of 124 bacterial organisms were isolated from 96 patients among which 47% were gram positive and 53% were gram negative organisms; 16.1% of the patients had septicaemia. Coagulase Negative Staphylococci (CoNS) were the most common gram positive and *E coli* was the most commonly isolated gram negative organism. Most of the gram positive organisms were isolated from blood (67%). There was emerging resistance to all commonly used antibiotics including imipenem, cloxacillin, vancomycin and amikacin. The average duration of neutropenia was 6.4 days. The mortality rate was 6%.

Conclusion: There is increasing trend of gram negative organisms developing resistance to commonly used antibiotics. Gram positive bacteria including *Enterococcus* spp. and CoNS are also showing emerging resistance to vancomycin (JPMA 54:357;2004).