

Original

Pattern of Infections in patients with Neutropenia and their Outcome.

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Abstract: Neutropenic patients are predisposed to a number of infections by bacteria, fungi and viruses. Fifty (50) patients with absolute neutrophil count (ANC) $\leq 1000/\text{mm}^3$ were analyzed for the pattern of infections and their outcome. Leukemia was the most common diagnosis in study group. Fever was the common clinical feature. Only 48% of patients had positive cultures. Main sites of isolation were blood (20%), urine (20%), and respiratory tract (12%). Gram-negative pathogens were isolated in 16 patients (53.3%), gram-positive pathogens in 13 patients (43.3%) and fungal pathogen in 1 patient (3.3%). E.coli was the predominant organism isolated from urine in the study (36.3%), followed by staphylococcus aureus (16.6% Patients). 60% of patients with neutropenia survived, while 30% died and 10% were lost to follow up. Gram-negative septicemia was the leading cause of mortality.

Treatment consisting of adequate gram-negative and gram-positive antibiotic cover should be initiated in patients who are culture negative.

Keywords: Neutropenia, Pattern of Infections.

INTRODUCTION

Neutrophils are the first of defense of our body. Neutrophils are associated with the function of phagocytosis. Therefore, neutropenia predisposes the patients to a number of infections by bacteria, fungi and viruses. Neutropenia is defined as absolute neutrophil count $< 500/\text{mm}^3$ or $< 1000/\text{mm}^3$ with a predicted decrease to $< 500 \text{ cell}/\text{mm}^3$. Neutropenia is graded as moderate when ANC is between $500-1000/\text{mm}^3$ and severe, when it is less than $500/\text{mm}^3$. Different risk categories can be identified according to the duration of neutropenia: low risk (≤ 5 days), intermediate risk (6-9 days) and high risk (> 10 days). Fever is associated with microbiologically documented infection in 30% of patients, with bacteremia accounting for about half of the cases; in another 30-40%, the infection is clinically documented. Treatment depends mainly on the underlying cause of neutropenia, duration of neutropenia and the microorganism infecting the patients. The present study was undertaken to analyze the pattern of infection in neutropenic patients and their outcome in a tertiary care center in order to evaluate the various types of infections occurring in patients having neutropenia and also to assess the outcome of these infections. Cases where neutropenia was due to infection were excluded from the study.

MATERIALS AND METHOD

Fifty (50) patients of neutropenia (ANCL $< 1000/\text{mm}^3$) over a period of 5 days attending the hospital and fulfilling the inclusion criteria, were included in the study; the causes were (i) drug induced neutropenia (ii) idiopathic aplastic anemia.

A detailed history was recorded and clinical examination was done. The following investigations were done at the time of admission: complete blood count; renal function tests; liver function test; chest X-ray; urine routine; urine culture and sensitivity; blood culture and sensitivity; sputum culture and sensitivity; I/V catheter tip culture sensitivity; urinary catheter tip culture & sensitivity; stool culture sensitivity; ultrasound abdomen; vaginal swab culture & sensitivity; pleural fluid culture & sensitivity;

Repeat sampling was done as per the response to antibiotics and according to the initial reports. Samples were collected under all aseptic precautions. Blood cultures were sent in aerobic bottles. Urine for culture, catheters tip (both I/V and urinary), were sent in sterile

plasticon-fainers. The outcome of patients was also determined in respect of mortality, morbidity or improvement. The condition was considered fatal when death has occurred because of infection acquired during neutropenia and not due to primary cause or other medical problems. The data was analyzed using coefficient of correlation and test of proportion wherever applicable.

RESULTS

Demographic Data

29 patients (58%) were males and 21 (42%) were female; leukemia was the most common primary diagnosis in study group seen in 64% of patients; aplastic anemia and drug-induced pancytopenia were the next common diagnosis seen in 12% of patients and 6% patients had lymphomas as primary diagnosis. Fever was the most common presenting complaint (100%) followed by bleeding diathesis (34% patients).

Culture results

In this study, 48% of neutropenic patients were culture positive, while 52% were culture negative. 21 patients (87.5%) had positive from a single site, two patients had two sites of culture positivity and one patient had culture positive from three sites. Gram-negative bacteremia was observed in 60% of patients and gram positive bacteremia in 40% of patients. Sputum cultures were positive in 2 of 5 patients, pleural fluid in 2 of 4; throat swab culture was positive in all 4; stool culture was negative in one patient sent.

Pathogens isolated:

Total of 30 microorganisms were isolated in the study. Out of 30 microorganisms 53.3% were gram-negative and 43.3% were positive table 1. One fungal isolate (candida tropicalis) was also cultured. Various pathogens isolated from various sites are shown in table 2. Out of 30 microorganisms isolated, E. coli was the most common, constituting 36% of all isolates, followed by staphylococcus aureus (16.6%). Among gram-negative organisms, klebsiella and pseudomonas were other microorganisms, staphylococcus epidermidis and non-hemolytic streptococci constituted 10% each. E. coli was the predominant microorganism isolated from the urine.

Antibiotics Used

In the study group, 26 different antibiotic molecules were used. Average number of antibiotics used in a patient was five; Amikacin,

Table 1: Distribution according to micro-organism isolated

Micro-Organism	Number Of Patients
Gram-Negative (A)	16 (53.3%)
Gram-Positive (B)	13 (43.3%)
Fungal (C)	1 (3.3%)
Total	30

	Z-value	p-value
A v/s B	0.78	>0.10
Av/s C	4.30	<0.01
B v/s C	3.66	<0.01

Table 2: Pathogens isolated from various sites

Pathogen Isolated	Blood	Urine	Sputum	Pleural Fluid	Throat Swab	Pus Culture
Total No. Of Patients With Positive Culture (N)	10	10	2	2	2	4
1.E.coli	4 (40%)	2	2	—	1	2
2. Klebsiella	1	—	—	1	—	1
3.Pseudomonas	1	1	—	—	—	—
4. Staph aureus	—	4 (40%)	—	1	1	—
5.Staph epidermidis	2	—	—	—	—	—
6. Non hemolytic	1	2	—	—	—	—
7. Strep. viridens	1	—	—	—	—	—
8. Strep. faecalis	—	—	—	—	—	1
9. Candida	—	1	—	—	—	—

ceftizidime and cefotaxime were the most commonly antibiotic used in 68%, 62% and 38% patients respectively. Glycopeptides molecules (teicoplanin and vancomycin) were also used in six patients each

Outcome

Out of 50 patients, 30 patients (60%) were discharged, 15 (30%) died and 5 (10%) were lost to follow up as they had left the hospital against medical advice. 14 patients (93%) died due to septicemia and one patient (7%) died due to intracerebral hemorrhage (Table 3). In **culture positive group**, 13 were discharged, 7 expired and 4 left against medical advice. In **culture negative group**, 17 patients were discharged, eight expired and one left against medical advice table 3. There was no significant difference in mortality among culture positive patients who were treated with antibiotics according to culture & sensitivity and those who were treated, empirically. It was found that mortality in patients presenting with ANC<100 cell/mm³ was 40% while in patients presenting with ANC<500 cell/mm³, it was 25% (table 4). Therefore it was observed that ANC had inverse relation with mortality.

Table 3: Comparison of outcome in culture positive patients versus culture negative patients

Culture Growth	Discharged	Death	Left Against Medical Advice	Total
Positive	13 (54%)	7 (29.1%)	4 (16.6%)	24
Negative	17 (65%)	8 (30%)	1 (3.8%)	26

Table 4: Comparison between Absolute Neutrophil Count (ANC) and outcome

Anc	Discharge	Death	Left Against Medical Advice	Total
≤100	7(46.6%)	6(40%)	2(13.3%)	15(100%)
101-500	12(63%)	5(26%)	2(10.5%)	19(100%)
>501	11(68%)	4(25%)	1(6.2%)	16
Total	30	15	5	50

DISCUSSION

Bodey in 1966 first defined the role neutropenia as a major host defense defect when he demonstrated that as the absolute neutrophil count (ANC) dropped below 500-1000/mm³. The incidence of severe infection, the number of days spent on antibiotics and the number of days of fever increase⁴. In the present study, 50 patients with ANC<1000/mm³ were evaluated. More than half of patients in study group were less than 30 years of age (55% males and 57% females). This was because majority of patients studied were having hematological malignancies, which present at a younger age group. Pizzo PA⁵ reported that fever is often the sole sign of infection in neutropenic patients because they are unable to mount a full inflammatory response. Unfortunately, fever is associated with microbiologically documented infection in approximately 30% of patients with bacteremia accounting for about half of cases. Hughes et al¹ noted that at least one half of neutropenia patients who become febrile have an established or occult infection and at least one-fifth of patients with neutrophil counts of <100/mm³ have bacteremia. In the present study, fever was present in all the patients (100%)

Microbiologically-documented infections were seen in 48% of patients, which was consistent with that noted by Hughes et al¹. 20% patients had bacteremia and 20% had urinary tract infection (UTI). In the present study, 30 culture isolates were found. Gram-negative organisms constituted 53% gram-positive organism constituted 43% and one fungal isolate was found. E coli (36.3%) were the UTI (20%) were the predominant infections found in the present study. Urine culture was positive for E coli (20%) pseudomonas (10.0) and staphylococcus aureus (40.4%). Gram-negative was observed in 60% of patients and gram-positive bacteremia was observed in 40% of patients. This was similar to the trend seen in EORTC trials conducted in 1980-1985 in USA and Western Europe⁶.

Microbiological data derived from EORTC trials (European Organization for Research and Treatment of Cancer) performed over a period of >20 years, have shown clear shift from gram-negative to gram-positive bacteremia⁶. In the first EORTC trial (1973-1976), out of total 145 isolates, 103 (71%) were gram-negative and 42 (29%) gram-positive whereas that conducted from 1991-1993 (EORTC) showed 161 isolates with 53 (33%) gram-negative and 108 (67%) gram-positive organisms. Zinner SH⁷ reported that new gram positive and gram-negative organisms is believed to be due to factors like oral mucositis, profound and prolonged neutropenia, increasing use of long dwelling I/V catheters, fluoroquinolones, sulfamethoxazole-trimethoprim prophylaxis and use of antacids and histamineblockers. However, in developing countries like India, gram-negative organisms especially E coli, pseudomonas aeruginosa and klebsiella species, still predominate. Kumar et al⁸ studied 153 febrile neutropenic episodes in patients with acute myeloid leukemia. Infective episodes could be documented microbiologically in 58.2% and clinically in 30% of patients. Microbiologically, gram-negative organisms were most common cause for infective episodes. Similarly, study done by Das⁹ showed that gram-negative organisms (predominantly E. coli) were the most common organisms responsible for febrile episodes in 30 hematological malignancy cases. Our study had also shown predominance of gram-negative organisms in causing infections in neutropenic patients.

Hughes et al¹ stated that as the progression of infection in neutropenic

patient can be rapid and because such patients with early bacterial infections cannot be reliably distinguished from noninfected patients at presentation, empirical antibiotic treatment should be administered promptly to all neutropenic patients at the onset of fever. Afebrile patients who are neutropenic but who have signs or symptoms compatible with an infection should also have empirical antibiotic treatment beginning in same manner as do febrile patients. In the selection of the initial antibiotic regime, one should consider the most probable pathogen and antibiotic susceptibility of bacterial isolates recovered from other patients at the same hospital. The use of antibiotic by the oral route may be considered only for patients who have no focus of bacterial infection or symptoms or signs suggesting systemic infection other than fever. Several studies have shown no striking differences between monotherapy and multidrug treatment combination for empirical treatment uncomplicated episodes of fever in neutropenic patients¹⁰. Advantages of combination treatment are synergistic effects against some gram-negative bacilli and minimal emergence of drug resistance.

Before modern management, the all cause mortality among high-risk neutropenic patients with bacteremia was 84% in 1965; it decreased to 44% in 1972 with the introduction of early empirical broad-spectrum antibiotic treatment and to 20%-36% more recently¹¹. In our study, 30% mortality was seen. In randomized controlled trials, mortality rates are lower, reflecting patient selection, but the same improvement in survival can be observed. In a series of trials conducted by EORTC between 1978 and 1994, the all cause mortality among neutropenic patients with bacteremia decreased from 21% to 7%.⁹

In our study, 40% of patients who presented with ANC<100/mm³

expired, while in patients who had an ANC>500/mm³ at presentation, 25 mortality was noted. The result were in close comparison with that observed by Schimpff¹² who noted that when neutrophils are less than 100/mm³, sepsis was lethal in 47% of infected patients versus 14%, when neutrophils were >1000/mm³.

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DRUG PROFILE

Febuxostat

Febuxostat is an orally administered, non-purine, selective inhibitor of xanthine oxidase approved for the management of chronic hyperuricaemia in patients with gout. In a randomized, double-blind, dose-ranging study in patients with gout and hyperuricaemia, significantly more recipient of febuxostat 40-120 mg/day than placebo had serum urate levels of <6.0 mg/dL after 4 weeks of treatment. Serum urate levels were reduced below 6.0 mg/dL at the last three monthly observations in a significantly greater proportion of patients with gout and hyperuricaemia receiving febuxostat 80 or 120 mg once daily than in those receiving allopurinol 300 mg once daily in a 52-week, randomized, double-blind trial (FACT). Similarly, febuxostat 80, 120 or 240 mg once daily showed significantly greater urate-lowering efficacy than allopurinol 100 or 300 mg once daily in a 28-week, randomized, double-blind, placebo-controlled trial (APEX) in patients with gout and hyperuricaemia. Long-term treatment with febuxostat for up to 4 years or more reduced the incidence of gout flares to (or close to) zero. **Dosage & Administration:** The recommended dosage of febuxostat is 80 mg orally once daily without regard to food, and the therapeutic target is to reduce and maintain sUA below 6.0 mg/dL. Urate-lowering therapy is typically initiated 2-8 weeks after resolution of an acute gout attack [8,9]. Anti-inflammatory therapy with low-dose, oral colchicines or an NSAID is recommended during the first few months of maintenance treatment and may be required for 12 months or more, depending on the sUA level. [8,9] Urate-lowering maintenance treatment of gout is effective only if it is continuous (not intermittent) and life long, an sUA level of <6 mg/dL is regarded as a suitable goal of urate-lowering therapy. However, reduction of sUA levels below 5 mg/dL might be necessary to promote resorption of tophi (urate deposits). **Drug Interaction:** Febuxostat has no clinically significant interactions with colchicine, indomethacin, hydrochlorothiazide or warfarin in adults in randomized, crossover studies. Although coadministration of naproxen 500 mg twice daily with febuxostat 80 mg once daily increased the C_{max} and AUC₂₄ of febuxostat by 28% and 41%. **Adverse Effect:** The most frequent adverse events (>5 events/100 patient-years) were upper respiratory tract infections, musculoskeletal, connective tissue or joint signs and symptoms, headache and diarrhoea; the incidences of events were similar in febuxostat and allopurinol recipients. The incidences of serious adverse events were also similar between febuxostat (10 events /100 patient – years) and allopurinol (11 events /100 patients-years) recipients. In each group, cardiac disorders (3 events/ 100 patient- years) were the most common serious adverse events.