

## **Neutropenia in a Tertiary Hospital: Epidemiology and Culture Isolates**

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**Objective:** To study the causes, severity, and the frequency of neutropenia.

**Design:** Retrospective medical chart review of patients with neutropenic episodes.

**Setting:** King Khalid University Hospital, Riyadh, Saudi Arabia.

**Method:** Consecutive patients with a diagnosis of neutropenia were reviewed and analyzed between January 1995 and December 2006. Personal characteristics and absolute neutrophil counts were documented.

**Result:** Ninety-seven patients, 39 males and 58 females, with 113 episodes comprised the study group. Mean age was  $38 \pm 24.8$  years. Mean absolute neutrophil count was  $1184 \pm 396$  cells/mm<sup>3</sup>. There were 88 (90.7%) with mild neutropenia and 9 (9.3%) had moderate neutropenia. An infective focus was identified in 75 (77.3%) patients. Patients with mild neutropenia were significantly younger compared to patients with moderate neutropenia ( $p=0.0185$ ) and had foci of infection in 81.8% of cases. Moderate neutropenia was seen in cancer patients and in those receiving chemotherapy. Fever was present in 84.5% of patients, who were younger and with shorter duration of neutropenic episodes compared to those who did not have fever. However, mortality was significantly greater among non-febrile patients than those with febrile episodes were ( $p=0.0294$ ).

**Conclusion:** There is a need to consider a variety of factors such as age, sex, infectious foci, presence of fever and even the duration of neutropenia for initiation of appropriate management protocols. The absence of fever may mislead physicians regarding the severity of the condition.

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Neutropenia is a hematological disorder characterized by an abnormally low number of neutrophil granulocytes. It is defined as an absolute neutrophil count of less than 1500 cells/mm<sup>3</sup> and can be graded as mild (1000-1500 cells/mm<sup>3</sup>), moderate (500-1000 cells/mm<sup>3</sup>), or severe (<500 cells/mm<sup>3</sup>)<sup>1</sup>. Neutropenia can develop in one or more conditions including decreased bone marrow production, the sequestering of neutrophils and increased destruction of neutrophils in the peripheral blood. Decreased production in the bone marrow is seen in hereditary disorders, cancer, use of certain medications<sup>2-7</sup>. Increased destruction of neutrophils is seen in aplastic anemia, autoimmune disorders and chemotherapy<sup>8-11</sup>.

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Neutropenia leads to an increased risk of infection. Neutropenia is classified according to the etiology as congenital or acquired, with the latter further defined according to the etiology or pathology<sup>12</sup>.

Neutropenia may be undetected and generally discovered when a patient has developed severe infections or sepsis. Patients usually present with fever, frequent infections, mouth ulcers, diarrhea, burning sensation when urinating, sore throat and shortness of breath or shaking chills.

Recent studies on isolates from patients with febrile neutropenia showed *Staphylococcus*, *Streptococcus viridans*, *Escherichia coli*, *Pseudomonas aeruginosa* *Mucor* spp and *Candida albicans* as the common bacterial and fungal isolates<sup>3,13-17</sup>.

The estimated incidence of severe chronic neutropenia is approximately one case per 100,000 in the USA. Cyclic neutropenia is the rarest with an estimated frequency of one per million in the USA. Severe chronic neutropenia is most frequently encountered as a pediatric problem. However, clinical symptoms tend to diminish with increasing age. Morbidity usually involves infections during severe, prolonged episodes of neutropenia. Serious medical complications occur in 21% of patients with cancer and neutropenic fever. Neutropenia occurs more commonly in females than males and the elderly have a higher incidence rate than younger individuals<sup>18-19</sup>. Mortality correlates with increased risk of severe and rapidly progressing infections caused by bacteria and fungi, thus, a rapid empirical antibiotic therapy should be administered at the onset of fever<sup>3</sup>.

This study was conducted to study the causes, severity, and the frequency of neutropenia.

## **METHOD**

A retrospective review of medical files of all patients with neutropenia seen from January 1995 to December 2006 was performed. Diagnosis of neutropenia was confirmed from the doctor's diagnosis. Neutropenia patients were reviewed for personal characteristics, hospital course, history, neutropenia status, dates and duration of neutropenia, management and interventions. Absolute confidentiality of the patients' vital information was maintained for ethical purposes. Ethical approval was not considered due to the retrospective nature of the study; neither personal interviews nor questionnaire requiring direct contact with patients were performed.

Inclusion criterion: All patients diagnosed with neutropenia (no age and sex limitations) seen between January 1995 to December 2006 were included in the study.

Exclusion criteria: Patients who were diagnosed with neutropenia but without available laboratory results and incomplete patients' records were excluded from the study.

## **RESULT**

A total of 97 patients, 39 (40.2%) males and 58 (59.8%) females were diagnosed with neutropenia. Mean age was  $38 \pm 24.8$  years (range: 1 month to 92 years). There was a total

of 113 neutropenia episodes in 97 patients; 82 (84.5%) patients with a single neutropenia episode, 14 (14.4%) with 2 episodes and 1 (1%) patient with 3 episodes. Mean duration of neutropenia was  $2.4 \pm 1.3$  days (range: 1-7 days). Mean hospital stay was  $12 \pm 14$  days (range: 2-74 days). Mean absolute neutrophil count (ANC) was  $1184 \pm 396$  cells/mm<sup>3</sup> (range: 800 – 1500 cells/mm<sup>3</sup>). Eighty-eight (90.7%) patients had mild neutropenia and 9 (9.3%) had moderate degree of neutropenia according to WHO classification<sup>1</sup> (see Table 1).

**Table 1: Personal Characteristics of Neutropenic Patients (N=97)**

<b>Sex distribution</b>	
Males	39 (40.2%)
Females	58 (59.8%)
<b>Age (mean <math>\pm</math> SD)</b>	
	38 $\pm$ 24.8 years (1 month-92 yrs)
<b>Duration of neutropenia (mean <math>\pm</math> SD)</b>	
	2.4 $\pm$ 1.3 days (1-7 days)
<b>Absolute neutrophil count (mean <math>\pm</math> SD)</b>	
	1184 $\pm$ 396 cells/mm <sup>3</sup> (800-1500)
<b>Causes</b>	
Infection	75 (77.3%)
Malignancy	10 (10.3%)
Prematurity	5 (5.2%)
Other	7 (7.2%)
	Intracranial hematoma (4)
	ESRD* on hemodialysis (2)
	Myasthenia gravis (1)

\*end stage renal disease

An infective focus was seen in 75 (77.3%) patients, cancer patients on chemotherapy in 10 (10.3%), prematurity in 5 (5.2%) and other causes in 7 (7.2%) patients. No patient was seen with benign cyclic neutropenia. Eighteen patients (18.6%) required insertion of a catheter, 8 (8.2%) needed a ventilator and 2 patients (2.1%) had nasogastric tube (NGT) inserted. Fever was present in 82 (84.5%) patients.

Patients with mild neutropenia were significantly younger (mean of  $30.67 \pm 25.3$  years) compared to those with moderate neutropenia (mean of  $51.33 \pm 15.4$  years) ( $p=0.0185$ ). Positive blood culture findings were similar in both mild and moderate neutropenia. Gram positive cocci, Gram negative bacilli and *Candida albicans* were the most common isolates in mild neutropenia compared to *Pseudomonas aeruginosa* in moderate neutropenia. Urine culture was positive in 18 patients (20.5%) out of 88 with mild neutropenia. *Escherichia coli*, *Pseudomonas aeruginosa* and *Streptococcus viridans* were isolated. Urine cultures were negative in all moderate neutropenia cases. Mortality was significantly higher ( $p<0.0001$ ) in patients with moderate neutropenia ( $n=8/9$ , 88.9%) compared to patients with mild neutropenia ( $n=7/88$ , 7.9%). No gender predilection on the degree of neutropenia was identified. Infectious foci were identified in 72 patients with mild neutropenia whereas cancer and chemotherapy effect were identified in moderate neutropenia (see Table 2).

**Table 2: Comparative Analysis of Mild versus Moderate Neutropenia According to Duration and Culture Results**

	<b>Mild</b>	<b>Moderate</b>	<b>p-values</b>
<b>No. of patients</b>	88	9	
<b>Age (mean ± SD)</b>	30.67 ± 25.3 yrs	51.33 ± 15.4 yrs	0.0185
<b>Duration of neutropenia (mean ± SD)</b>	2.3 ± 1.17 days	2.67 ± 2.6 days	0.4355
<b>Blood culture positivity</b>	40 (45.5%)	4 (44.4%)	0.9497
<b>Urine culture positivity</b>	18 (20.5%)	None	
<b>Mortality</b>	7 (7.9%)	8 (88.9%)	<0.0001
<b>Presence of infective foci</b>	72 (81.8%)	4 (44.5%)	0.0313
<b>Blood culture isolates</b>	Gram positive cocci Gram negative bacilli Candida albicans	Pseudomonas aeruginosa	

Febrile neutropenia was seen in 82 patients (84.5%) compared to 15 Neutropenia patients (15.5%) without fever. Those with fever were relatively younger ( $37.7 \pm 25.6$  versus  $39.82 \pm 21.1$  years,  $p=0.7632$ ) and with shorter duration of neutropenic episodes ( $2.33 \pm 1.3$  versus  $2.53 \pm 1.8$  days,  $p=0.6083$ ). Foci of infection were identified in 85.4% of febrile neutropenia, significantly greater than 40% in non-febrile neutropenia ( $p=0.0009$ ). Blood culture positivity was significantly greater in febrile neutropenia than non-febrile neutropenia (50% versus 20%,  $p=0.0120$ ). However, mortality was significantly lower in non-febrile than in febrile neutropenia (11% vs. 40%,  $p=0.0294$ ). In 82 patients (84.5%), neutropenia eventually resolved before being discharged from the hospital (see Table 3).

**Table 3: Comparison between Febrile and Non-febrile Neutropenia in 97 Neutropenia Cases**

	<b>With Fever</b>	<b>Without Fever</b>	<b>p-values</b>
<b>No. of patients</b>	82	15	
<b>Age (mean ± SD)</b>	$37.7 \pm 25.6$ yrs	$39.82 \pm 21.1$ yrs	0.7632
<b>No. of hospital days (mean ± SD)</b>	$9.77 \pm 7.8$ days	$24.47 \pm 28.3$ days	0.0001
<b>Duration of neutropenia (mean ± SD)</b>	$2.33 \pm 1.3$ days	$2.53 \pm 1.8$ days	0.6083
<b>Absolute Neutrophil count (mean ± SD)</b>	$1183.3 \pm 243$	$1020 \pm 355$	0.1377
<b>Focus of Infection present</b>	70 (85.4%)	6 (40%)	0.0009
<b>Blood culture positivity</b>	41 (50%)	3 (20%)	0.0120
<b>Urine culture positivity</b>	14 (17%)	4 (26.7%)	0.4307
<b>Mortality</b>	9 (11%)	6 (40%)	0.0294
<b>Common isolates</b>	Gram negative bacilli Gram positive cocci	Candida albicans Pseudomonas	

## DISCUSSION

Based on the WHO classification, our study showed that neutropenia occurs more commonly in females and that elderly individuals have a higher incidence rate than younger individuals as previously described in the literature<sup>1,2,3,18,19</sup>. The high number of infection as a cause of neutropenia is often discovered in the course of an acute infection and the neutropenia is secondary to the infection itself rather than a predisposing factor<sup>4</sup>. Several other factors may have contributed to the neutropenic status of our patients such as immunosuppressive drugs and the condition of the immune system<sup>5-11</sup>. These have limited the result of our study. Elderly individuals tend to have a more severe degree of neutropenia as shown in our results, with higher complication and mortality rate. Our study showed that elderly individuals have a more severe degree of neutropenia. This is in contrast to studies done in children where high incidence of a more severe degree of neutropenia has been reported<sup>13</sup>. The high incidence of fungal isolates from patients presenting with neutropenia have been reported. Our study has shown *Candida albicans* isolated from a non-febrile patient<sup>14</sup>. Furthermore, Gram positive and Gram negative organisms such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Streptococcus viridans* were common isolates, similar to previous studies<sup>13-17</sup>. Fever served as an alarm for the physicians to aggressively investigate and manage the cause of neutropenia. This is why the mortality rate was relatively higher among patients who did not present with fever since physicians were caught unaware of the seriousness of the condition. This is true of the fact that neutropenia in these cases went undetected and discovered only when patients presented with fever, developed a serious infection or was in a life-threatening condition. Patients with neutropenia should be considered initially for risks assessment and initiation of more aggressive management protocols.

## CONCLUSION

**Our study suggests that in neutropenia, there is a need to consider a variety of factors such as age, sex, infectious foci, presence of fever and even the duration of neutropenia for the initiation of appropriate management protocols.**

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