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Original Research Article

Evaluation of non-malignant neutropenia in children at tertiary care hospital of South Gujarat

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ABSTRACT

Introduction: Neutropenia is defined as absolute neutrophil count <1500cells/mm^3. This condition is observed in different situations - from a variant of the normal to life-threatening acquired and congenital diseases. Diseases like Tuberculosis, malaria, pertussis, typhoid, dengue, HIV, etc. can cause neutropenia. Mild cases are usually asymptomatic. But severe cases are extremely susceptible to infections, mainly viral infections like CMV, EBV, HIV, etc. Clinical manifestations, like complications, depend on the severity of neutropenia. The clinical manifestations of isolated neutropenia are diverse, including the frequency of infectious episodes. A thorough infectious history of neutropenic patients is the initial step of the evaluation.
Aim & Objective: To enlist the causes and clinical features, to document various treatment modalities, and to assess the outcome of children with non-malignant neutropenia.
Materials and Methods: Hospital based prospective cross-sectional study was conducted for 20 months among 42 patients at Department of Pediatrics of tertiary care Hospital. Study was conducted from February 2021 to August 2022.
Result: Total 20 were males and 22 were females. Among the study participants, 36 were >2 years of age and 6 were <2 years of age had nonmalignant neutropenia. Among the study participants, 40 were from urban area and 2 were from rural area. More number of patients had come with chief complaint of fever.
Conclusion: The current population of children in India is close to 1.41 billion and 10.2% of it suffering from neutropenia makes it an important health problem that needs to be thoroughly evaluated.

1. Introduction

Neutrophils also known as polymorphonuclear leukocytes are the main type of immune cells in human blood, where they guard us from pathogens and diseases. WBCs travel to the site of infection, where they abolish the microorganisms by ingesting them and releasing enzymes. They are indispensable for preventing and controlling bacterial and fungal infections. Neutrophils develop in the bone marrow from haematopoietic progenitor stem cells via "granulopoiesis". Approximately 1–1.5×10^9/kg neutrophils are produced daily and are established in the storage pool inside the bone marrow. About 2–5% enter the circulation where a portion of these cells are located on the vascular wall.[1] The average lifespan of neutrophils is approximately 5 days.[2] Neutropenia (granulocytopenia), as a haematological condition, is most characteristic of childhood. Neutropenia is defined as absolute neutrophil count <1500cells/mm.[3] This condition is observed in different situations - from a variant of the normal to life-threatening acquired and congenital diseases.[3,4] Diseases like Tuberculosis, malaria, pertussis, typhoid, dengue, HIV, etc. can cause neutropenia. Mild cases are usually asymptomatic. But severe cases are extremely susceptible

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to infections, mainly viral infections like CMV, EBV, HIV, etc. Clinical manifestations, like complications, depend on the severity of neutropenia.[5] The severity of neutropenia depends on the ANC: For patients older than 1yr of age, neutropenia is defined mild with an ANC between 1 and 1.5 x 10^9 /l, moderate with an ANC between 0.5 and 1 x 10^9 /l, and severe when ANC is below 0.5 x 10^9 /l[5]. The number of neutrophils is influenced by inherited and acquired conditions. Several congenital disorders such as Kostmann syndrome, Shwachman–Diamond syndrome, X linked agammaglobulinemia, Chediak - Higashi syndrome, and cyclic neutropenia have been associated with severe neutropenia. On the other hand, several acquired conditions such as exposure to cytotoxic or immunosuppressive drugs, anticonvulsants, anti-inflammatory medications, antihistamines, antibiotics or exposure to chemical agents, thyroid dysfunction, autoimmune disorders, bone marrow infiltration by tumour, and aplastic anaemia are associated with low neutrophils. However, the most common cause of acquired neutropenia is infection.[6] The clinical manifestations of isolated neutropenia are diverse, including the frequency of infectious episodes. A thorough infectious history of neutropenic patients is the initial step of the evaluation. Family and social history, information about living conditions, and the presence of pets are important. Inflammation of the oral cavity (stomatitis, gingivitis, periodontitis, tooth loss), other common infectious processes (cellulitis, sinusitis, otitis media, pharyngitis, pneumonia, gastrointestinal syndrome, phlegmon, neutropenic colitis, sepsis) - all these conditions require careful clinical analysis. With neutropenia, the general inflammatory response is reduced, typical symptoms of inflammation (pain, tension, tissue hyperaemia) are vague or absent altogether.[4] Neutropenic syndromes in children are pathogenetically a consequence of myelopoiesis disorder in the bone marrow, in some cases associated with genetic defects, a consequence of the process of redistribution of neutrophils in the parietal and circulating cell pool and increased destruction of granulocytes in the peripheral blood. A combination of these pathogenetic mechanisms is also possible. Untimely intervention can lead to secondary infections and eventual mortality.[4] Variants of neutropenic conditions in children are very numerous and correct determination of the pathogenetic mechanism of the development of neutropenia in a patient is necessary to determine the tactics of management, monitoring and conducting optimal therapy. The prevalence of neutropenia in Indian children is 10.2%.[7] Neutropenia is common in people from North Africa, the Middle East and South Asia. A neutropenia frequency of up to 30% from Africa has been observed while it is 4.4% among African Americans. In United Arab Emirates (UAE), 10.7% of the native population has absolute neutrophil counts less than 1.5×109 /L. The neutrophil counts were highest at birth, decreased in the first seven days of life, and reached the lowest values in the fourth week of life. Thereafter, the counts increased until 6 months of age and changed a little from six months to six years.[7] Asymptomatic or benign reductions in neutrophils are observed in individuals of all ethnic backgrounds but may be more common in those of African descent. Benign ethnic neutropenia has been described in Africans, African-Caribbean persons, West Indians, Ethiopians, Yemenite Jews, and certain Arabs. Prevalence estimates range from 10% to more than 30%.[8] The prevalence of neutropenia in Indian children is 10.2%.[7]

2. Aim & Objectives

To study the non-malignant neutropenia in children, to enlist the causes and clinical features of non-malignant neutropenia in children, to document various treatment modalities of non-malignant neutropenia in children, to assess the outcome of children with non-malignant neutropenia.

3. Materials and Methods

Hospital based prospective cross-sectional study was conducted for 20 months among 42 patients at Department of Pediatrics of tertiary care Hospital. Study was conducted from February 2021 to August 2022.

3.1. Inclusion criteria

1. Children between the age of 1 month to 12 years with laboratory confirmed Neutropenia admitted in the paediatric ward at a tertiary care hospital of South Gujarat.

3.2. Exclusion criteria

1. Children suffering from malignancy.
2. Children whose parents were not given a valid informed written consent.

All cases of inclusion criteria mentioned below were taken in this study expect cases mentioned in exclusion criteria. All patient from date of approval from ethical committee to submission of dissertation were included. Informed written consent from parents and caregiver was taken prior the start of study. Initially in all patients of non- malignant neutropenia, brief history regarding presenting complaints was taken and patient was examined for signs and symptoms of complications and managed in emergency department, paediatric intensive care unit and paediatric ward to stabilize airway, breathing and circulation. Symptomatic and Supportive care was given to all patients with specific treatment according to standard management protocol. Detailed general and systemic examination was carried out. All data of history, examination, investigations,

diagnosis and management was recorded systemically in Proforma. All routine investigations like complete blood count, Absolute neutrophil count, ABGA, ESR, CRP, renal function test, liver function test, chest x-ray, USG, etc and Special investigations like Viral markers, Bone marrow examination, Sputum CBNAAT, Blood culture, Anti neutrophil antibodies, Vitamin B12 level, Vitamin Folic acid level, etc. were done as and when required according to the condition of the patients. Patients were closely monitored for complications. This study was approved by Institutional Ethical Committee of this institute. Written informed consent was taken prior to the study of each participant. Data was collected by case record form and entered into Microsoft excel 2016. Data analysis was done in SPSS Software version 26.

4. Results

Hospital based prospective cross-sectional study was conducted for 20 months among 42 patients at Department of Pediatrics of tertiary care Hospital. Study was conducted from February 2021 to August 2022.

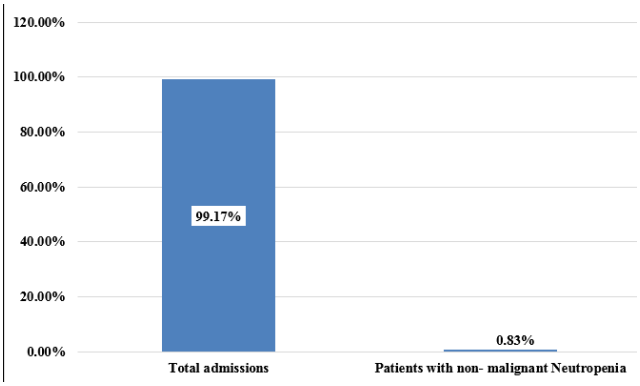

Figure 1: Frequency of non-malignant neutropenia

Figure 1 shows that in Present Study, the total number of admissions 5029 and patients with neutropenia were 42. Hence the frequency of Non-Malignant Neutropenia in Present Study is 0.83%.

Figure 2 shows in Present Study, Total 20 were males and 22 were females. Female to male cases ratio is 1.1:1.

Table 1: Age group wise distribution among study participants

Age group (in Years)	Number of patients	Percentage (%)
1 month – 1 year	2	4.8
1 year – 2 years	4	9.5
>2 years	36	85.7
Mean age	5.6 + 3.7 years	

Table 1 shows that in Present Study, out of 42 majority 36 (85.7%) patients belonged to >2 years age group followed

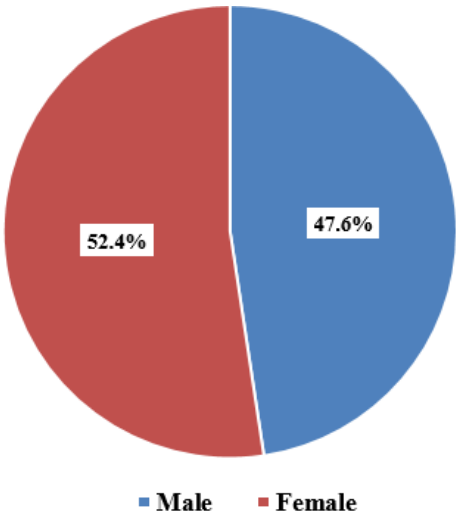

Figure 2: Gender wise distribution among study participants

by 4 (9.5%) belonging to 1-2 years of age group. Only 2 cases were aged less than 1 year. The mean age is 5.6 years.

In the Present Study, 40 (95.2%) patients were from urban areas, and the remaining 2 (4.8%) patients were from Rural areas.

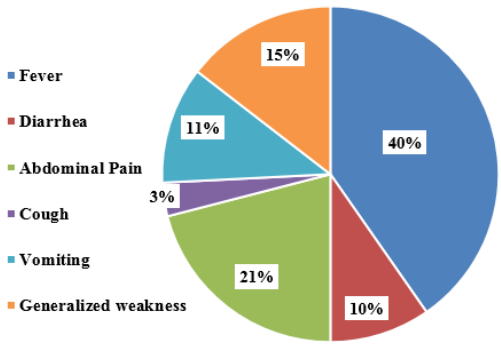

Figure 3: Presenting chief complaints among study participants

Figure 3 shows that in Present Study, out of 42 majority 25 cases had chief complaint of fever, followed by 13 cases having complaint of Abdominal pain, 9 cases having generalized weakness, 13 cases patient had complaint of diarrhoea & vomiting and 2 patients had history of cough.

Table 2: Immunization status among study participants

Immunization Status	Number of patients	Percentage (%)
Fully immunized	35	83.3
Partial immunized	7	16.7
Unimmunized	0	-

Table 2 shows that in Present Study, 83.3% cases were immunized completely up to their age, while 16.7% patients

were partially immunized in the study.

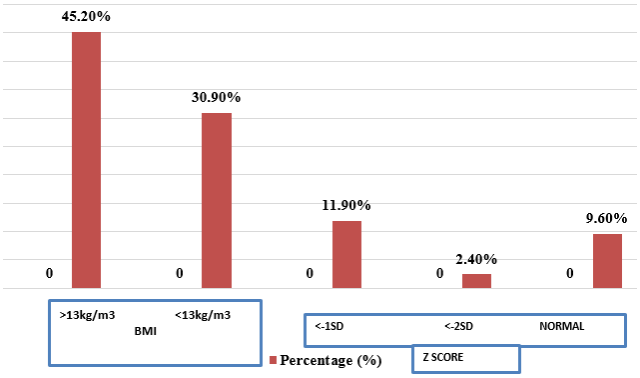

Figure 4: Anthropometric parameters among patients

Figure 4 show that in Present Study, 20(47.6%) patients were undernourished and 22(52.4%) patients were adequately nourished.

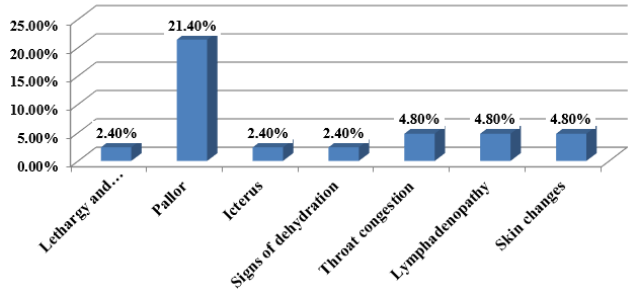

Figure 5: General examination findings among study participants

Figure 5 show that in Present Study, Total 9 patients were found to have pallor on general examination. Icterus and signs of dehydration were seen in 1 patient each. Also throat congestion, lymphadenopathy and skin changes were seen in 2 patients each.

Table 3 shows that in Present Study, Overall increase level in Total leucocyte count, Platelet count, ESR as well as CRP was found among study participants.

Table 4 shows that in Present Study, 9.5% patients had presence of Hypoplastic Marrow on bone marrow examination. On Blood culture sensitivity examination, one sample showed salmonella typhi growth. 14.2 % patients tested positive via Antigen antibody test for various infectious diseases.

Table 5 shows that in Present Study, majority of the patients suffered from Enteric fever (28.4%) followed closely by viral fever (26.1%). Other common diagnosis seen are Aplastic anaemia, Liver diseases, Dengue fever and Drug induced neutropenia.

Figure 6 shows that in Present Study, out of 42 participants, 78.5% patients were found to have mild

Table 3: Blood Investigation parameters among study participants

Blood Investigation parameters	Mean + SD
Hemoglobin (g/dl)	7.81 + 4.63
Total Leucocyte count (/mm^3)	3254.3 + 2746.9
Platelet count (/mm^3)	224517.3 + 10556.4
ANC (/mm^3)	1261.7 + 240.8
HCT (%)	31.22 + 9.7
ESR (mm in 1 hr)	75.6 + 25.41
CRP (mg/l)	19.33 + 4.52
ALT (U/l)	51.7 + 10.47
S. Bilirubin (mg/dl)	0.94 + 0.12
S. Creatinine (mg/dl)	0.62 + 0.31
S. Sodium (mmol/L)	139.7 + 2.45
S. Potassium (mmol/L)	4.1 + 1.61
S. Calcium (mg/dl)	8.7 + 2.6

Table 4: Special Investigations done among study participants

Special Investigation	Number of patients	Percentage (%)	Number of patients with abnormal result	Percentage (%)
Bone Marrow	5	11.9	4	9.5
Blood Culture	8	19.04	1	2.4
Viral markers	9	21.42	0	-
Antigen Antibody test	33	78.5	6	14.2

Table 5: Diagnosis among study participants

Diagnosis	Number of patients	Percentage (%)
Enteric Fever	12	28.4
Viral Fever	11	26.1
Aplastic Anemia	4	9.6
Liver Disease	3	7.1
Drug Induced Neutropenia	2	4.8
Dengue Fever	2	4.8
Malaria	1	2.4
Submandibular Cellulitis	1	2.4
Congenital Myasthenia Gravis	1	2.4
Brucellosis	1	2.4
Pyoderma	1	2.4
Acute Gastroenteritis	1	2.4
Polyarthralgia	1	2.4
Acute Bronchiolitis	1	2.4

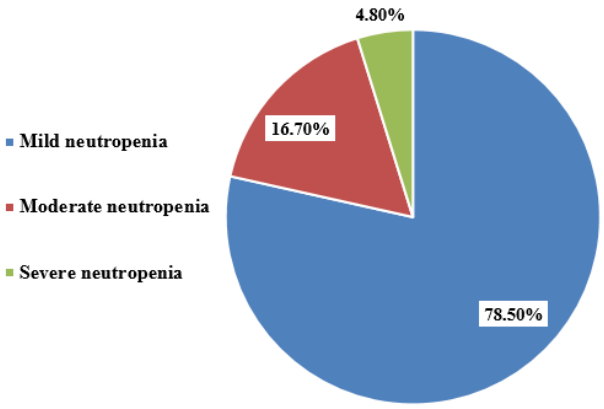

Figure 6: Classification of neutropenia according to severity

neutropenia, 16.7% moderate neutropenia and 4.8% had severe neutropenia.

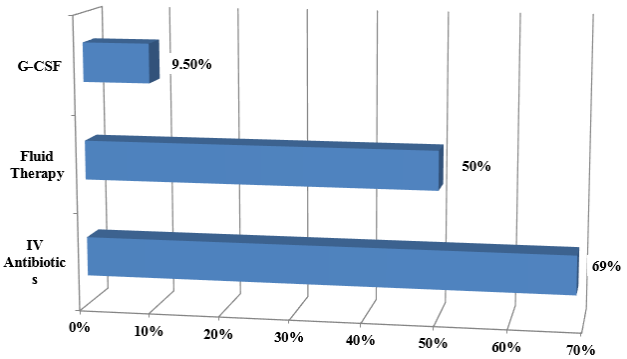

Figure 7: Treatment given to patients

Figure 7 shows that in Present Study, 69% patients were given antibiotics and 50% patients required IV fluid therapy. 9.5% patients required treatment with G-CSF.

Table 6: Outcome of study participants

Outcome	Number of patients	Percentage (%)
Discharged	40	95.2
LAMA	2	4.8
Expiry	0	-

Table 6 show that in Present Study, 95.2% patients were discharged, 4.8% patients took LAMA and no expiry was noted.

5. Discussion

Neutropenia is a clinically significant entity due to its association with increased risk of infection. The severity of neutropenia is associated with the susceptibility to pyogenic infection.[15] Additional factors, such as bone marrow myeloid reserves, speed of onset and duration of the neutropenia, absolute monocyte count, and the capacity of phagocytes, influence the susceptibility to infection in neutropenic patients. Based on duration, neutropenia can be further divided into acute (or transient) and chronic forms.[16] Cytotoxic effects of drugs or infectious agents often cause the acute form. Chronic neutropenia has four principal clinical categories: congenital, cyclic, idiopathic, and autoimmune.[17] The congenital and cyclic categories are regarded as congenital neutropenia, while the idiopathic and autoimmune categories are acquired. In Present Study, the frequency of Non-Malignant Neutropenia was found to be 0.83% which was slightly lesser but still comparable with other studies like Battini et al (1.91%),[9] Jiunn-Ming Sheen et al (2.16%),[12] Kyriaki Karavanaki et al (2%).[11] Females were more than males, while in other studies of Joanna Konieczek et al,[18] Tschenin et al,[19] and Akanksha Mahajan et al[19] as well as Kyriaki Karavanaki et al[11] studies Males were more as compared to female study participants. 85.7% patients belonged to>2 years of age group which is comparable with Nguyen S.N et al[10] while in study of Jiunn-Ming Sheen et al[12] and Kyriaki Karavanaki et al[11] majority patients were below 1 year of age. In Present Study, mean age of the cases is more than 5 years which is comparable with Vasiliki Vlacha et al[6] and Battini et al.[9] In Nguyen S.N et al,[10] Kyriaki Karavanaki et al[11] and Jiunn-Ming Sheen et al[12] mean age of the cases is less than 5 years.

Table 7: Comparison of mean age

Study	Mean age
Present Study	5.6 + 3.7 years
Vasiliki Vlacha et al[6]	8.8 Years
Battini et al[9]	10 years
Nguyen S.N et al[10]	25 months
Kyriaki Karavanaki et al[11]	0.7 years
Jiunn-Ming Sheen et al[12]	31.3 months

In Present Study, 95.2% patients were residing at urban area, on counterpart, Nguyen S.N et al[10] study 33.02% patients were residing at urban area. More cases belonging to urban region in the present study can be because of the urban location of the hospital in tier 2 city. majority patients (40%) had complaint of Fever which was comparable with other studies like Tschernin D et al, Akanksha Mahajan et al. Abdominal pain and vomiting were other complaints seen in Present Study. Present Study shows the mean hemoglobin level is 7.8g/dl whereas Vasiliki Vlacha et al[6] and Ozdemir et al[13] have higher mean hemoglobin level. While mean ESR in our study was 75.6 mm in 1 hr and In Vasiliki Vlacha et al[6] study was 21 mm in 1 hour. 2.4% patients had positive blood culture report which was comparable with Ozdemir ZC et al study,[13] while in Study of Akanksha Mahajan et al,[14] 18.1% patients had positive blood culture report.

Table 8: Comparison of diagnosis

Diagnosis	Present Study (%)	Ozdemir ZC et al[13] (%)	Akanksha Mahajan et al[14] (%)	Kyriaki Karavanaki et al[11] (%)
Enteric fever	28.5	-	18.3	-
Viral fever	26.1	58.5	-	29.8
Aplastic anemia	9.6	-	7.3	-
Liver disease	7.1	-	-	-
Drug induced neutropenia	4.8	6.3	-	-
Dengue fever	4.8	-	36.6	-
Malaria	2.4	-	7.3	-
Submandibular cellulitis	2.4	-	-	-
Congenital Myasthenia Gravis	2.4	-	-	-
Brucellosis	2.4	-	-	-
Pyoderma	2.4	-	-	-
Acute Gastroenteritis	2.4	-	-	5.9
Poly arthralgia	2.4	-	-	-
Acute Bronchiolitis	2.4	2	-	14.9

Present Study shows Enteric fever (bacterial infection) was the most common cause closely followed by viral fever. In contrast to this, Akanksha Mahajan et al[14] study has most common cause of Non-Malignant Neutropenia as Dengue fever (viral infection). Drug induced neutropenia was seen in 4.8% patients in Present Study which is comparable with Ozdemir Z C et al[13] study. Frequency of viral fever is comparable with Kyriaki Karavanaki et al[11] study.

Most cases of non-malignant neutropenia occurred due to infection and similar findings were observed in other studies. Majority patients (78.5%) had Mild neutropenia and Severe Neutropenia (4.8%) was least common. Similar findings were seen Korematsu T et al,[20] Ozdemir ZC et al[13] and Kyriaki Karanavakiet al[11] study while in Vasiliki Vlacha et al[6] severe neutropenia was most commonly seen. In Present Study, 9.5% patients required G-CSF treatment which was comparable to Vishnu Nagalapuram et al[21] study, while in G-CSF treatment was required in study of Joanan Konieczek et al[18] and Susan Kirk et al[22] for 21.1% and 17% of patients respectively. Majority of patients (95.2%) were discharged which is comparable with other studies. No expiry was noted while 1.2% in study of Akanksha Mahajan et al,[14] 1.8 % in Ozdemir ZC et al[13] study and 0.17% in Jiunn-Ming Sheen et al[12] study, expiry was noted.

6. Conclusion

Patients presenting with recurrent fevers, mouth ulcers, and gingivitis should be evaluated for neutropenia. The most commonly encountered causes of neutropenia in childhood are viral-induced neutropenia and immune-mediated neutropenia. Patients who have disorders of neutrophil production and release from the bone marrow carry a greater risk of bacterial infection than patients who have peripheral neutropenia associated with a normal bone marrow because the bone marrow is not able to produce new neutrophils sufficiently in times of need (ie, infection). Neutropenia unrelated to chemotherapy toxicity occurs in a number of clinical settings. The most common conditions associated with neutropenia are those that are acquired, including viral infection, neutropenia associated with various medications, and immune neutropenia. Inherited neutropenias are rarer and often more pro found. These disorders include the dominant or sporadic types of severe congenital neutropenia (often with mutations in the ELA2 gene), the recessive type or Kostmann syndrome, and the marrow failure syndromes such as Fanconi anaemia. Cyclic neutropenia may be severe at the nadir of the cycle. Of particular concern is the occurrence of fever in conjunction with neutropenia. This combination creates a medical emergency that must be addressed with appropriate evaluation and prompt administration of antibiotics. The actual risk of severe infection and the likelihood of recovery depend not only on the level of the ANC, but on the duration of the neutropenia. If recovery from the neutropenia is not expected, as in severe congenital types, G-CSF administration may be indicated. Patients receiving immunosuppressive therapy (eg, chemotherapy) are at significantly higher risk for serious bacterial infection compared with those who have isolated neutropenia due to the compounding T-cell and B-cell dysfunction. The use of recombinant human granulocyte colony stimulating factor in the management of cyclic neutropenia and severe congenital neutropenia has dramatically decreased clinical symptoms and has decreased mortality from infectious causes.

7. Source of Funding

None.

8. Conflict of Interest

None.

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