Infectious Causes of Diarrhea Among Neutropenic Children

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ABSTRACT

Background: Intestinal infections are frequently occur among children with cancer who receive chemotherapy. On the other hand, diarrhea is especially common and severe among cancer patients that develop neutropenia, either due to the disease itself or due to the intensive chemotherapy. There are many causes of diarrhea among those patients, but intestinal infections still an important etiology among them.

Objectives: to study the frequency of diarrhea among neutropenic children, with its infectious etiologies, especially the bacterial, fungal and parasitic causes.

Type of the study: Cross-sectional study.

Methods: the study was done in the Oncology Department of Nanakali Hospital for Haematological diseases and malignanciesin Erbil City, on pediatric age group. One hundred six children with cancer were followed up during the period between January – May 2017, of them only 50 patients who full fill the criteria of being (neutropenic, diarrheic, and age < 14 years), and those were regarded as the study group, compared to 20 patients who had the same criteria (diarrheic, and age < 14 years) but notneutropenic.They were investigated for the infectious causes of diarrhea especially bacterial, parasitic, and fungal agents. Data were analyzed statistically using SPSS program and Correlation test was also used. The results were regarded significant with $p < 0.05$.

Results: A total of 70 diarrheal episodes in 106 cancer children were detected, 50 of them were neutropenic while 20 were not. Intestinal infections were detected in 62% of the 1st group and in 45% of the 2nd one, while the causes in the remaining cases of diarrhea (38%) cannot be identified. Bacterial pathogens were the main agents that causes diarrhea followed by fungi then parasites with an infectious rates of (28%, 20%, and 14% respectively).

Conclusions: Diarrhea commonly developed among cancer children with neutropenia. Bacteria are the most incriminated pathogens followed by *Candida* and parasites. This study noticed the presence of other etiologies for diarrhea beside infectious causes that should be considered and investigated in the future researches and during management of diarrhea in those patients.

Keywords: Children, Neutropenia, Diarrhea, Cancer, Infection.

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Neutropenia is defined as an absolute neutrophils count (ANC) of less than (500 cell/ µl) of blood (1). It is a common finding in patients with malignancies as a result of the disease itself or the effect of chemotherapy, where neutropenia could be severe in which ANC may reach less than 500 cells/µl of blood (2). Neutropenic patients had a great liability for intestinal tract infections (3). Those patients may present with diarrhea, abdominal pain, and vomiting, but these symptoms may result from non-infectious causes such as the effect of intensive chemotherapy which may lead to Necrotizing Enterocolitis, beside other etiologies (4). On the other hand, clinical differentiation between infectious and non-infectious causes of abdominal manifestations in neutropenics is difficult, but it could be done primarily by imaging methods such as ultrasound and CT- scan which shows thickening in the wall of distal colonin case of Necrotizing Enterocolitis to be excluded easily (5). Also, differentiation is important to determine severity of the condition and to choose the suitable therapeutic method. Incase of infectious enterocolitis it should be treated with antimicrobialswhile non-infectious one is life threatening condition and must be treated surgically (6).Many conventional gastrointestinal pathogens could be responsible for incidence of infectious enterocolitis among neutropenic patients include (*Escherichia coli, Shigella, Salmonella, Campylobacter species, Klebsiella spp., Proteus spp.,Entamoebahistolytica, Giardia intestinalis, fungi,* and *virus*es)(3). This study was aimed to determine the frequency of diarrhea in neutropenic cancer children and to investigate its underlying microbial causes.

Methods: 106 of the ambulatory and hospitalized cancer patients who attended the Oncology Department of Nanakali Hospital for Haematological diseases and Malignancies in Erbil City, were studiedin the period between January and May 2017. Detailed history, personal data, and complete blood count was done for them in order to full fill the following criteria (age <14 years, diagnosed with malignancy, neutropenic, and presented with diarrhea). According to the previous characteristics only 50 children were selected and included as a study group, who were 23 males and 27 females, while 20 children (10males and 10

females)who matched them in their criteria but not neutropenic were regarded as a control group.

Samples collection: A blood sample was taken from each child and CBP was done to assess neutrophil count and to determine severity of neutropenia. Neutropenia was considered severe with an absolute neutrophils count of< 200 cell/µml.Also, a stool specimen was taken from each diarrheic child and divided into two parts that were kept in a wide mouth tightly closed, labeled plastic containers one of them for direct examination and bacterial isolation, while the other part was kept in containers that contain 10% formalin as a preservative solution for further assessment.

Microbiological assessment: Stool samples were examined microscopically using direct microscopic examination, concentration technique,Lugol's iodine, modified Ziehl-Neelsen stain, and Grams stain (7,8). Moreover, samples were inoculated using standard culture techniques including MacConkey's agar, Blood agar, Salmonella-Shigella agar, and Sabouraud dextrose agar (9,10).Above techniques help us to detect bacterial, parasitic, and fungal pathogens that causing diarrhea. Besides that, final identification was done with biochemical tests using API 20E (Analytic Profile Index 20E Identification System) (11).

Statistical analysis: Data storage and statistical tests were done using the Statistical Package for the Social Sciences (SPSS) and Correlation test to detect the relationship between severity of neutropenia and intestinal infections. All P values < 0.05 were considered statistically significant (12).

Results and Discussion: Intestinal infections are frequently seen among cancer patients due to decreased immunity which result from the malignant disease or the use of chemotherapy. Diarrhea in children is still one of the preventable leading causes of mortality and disease burden in developing countries (13,14,15). The results of the present study had been demonstrated that intestinal infection rate among neutropenic children was 62%, compared with 45% in the control group with a non-significant statistical difference P > 0.05 (Fig. 1). This result is lining with but slightly lower than a result found in a study done by Laila *et al* in Egypt, who noticed an intestinal infection rate of 75% among neutropenic children who presented with diarrhea (16). Moreover, it is in agreement with a study done on neutropenic adult population and detected an intestinal infection rate of 50.8% (17). Such variations in the infection rates can be explained on the basis of studied patients populations and the differences of epidemiological patterns and distribution of pathogenic agents in different regions of the world (18,19). Bacterial pathogens were the most frequently detected agents found in 14 (28%) of neutropenic children with diarrhea, followed by fungal 10 (20%), then parasitic causes 7 (14%)(Table 1). Our findings were in line with many studies in Iraq and other countries which revealed that bacteria are the most frequently detectable cause of pediatric diarrhea (7,20). Furthermore, the etiology of diarrhea in 19 (38%) children could not be identified (Table 1). It may be due tothe effect of intensive chemotherapy that leads to necrotizing enterocolitis, or other pathogenic agents likeviral causes includingrota, CMV, adenovirus etc… that could not be detected by investigation techniques used in the study(19). However, the most commonly isolated organism in stool samples of neutropenic patients was *Candidaalbicans* 10(20%), followed by *Klebsiellaoxytoca* 5(10%) and they were significantly associated with diarrhea, while in the control group *Escherichia coli* was the most commonly detected pathogen 3(6%) (Table 1). These findings were in agreement with Aksoy*et al* study who suggested*Candida* to be the most frequent cause, followed by *Klebsiellaoxytoca* among neutropenic patients with diarrhea (17). On the other hand, Marcus *et al* demonstrated that the greatest intestinal infection rate among cancer patients who were diarrheic and non-neutropenic was due to*E. coli*(5). *Giardia intestinalis* was the most incriminated parasite found in 4 (8%) of the 50 neutropenic children (Table 1). So, parasitic infections should be considered in the diagnostic workup of diarrhea in neutropenic patients. It is important to know that all above differences in the infection rates of different pathogens were statistically non-significant with p value of > 0.05.Neutropenic patients were divided into 27 females and 23 males. A higher infection rate was seen among males than females (77.8%, 51,9% respectively), but those differences were statistically non-significant P > 0.05 (Fig. 2).Again, neutropenic children were divided according to the severity of neutropenia into two groups, the 1st one with severe neutropenia that Absolute Neutrophil Count< 200 (cell/µl blood) and the 2nd group with ANC > 200 (cell/µl blood).The infection rate in the 1st group was (32.3%) which is less than that in the other group (67.7%). This difference was statistically significant (P = 0.001) but no relationship was seen between intestinal infections and severity of neutropenia. This result is similar to that of Laila *et al* who found an infection rate of (31%) among children with ANC < 200 (cell/µl blood) and (69%) among those with ANC > 200 (cell/µl blood) (10). These could be attributed to the isolated neutropenia that resulted from cancer chemotherapy and otherwise intact immune system. In such condition it is expected to have a lower risk of infection even with severe neutropenia (21).

Conclusion: This study revealed that diarrhea is a common complication among neutropenic patients of pediatric age group with malignancies. Bacterial pathogens had a higher incidence rate than other causes of diarrhea and dominated by gram negative bacteria. Candida also showed a moderately high incidence rate in those patients.

Recommendations: Other causes of diarrhea should also be investigated in the future studies and in addition to that, diagnosis of one etiology of diarrhea should not be a cause to give up further investigations during management of such patients.

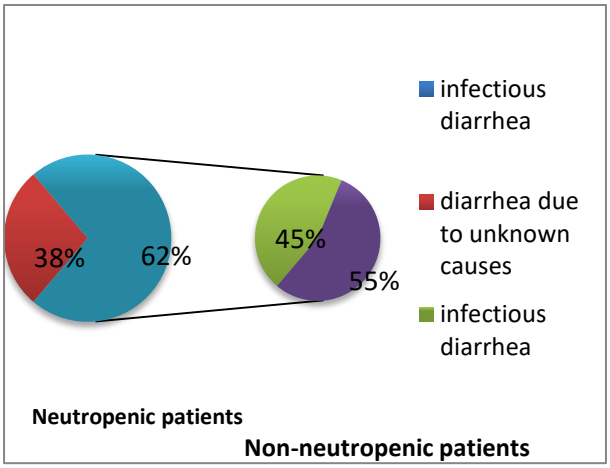

Fig. 1: Types of diarrhea among neutropenic and non-neutropenic groups

The difference in the infection rates between study and control groups is statistically non-significant with P > 0.05.

Table 1: Microbial evaluation of the stool samples in the neutropenic and non-neutropenic groups

Causative agent	Type of isolate	Neutropenic patients No. =50	Total No. of isolate 31 (62 %)	Non-neutropenic patients No. =20	Total No. of isolate 9(45 %)
Bacteria	*Klebsiellaoxytoca*	5 (10%)	14 (28 %)	1 (5%)	6 (30%)
	Escherichia coli	3 (6%)		3 (15%)	
	Salmonella spp.	3 (6%)		2 (10%)	
	Shigellaspp	2 (4%)		---	
	Citrobacterbraakii	1 (2%)		---	
Fungi	*Candida albicans*	10 (20%)	10 (20 %)	1 (5%)	1 (5%)
Parasites	*Giardia intestinalis*	4 (8%)	7 (14 %)	1 (5%)	2 (10%)
	G. *intestinalis* + *Cryptosporidium spp.*	2 (4%)		1 (5%)	
	Entamoebahistolytica	1 (2%)		---	

Unknown causes	Non	19 (38%)	---	---	---

All above differences in infection rates are statistically non-significant P > 0.05

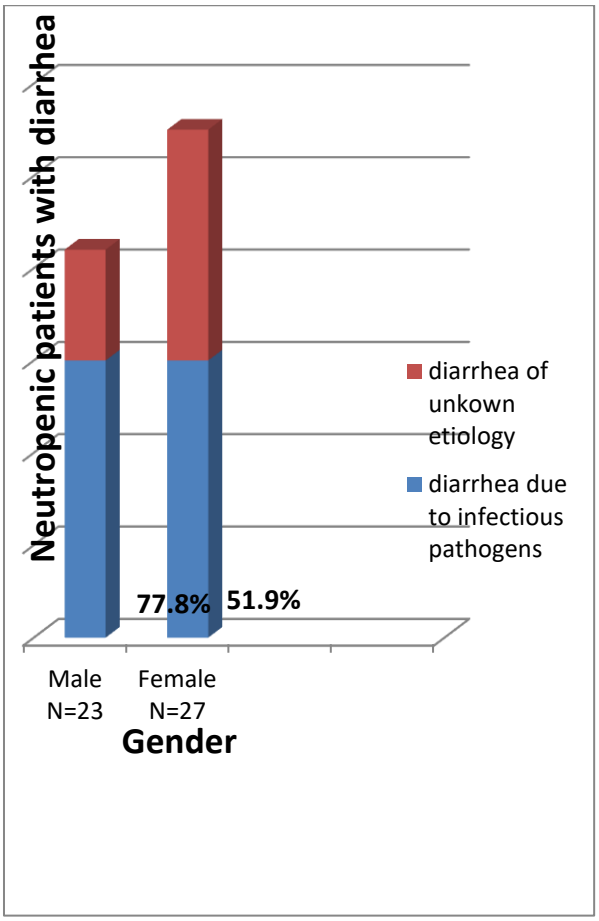

Fig. 2: Distribution of diarrheal cases according to gender of the patients.

No statistically significant difference in the infection rates between males and females (p > 0.05).

Table 2: Association between severity of neutropenia and type of diarrhea.

Characteristic of neutropenia	Neutropenic patients N=50	Identified cause of diarrhea N=31	Non-Identified cause of diarrhea N=19
Severe ANC < 200 cell/µml	15 (30%)	10 (32.3%)	5 (26.3%)
Not severe ANC > 200 cell/µl	35 (70%)	21 (67.7%)	14 (73.7%)

The difference in the infection rate between two groups of neutropenic patients is statistically significant (P = 0.001). No relationship was seen between the severity of neutropenia and intestinal infection

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