Diarrhea in neutropenic children with cancer: An Egyptian center experience, with emphasis on neutropenic enterocolitis

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ABSTRACT

Background: Diarrhea is a frequent complication in children with cancer who received intensive chemotheraputic regimens. It may be caused by several factors, neutropenic enterocolitis (NE) being the most serious. **Aim:** To study diarrhea in neutropenic cancer patients in the pediatric age group, with its underlying etiologies and risk factors, especially the bacterial causes, with special concern on NE. **Materials and Methods:** This study was carried out at the Pediatric Hematology and Oncology Units, Zagazig University Hospitals, Egypt, from January 2009 to September 2010. All children with malignant diseases who are ≤12 years of age were included. Patients who were neutropenic (<500/mm^3) on admission or who became neutropenic during their stay in the hospital were monitored regularly (daily) for diarrhea. Neutropenic cancer patients with diarrhea were grouped into two groups: Group 1, with NE, and group 2, with neutropenic diarrhea rather than NE. On the first day of diarrhea, patients were subjected to complete blood count, blood cultures, stool microscopy and culture. Abdominal ultrasonography was carried out within 3 days of diarrhea. **Results:** A total of 200 children ≤12 years old, suffering from different malignancies, with a total of 180 neutropenic episodes were followed. Diarrhea was observed in 100 episodes (55.5%). NE constituted 16% of these diarrheal episodes. All patients with NE had significantly more severe neutropenia, and this was of longer duration than the other group. All patients with NE were febrile, with 100% positive blood culture. Stool analysis diagnosed giardiasis in 4.8% of the non-NE patients and in none of the NE patients, while stool culture was positive in 75% of the NE patients compared with 40.5% of the other group. **Conclusions:** Diarrhea is a common complication in neutropenic cancer children. Gram negative bacteria and Candida are the most incriminated pathogens. Duration and severity of neutropenia carry a great risk for the development of NE.

Key words: *Cancer, children, diarrhea, neutropenia, neutropenic enterocolitis*

INTRODUCTION

Diarrhea is a frequent complication in children with cancer.[1] Possible etiologies include radiotherapy, chemotherapy, graft versus host disease and infections.[2]

Diarrhea can be debilitating and, in some cases, life-threatening, causing volume depletion, renal failure and electrolyte disorders.[3]

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Neutropenic enterocolitis (NE) is a specific disease entity, usually manifesting itself with diarrhea.[4] It is a severe complication of chemotherapeutic regimens.[5] The acute inflammatory disease may involve cecum, colon and the terminal part of the ileum.[6] The mechanism by which NE occurs is mutifactorial and thought to result from a combination of multiple factors, including neutropenia, chemotherapy- or radiotherapy-induced destruction of normal mucosa, intramural hemorrhage caused by severe thrombocytopenia and change in normal gastrointestinal flora caused by antibiotics, antifungal agents and colonization by hospital flora.[7] Prolonged neutropenia appears to be the pre-requisite factor in conjunction with injury to the bowel mucosa.[8]

The diagnosis of NE may be delayed because the presenting clinical features (fever, abdominal pain and diarrhea) are

not specific and may suggest other abdominal diseases.[9,10] To support the clinical diagnosis of NE, imaging techniques have therefore been used, including abdominal ultrasonography[11,12] and computed tomography.[13-15]

Current data on diarrhea in neutropenic cancer children are limited.[5] We conducted a prospective study over a period of 21 months to determine the incidence, risk factors and causes of diarrhea in neutropenic children with cancer.

MATERIALS AND METHODS

The current study was conducted at the Pediatric Hematology and Oncology Units, Zagazig University Hospitals, Egypt, from January 2009 to September 2010 on children with malignant diseases ≤12 years of age regardless of their underlying malignancy and phase of treatment. Patients who were neutropenic (≤500/ mm^3) on admission or who became neutropenic during their hospital stay were monitored regularly (daily) until discharge or recovery from neutropenia, whichever occurred earlier, to monitor the presence of diarrhea. Those who developed diarrhea were grouped into two groups: Group 1, with NE, and group 2, with neutropenic diarrhea rather than NE. The study was approved by the research and ethical committee - Zagazig university.

All the parents of eligible children were consented at the beginning of the study for inclusion of their children in the study.

Data regarding demographic characteristics (age, gender, underlying disease and the status of the disease), duration and severity of neutropenia and risk factors for diarrhea were recorded. All patients were subjected to complete history taking and thorough clinical examination. Vital signs and physical examination findings were monitored regularly (daily) in patients who developed diarrhea till recovery. Routine investigations included complete blood count (CBC), creatinine, urea, alanine transaminase, aspartate transaminase, sodium (Na), potassium (K), C-reactive protein (CRP) and arterial blood gases.

On the first day of diarrhea, CBC, blood cultures, stool microscopy for red and white blood cells, parasitic cysts and ova examination and stool culture for specific pathogens were collected. All microbiological tests were repeated on the following day.

For isolation of Salmonellae and Shigellae, enrichment using tetrathionate broth for 18-24 h was performed, followed by plating on Salmonella-Shigella agar and incubation at 37°C for 18-24 h. For isolation of Campylobacter,[16] Skirrow's Campylobacter medium with vancomycin, polymyxin B and trimethoprim and aerotolerance growth supplements (Oxoid) were used and incubated for 48 h at 42-43°C in a candle jar. For isolation of Enterohemorrhagic *E. coli* (*E. coli* O157), specimens were plated on Sorbitol MacConkey's agar.[17] Stool samples were also inoculated on blood agar (5%) and MacConkeys agar (Oxoid) and incubated at 37°C for 18-24 h. Colonies were identified by Gram stain, conventional biochemical tests and Api20E (BioMérieux, Marcy, L'Etoile, France). Quantitative cultures were carried out for Candida spp. 0.1 ml of the 1/10 diluted stool sample was inoculated into sabouraud dextrose agar and incubated at room temperature for 24-48 h ≥10^5 colonies considered significant).[18] Blood cultures were carried out using Oxoid and then subcultured on blood and MacConkeys agar. Gram +ve cocci were identified as enterococci by their ability to grow on MacConkey broth containing 6.5% NaCl and esculin hydrolysis.[19]

Abdominal ultrasonography was carried out very early, within 3 days of the onset of diarrhea, for assessment of bowel wall thickness (thickness ≥3 mm was considered abnormal), pneumatosis intestinalis, irregularity of bowel loop, mucosal enhancement and dilatation of bowel loop, aiming to differentiate NE from neutropenic diarrhea due to other causes.

RESULTS

A total of 200 children ≤12 years old, range 9 months to 12 years, suffering from different malignancies were included in the current study. Forty-six percent of them were males and 54% were females. A total of 180 neutropenic episodes in these patients were followed. The underlying disease was a hematological malignancy in most (92%) of the cases [Table 1]. Diarrhea was observed in 100 episodes (55.5%). NE constituted 16% of these diarrheal episodes. Cytarabine (48%) was the most common cytotoxic chemotherapeutic agent used in our patients. Methotexate and mitoxantrone were associated significantly with the development of NE [Table 2]. All the patients who developed diarrhea received antimicrobial therapy before the onset of diarrhea. Co-trimoxazole, ceftazidime and metronidazile were the most commonly used while carbapenems were most commonly associated with NE (P=0.02 for imipenem and 0.001 for meropenem).

Acute leukemia was the most common malignancy in both groups. Acute lymphoblastic leukemia was the most prevalent in diarrhea other than NE (66.7%), while acute myeloid leukemia dominated in patients with NE (50%). Most of the diarrheal episodes occurred during the induction phase of chemotherapy (42%). Neutropenia was significantly longer in duration and more severe in

Table 1: Demographic characteristics of the patients studied

Characteristics	All neutropenic patients with diarrhea (*n*=100)	Neutropenic diarrhea rather than NE (*n*=84)	NE (*n*=16)	*P*
Age in years (mean±SD)	6±3.7	6±3.5	4.8±3.88	0.21
Gender (M/F)	46/54	40/44	6/10	0.45
Underlying disease, *n* (%)				
ALL	62 (62)	56 (66.7)	6 (37.5)	0.001**
AML	14 (14)	6 (7.1)	8 (50)	0.001**
Neuroblastoma	6 (6)	6 (7.1)	0 (0)	0.59
Non-hodgkin's lymphoma	16 (16)	14 (16.7)	2 (12.5)	0.96
Rhabdosarcoma	2 (2)	2 (2.4)	0 (0)	0.72
Status of underlying disease, *n* (%)				
Induction	42 (42)	32 (38)	10 (62)	0.06
Remission	22 (22)	20 (23)	2 (12.5)	0.56
Refractory to treatment	10 (10)	8 (9)	2 (12.5)	0.92
Relapse	20 (20)	18 (21)	2 (12.5)	0.63
Progressive	6 (6)	6 (7)	0 (0)	0.59
Duration of neutropenia in days (mean±SD)	6.6±4	5.5±2.5	12.4±6.4	0.002**
Severity of neutropenia, *n* (%)				
Absolute neutrophilic count<200	38 (38)	26 (31)	12 (75)	0.001**
Absolute neutrophilic count>200	62 (62)	58 (69)	4 (25)	

**Highly significant statistically; ALL - Acute lymphoblastic leukemia; AML - Acute myeloid leukemia; ANC - Absolute neutrophilic count; NE - Neutropenic enterocolitis

Table 2: Chemotheraputic agents used in the treatment of the study population

Chemotherapeutic agent	Neutropenic diarrhea rather than NE (*n*=84)		NE (*n*=16)		*P*
	No.	%	No.	%	
Cyclophosphamide	7	16.7	0	0.0	0.49
Cytarabine	21	50.0	3	37.5	0.51
Methotrexate	7	16.7	4	50.0	0.009*
6MP	4	9.5	0	0.0	0.84
Doxorubicin	5	11.9	1	12.5	0.58
Thioguanine	2	4.8	1	12.5	0.97
Idarubicin	2	4.8	1	12.5	0.97
Etoposide	4	9.5	1	12.5	0.69
Mitoxantrone	0	0.0	1	12.5	0.02*
Actinomycin D	1	2.4	0	0.0	0.34

*Significant statistically; NE - Neutropenic enterocolitis

patients with NE compared with the other group (P<0.001) [Table 1]. There was no mortality recorded in either group. Abdominal pain was the most frequent symptom in all patients (88%). Right lower quadrant abdominal pain and abdominal tenderness with increased body temperature and heart rate were the significant clinical findings in patients with NE when compared with the other group. The mean number of bowel motions in patients was 4.8 per day, with no significant difference between the two groups. In 82% of the patients, the stool had no mucous or blood [Table 3].

High fever and positive CRP were indefinite findings in all patients with NE compared with 38% with fever and 45.2% with positive CRP in the other group, with high statistical significance (P=0.001) [Table 2]. This might indicate that diarrhea in patients with NE was caused by infectious agents. This was supported by the positive blood culture in all NE patients compared with only 37.5% in the other group (P=0.001). Stool culture was positive in 75% of the NE patients compared with 40.5% in the other group, with no statistical difference. The most common isolated organisms in stool were *Klebsiella oxytoca* and Candida in patients with NE, while it was *E. coli* in the second group. Giardiasis was detected in the stool samples of four patients from the second group. All these data are presented in Tables 4 and 5.

Ultrasonographic evaluation using a high-resolution probe was carried out in all the studied patients [Table 6]. Bowel wall thickness was increased significantly in patients with NE (mean: 5.2±0.7 mm) than in the other group (mean: 2.1±0.4 mm), with P<0.001. Pneumatosis intestinalis and irregular bowel wall were solely found in patients with NE, P<0.001. There was a highly significant mucosal enhancement (P<0.001) and significant bowel wall dilatation in patients with NE when compared with the second group (P=0.002).

DISCUSSION

Diarrhea is a frequent complication of cytotoxic chemotherapy; its true incidence, risk factors and clinical course have rarely been investigated prospectively. To the best of our knowledge, this is the largest prospective study

Table 3: Clinical characteristics of the studied patients with diarrhea

Signs and symptoms, *n* (%)	All neutropenic patients with diarrhea (*n*=100)	Neutropenic diarrhea rather than NE (*n*=84)	NE (*n*=16)	*P*
Number of bowel motions/day Mean±SD (range)	4.8±1.6 (3-12)	4.7±1.7 (3-12)	5.8±1.9 (4-10)	0.11
Stool properties				
Bloody	6 (6)	4 (4.7)	2 (12.5)	0.53
Mucoid	10 (10)	8 (9.5)	2 (12.5)	0.92
Bloody and mucoid	2 (2)	2 (2.4)	0 (0)	0.72
Without blood or mucous	82 (82)	70 (83.6)	12 (75.5)	0.65
Abdominal pain				
Right lower quadrant	16 (16)	8 (9.5)	8 (50)	0.001**
Generalized	28 (28)	26 (31)	2 (12.5)	0.22
Left lower quadrant	40 (40)	32 (38.1)	6 (37.5)	0.37
Periumblical	4 (4)	4 (4.8)	0 (0)	0.84
Nausea	16 (16)	10 (11.9)	6 (37.5)	0.02*
Vomiting	46 (46)	34 (40.5)	12 (75)	0.01*
Distension	10 (10)	6 (7.1)	4 (25)	0.08
Tenesmus	10 (10)	6 (7.1)	4 (25)	0.08
Abd. tenderness	16 (10)	6 (7.1)	10 (62.5)	0.001**
Vital signs, mean±SD				
Temperature	37.8±0.5	37.6±0.67	39.15±0.35	0.001**
HR	83.7±9.9	81.2±9	94.5±8.7	0.001**
Blood pressure systolic/diastolic	104.8±6.4/64.2±6.3	105.8±6.4/64.7±5.9	103±6.4/63.75±7.4	0.5/0.61
RR	19.1±4.5	18.5±3.9	21.2±7.6	0.12

*Significant statistically, **Highly significant statistically; NE - Neutropenic enterocolitis; HR - Heart rate; RR – Respiratory rate

Table 4: Laboratory findings in the studied population

Laboratory results, Mean±SD	All neutropenic patients with diarrhea (*n*=100)	Neutropenic diarrhea rather than NE (*n*=84)	NE (*n*=16)	*P*
White blood cell count (per mm^3)	1300±530	1300±680	2300±2900	0.06
ANC (per mm^3)	242.2±161.1	269.6±158.1	191.9±167.2	0.11
Hemoglobin (g/dl)	9.72±1.78	9.7±1.8	9.74±1.77	0.94
Hematocrit (%)	29.1±5.7	30.1±9.1	28.2±3.9	0.11
Platelets (per mm^3)	52300±32200	63600±67700	28200±12600	0.001**
Blood urea nitrogen (mg/dl)	22.1±12.9	21.5±11.6	24±15.7	0.8
Creatinine (mg/dl)	0.69±3.1	0.67±0.2	0.71±0.53	0.7
ALT (IU/ml)	49.1±25.9	52.3±31.2	40±23.1	0.08
AST (IU/ml)	34.2±17.6	36.4±21.6	30.2±15.6	0.1
Sodium (mEq/l)	132.1±5.3	135.6±6.5	127.5±4.6	0.001**
Potassium (mEq/l)	3.4±0.8	3.55±0.7	2.97±1.1	0.02*
pH (normal/metabolic acidosis)	40/16	36/4	4/12	0.001**
CRP (-ve/+ve)	46/52	46/38	0/16	0.001**

*Significant statistically. **Highly significant statistically; NE - Neutropenic enterocolitis; ANC - Absolute neutrophilic count; ALT - Alanine transaminase; AST - Aspartate transaminase; CRP - C-reactive protein

in children to date, which evaluates diarrhea in neutropenic children with cancer. Most of the data in the literature rely on case reports, case series and retrospective studies.[20] The study carried by McCarville *et al*.[21] is the largest retrospective study to date on typhlitis in childhood cancer, which discussed 83 children with typhlitis.

In the current study, diarrhea was observed in 55.5% (100 episodes) of all episodes of neutropenia (180 episodes) experienced by the study group.

In our study, we used specific quantifiable bowel wall measurements of ≥3 mm obtained by ultrasonography (US) imaging in addition to the constellation of neutropenia and diarrhea and/or abdominal pain and/or fever to label the patients as having NE.

The reported incidences of NE in literature in adults vary considerably from 0.8% to 26%,[22,23] while studies in pediatric population demonstrated incidence rates of 0.35-6.1%.[24,25] These results, although variable in different

Table 5: Microbial evaluation of the stool and blood samples in the studied patients

Result *n* (%)	All neutropenic patients with diarrhea (*n*=100)	Neutropenic diarrhea rather than NE (*n*=84)	NE (*n*=16)	*P*
Microscopic examination				
Giardia	4 (4)	4 (4.8)	0 (0)	0.84
Stool culture				
Aeromonas hydrophilia	2 (2)	2 (2.4)	0 (0)	0.72
E. coli	18 (18)	16 (19)	2 (12.5)	0.78
EHEC	2 (2)	0 (0)	2 (12.5)	0.02*
Klebsiella oxytoca	4 (4)	0 (0)	4 (25)	0.001**
Salmonella	6 (6)	6 (7.1)	0 (0)	0.59
Shigella	4 (4)	4 (4.8)	0 (0)	0.84
Yersinia enterocolitica	2 (2)	2 (2.4)	0 (0)	0.72
Candida	4 (4)	0 (0)	4 (25)	0.001**
Blood culture				
Klebsiella	6 (6)	2 (2.4)	4 (25)	0.003*
E. coli	2 (2)	0 (0)	2 (12.5)	0.02*
Enterococci	4 (4)	2 (2.4)	2 (12.5)	/0.23
Candidemia	4 (4)	2 (2.4)	2 (12.5)	0.23
Staph. aureus	10 (10)	6 (7.1)	4 (25)	0.08
Serratia orodrifera	2 (2)	0 (0)	2 (12.5)	0.02*

*Significant statistically. **Highly significant statistically; NE - Neutropenic enterocolitis; EHEC - Enterohemorrhagic *E. coli*

Table 6: Abdominal ultrasonographic finding in the studied patients

Ultrasonographic finding	All neutropenic patients with diarrhea (*n*=100)	Neutropenic diarrhea rather than NE (*n*=84)	NE (*n*=16)	*P*
Bowel wall thickness Mean±SD (range)	2.6±0.5 mm (1.4-6.2)	2.1±0.4 (1.4-3.3)	5.2±0.7 (4-6.2)	<0.001**
Dilataion (negative/positive)	36/14	66/18	6/10	0.002*
Regularity (regular/irregular)	45/5	84/0	6/10	<0.001**
Pneumatosis intestinalis (negative/positive)	47/3	84/0	10/6	0.001**
Mucosal enhancement (negative/positive)	42/8	78/6	6/10	<0.001**

*Significant statistically. **Highly significant statistically; NE - Neutropenic enterocolitis

patient populations, underscore the importance of NE as a clinical problem.[7]

These variations can be explained on the basis of the patient population studied and that in most of these studies, the focus was on typhlitis, which may be regarded as a localized form of NE limited to caecal inflammation.[26]

We found a clear significant high incidence of NE (16%) among the children treated for cancer at our institution as compared to other studies. We attribute this increase, at least in part, to our policy of performing abdominal ultrasonography very early within 3 days from the development of diarrhea in neutropenic children without waiting for the clinical triad of diarrhea, fever and abdominal pain to be fulfilled. We found that the clinical triad is always completed during the course of the hospital stay, indicating that this policy helped to pick up early cases before the development of the full blown picture of NE, which is later reflected on the favorable outcome with resolution of NE without any surgical morbidity and without any reported mortality. The difference in mortality rate as compared with other studies in literature might also be attributed to the difference in the age group of the studied population, which was ≤12 year old in our study. The two mortalities in the McCarville's[21] study group were in 14- and 15-years old. Overall, patients >16 years old were at a significantly greater risk of NE and its associated morbidity and mortality than younger patients. Age is noteworthy a significant demographic variable associated with the development of typhlitis.[21] Older patients not only are at a greater risk of typhlitis but may also not respond as well as compared to younger patients to its management.[25]

In agreement with McCarville *et al*.,[21] the imaging and clinical features that we found to be significantly associated with NE were the duration and severity of neutropenia, bowel wall thickness as measured by US imaging, fever

and abdominal tenderness. Jain *et al*.[25] and Aksoy *et al*.[4] also agreed with us regarding the duration of neutropenia. Aksoy *et al*.[4] agreed as well as regards the severity of neutropenia while Dietrich *et al*.[27] had significant results like ours regarding fever.

Right lower quadrant abdominal pain was another significant clinical finding in patients with NE. That was in agreement with the results of Merine *et al*.[28] and Alioglu *et al*.[29]

The development of typhlitis has historically been attributed to previous drug therapy.[21] Our findings suggest that several drugs can affect the development of typhlitis in children. Methotrexate and mitoxantrone were significantly associated with NE in our patients, while anthracyclines showed no significant statistical difference in our work. Akosy *et al*.[4] agreed with us regarding mitoxantrone, while disagreed regarding anthracyclines. Boukhettala *et al*.[30] and Hogan *et al*.[31] found that antimetabolites were the most commonly implicated chemotherapeutic agents with development of NE. Diarrhea induced by cytotoxic compounds is most likely due to mucositis, but may also be due to the alteration of the bacterial flora of the gut.[32]

There were no significant differences in laboratory finding between episodes with or without NE apart from hyponatremia and hypokalemia that were associated with NE, which may be attributed to the marked morbidity and prolonged course of diarrhea in patients with NE. Aksoy *et al*.[4] found no significant electrolyte abnormalties, which may be explained by the different sample age as Aksoy *et al*. carried their study in adults who may have higher ability to withstand diarrheal sequlae. The different modes of chemotherapeutic combinations in the two studies may be another factor.

Stool culture was positive in 75% of the NE patients, with Candida being the most commonly revealed organism, followed by Klebsiella, which were both significantly associated with NE, while *E. coli* was most common in the other group, followed by Salmonella and Shigella. Aksoy *et al*.[4] in his adult population found Candida to be the most common organism, followed by Klebsiella in cases of NE. Cartoni *et al*.[6] found a great proportion of Candida and Gram negative bacteria in their patients.

Parasitic infestations should also be considered in the diagnostic work-up of diarrhea in certain settings; they were detected in four diarrheal episodes (giardiasis) among patients in group 2.

Blood culture was positive in all cases of NE, with Klebsiella and *Staph. aureus* being the most commonly revealed organisms, followed by *E. coli*, Enterococci, Candida and *Serratia orodrifera*. *Klebsiella*, *E. coli* and *Serratia orodrifera* were significantly associated with NE. This was some what similar to the results of McCarville *et al*.,[21] who found *E. coli*, *Klebsiella*, *Enterococcus*, *Staphylococcus* and *Streptococcus* species to be the most incriminated organisms. Dietrich *et al*.[27] had 57% positive blood cultures in patients with NE while Cardona Zorrilla *et al*.[33] had only 51% positive blood cultures.

Abdominal ultrasonography using a high-resolution probe was the preferred imaging technique in our institution as a screening for NE. Bowel wall thickness ≥3 mm, bowel dilatation, bowel wall irregularity, pneumatosis intestinalis and mucosal enhancement were all significantly associated with NE. McCarville *et al*.[34] suggested using the cut-off value for bowel wall thickness of ≥3 mm on US to increase both the sensitivity and the accuracy of diagnosis of NE.

Finally, the unavailability of tests for viral etiologies in the stool specimens is considered a limitation in our study as diseases like Cytomegalovirus enterocolitis, which may resemble NE, may be overlooked.

CONCLUSION

This study revealed that diarrhea is a common finding in neutropenic cancer children. Gram negative bacteria and Candida species were the most commonly incriminated organisms. Duration and severity of neutropenia carry a great risk for the development of NE. NE should be highly anticipated during the induction phase of chemotheraputics. Fever, abdominal pain and tenderness are considered red alerts for the oncologists in any neutropenic cancer children with diarrhea.

It is likely that the application of strict, quantitative imaging criteria together with the use of clinical signs and improved antibiotic therapy can reduce the rate of NE-associated morbidity and mortality. Even in the absence of typical clinical findings, the diagnosis of NE can be made when clinical suspicion is confirmed with imaging.

REFERENCES

1. Madani TA. Clinical infections and bloodstream isolates associated with fever in patients undergoing chemotherapy for acute myeloid leukemia. Infect 2000;28:367-73.
2. Davila M, Bresalier RS. Gastrointestinal complications of oncologic therapy. Nat Clin Pract Gastroenterol Hepatol 2008;5:682-96.
3. Maroun JA, Anthony LB, Blais N, Burkes R, Dowden SD, Dranitsaris G, *et al*. Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: A consensus statement by the canadian working group on chemotherapy-induced diarrhea. Curr Oncol 2007;14:13-20.

4. Aksoy DY, Tanriover MD, Uzun O, Zarakolu P, Ercis S, Erguven S, *et al*. Diarrhea in neutropenic patients: A prospective cohort study with emphasis on neutropenic enterocolitis. Ann Oncol 2007;18:183-9.
5. Alt B, Glass NR, Sollinger H. Neutropenic enterocolitis in adults: Review of the literature and assessment of surgical intervention. Am J Surg 1985;149:405-8.
6. Cartoni C, Dragoni F, Micozzi A, Pescarmona E, Mecarocci S, Chirletti P, *et al*. Neutropenic enterocolitis in patients with acute leukemia: Prognostic significance of bowel wall thickening detected by ultrasonography. J Clin Oncol 2001;19:756-61.
7. Ullery BW, Pieracci FM, Rodney JR, Barie PS. Neutropenic enterocolitis. Surg Infect (Larchmt) 2009;10:307-14.
8. Song HK, Kreisel D, Canter R, Krupnik AS, Stadtmauer EA, Buzby G. Changing presentation and management of neutropenic enterocolitis. Archiv Surg 1998;133:979-82.
9. Vlasveld LT, Zwaan FE, Fibbe WE, Tjon RT, Tham TA, Kluin PM, *et al*. Neutropenic enterocolitis following treatment with cytosine arabinoside-containing regimens for hematological malignancies: A potentiating role for amsacrine. Ann Hematol 1991;62:129-34.
10. Micozzi A, Cartoni C, Monaco M, Martino P, Zittoun R, Mandelli F. High incidence of infectious gastro-intestinal complications observed in patients with acute myeloid leukemia receiving intensive chemotherapy for first induction of remission. Support Care Cancer 1996;4:294-7.
11. Gootenberg JE, Abbondanzo SL. Rapid diagnosis of neutropenic enterocolitis (typhlitis) by ultrasonography. Am J Pediatr Hematol Oncol 1987;9:222-7.
12. Patel U, Leonidas JC, Furie D. Sonographic detection of necrotizing enterocolitis in infancy. J Ultrasound Med 1990;9:673-5.
13. Tjon A Tham RT, Vlasveld LT, Willemze R. Gastrointestinal complications of cytosine-arabinoside chemotherapy: Findings on plain abdominal radiographs. AJR Am J Roentgenol 1990;154:95-8.
14. Wall SD, Jones B. Gastrointestinal tract in the immunocompromised host: Opportunistic infections and other complications. Radiol 1992;85:327-35.
15. Fishman EK, Kavuru M, Jones B, Kuhlman JE, Merine DS, Lillimoe KD, *et al*. Pseudomembranous colitis: CT evaluation of 26 cases. Radiol 1991;180:57-60.
16. Skirrows MB, Benjamin J. Differentiation of enteropathogenic campylobacter. J Clin Pathol 1980;33:1122.
17. Smith HR, Scotland SM. Isolation and identification methods for *Escherichia coli* O157 and other verocytotoxin producing strains. J Clin Pathol 1993;46:10-7.
18. Krause R, Schwab E, Bachhiesl D, Daxbock F, Wenisch C, Krejs GJ, *et al*. Role of Candida in antibiotic-associated diarrhea. J Infect Dis 2001;184:1065-9.
19. Ross PW. *Streptococcus* and *Enterococcus*. In: Collee JG, Fraser AG, Marmion BP, Simmons A, editors. Mackie and McCartney Practical Medical Microbiology. 14th ed. Edinburgh: Churchill Livingstone; 1996. p. 263-74.
20. Gorschlüter M, Mey U, Strehl J, Ziske C, Schepke M, Schmidt-Wolf IG, *et al*. Neutropenic enterocolitis in adults: Systematic analysis of evidence quality. Eur J Haematol 2005;75:1-13.
21. McCarville MB, Adelman CS, Li C, Xiong X, Furman WL, Raz- zouk BI, *et al*. Typhlitis in childhood cancer. Cancer 2005;104:380-7.
22. Salazar R, Solá C, Maroto P, Tabernero JM, Brunet J, Verger G, *et al*. Infectious complications in 126 patients treated with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1999;23:27-33.
23. Jones GT, Abramson N. Gastrointestinal necrosis in acute leukemia: A complication of induction therapy. Cancer Invest 1983;1:315-20.
24. Sloas MM, Flynn PM, Kaste SC, Patrick CC. Typhilitis in children with cancer: A 30-year experience. Clin Infect Dis 1993;17:484-90.
25. Jain Y, Arya LS, Kataria R. Neutropenic enterocolitis in children with acute lymphoblastic leukemia. Pediatr Hematol Oncol 2000;17:99-103.
26. Wagner ML, Rosenberg HS, Fernbach DJ, Singleton EB. Typhlitis: A complication of leukemia in childhood. Am J Roentgenol Radium Ther Nucl Med 1970;109:341-50.
27. Dietrich CF, Hermann S, Klein S, Braden B. Sonographic signs of neutropenic enterocolitis. World J Gastroenterol 2006;12:1397-402.
28. Merine DS, Fishman EK, Jones B, Nussbaum AR, Simmons T. Right Lower Quadrant Pain in the Immunocompromised Patient: CT Findings in 10 Cases. AJR Am J Roentgenol 1987;149:1177-9.
29. Alioglu B, Avci Z, Ozcay F, Arda S, Ozbek N. Neutropenic enterocolitis in children with acute leukemia or aplastic anemia. Int J Hematol 2007;86:364-8.
30. Boukhettala N, Leblond J, Claeyssens S, Faure M, Le Pessot F, Bôle-Feysot C, *et al*. Methotrexate induces intestinal mucositis and alters gut protein metabolism independently of reduced food intake. Am J Physiol Endocrinol Metab 2009;296:E182-90.
31. Hogan WJ, Letendre L, Litzow MR, Tefferi A, Hoagland HC, Pruthi RK, *et al*. Neutropenic colitis after treatment of acute myelogenous leukemia with idarubicin and cytosine arabinoside. Mayo Clin Proc 2002;77:760-2.
32. Jarvis B, Sheychuk YM. Recurrent Clostridium difficile diarrhea associated with mitoxantrone and etoposide: A case report and review. Pharmacotherapy 1997;17:606-11.
33. Cardona Zorrilla AF, Bereiz Herault L, Casasbuenas A, AponTe DM, Ramos PL. Systematic review of case reports concerning adults suffering from neutropenic enterocolitis. Clin Transl Oncol 2006;8:31-8.
34. McCarville MB, Thompson J, Li C, Adelman CS, Lee MO, Alsammarae D, *et al*. Significance of appendiceal thickening in association with typhlitis in pediatric oncology patients. Pediatr Radiol 2004;34:245-9.

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