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Systematic review of case reports of neutropenic enterocolitis in children with hematologic malignancies

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Abstract

Neutropenic Enterocolitis (NE) is a gastrointestinal disease that is a quite rare disease but life threatening and one of the primary cause of mortality, NE predominantly affect immunocompromised children. Pediatric malignancies, specifically pediatric leukemia, are one of the primary causes of mortality. Leukemias, including Acute Lymphoblastic Leukemia (ALL), Acute Myeloblastic Leukemia (AML), and Chronic Myeloblastic Leukemia (CML), are a substantial component of juvenile cancers. Of these, ALL is the most common, with the highest occurrence between the ages of 2 and 5. Chemotherapy is the major treatment for juvenile leukemia and has been successful in obtaining survival rates of above 90%. Nevertheless, there are consequences associated with it, such as Neutropenic Enterocolitis (NE). Neutropenic patients may get Necrotizing Enterocolitis (NEC), which can occur when bacteria pass through the weakened intestinal lining as a result of chemotherapy. Common symptoms of this condition encompass stomach pain, diarrhea, and neutropenia, while severe complications may involve sepsis and gastrointestinal hemorrhage. Early detection and comprehension are crucial due to the non-specific nature of its presentation. Further emphasize the importance of NE management in the field of pediatric oncology.

Keywords: Leukemia; Neutropenic Enterocolitis; Pediatric; Chemotherapy; Typhlitis

1. Introduction

1.1. Pediatric Leukemia

Malignancies or cancer is a broad term for diseases with high progressivity. Malignancy is referred to as a presence of cancerous cells that have the ability to metastasize and invade other organs of the body to destroy cells within that organ [3]. Paediatric cancer can be defined as cancers that affect children ranging from infants to age 14 and teenagers ranging from age 15 to 19. Paediatric cancer ranks as one of the leading causes of death in the world, where the American Cancer Society estimates that 415 in 1 million children and teenagers may suffer from one of these in cancers based on data in 2023. Common types of paediatric cancers are leukaemia's, lymphomas, brain tumours and solid tumours [19]. From all the groups of paediatric cancers, leukaemia's are the most common, with an estimate of 53 in a million and 35 teenagers in a million will suffer from leukaemia. For paediatric leukaemia, there are three main types which are Acute Lymphoblastic Leukaemia (ALL), Acute Myelogenous Leukaemia (AML), and Chronic Myelogenous Leukaemia (CML). The first type is Acute Myelogenous Leukaemia (AML) which represents 15-20% of leukaemia's in children. Age contributes heavily as a prognostic factor, where if age increases, there will be a decrease in prognosis. Recent studies show that aside from age, other aspects such as genetic mutation is shown to be a significant prognostic factor. Over the past 20 years, children suffering from AML experienced an increase in overall survival rate (5-year overall survival rate 60-75%) [28]. Chronic Myelogenous Leukaemia (CML) is widely known as a disease of older adults with an average age

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of 65 years. However, CML does not only often occur in adults, but also in children as well. Annually, it is estimated that there are around 2.5 million cases of CML in children [25].

From the three leukaemia's**,** the most notably frequent type is Acute Lymphoblastic Leukaemia (ALL). Though most children diagnosed with ALL are usually cured, most of them suffer prolonged complications where prevention efforts are needed. Around 60% of all cases arise in adolescents and children under years of age, with a yearly occurrence of 36.2 per 1 million people and a peak age of incidence of 2-5 years. ALL is found more frequently in male then female with a ratio of approximately 1.3:1. Contrary to most paediatric cancers, studies implicate that few environmental, infectious and dietary factors play a role in the pathophysiology of ALL. For instance, traffic emissions, smoke, pesticides, etc show a significant correlation towards the risk of children suffering from ALL [11].

A potent medication for Leukaemia is chemotherapy. Data shows that the survival of paediatric patients with Leukaemia treated in developed countries exceeds 90%. Treatments like chemotherapy is given to paediatric Leukaemia patients in four important phases: remission induction, consolidation, reinduction and continuation. Though it may be potent, there are some dreaded complications that must be anticipated. One of the complications caused is Neutropenic Enterocolitis (NEC) or Typhlitis [12].

Neutropenic Enterocolitis or Typhlitis is known to be a severe gastrointestinal disorder that occurs in neutropenic patients. Some studies state that NEC is caused by a translocation of bacteria through weak intestinal mucosa that is damaged due to chemotherapy. Incidences of NEC vary through many studies. A systematic review conducted by Gorschlüter et al., states that the incidence rate from 21 studies was 5.3% in hospitalized patients suffering from hematologic malignancies, and high-dose chemotherapy for aplastic anaemia and solid tumours [5].

The pathophysiology of Neutropenic Enterocolitis is not fully understood, but studies show that damaged intestinal mucosa added with neutropenia and immunodeficiency that may lead to enlargement of vessels, edema, vascular congestions and fungal, bacterial or viral infections [16].

Since Neutropenic Enterocolitis is a rare condition that presents itself in a non-specific way, it may resemble other diseases. The diagnosis can possibly be indicated by concurrent symptoms such as diarrhoea, abdominal pain, neutropenia, nausea, thickening of abdominal wall and fever. Neutropenic Enterocolitis may also lead to sepsis (mostly *Citrobacter freundii, Stenotrophomonas maltophilia, C. septicum*), gastrointestinal haemorrhage and even perforations requiring surgery. Mortality rates vary from 23% in ICU patients with 42.2% of those patients needing surgical treatment. In conclusion, it is imperative to get a comprehensive grasp of neutropenic enterocolitis in children with hematologic malignancies, as they have heightened susceptibility to neutropenic diseases face an elevated risk of mortality. Through case reports, the reviewer aims to further our understanding of the symptoms, treatments, and diagnostic methods associated with neutropenic enterocolitis [5].

2. Material and methods

2.1. Search Strategy

The reviewers searched on Medline (Ovid) and keywords on October 2023 for all references. The keywords used in the search are as follows: ("Neutropenic Enterocolitis" or "Necrotizing Enteropathy" or "Agranulocytic Lesions" or "Typhlitis" or "Cecitis" or "Bowel complications" or "Intestinal inflammation" or "Chemotherapy-induced enterocolitis") AND ("Child" or "Pediatric" or "Childhood") AND ("Leukemia" or "Lymphoma" or "Blood cancer" or "Hematologic malignancies") AND ("Chemotherapy" or "Antineoplastic agents"). Key terms used in the Medline search strategy were pediatric leukemia, Neutropenic Enterocolitis, Typhlitis, Chemotherapy, Acute Lymphoblastic Leukemia. The key terms were combined with Boolean operator “AND”. All search results were then compiled and exported to Rayyan to help in screening and managing the references.

2.2. Study Selection

Screening of the search result was done by two independent reviewers (JB and GZ) through the title and abstract. Identified articles were then retrieved in full to assess eligibility. Any disagreements were resolved by consensus and through a third reviewer (FM) when necessary

Case reports of children with hematologic malignancies that were Neutropenic Enterocolitis were included in this review. Exclusion criteria were review studies, cohort or cross-sectional studies and studies in languages other than English are also excluded.

2.3. Data Extraction and Management

The search results from all databases were uploaded into Rayyan, where the duplicates were removed. A custom data extraction form was created by one of the reviewers (FM), and the extracted data were put into an Excel sheet. The following data were extracted: Author, Year, number of cases, patient demographics (gender, age, diagnosis, previous cancer treatment), Typhlitis and NEC diagnostic method, neutrophil count and Typhlitis treatment. Individual patient data were extracted, if there were multiple cases in the study.

2.4. Method of Quality Assessment

Quality assessment was done according to the JBI Critical Appraisal Checklist for Case Reports. The checklist assessed case report studies through eight guiding questions. The questions assess the clarity and robustness of the case report being assessed. The JBI Critical Appraisal Checklist for Case Reports questions are clear descriptions of the patient's demographic characteristics, the patient's history and timeline, the current clinical condition, diagnostic tests or assessment methods, the intervention or treatment, post-intervention clinical condition, adverse events or unanticipated events, and takeaway lessons from the case report. Each guiding questions are numbered from one to eight accordingly.

The Critical Appraisal checklist gives four option for each questions, the options are Yes, No, Unclear or Not Applicable. The reviewer would then assess the overall appraisal of each case report as Include, Exclude or Seek Further info. I this review the overall appraisal is set as Clear, Somewhat Clear, or Ambiguous.

Quality assessment of the included studies is done with a custom Excel sheet created by the reviewer (FM) Quality assessment was done by two reviewers (FM and GB).

3. Results and discussion

The result of the search yields 65 studies, which were then screened through the abstract and title into 19 studies. There were in total 46 excluded studies from screening with the following reasons : wrong population (n=9), wrong study design (n=14), wrong publication type (n=23). The reviewer then sought the full text of the 19 studies, and there were 17 studies found with full text. Lastly the included studies amount to 12, with 2 studies excluded from full text eligibility due to wrong publication type. A clear description of the work flow can be found in Figure 1.

Table 1 shows the result of critical appraisal using the JBI Critical Appraisal Checklist for Case Reports. There are a total of six studies that provide clear descriptions of the cases, while another six research offer somewhat clear descriptions of the cases. There are no research that appear to justify more investigations or require exclusion.

Since the 1980s, there have been notable case studies conducted on neutropenic enterocolitis in children with hematologic malignancies. McNamara, M.J., and Chalmers, A.G. recorded instances in 1986 that concerned children between the ages of 9 and 10 years. In 1988, Alexander, J.E., et al. provided data on children aged 7 and 17 years.

During the 1990s, there were several studies conducted. Two distinct investigations were conducted in 1994. Paulino, F.G. et al. documented the case of a 3-year-old child, whereas Gavan, D.R., and Hendry, G.M.A. conducted research on children aged 3, 9, and 7 years.

In 2001, Thomas, K.L., et al. drew attention to the condition in a 12-year-old child as the new millennium started. In 2003, Özcan, Eğe, Kavieç, Sinan, Mabak, and Özbek published a case report about a 10-year-old child. In 2004, Wilson, David B. et al. reported a case involving a 2-year-old child.

Subsequent to it, the next ten years witnessed additional contributions. In 2007, Ianic, Dragana et al. recorded a case involving a 4-year-old child. In 2012, Gupta, Shivani, and their colleagues presented another legal case involving a youngster who was 6.5 years old. In 2014, McAteer and colleagues published a study on a youngster who was 8 years old. In 2019, Totadri, Sidharth, et al. published a report on a child who was one year old. The latest study conducted in 2021 by Amani, Ali, et al. reported findings from instances involving children aged 7 and 9 years.

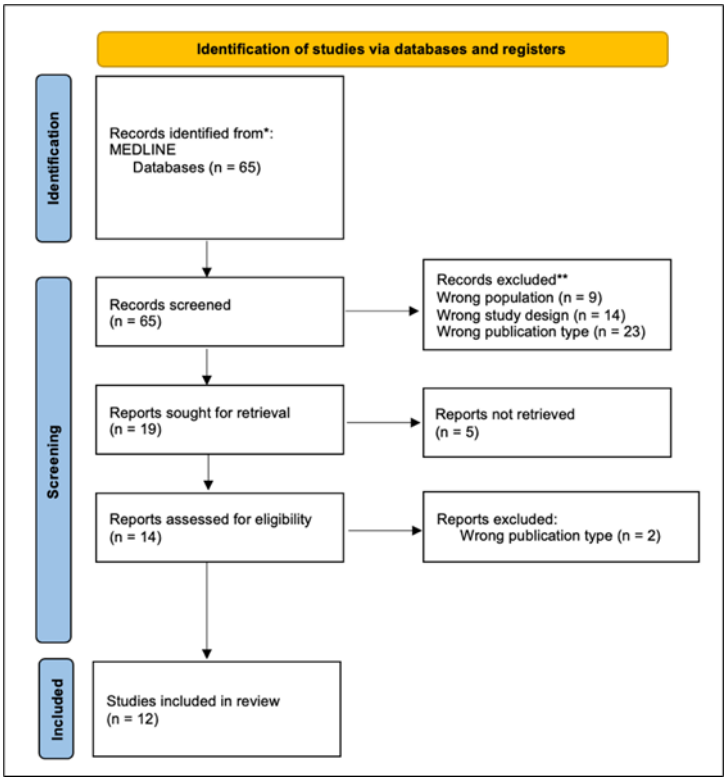

Figure 1 PRISMA Flowchart

Table 1 Quality Assessment With JBI Critical Appraisal Checklist for Case Reports

Author	1	2	3	4	5	6	7	8	Overall
Paulino, Augusto F.G., et. Al, 1994	C	C	C	C	QC	N/A	N/A	C	QC
Janic, Dragana et. al, 2007	C	C	C	C	C	QC	QC	C	C
McAteer, Jarod P., et. al, 2014	C	C	C	C	QC	QC	QC	QC	QC
Özçay, Figen., Kayiran, Sinan Mahir., and Özbek, Namik., 2003	C	C	C	C	C	QC	C	C	C
Wilson, David B., et.al, 2004	C	C	C	C	QC	QC	C	C	QC
Gavan. D. R., and Hendry. G. M. A, 1994	C	QC	C	QC	C	C	QC	C	QC
Totadri. Sidharth., et. al, 2019	C	QC	QC	C	QC	QC	C	C	QC
Amanati. Ali., et. al, 2021	C	C	C	QC	C	C	C	C	C
Alexander. J. E., et. al, 1988	C	QC	C	C	QC	QC	QC	QC	QC
Thomas. K. L., et. al, 2001	C	C	C	C	C	C	QC	C	C
McNamara. M. J., Chalmers. A. G., Morgan. M., and Smith. S.E.W., 1986	C	QC	C	C	C	C	C	C	C
Gupta. Shuchita., et. al, 2012	C	C	C	C	C	C	C	QC	C

C: Clear; QC: Quite clear; N/A: Not Applicable;

Table 2 Case Reports of Neutropenic Enterocolitis in Children with Hematologic Malignancies

Author	Year	Country	Research Design	Gender		Age
				F	M	
Paulino, Augusto F.G., et. al	1994	USA	Case Report	0	1	3
Janic, Dragana et. al	2007	Serbia	Case Report	0	1	4
McAteer, Jarod P., et. al	2014	USA	Case Report	1		8
Özçay, Figen., Kayiran, Sinan Mahir., and Özbek, Namik.	2003	Turkey	Case Report	0	1	10
Wilson, David B., et.al	2004	USA	Case Report	0	1	2
Gavan. D. R., and Hendry. G. M. A	1994	United Kingdom	Case Report	1	3	3, 9, 7
Totadri. Sidharth., et. al	2019	India	Case Report	1	0	1
Amanati. Ali., et. al	2021	Iran	Case Report	0	2	7, 9
Alexander. J. E., et. al	1988	USA	Case Report	1	1	7, 17
Thomas. K. L., et. al	2001	Denmark	Case Report	0	1	12
McNamara. M. J., Chalmers. A. G., Morgan. M., and Smith. S.E.W.	1986	UK	Case Report	1	1	9, 10
Gupta. Shuchita., et. al	2012	India	Case Report	1	0	6.5

3.1. Malignancies and Manifestations of Neutropenic Enterocolitis in Children

Leukemia is the most common malignancy in childhood. It is defined by the uncontrolled growth of leukocytes or their early forms and is mostly caused by a disruption in the regulation of the bone marrow. Childhood leukaemia is classified into two main types: acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML). ALL is characterised by the abnormal growth of B and T lymphocyte precursors, while AML is characterised by the invasion of lymphatic tissues by cancerous hematopoietic cells [2,3]. Chronic myeloid leukaemia (CML) is a cancerous condition where there is an abnormal growth of hematopoietic stem cells, causing an excessive production of myeloid and erythroid cells as well as platelets, leading to an overgrowth of bone marrow [4].

The diagnosis of leukaemia involves a comprehensive set of examinations, such as complete blood count (CBC), coagulation studies, and chemical profile (mostly liver and kidney function tests). The physical characteristics of bone marrow aspiration are employed to differentiate between different kinds of leukaemia [5]. The treatment of leukaemia is contingent upon its classification and the extent of its severity. The mainstay of childhood leukaemia treatment consists of multi-agent chemotherapy, immunotherapy, targeted therapy, and bone marrow transplantation.

Table 3 presents case reports detailing the onset of Typhlitis-like symptoms in children following the diagnosis of cancer. The majority of cases primarily involve Acute Lymphoblastic Leukaemia (ALL). Additionally, there are occurrences of Acute Myeloblastic Leukaemia (AML), T-cell Lymphoblastic Lymphoma stage III, and Acute Lymphocytic Leukaemia. The therapy regimens mentioned exhibit a wide range of variations. The treatments include chemotherapy, which involves the use of medication combinations such as prednisone, vincristine, daunorubicin, and L-asparaginase. Certain instances utilised medications such as cytarabine, etoposide, and dexamethasone, along with supplementary preventive measures like trimethoprim/sulfamethoxazole to prevent Pneumocystis jirovecii pneumonia. The occurrence of symptoms exhibits significant variation among different cases. A few children displayed symptoms such as fever, bacteremia, and discomfort shortly after commencing medication. Conversely, other patients exhibited these symptoms over a period of many weeks to months following the start of treatment.

Table 3 Case Reports of Onset of Typhlitis Like Symptoms after Cancer Diagnosis in Children

Author	Diagnosis (cancer)	Cancer Treatment	Onset of Typhlitis Like Symptoms

Paulino, Augusto F.G., et. al	Acute lymphoblastic leukemia	Not yet	On arrival
Janic, Dragana et. al	Acute lymphoblastic leukemia	Prednisone pre-phase, followed by vincristine, daunorubicin on the day 8 and 15 and L-asparaginase on day 12 and 15	Day 15 of treatment
McAteer, Jarod P., et. al	Acute lymphoblastic leukemia	Induction therapy for relapse	day 2 of treatment (fever and pesudomonas bacteremia, day 14 new onset RLQabd pain
Özçay, Figen., Kayiran, Sinan Mahir., and Özbek, Namik.	Acute lymphoblastic leukemia	Prednisolone, L-asparaginase, vincristine, and daunorubicin	three days after second dose
Wilson, David B., et.al	Acute lymphoblastic leukemia		
Gavan. D. R., and Hendry. G. M. A	Acute lymphoblastic leukemia	Case 1: vincristine, prednisolone, adriamycin, operation Case 2: allopurinol, vincristine, steroids, adriamycin, antibiotics Case 3: steroids, salazopyrine Case 4: adriamycin, vincristine, oral steroids.	Case 1: Day 11 of treatment Case 2: Day 8 of treatment Case 3: 4th week of treatment Case 4: 1st week of treatment
Totadri. Sidharth., et. al	Acute lymphoblastic leukemia	Chemotherapy, broad spectrum antibiotics, emergency laparotomy, transfusion support.	-
Amanati. Ali., et. al	Acute Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia	Case 1: Reinduction chemotherapy started with cytarabine (300 mg/m^2 as loading dose day 1 and 2 and continued by 150 mg/m^2 from day 3), etoposide, idarubicin (0.5 mg/kg; day 3, 5, and 7), and dexamethasone 1.5 mg/8 h (protocol BFM-2012). Trimethoprim/sulfamethoxazole 2.5 mg/kg twice/day three times/week to prevent Pneumocystis jirovecii pneu-moniae (PJP) and antifungal prophylaxis with liposomal amphotericin-B (L-AmB) 2.5 mg/kg every other day concurrently. Case 2: She received a reinduction regimen including cytarabine (100 mg/ m^2), etoposide, weekly vincristine, and dexamethasone 2 mg/8 h. She also received trimethoprim/sulfamethoxazole 200/40 mg twice/day three times/week for PJP prophylaxis and antifungal prophylaxis with L-AmB 2.5 mg/kg every other day	Case 1: After a week of treatment Case 2: After 10 days of treatment
Alexander. J. E., et. al	Acute Lymphocytic Leukemia (ALL), Acute Myeloblastic Leukemia (AML)	Case 1: - Case 2: chemotherapy	Case 1: - Case 2: 4 months after being diagnosed with

			AML and in second remission of chemotherapy
Thomas. K. L., et. al	Acute Lymphocytic Leukemia	Vincristine, methotrexate, cyclophosphamide, mercaptopurine, prednisolone, cytarabine, adriamycin, and thioguanine for a period of 10 months under which remission was achieved. After 4 months of maintenance therapy with mercaptopurine, 75 mg every day, and methotrexate, 20 mg every week.	After 4 months of maintenance therapy
McNamara. M. J., Chalmers. A. G., Morgan. M., and Smith. S.E.W.	Acute Lymphoblastic Leukemia, Acute Myelomonocytic Leukemia	Chemotherapy comprising daunorubicin, vincristine, L-asparaginase and prednisolone, broad-spectrum antibiotics, vancomycin	10 days after treatment
Gupta. Shuchita., et. al	T cell lymphoblastic lymphoma stage III	MCP-841 protocol (medium risk) and had received a cumulative dose of 728 mg of prednisolone, 40 g of L-asparaginase, 40 mg of daunorubicin, and 5 mg of vincristine during Induction-I, along with 36 mg of intrathecal methotrexate. Induction-II was modified as per the ALL-BFM 95 protocol, avoiding pre-symptomatic cranial radiotherapy, and child was given a total dose of 500 mg of cyclophosphamide, 840 mg of 6-mercaptopurine and 600 mg of cytarabine.	2 days after reinduction phase

Neutropenic enterocolitis (NE) was first observed in children with hematologic malignancies. From there the syndrome has been associated with a variety of chemotherapeutic drugs. The medications that have been specifically implicated include taxanes, 5-Fluorouracil, epirubicin, cyclophosphamide, platinum derivatives, vinorelbine, ifosfamide, etoposide, pegylated interferon, cytosine arabinoside, vinca alkaloids, sulfasalazine, procainamide, gemcitabine, pemetrexed, and alemtuzumab[1,2,10,11,14,22,23,27,28].

Among these, taxanes, whether used alone or in combination, seem to be associated with an increased risk of NE [5]. Prolonged administration schedules of chemotherapy are also recognized as potential contributing factors [2]. An occurrence of NE has been linked to taxanes, which are recognized for causing a halt in the division of mucosal cells and the death of epithelial tissue in the gastrointestinal tract [2,12,14]. In addition, it has been observed that NE is more common in patients treated with 5-FU who have a deficiency in DPD (dihydropyridine dehydrogenase) [1,2,15]. Reports suggest that individuals who maintain normal neutrophil counts after treatment can nonetheless experience manifestations of NE. The full understanding of the consequences for NE incidence and its subsequent treatment results is still pending due to the growing incorporation of novel compounds and targeted medicines into chemotherapy regimens.

Table 4 presents an extensive compilation of case reports of children who have been diagnosed with Typhlitis. A wide range of diagnostic techniques have been used in these cases, including clinical examinations, laboratory tests, and imaging procedures. Several cases depended on investigative methods, such as post-mortem autopsies, examination of surgical specimens, or the use of modern imaging equipment such abdominal CT scans.

The neutrophil counts at the time of the Typhlitis diagnosis exhibited significant variation, ranging from as low as $20/mm^3$ to $0.2x10^9/L$. In certain instances, the precise number was not stated.

There was a wide range of therapy approaches. Several children received surgical interventions, including procedures such as appendix resection or removal of specific parts of the colon. In other instances, medicinal treatment protocols included the administration of antibiotics such as meropenem, cefazidime, and amikacin, or antifungal medications like

fluconazole. Additional treatment approaches utilised included nasogastric decompression, temporary cessation of bowel activity, intravenous fluid infusion, complete parenteral nourishment, and more intricate operations, such as the placement of thoracic catheters.

The survival or outcome of each case also differs accordingly. A significant number of children successfully survived after receiving treatment. Nevertheless, there were unfortunate occurrences in which certain patients did not survive, either due to complications related to Typhlitis or because of their underlying condition, such as leukemia.

Table 4 Case Reports regarding Typhlitis Diagnostic Method, Neutrophil Count, Treatment and Outcome in Children

Author	Typhlitis, NE, Diagnostic Method	Neutrophil Count at Time of Typhlitis Diagnosis	Typhlitis Treatment	Outcome
Paulino, Augusto F.G., et. al	Postmortem autopsy	3%; $0.09x10^9$/L	Not yet	Died before typhlitis treatment
Janic, Dragana et. al	Clinical, laboratory, and imaging	-	Conservative, into surgical ileum, cecum and partial colon resection	Alive
McAteer, Jarod P., et. al	Pathology of surgical specimen	20/mm^3	Surgical resection of appendix with 14 day course of meropenem and trimethoprim/sulfamethoxazole	Alive
Özçay, Figen., Kayiran, Sinan Mahir., and Özbek, Namik.	Clinical, laboratory, CT abdomen	$0.2x10^9$/L	NG decompression, bowel rest, IV fluid, total parenteral nutrition, antibiotic based on blood urine stool and throat (ceftazidime, amikacin, metronidazole and fluconazole), G-CSF, Dopamine	Alive
Wilson, David B., et.al	CT abdomen, serial Xray, Doppler USG	-	Ceftazidime, bowel rest, nasogastric drainage, vancomycin, clindamycin, gentamicin, fluconazole, mechanical ventilation, thorax catheter. Perforation 24th day, resection of the splenic flexure and proximal descending colon with formation of end-transverse colostomy and distal descending colon Hartmann's pouch.	-
Gavan. D. R., and Hendry. G. M. A	**Case 1**: Ultrasound **Case 2:** Ultrasound and water-soluble contrast enema (no evidence of typhlitis) **Case 3:** Ultrasound **Case 4:** Laparotomy, biopsy, contrast enema	-	**Case 1**: Operation to reduce ileo-colic intussusception. **Case 2:** Operation to reduce ileo-colic intussusception. **Case 3:** steroids and salazopyrine. **Case 4:** formal defunctioning colostomy	All Alive
Totadri. Sidharth., et. al	Contrast-enhanced computerized tomography, laparotomy	-	Not yet	Alive
Amanati. Ali., et. al	**Case 1:** Laboratory, Abdominopelvic ultrasonographic examination **Case 2:** laboratory, imaging	**Case 1:** 100/mm^3 and continue decreasing to 50/mm^3 **Case 2:** <500/mm^3	**Case 1**: meropenem (20 mg/kg/dose/6 h) and amikacin (15 mg/kg/dose/ day), and the patient's diet changed to NPO (nil per os). **Case 2:** colistin (150,000 units/kg as a loading dose then 75,000 units/kg/12 h) and amikacin (15 mg/kg/day)	**Case 1:** Dead **Case 2:** Alive

Alexander. J. E., et. al	**Case 1:** Ultrasound, Laboratory **Case 2:** Imaging, clinical	**Case 1:** - **Case 2: -**	**Case 1:** - **Case 2 :** Appendectomy and antibiotics	**Case 1:** Alive **Case 2:** Alive
Thomas. K. L., et. al	Laboratory and imaging	-	Hydrocortisone 100 mg every 8 hours, surgery	Alive
McNamara. M. J., Chalmers. A. G., Morgan. M., and Smith. S.E.W.	Barium follow-through examination	-	Vancomycin	Died due to leukemia
Gupta. Shuchita., et. al	Laboratory	300/mm^3	The child was managed conservatively on intravenous fluids with continuous nasogastric drainage and broad-spectrum antibiotics (meropenem, vancomycin and metronidazole).	Alive

The diagnosis of neutropenic enterocolitis (NE) mostly relies on radiologic imaging, where intestine wall thickness (BWT) is identified using CT or ultrasonography, acting as the main criteria [9]

CT imaging and ultrasonography provide higher sensitivity compared to radiography and barium investigations in detecting intestinal wall thickening. Additionally, they help differentiate NE from other medical disorders [1]. Nevertheless, the conclusive significance of BWT in the diagnosis of NE is still a subject of controversy, prompting the need for comprehensive research to validate its radiological sensitivity and specificity. However, certain authors propose improving the precision of diagnosing NE by integrating radiological observations with symptoms and physical indicators. They suggest diagnostic criteria that include fever, abdominal pain, and a BWT (bowel wall thickness) exceeding 4 mm (in transverse scan) or 30 mm (in longitudinal scan) as determined by ultrasound or CT scanning [4]

The management of NE is still a subject of debate in the field of medicine because there are no published prospective randomized trials on the topic. The current therapy recommendations are based on retrospective investigations, clinical experience, and insights from respected authority. For uncomplicated instances, the first step in treatment comprises non-surgical methods such as resting the intestine, providing fluids through an IV, giving total parenteral nutrition, and administering a wide range of antibiotics [19,23]

The 2003 guidelines from the Infectious Diseases Society of America recommend a broader range of antibiotics for individuals with weakened immune systems. They propose using combinations such as meropenem, imipenem/cilastatin, or piperacillin/tazobactam, among others [21]. Nevertheless, the efficacy of these antibiotics, particularly in NE-specific situations, has not been definitively confirmed. In order to achieve a strong recovery from NE, it is crucial to normalize the leukocyte count. One suggested approach to expedite this process is the use of granulocyte colony-stimulating factor (G-CSF). However, there is limited evidence available on the effectiveness of G-CSF in treating NE [15]. Surgical surgery is only performed in cases of serious consequences such as persistent gastrointestinal bleeding, intra-abdominal perforation, or clinical worsening despite medicinal therapy [18]. During surgical situations, the method used can differ, although it is generally recommended to avoid doing primary bowel anastomosis when a person has continuous leukopenia, according to the agreement [7, 24].

4. Conclusion

To summarize, this review comprises twelve case reports discussing neutropenic enterocolitis in children diagnosed with hematologic malignancies. The descriptions in the case reports are either very clear or clear. The symptoms of the illness usually exhibit various patterns of abdominal pain, and relying on clinical indications and demographic data seems to be quite informative. Key indicative indicators include a noticeable increase in the thickness of the intestinal wall and a decreased quantity of neutrophils. Timely and precise administration of appropriate medication significantly improves the survival prospects of patients diagnosed with neutropenic enterocolitis.

Compliance with ethical standards

Disclosure of Conflict of interest

There is no conflict of interest in all Authors.

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