Incidence, Risk Factors, and Outcomes of Enteritis, Typhlitis, and Colitis in Children With Acute Leukemia

Amy Shafey, MD, Marie-Chantal Ethier, BSc, Jeffrey Traubici, MD, Ahmed Naqvi, MD, and Lillian Sung, MD, PhD

Summary: This retrospective chart review describes pediatric patients with acute lymphoblastic leukemia or acute myeloid leukemia diagnosed between January 1999 and January 2008, who were identified with enteritis, typhlitis, or colitis. Among the acute leukemia patients, 33/449 (7.3%) with acute lymphoblastic leukemia and 13/89 (14.6%) with acute myeloid leukemia experienced 51 episodes of enteritis (n = 8), typhlitis (n = 15), colitis (n = 19), or enterocolitis (n = 9). Twenty-five (49%) patients were exposed to corticosteroids within 14 days of the episode and 35 (68.6%) had fever and neutropenia concurrent with the episode. Forty-eight (94%) patients were treated with complete bowel rest and broad-spectrum antibiotics. However, 3 patients received no therapy and had uneventful courses. Complications included sepsis in 7/51 (13.7%) and intestinal obstruction in 3/51 (5.9%). One child required surgery for abscess drainage and 2 children died of causes unrelated to their colitis. Enteritis, typhlitis, or colitis occurred in 8.6% of children treated for leukemia. The optimal management approach is uncertain.

Key Words: typhlitis, enterocolitis, colitis, children, leukemia

(*J Pediatr Hematol Oncol* 2013;35:514–517)

Children with cancer are at increased risk of gastrointestinal (GI) complications and in particular, enteritis, typhlitis, and colitis have been increasingly recognized over the last few decades.[1] These diagnoses represent inflammatory conditions of the small bowel, cecum, and large bowel, respectively, and about 5% to 10% of children with cancer will experience these complications during therapy.[2–4] The etiology of these conditions is thought to be a combination of immunosuppression, mucosal injury, and bacterial invasion,[5] leading to bowel edema, engorged blood vessels, and tissue necrosis.[5,6] Mortality may be as high as 10% to 100% in these patients.[6–10]

Children with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) may be at particular risk of these GI complications related to corticosteroid exposure, prolonged periods of neutropenia, frequent antibiotic administration, and recurrent episodes of infection.[11] Therapies for pediatric ALL and AML have changed over time, with better risk stratification for children with ALL and increasingly intensive chemotherapy for children with AML.[12,13] Little is known about the incidence, risk factors, and outcomes for children with enteritis, typhlitis, and colitis with contemporary therapies. Better understanding of these conditions may help to improve timely diagnosis and increase our knowledge of potentially effective treatments. Ultimately, such knowledge will be critical before planning and conducting preventative and interventional trials.

Consequently, our objective was to describe the incidence, risk factors, symptoms, treatments, and outcomes of enteritis, typhlitis, and colitis in children with acute leukemia.

MATERIALS AND METHODS

Patients

Children 1 to 18 years of age diagnosed with initial or relapsed ALL or AML at The Hospital for Sick Children (SickKids) between January 1999 and January 2008 were included. Exclusion criteria were age less than 1 year at diagnosis and patients with mature B-ALL (L3) and acute promyelocytic leukemia. Episodes occurring following hematopoietic stem cell transplantation were also excluded from the analysis.

Study Design

This retrospective chart review received institutional research ethics board approval from SickKids. For all eligible children, radiology reports through to January 31, 2009 were reviewed by a single investigator (A.S.). Any abdominal imaging modality including ultrasounds, computed tomography (CT) scans, and plain radiographs were reviewed. Cases were classified as enteritis, typhlitis, colitis, or enterocolitis depending on whether there was noted thickening of the small bowel, the cecum, the large bowel, or both the small and large bowel, respectively. Cases were chosen if significant radiographic thickening was reported by the reviewing radiologist. If there was uncertainty about the diagnosis or location, the abdominal imaging was reviewed by a pediatric radiologist (J.T.).

For all patients with enteritis, typhlitis, colitis, or enterocolitis, the clinical presentation, treatments, and outcomes were abstracted from the patient chart. Predisposing factors including corticosteroid use within 14 days and noncorticosteroid systemic chemotherapy treatment within 30 days were retrieved.

The date at onset of the episode was defined as the first day of GI symptoms or the first day of radiographic abnormality in a patient without GI symptoms. The end date was defined as the last day of symptoms or the last day of treatment, whichever occurred later.

Received for publication January 26, 2013; accepted April 3, 2013.
From the Departments of Pediatrics and Diagnostic Imaging, and Program in Child Health Evaluative Sciences, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada.
The authors declare no conflict of interest.
Reprints: Lillian Sung, MD, PhD, Division of Haematology/Oncology, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G1X8, Canada (e-mail: lillian.sung@sickkids.ca).

Statistics

The demographics, clinical presentation, treatments, and outcomes were described as proportions for categorical variables and medians with interquartile ranges (IQR) for continuous variables. Proportions were compared between ALL and AML patients using the χ^2 test. Analysis was conducted using the SAS statistical program (SAS-PC, version 9 · 3; SAS Institute Inc., Cary, NC).

RESULTS

During the study period, there were 449 patients with ALL and 89 patients with AML who met the eligibility criteria. There were 46 patients who experienced 51 episodes of enteritis, typhlitis, colitis, or enterocolitis during the study time frame. Four patients had repeat episodes: 3 had 2, and 1 had 3 episodes. Among the 46 patients, complications were significantly less common in patients with ALL (33/449, 7.3%) compared with AML (13/89, 14.6%; $P = 0.04$).

Demographics of the 51 episodes are illustrated in Table 1; these consisted of enteritis (8, 15.7%), typhlitis (15, 29.4%), colitis (19, 37.2%), and enterocolitis (9, 17.6%). The median time from symptom onset to date of the GI complication diagnosis was 3.0 (IQR, 0.0 to 5.0) days. Typically, complications occurred soon after leukemia diagnosis with a median time to onset of 3.0 (IQR, 1.0 to 9.0) months. In terms of phase of treatment, in the ALL group, episodes occurred before initiation of chemotherapy (n = 3), during induction (n = 7), consolidation (n = 4), delayed intensification (n = 7), and maintenance (n = 12), and while receiving chemotherapy for relapsed disease (n = 3). More specifically, the episodes occurred in the following phases: dexamethasone-based induction (n = 3), prednisone-based induction (n = 4), cyclophosphamide-based and cytarabine-based consolidation (n = 2), dexamethasone-based delayed intensification (n = 5), and non–dexamethasone-based delayed intensification (n = 2). In the AML group, episodes occurred in induction (n = 7), or consolidation/intensification (n = 8).

Table 1 also illustrates that 49% of patients had exposure to corticosteroids within 14 days of episode onset. For these patients, the median length of steroid use was 6.0 (IQR, 3.0 to 11.0) days. The most prevalent steroid was dexamethasone; the frequency of each steroid type administered is outlined in Table 1. Once enteritis, typhlitis, or colitis had been diagnosed, steroids were continued or administered in 22 (43.1%). Noncorticosteroid systemic chemotherapy administration within 30 days before episode onset occurred in 39 (76.4%) patients. The median length of time between chemotherapy administration and episode onset was 5.0 (IQR, 3.0 to 9.0) days. Table 2 describes the noncorticosteroid systemic chemotherapeutic drug exposures within 30 days of episode onset in ALL and AML patients.

Clinical presentation at onset of the episode and symptoms experienced during the episode are illustrated in Table 3. Fever was very common and 28 (54.9%) patients were febrile at the onset of the episode. Other common symptoms at presentation were abdominal pain, diarrhea, vomiting, and nausea. There were 3 episodes that presented solely with fever without any GI symptom; all ultimately developed diarrhea, vomiting, or abdominal distension. One episode was asymptomatic throughout the course and was an incidental finding on imaging to follow-up an *Aspergillus* infection. Diarrhea was the most common symptom throughout the episode. Thirty-five (68.6%) patients had fever and neutropenia at any time during the episode. The median length of the episode was 8.0 (IQR, 3.5 to 14.3) days.

The imaging modality used to detect the complication was most commonly ultrasound (30, 58.8%) followed by CT scan (18, 35.3%) and plain radiograph (3, 5.9%). No cases were diagnosed by magnetic resonance imaging. Positive cultures were found in 27 (52.9%) episodes. Seven stool specimens were positive for *Clostridium difficile* toxin, and 5 were positive for Torovirus. Five blood cultures were

TABLE 1. Demographics of Episodes of Enteritis, Typhlitis, and Colitis in Pediatric Acute Leukemia Patients (N = 51)

Characteristics	Value
Male (%)	26 (50.9)
Median age at diagnosis at episode onset in years (IQR)	
ALL	7.0 (4.0 to 13.0)
AML	10.0 (5.0 to 15.0)
Median months to onset of complication from leukemia diagnosis (IQR)	3.0 (1.0 to 9.0)
Type of leukemia (%)	
ALL	36 (70.6)
AML	15 (29.4)
Phase of leukemia therapy (%)	
Prechemotherapy	3 (5.9)
Nonrelapse chemotherapy	45 (88.2)
Relapse chemotherapy	3 (5.9)
Neutropenia (ANC $< 0.5 \times 10^9$/L) at onset of episode (%)	38 (74.5)
Corticosteroid administration within 14 d (%)	25 (49.0)*
Dexamethasone	20 (80)
Prednisone	5 (20)
Hydrocortisone	3 (12)
Chemotherapy administration within 30 d (%)	39 (76.4)
Type of complications	
Enteritis	8 (15.7)
Typhlitis	15 (29.4)
Colitis	19 (37.2)
Enterocolitis	9 (17.6)

*Multiple corticosteroid types could be administered.

ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; IQR, interquartile range.

TABLE 2. Systemic Chemotherapy in the 30 Days Before Episode Onset

Chemotherapy	Acute Lymphoblastic Leukemia (N = 36)	Acute Myeloid Leukemia (N = 15)
Cytarabine	5	12
Vincristine	17	
Daunorubicin	7	5
Mercaptopurine	12	
L-asparaginase	11	
Methotrexate	11	
Etoposide	1	6
Amsacrine		6
Thioguanine	2	3
Cyclophosphamide	3	
Mitoxatrone		1

TABLE 3. Clinical Findings of Typhlitis, Enteritis, and Colitis in Children With Acute Leukemia at Onset of the Episode and at Any Time During the Episode (N = 51)

Symptoms	At Onset of Episode	During the Episode
Fever	28	43
Diarrhea	17	34
Abdominal pain	28	28
Vomiting	16	25
Abdominal distension	4	21
Abdominal tenderness	8	19
Decreased appetite	8	16
Nausea	10	14
Melena	2	12
Tachycardia	3	12
Hypotension	2	7
Hematemesis	1	5
Constipation	3	2
Heartburn	0	2
Headache	1	1

TABLE 4. Treatment of Episodes and Duration of Therapy for Enteritis, Typhlitis, and Colitis in Children With Acute Leukemia

Treatment	No. Episodes (%)	Median Days (IQR)
Nothing to eat or drink	27 (52.9)	7 (4.0 to 9.5)
Total parenteral nutrition	36 (70.5)	15.5 (8.0 to 18.3)
Antibiotics	48 (94.1)	18 (6.0 to 19.0)
Metronidazole	32	
Vancomycin	29	
Tobramycin	25	
Gentamicin	20	
Meropenem	19	
Piperacillin-tazobactam	18	
Piperacillin	14	
Ciprofloxacin	12	
No treatment	3 (5.9)	
Hospital admission	48 (94.1)	
Intensive care unit	7 (13.7)	

IQR indicates interquartile range.

positive for coagulase-negative *Staphylococcus* and 4 were positive for *Escherichia coli*.

Treatment was variable and is summarized in Table 4. Most patients were not permitted to eat or drink and received total parenteral nutrition. Almost all patients were treated with broad-spectrum antibiotics. Almost all patients were admitted to hospital and about 14% were in the intensive care unit. However, 3 patients did not receive any treatment including not permitted to eat or drink, total parenteral nutrition, or antibiotics. Two of these patients had imaging performed for abdominal pain noted during a clinic visit, whereas 1 patient had nausea and abdominal pain during an admission for chemotherapy. All the 3 episodes had symptom resolution with no further complications.

The most common complication was temporally associated sepsis in 7/51 (13.7%) episodes, with 3/51 (5.9%) possibly causally associated with the GI complication, and obstruction in 3/51 (5.9%). One patient required surgery for abscess drainage related to typhlitis which resulted with resolution of the abscess and no further complications.

Two patients died within 2 weeks of episode diagnosis. One 2.5-year-old patient with ALL had completed the consolidation phase. This patient had an unusual course with protracted cytopenia, hepatosplenomegaly, lymphadenopathy, and fever of unknown origin. He was being investigated for disseminated Epstein-Barr virus infection and primary immunodeficiency. Because of these complications, chemotherapy was held and he did not receive any chemotherapy within 30 days of the episode. He died 7 days after colitis onset; the cause of death was not attributed to colitis. The second patient was 4.5 year old with ALL on day 43 of induction, who died 13 days following onset of colitis. The patient had coagulase-negative staphylococci in blood and a ring-enhancing lesion in the brain. This child had persistent fever and progressive respiratory insufficiency thought to be secondary to sepsis. Death was not attributed to colitis.

DISCUSSION

We found that 8.6% of children with acute leukemia experienced enteritis, typhlitis, colitis, or enterocolitis, and these complications were more common in AML compared with ALL. The complications typically occurred early during therapy and may occur before the initiation of chemotherapy. Fever, diarrhea, vomiting, and abdominal pain were the most common symptoms. Infections with GI pathogens and bacteremia were relatively common. Finally, outcomes were good with conservative management. Some patients did not need any therapy.

Our findings are similar to a recent single-center study conducted in the United Kingdom[14] in which the records of 596 children with cancer who underwent radiologic investigations for abdominal pain were reviewed. Typhlitis was found in 11.6% of patients who received chemotherapy. In contrast, in a recent case-control study, El-Matary et al[10] identified 9/410 (2.2%) children with cancer who had typhlitis using the diagnostic criteria of fever, abdominal pain, abdominal wall thickness of >0.4 cm, and neutropenia. The higher prevalence of enteritis, typhlitis, and colitis in our series likely relates to the diagnosis being defined only by radiologic criteria, capture of enteritis, and colitis in addition to typhlitis and restriction to a population of children with acute leukemia rather than all children with cancer. Clinical presentation was similar across studies. McCarville et al[15] reviewed the records of 3171 children diagnosed with radiologic and clinical confirmation of typhlitis. The predominant features in that series were fever (84%), abdominal pain (92%), abdominal tenderness (82%), and diarrhea (72%).

We could not identify the optimal criteria for defining enteritis, typhlitis, colitis, and enterocolitis. We relied purely on radiologic findings as the diagnostic criteria. Although many studies relied upon radiologic confirmation by CT or ultrasound, there are no strict radiologic definitions of typhlitis or enterocolitis.[7,8] A bowel wall thickening of >3 mm using CT or ultrasound has been considered a diagnostic criteria by some investigators.[16,17] Support for this approach comes from a study of neutropenic enterocolitis in which an association between the degree of bowel wall thickness and longer duration of symptoms was observed.[18] Patients with a bowel wall thickness of >10 mm had a significantly higher mortality rate (60%).

Our study demonstrated that the most common corticosteroid administered before the episode was dexamethasone. Previous studies have suggested that

dexamethasone is associated with more toxicity and infectious complications compared with prednisone.[19,20] The pathophysiology behind this association is not clear and may relate to uncertainty in bioequivalence of dosing with respect to both efficacy and toxicity. It is also possible that dexamethasone has unique toxicities with respect to GI integrity and immunity compared with prednisone.[21,22]

Similar to others, we found that conservative management consisting of bowel rest, parenteral nutrition, and broad-spectrum antibiotics was associated with good outcomes.[7] However, because of the observational nature of our study, we do not know whether all of these treatments are necessary. In particular, the observation of 3 untreated patients without complications highlights that some children may not need therapy although accurate identification of such cases remains a challenge. We also demonstrated that some children can safely continue corticosteroid therapy.

The strength of our study is the large number of children with acute leukemia included. However, this study has several limitations. Because of the retrospective nature of the study, symptoms were only known if documented in the patient chart. Therapies were not standardized and thus, we do not know which components of treatment were most important to recovery. Finally, as diagnosis relied upon imaging, our study would not have identified children with these complications who did not undergo radiography.

In conclusion, enteritis, typhlitis, and colitis were common complications in children with ALL and AML. The presence of fever, diarrhea, and abdominal pain are common symptoms and should prompt a consideration of these diagnoses. Patients generally have a good outcome with conservative management. Some patients may not need any therapy. Future research should focus on identifying minimum diagnostic criteria and optimum management strategies for these patients.

REFERENCES

1. Gray TL, Ooi CY, Tran D, et al. Gastrointestinal complications in children with acute myeloid leukemia. *Leuk Lymphoma*. 2010;51:768–777.
2. Wade DS, Nava HR, Douglass HO Jr. Neutropenic enterocolitis. Clinical diagnosis and treatment. *Cancer*. 1992;69:17–23.
3. Davila ML. Neutropenic enterocolitis. *Curr Treat Options Gastroenterol*. 2006;9:249–255.
4. Alioglu B, Avci Z, Ozcay F, et al. Neutropenic enterocolitis in children with acute leukemia or aplastic anemia. *Int J Hematol*. 2007;86:364–368.
5. Katz JA, Wagner ML, Gresik MV, et al. Typhlitis. An 18-year experience and postmortem review. *Cancer*. 1990;65:1041–1047.
6. Bavaro MF. Neutropenic enterocolitis. *Curr Gastroenterol Rep*. 2002;4:297–301.
7. Davila ML. Neutropenic enterocolitis. *Curr Opin Gastroenterol*. 2006;22:44–47.
8. Sloas MM, Flynn PM, Kaste SC, et al. Typhlitis in children with cancer: a 30-year experience. *Clin Infect Dis*. 1993;17:484–490.
9. Fike FB, Mortellaro V, Juang D, et al. Neutropenic colitis in children. *J Surg Res*. 2011;170:73–76.
10. El-Matary W, Soleimani M, Spady D, et al. Typhlitis in children with malignancy: a single center experience. *J Pediatr Hematol Oncol*. 2011;33:e98–e100.
11. Dix D, Cellot S, Price V, et al. Association between corticosteroids and infection, sepsis, and infectious death in pediatric acute myeloid leukemia: results from the Canadian infections in AML Research Group. *Clin Infect Dis*. 2012;55:1608–1614.
12. Pui CH, Mullighan CG, Evans WE, et al. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? *Blood*. 2012;120:1165–1174.
13. Burnett A, Wetzler M, Lowenberg B. Therapeutic advances in acute myeloid leukemia. *J Clin Oncol*. 2011;29:487–494.
14. Mullassery D, Bader A, Battersby AJ, et al. Diagnosis, incidence, and outcomes of suspected typhlitis in oncology patients—experience in a tertiary pediatric surgical center in the United Kingdom. *J Pediatr Surg*. 2009;44:381–385.
15. McCarville MB, Adelman CS, Li C, et al. Typhlitis in childhood cancer. *Cancer*. 2005;104:380–387.
16. Fisher JK. Normal colon wall thickness on CT. *Radiology*. 1982;145:415–418.
17. Vas WG, Seelig R, Mahanta B, et al. Neutropenic colitis: evaluation with computed tomography. *J Comput Tomogr*. 1988;12:211–215.
18. Cartoni C, Dragoni F, Micozzi A, et al. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. *J Clin Oncol*. 2001;19:756–761.
19. Hurwitz CA, Silverman LB, Schorin MA, et al. Substituting dexamethasone for prednisone complicates remission induction in children with acute lymphoblastic leukemia. *Cancer*. 2000;88:1964–1969.
20. Teuffel O, Kuster SP, Hunger SP, et al. Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. *Leukemia*. 2011;25:1232–1238.
21. Urbach DR, Rotstein OD. Typhlitis. *Can J Surg*. 1999;42:415–419.
22. Keidan RD, Fanning J, Gatenby RA, et al. Recurrent typhlitis. A disease resulting from aggressive chemotherapy. *Dis Colon Rectum*. 1989;32:206–209.