

Typhlitis in Childhood Cancer

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BACKGROUND. Typhlitis is increasingly recognized in children undergoing chemotherapy but is poorly characterized. The authors investigated the demographic, clinical, and imaging (ultrasonography and computed tomography [CT] scans) variables related to the diagnosis, risk, and outcome of typhlitis.

METHODS. The authors reviewed the records of patients who had typhlitis (bowel wall thickness ≥ 0.3 cm plus clinical findings) during treatment at St. Jude Children's Research Hospital (Memphis, TN) between 1990 and 2001. They assessed whether duration of typhlitis was related to bowel wall thickness, extent of colonic involvement, ascites, demographics, primary diagnosis, symptoms of typhlitis, or duration of neutropenia. To identify risk factors for typhlitis, the authors compared the demographic data and previous drug therapy of 78 patients who had typhlitis and 1231 identically treated children who did not.

RESULTS. Of 3171 children, 83 (2.6%) developed typhlitis. Frequent symptoms were abdominal pain (91%), fever (84%), abdominal tenderness (82%), and diarrhea (72%). Twelve percent of the patients were not neutropenic. Duration of typhlitis was associated with bowel wall thickness measured by ultrasonography ($n = 68$; $P = 0.05$) but not CT scan ($n = 48$; $P = 0.67$) and was associated with duration of neutropenia ($P = 0.02$), fever ($P = 0.01$), and abdominal tenderness ($P = 0.04$). Age >16 years at cancer diagnosis was the only demographic factor associated with typhlitis ($P = 0.03$). Two patients died of typhlitis.

CONCLUSIONS. Ultrasonography was a useful imaging modality for children with suspected typhlitis. The classic triad of abdominal pain, fever, and neutropenia may be absent. The severity of typhlitis was related to the duration of neutropenia and the presence of fever or abdominal tenderness. *Cancer* 2005;104:380-7.

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Typylitis is a potentially life-threatening necrotizing inflammation of the cecum and colon that was recognized initially as a complication of childhood leukemia but is now known to occur in both adults and children with a variety of hematologic and solid malignancies, in patients with acquired immunodeficiency syndrome, and as a complication of bone marrow transplantation (BMT).¹⁻⁷ Originally, the diagnosis of typhlitis hinged on the clinical triad of neutropenia, abdominal pain, and fever and was supported by indirect evidence of right colon inflammation as evidenced on plain radiography or barium enema.^{1,8,9} Today, ultrasonography (US) and computed tomography (CT) scans allow direct visualization of the bowel wall and its surrounding mesentery.¹⁰⁻¹² Previous investigations have shown that a colon wall thickness > 0.3 cm is abnormal in adult patients when measured by either CT scan or US imaging.¹²⁻¹⁴ However, there has been no systematic evaluation of the optimal imaging modality for the diagnosis and/or management of typhlitis in children treated for cancer.¹⁵⁻²⁰ In our retrospective study, we investigated whether im-

aging findings, clinical findings, and demographic factors are associated with the outcome of typhlitis. A secondary objective of our study was to determine whether demographic variables or previous drug therapy are associated with the risk of typhlitis in these children.

MATERIALS AND METHODS

The current study, performed retrospectively, was approved by the institutional review board at St. Jude Children's Research Hospital (Memphis, TN). Because we had previously performed a study of typhlitis that included children treated between 1962 and 1992, we chose to study only patients from the most recent era beginning with January 1990. We searched our institution's diagnostic imaging database for reports of CT scan and US imaging studies obtained between January 1, 1990 and May 5, 2001 in which the words "typhlitis," "colitis," or both were included in the indication for imaging, the body of the report, or the final impression.⁵ We selected reports containing statements that the patient had typhlitis, colitis, bowel wall thickening, or pericolic inflammatory changes or those containing any other suggestion of typhlitis (e.g., "possible typhlitis" and "typhlitis not readily excluded"). The study radiologist retrospectively measured each patient's colon wall thickness on the corresponding CT scan and US images by using handheld or electronic calipers. Measurements were made on either the transverse or longitudinal images of the bowel segment, whichever best demonstrated the bowel wall. On the basis of previous reports, we defined a colon wall thickness ≥ 0.3 cm on either CT scans or US imaging as abnormal.¹²⁻¹⁴ We defined typhlitis as bowel wall thickness ≥ 0.3 cm accompanied by ≥ 1 clinical sign suggestive of typhlitis (fever, abdominal tenderness, diarrhea, nausea, emesis, abdominal pain, and/or constipation). Only patients who met these criteria (both thickened bowel wall and clinical evidence of typhlitis), who did not have other diagnoses of bowel disease (such as graft vs. host disease, Burkitt lymphoma of bowel, or other), and who underwent imaging examination within 3 days of a clinical diagnosis of typhlitis were included in the study, to ensure that measurements of bowel wall thickness were obtained when typhlitis was clinically suspected.

We recorded the greatest bowel wall thickness measured on the images of the colon. Between 1990 and 1994, CT scans were performed on a Somatom DRH scanner (Siemens, Iselin, NJ) using 93 mA and 125 kV. From 1994 to 2001, either a Somatom Plus S or Plus 4 helical scanner (Siemens) was used with 150 mA and 120 kV and breath-holding when possible. Con-

tiguous axial images were obtained using a 5-mm slice thickness for patients < 5 years and an 8-mm thickness for patients ≥ 5 years. From 1990 to 1997, US imaging was performed with an Acuson model 128 instrument (Mountain View, CA) and from 1997 to 2001 with an Acuson Sequoia instrument. Most US images of the bowel wall were obtained using a high-resolution, 8-MHz, linear transducer. For US examinations that included the entire colon, we recorded the number of abnormal segments of colon among a total of six segments: cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The presence and amount of ascites was evaluated only in US examinations that included images of the splenorenal fossa, Morrison's pouch, and the cul-de-sac or Pouch of Douglas. The amount of ascites was graded as small (pelvic fluid only), moderate (pelvic and upper abdominal fluid), or large (pelvic, upper abdominal, and interloop fluid).

The study investigators trained two undergraduate students and one medical student, who were participating in our institutional Professional Oncology Education Program, to review patient charts and collect clinical data. These students and several oncology nurse practitioners collected all clinical information. The data collection forms were reviewed by the study principal investigator (PI) for completeness and accuracy. When information was missing or unclear, the PI resolved the deficiencies by reviewing the patients' chart. From the patients' medical records, we obtained the following information: demographic data; primary diagnosis; treatment protocol; phase of therapy at the onset of typhlitis; types of chemotherapeutic agents, antibiotics, and steroids received within 1 month before the onset of typhlitis symptoms; and narcotics received within 2 weeks of the onset of symptoms. The duration of typhlitis was defined as the total duration of associated symptoms. We recorded the type and duration of typhlitis symptoms (nausea, emesis, abdominal pain, abdominal tenderness on palpation, constipation, diarrhea, and fever [defined as an oral temperature ≥ 38 °C]) and the absolute neutrophil count (ANC) on the day that symptoms began, the day that typhlitis was diagnosed, and the day of resolution of symptoms. If the patient was neutropenic (ANC < 500 cells/ μ L) on any of these dates, the duration of neutropenia was recorded. Results of blood and stool cultures obtained during the course of typhlitis were recorded, as was clinical management, including any delay in chemotherapy, nothing passed orally (NPO) status, nasogastric tube placement, administration of total parenteral nutrition (TPN), use and type of antibiotics, surgery or other interventional procedure, and outcome of typhlitis.

TABLE 1
Drugs Significantly Associated with the Development of Typhlitis by Univariate Analysis ($P < 0.05$)^a

Drug ^b	<i>P</i> value	OR (drug vs. no drug)	95% CI of OR
G-CSF	< 0.0001	2.70	1.65–4.40
Topotecan	< 0.0001	4.37	2.52–7.59
Atovaquone	0.0002	4.06	1.96–8.43
PEG-L-asparaginase	0.0002	4.06	1.96–8.43
Idarubicin	0.001	3.02	1.56–5.84
Cytosine arabinoside	0.002	0.48	0.30–0.77
Trimethoprim-sulfamethoxazole	0.004	0.46	0.27–0.78
Hydrocortisone	0.04	0.62	0.39–0.99
Methotrexate	0.04	0.62	0.39–0.99
Carboplatin	0.05	1.85	0.99–3.46

95% CI: 95% confidence interval; OR: odds ratio; G-CSF: granulocyte—colony-stimulating factor; PEG: polyethylene glycol.

^a Drugs that were investigated but did not show a significant association with development of typhlitis: ifosfamide, mitoxantrone, irinotecan, cyclophosphamide, vincristine, sodium mercaptoethanesulfonate, cisplatin, mercaptopurine, doxorubicin, prednisone, leucovorin, interferon, interleukin-2, vinblastine, etoposide, dexamethasone, L-asparaginase, 2-chlorodeoxyadenosine, daunorubicin, triethylenethiophosphoramide, *Escherichia coli* asparaginase, Erwinia asparaginase, fludarabine, teniposide, doxorubicin, 6-thioguanine, dacarbazine, recombinant urate oxidase (rasburicase), and nonrecombinant urate oxidase (Uricozyme).

^b Four additional drugs were included in the pair-wise drug synergism analyses ($0.05 < P < 0.10$) were ifosfamide, mitoxantrone, irinotecan, and cyclophosphamide.

Statistical Analysis

All statistical analyses were performed with SAS, version 8.2 (SAS Institute, Cary, NC). The statistical significance level was set at an alpha value of 0.05, unless indicated otherwise. The *P* values are not adjusted for multiple testing. Analyses of the association of factors with the duration of typhlitis were based on the number of episodes of typhlitis rather than on the number of patients. We evaluated demographic data, duration of neutropenia, the presence and number of typhlitis symptoms, US imaging measures of bowel thickness, CT scan measures of bowel thickness, number of colonic segments involved, presence and amount of ascites, and previous drug therapy as possible correlates of the duration of typhlitis. In the univariate analysis, a simple regression model was used for continuous risk factors. For categorical risk factors, we used a one-way analysis of variance and the Wilcoxon rank-sum test. The multiple regression analyses included all factors with $P < 0.10$ in the univariate analysis.

To analyze risk factors for development of typhlitis, we compared the demographics and previous drug therapies of 78 episodes of typhlitis (in 78 patients) with those of 1231 patients treated with the same protocols during the same time period who did not have typhlitis. The 21 other episodes of typhlitis occurred in 14 patients who were enrolled in multiinstitutional trials and for whom we could not obtain comparative data. We performed univariate analyses using the chi-square test and Fisher exact test. We analyzed the association between typhlitis and all chemotherapeutic agents, steroids, and antibiotics received within

30 days of typhlitis and all narcotics received within 2 weeks of typhlitis (Table 1).

We calculated the odds ratio (or exact OR) and 95% confidence intervals for the demographic risk factors in each of 4 broad disease groups: leukemia/lymphoma, brain tumors, other solid tumors, and BMT recipients. Drugs that were found by univariate analysis to have a P value ≤ 0.1 for the development of typhlitis were investigated for potential synergism by using a logistic regression model in which 2 drugs and their potential interaction were risk factors and typhlitis status was the response.

The incidence of typhlitis among all patients with cancer ($n = 3171$) treated at our institution during this era was estimated on the basis of the number of patients rather than on the number of typhlitis episodes. To determine the overall incidence of typhlitis among children treated for cancer, we excluded BMT recipients, who were a heterogeneous group, not all of whom were treated for malignancy. We also determined the incidence of typhlitis in each of the four individual disease groups (leukemia/lymphoma, brain tumors, other solid tumors, and BMT recipients).

RESULTS

Patients and Imaging Studies

Using our criteria of abnormal bowel wall thickness and ≥ 1 clinical sign or symptom of typhlitis, we identified 103 episodes of typhlitis in 94 patients. A complete set of clinical data was available for 99 episodes in 92 patients (66 Caucasians, 18 African Americans, and 8 of other ethnic origin). Forty-two patients

were female and 50 were male. The median age at diagnosis of typhlitis was 10 years (range, 1–22 years). Of the 92 patients, 4 had multiple episodes of typhlitis (3 patients had 2 episodes and 1 patient had 5 episodes). Patients were being treated for acute lymphoblastic leukemia (ALL) ($n = 33$), acute myeloblastic leukemia ($n = 17$), neuroblastoma ($n = 12$), lymphoma ($n = 8$), Ewing-family tumor ($n = 6$), brain tumor ($n = 4$), osteosarcoma ($n = 3$), rhabdomyosarcoma ($n = 3$), Wilms tumor ($n = 2$), and 1 each of 4 other malignancies. Nine patients developed typhlitis during BMT.

Seventy of the 99 episodes were assessed by US imaging and 51 by CT scans (46 by US only, 27 by CT scan only, and 24 by US imaging and CT scan). All the CT scan studies were performed with intravenous contrast. Oral contrast was not used uniformly because it is not required at our institution for evaluation of possible typhlitis. Twenty of the 51 CT scans were of the abdomen only (pelvis not included). In these cases, the cecum and rectum could not be completely evaluated. Sixteen of the 70 US examinations imaged only the cecum or the cecum and ascending colon. Two included the cecum through the sigmoid colon but did not include the rectum. The remaining 52 US evaluations included images of the entire colon, from the cecum through the rectum.

Incidence and Characteristics of Typhlitis

The incidence of typhlitis among all patients with cancer, excluding BMT recipients, was 2.6% (83 of 3171). The incidence was 3.3% (53 of 1603) among patients with leukemia/lymphoma, 2.4% (27 of 1106) among patients with solid tumors, 1.7% (9 of 538) among patients who received BMT, and 0.6% (3 of 462) among patients with brain tumors.

The signs and symptoms of typhlitis in order of frequency were abdominal pain, 91% (90 of 99); fever, 84% (83 of 99); abdominal tenderness, 82% (82 of 99); diarrhea, 72% (71 of 99); emesis, 64% (63 of 99); nausea, 59% (58 of 99); and constipation, 6% (6 of 99). The median duration of symptoms was 13 days (range, 3–61 days). The ANC was known for 97 of the 99 episodes. The median duration of neutropenia, when present, was 8 days (range, 0–42 days). There were 12 episodes of typhlitis (12%) in which the patient was never neutropenic. Blood cultures were obtained in 89 episodes, and 7 of these (8%) were positive. The organisms isolated were *Escherichia coli*, *Klebsiella*, *Enterococcus*, *Staphylococcus*, and *Streptococcus* species. Of 92 stool cultures performed, 18 (20%) were positive for *Clostridium difficile*. Of these 18 specimens, 15 were isolated from neutropenic patients.

Imaging Findings

In the 70 episodes imaged by US, the mean bowel wall thickness was 0.65 cm (range, 0.30–1.34 cm), whereas in the 51 episodes measured by CT scan, the mean bowel wall thickness was 1.4 cm (range, 0.60–3.0 cm) ($P = 0.009$). A paired comparison of US imaging and CT scan bowel wall measurements was possible for 12 episodes, and these measurements were significantly different (US mean, 0.88; standard deviation [SD], 0.30; CT mean, 1.26; SD, 0.32; $P = 0.001$). Bowel wall thickness as measured by US ($n = 68$) was significantly associated with the duration of typhlitis ($P = 0.05$), whereas measurements obtained by CT scan ($n = 48$) were not ($P = 0.67$). The duration of 2 of the 70 episodes evaluated by US imaging and 3 of the 51 episodes evaluated by CT scan was not clinically documented.

The entire colon was evaluated by US imaging in 52 patients. Only the right colon was involved in 31 patients (60%), and other segments were involved in 21 patients (40%) (in 9 patients the right colon was not involved). Forty-nine of the 52 patients had involvement of 1–4 segments, and the duration of typhlitis was similar among these patients (range, 3–51 days; median, 12 days; $P > 0.52$). Three patients had involvement of all six segments. Univariate analysis showed that the latter group had a significantly greater duration of symptoms (16–61 days; median, 28 days) than did those with involvement of 1–4 segments ($P < 0.02$). In the 67 patients with ascites documented by US imaging, neither the presence nor the amount (small, moderate, large) of ascites was significantly associated with the duration of typhlitis symptoms ($P = 0.15$ and $P = 0.42$, respectively).

Management and Outcome

Ninety-five episodes were treated medically with various antibiotics. The combination used most often was vancomycin, tobramycin, ceftazidime, and meropenem. Antibiotic selection at our institution has not changed significantly over the past 10 years. Eighty episodes were treated with bowel rest (NPO), 74 with TPN, and 30 with nasogastric tube placement. Thirty episodes resulted in a delay in chemotherapy. Four episodes were treated surgically, three of these with partial colectomy. The fourth patient underwent laparoscopy for a pneumoperitoneum diagnosed by plain film, but no bowel perforation was identified and no further surgical intervention was performed. These four patients had a mean bowel wall thickness of 0.81 cm (range, 0.54–1.10 cm) on US imaging. Three of these patients were in the induction phase of leukemia treatment and one was in the consolidation phase of

TABLE 2
ORs for Development of Typhlitis in Patients Aged ≤ 16 Years versus > 16 Years

Disease group	Age ^a	No. of patients with typhlitis	Total patients	No. of patients with typhlitis (%)	OR	95% CI for OR	P value
BMT	≤ 16	5	179	2.8	0.2	0.07-0.80	0.02
	> 16	6	55	10.9			
Leukemia/lymph nodes	≤ 16	37	741	5.0	0.4	0.2-0.8	0.02
	> 16	10	84	11.9			
Brain tumor	≤ 16	3	70	4.3	NA	NA	1.00
	> 16	0	3	0.0			
Solid tumor	≤ 16	16	135	11.9	4.7	0.7-202.9	0.1
	> 16	1	36	2.8			
All disease groups	≤ 16	61	1128	5.4	0.5	0.3-0.9	0.03
	> 16	17	178	9.6			

OR: odds ratio; 95% CI: 95% confidence interval; BMT: bone marrow transplantation.

^a The optimal cutoff point of age for predicting typhlitis is 16 years, determined objectively from data for all patients.

lymphoma treatment. Two patients underwent paracentesis. Transudative ascitic fluid was aspirated in one of these two patients, and the other underwent multiple percutaneous abscess drainage procedures.

Two deaths were caused by typhlitis (2% [2 of 92]). One patient had a bowel wall thickness of 3.0 cm as measured on CT scan (US imaging was not used) and the other had a thickness of 0.92 cm as measured on US imaging. One of these patients was in the reinduction phase of treatment for non-Hodgkin lymphoma and the other was in the induction phase of treatment for ALL. One was a 15-year-old boy who died after prolonged neutropenia and multiple percutaneous drainage procedures for an abscess that was probably due to bowel perforation. The other, a 14-year-old boy, succumbed to overwhelming sepsis that resulted in multiorgan failure.

Factors Associated with the Duration of Typhlitis

By univariate analysis, the number of typhlitis symptoms was significantly associated with the duration of typhlitis ($P = 0.0004$), as were individual signs and symptoms: abdominal tenderness on palpation ($P = 0.002$), fever (oral temperature ≥ 38 C; $P = 0.002$), diarrhea ($P = 0.02$), and nausea ($P = 0.03$). The duration of neutropenia, when present, was also highly related to the duration of typhlitis ($P = 0.0006$), as was the bowel wall thickness as measured by US imaging ($P = 0.05$). Of the drugs that were analyzed, only narcotics were significantly associated with the duration of typhlitis by univariate analysis ($P = 0.03$). Also, by univariate analysis, older patients had a longer course of typhlitis ($P = 0.04$).

In a multivariate analysis, factors that remained significantly associated with the duration of typhlitis were duration of neutropenia (the duration of typhlitis

increased 0.3 day per day of neutropenia; $P = 0.02$); US-measured bowel wall thickness (the duration of typhlitis increased 11 days per centimeter of bowel wall thickness; $P = 0.05$); presence of fever (the duration of typhlitis duration increased an average of 14 days with fever; $P = 0.01$); and the presence of abdominal tenderness (the duration of typhlitis increased an average of 4 days with abdominal tenderness; $P = 0.04$).

Factors Associated with Development of Typhlitis

In the overall study group, univariate analysis showed no association between age, race, or gender and the development of typhlitis. Within the subgroups of patients with leukemia/lymphoma or solid tumors, however, age was significantly associated with typhlitis. Patients in the leukemia/lymphoma subgroup who developed typhlitis had a greater mean age than those who did not ($P = 0.03$) and, conversely, in the solid tumor group, a younger mean age than patients who did not develop typhlitis ($P = 0.04$). On the basis of an OR analysis, patients in the overall study group who were > 16 years were significantly more likely to develop typhlitis than those who were younger ($P = 0.03$) (Table 2).

In a univariate analysis of all 39 drugs given to our patients within 1 month of the development of typhlitis, we found 10 to be significantly related to the development of typhlitis ($P < 0.05$) (Table 1). Drug combinations significantly associated with typhlitis by multivariate analysis were granulocyte—colony-stimulating factor and topotecan ($P = 0.0008$), topotecan and idarubicin ($P < 0.0001$), cyclophosphamide and hydrocortisone ($P < 0.0001$), cyclophosphamide and methotrexate ($P < 0.0001$), cyclophosphamide and

carboplatin ($P = 0.03$), and carboplatin and methotrexate ($P = 0.04$).

DISCUSSION

Sloas et al.⁵ of our institution previously reported on the management of typhlitis in 24 children treated for cancer between 1962 and 1992. These investigators defined typhlitis by subjective criteria (right colon inflammation on CT scan, US imaging, plain radiography, or barium enema, plus clinical findings) and found a 0.35% incidence among patients with childhood cancer during that era. We found an apparent increase in the incidence to 2.6% (81 of 3171) among children treated for cancer at our institution since 1990. We attribute this increase, at least in part, to improved detection of typhlitis with cross-sectional imaging and an increased use of CT scan and US imaging to evaluate these patients. Unlike previous studies, our study used specific, quantifiable bowel wall measurements, obtained by CT scan or US imaging, to reexamine the classic features associated with typhlitis. When we examined all patients who had a bowel wall thickness ≥ 0.3 cm in combination with typhlitis-associated clinical findings, we found that the classic triad of abdominal pain, fever, and neutropenia was absent in a considerable number of our patients: abdominal pain was absent in 9%, neutropenia in 12%, and fever in 16%. Furthermore, although typhlitis has classically been described as involving the cecum and right colon, we found the transverse and descending colon or the rectum to be involved in 40% of our patients. Our results point to the need for a heightened awareness of the possibility of typhlitis in pediatric oncology patients even in the absence of typical clinical findings.

In our study, the only demographic variable associated with the development of typhlitis was age. Patients with leukemia or lymphoma who developed typhlitis were on average older than those who did not, whereas in the solid tumor group, younger patients were more likely to develop typhlitis. In the overall study group, patients > 16 years were at significantly greater risk than younger patients. It is also noteworthy that the 2 patients in our cohort who died of complications of typhlitis were in the leukemia/lymphoma group and were slightly older (14 years and 15 years, respectively) than the mean age of that group (10 years). By univariate analysis, we found that the duration of typhlitis significantly increased with increasing age ($P = 0.04$). These findings suggest not only that older patients are at greater risk of typhlitis but also that they may not respond as well as younger patients to its management.

The development of typhlitis has historically been

attributed to previous drug therapy. Our findings suggest that several drugs can affect the development of typhlitis in children. Some of these (e.g., cytosine arabinoside, methotrexate, and irinotecan) are known to be associated with oral mucositis or gastrointestinal toxicity, including diarrhea. However, the multiagent nature of treatment regimens makes it difficult to definitively determine the contribution of a single agent or drug pair to the risk of typhlitis. The potential interaction of chemotherapeutic drugs with each other and with nonchemotherapeutic drugs cannot be fully addressed by our retrospective study. Larger, prospective clinical trials are necessary to fully evaluate and understand the effects of age, drugs, and other variables on the development of typhlitis in children.

The imaging and clinical features that we found to be significantly associated with the duration of typhlitis were duration of neutropenia, bowel wall thickness as measured by US imaging, fever, and abdominal tenderness. Importantly, bowel wall thickness measured by US imaging was significantly related to the duration of typhlitis, whereas thickness as measured by CT scan was not. Our goal was to determine whether imaging findings are associated with the duration of typhlitis. Therefore, we recorded only the greatest bowel wall thickness obtained by both imaging modalities currently in clinical use. Because we did not seek to determine the agreement between these two modalities we did not directly compare CT scan and US imaging measurements of the same segments of bowel. However, for the 12 cases in which a direct comparison could be made, the measurements were significantly different. A potential limitation of our study is that CT scans were performed without an orally administered contrast agent, which might have improved identification of the mucosal surface of the colon and allowed more precise measurement of the bowel wall, especially when the bowel was collapsed. However, the oral contrast agent could not have overcome the problem of intraluminal contents that adhere to the wall of the colon and preclude visualization of the mucosal surface (Fig. 1). An orally administered contrast agent is not mandated for CT scans performed for suspected typhlitis at our institution, because the children being examined are often nauseated and unable to tolerate an adequate quantity of these agents. Other limitations of our study include the retrospective design and the potential bias of the study radiologist who was aware of the preexisting radiology reports at the time that the bowel wall was remeasured for study purposes. Also, it is possible that the sonographer did not include the area of greatest bowel wall thickening in the images that were recorded. Finally, our data should be interpreted with



FIGURE 1. Computed tomographic scan of the abdomen shows thickening of the hepatic flexure of the colon (arrowheads). Intraluminal contents (straight arrow) and surrounding inflammatory changes (curved arrow) which make accurate measurement of the bowel wall difficult.

caution because adjustment was not made for multiple statistical testing.

The difference in the mean bowel wall measurements that we found between CT scans and US imaging may be explained by factors that can impair or facilitate imaging of the bowel by these methods. On CT scan images of the bowel, not only do intraluminal contents make identification of the mucosal surface difficult, but surrounding inflammatory changes may limit identification of the serosal surface as well (Fig. 1). It is possible that in such cases, CT scan measurements overestimate the thickness of the bowel wall. By contrast, a high-resolution US imaging probe often allows visualization of the individual layers of the bowel wall as alternating hyperechoic and hypoechoic layers (the “gut signature”) (Fig. 2).²¹ Therefore, US imaging may allow a more accurate bowel wall measurement. At our institution, the screening examination of choice for typhlitis is US evaluation of the entire colon using a high-resolution probe.

US offers a number of significant advantages over the CT scan. Perhaps, most importantly, US does not expose the patient to the potential harmful effects of ionizing radiation, an issue of considerable concern in the pediatric population. Further, it is well tolerated, does not require sedation, can be performed at the bedside, and is less expensive than a CT scan. However, a drawback of US imaging is its inability to detect free intraperitoneal air, a complication of typhlitis that is rare in children and is caused by bowel perforation. If perforation is a clinical concern, either plain radiography or a CT scan should be performed. The decision to perform a CT scan or US imaging to evaluate patients with sus-



FIGURE 2. Transverse ultrasound image of the cecum demonstrates the gut signature as alternating hyperechoic and hypoechoic layers corresponding to the five layers of the bowel wall. Electronic calipers placed on the mucosal and serosal surfaces allow accurate measurement of bowel wall thickness (0.50 cm).

pected typhlitis will be governed by institutional practice, sonographer experience, and the radiologist’s confidence level with these modalities.

Recently, Cartoni et al.,²² in their study of typhlitis in 88 adults with leukemia, used an US measurement of 0.5 cm as the threshold to define abnormal colon wall thickness. These investigators found that the mortality rate was 60% (12 of 20) among adult patients who had bowel wall thickness > 1.0 cm and 4.2% (1 of 24) when the bowel wall measured ≤ 1.0 cm by US imaging. On the basis of other reports, we used the lower threshold of ≥ 0.3 cm plus the presence of clinical signs or symptoms to define typhlitis.^{12–14} Previous investigators at our institution found a typhlitis-associated mortality rate of 8.2% among children treated for cancer between 1962 and 1992. We found a much lower associated mortality rate of 2.2% (2 of 90) among pediatric oncology patients treated since 1990. Because only two patients in our cohort died of complications of typhlitis, we were not able to determine whether bowel wall thickness is associated with mortality. However, of 8 patients with bowel wall thickness ≥ 1.0 cm by US imaging, 7 had resolution of typhlitis with medical management alone. Although the eighth patient developed a pneumoperitoneum and underwent exploratory laparoscopy, no bowel perforation was identified and no further surgical intervention was required. Of 3 patients who required surgical intervention for complications of typhlitis, only 1 had a bowel wall thickness > 1.0 cm on US imaging. One of the 2 patients who died of complications of typhlitis had a bowel wall thickness > 1.0 cm by CT scan but did not undergo US imaging.

It is possible that our use, both in the current

study and in our clinical practice, of a threshold lower than that used by Cartoni et al.²² has resulted in earlier diagnosis and better control of this complication in our pediatric patients. However, our findings also suggest that children < 16 years respond more favorably than older children and adults to the medical management of typhlitis, even when there is significant bowel wall thickening. It is likely that the application of strict, quantitative imaging criteria together with the use of clinical signs and improved antibiotic therapy have reduced the rate of typhlitis-associated mortality from that previously observed at our institution and reported in adult studies.

In conclusion, our study shows that even in the absence of typical clinical findings, the diagnosis of typhlitis can be made when clinical suspicion is confirmed with imaging. We routinely use US imaging rather than CT scan to evaluate children with suspected typhlitis because we believe that US imaging is superior to a CT scan for this diagnosis not only because it does not require ionizing radiation, but because US bowel wall measurement is significantly associated with the outcome of typhlitis, whereas a CT scan measurement is not. The US examination should include representative images and measurements of the entire colon from the level of the cecum to the rectum.

Although US imaging appears to be superior to a CT scan for the evaluation of patients with suspected typhlitis, the choice of imaging modality will depend on the institutional experience because US imaging is operator dependent and a CT scan may be simpler to perform. We found that when typhlitis is confirmed by US imaging and clinical findings, the early use of broad-spectrum antibiotics and bowel rest should control this complication in most patients. The bowel wall thickness on US images, the duration of neutropenia, the patient's age, and the patient's clinical signs are useful in tailoring the management of typhlitis in individual pediatric patients with cancer. Additional prospective clinical trials with larger cohorts of patients are needed to fully elucidate the impact of individual drugs and other variables on the development of typhlitis in children as well as the individual clinical features that are predictive of this complication.

REFERENCES

1. Wagner ML, Rosenberg HS, Fernbach DJ, et al. Typhlitis: a complication of leukemia in childhood. *AJR Am J Roentgenol.* 1970;2:341-350.
2. Sherman NJ, Woolley MM. The ileocecal syndrome in acute childhood leukemia. *Arch Surg.* 1973;107:39-42.
3. Katz JA, Wagner ML, Gresik MV, et al. An 18-year experience and postmortem review. *Cancer.* 1990;65:1041-1047.
4. Wade DS, Nava HR, Douglass HO Jr. Neutropenic enterocolitis. Clinical diagnosis and treatment. *Cancer.* 1992;69:17-23.
5. Sloas MM, Flynn PM, Kaste SC, et al. Typhlitis in children with cancer: a 30-year experience. *Clin Infect Dis.* 1993;17:484-489.
6. Ettinghausen SE. Collagenous colitis, eosinophilic colitis, and neutropenic colitis. *Surg Clin North Am.* 1993;73:993-1016.
7. Avigan D, Richardson P, Elias A, et al. Neutropenic enterocolitis as a complication of high dose chemotherapy with stem cell rescue in patients with solid tumors: a case series with a review of the literature. *Cancer.* 1998;83:409-414.
8. Del Fava RL, Cronin TG Jr. Typhlitis complicating leukemia in an adult: barium enema findings. *AJR Am J Roentgenol.* 1977;129:347-348.
9. Abramson SJ, Berdon WE, Baker DH. Childhood typhlitis: its increasing association with acute myelogenous leukemia. *Pediatr Radiol.* 1983;146:61-64.
10. Merine DS, Fishman EK, Jones B, et al. Right lower quadrant pain in the immunocompromised patient: CT findings in 10 cases. *AJR Am J Roentgenol.* 1987;149:1177-1179.
11. Adams GW, Rauch RF, Kelvin FM, et al. CT detection of typhlitis. *J Comput Assist Tomogr.* 1985;9:363-365.
12. Teefey SA, Montana MA, Goldfogel GA, et al. Sonographic diagnosis of neutropenic typhlitis. *AJR Am J Roentgenol.* 1987;149:731-733.
13. Horton KM, Corl FM, Fishman EK. CT evaluation of the colon: inflammatory disease. *Radiographics.* 2000;20:399-418.
14. Fisher JK. Abnormal colonic wall thickening on computed tomography. *J Comput Assist Tomogr.* 1983;7:90-97.
15. McNamara MJ, Chalmers AG, Morgan M, et al. Typhlitis in acute childhood leukaemia: radiological features. *Clin Radiol.* 1986;37:83-86.
16. Gootenberg JE, Abbondanzo SL. Rapid diagnosis of neutropenic enterocolitis (typhlitis) by ultrasonography. *Am J Pediatr Hematol Oncol.* 1987;9:222-227.
17. Alexander JE, Williamson SL, Seibert JJ, et al. The ultrasonographic diagnosis of typhlitis (neutropenic colitis). *Pediatr Radiol.* 1988;18:200-204.
18. Merine D, Nussbaum AR, Fishman EK, et al. Sonographic observations in a patient with typhlitis. *Clin Pediatr.* 1989;28:377-379.
19. Kamal M, Wilkinson AG, Gibson B. Radiological features of fungal typhlitis complicating acute lymphoblastic leukaemia. *Pediatr Radiol.* 1997;27:18-19.
20. Kaste SC, Flynn PM, Furman WL. Acute lymphoblastic leukemia presenting with typhlitis. *Med Pediatr Oncol.* 1997;28:209-212.
21. Rumack CM, Wilson SR, Charboneau JW. Diagnostic ultrasound. 2nd ed. St. Louis, MO: Mosby, 1998.
22. 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.