

## Sonographic signs of neutropenic enterocolitis

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### Abstract

**AIM:** To investigate the sonographic features at time of diagnosis and follow-up in patients with neutropenic enterocolitis.

**METHODS:** The sonographic findings in 14 patients with neutropenic enterocolitis were described and evaluated regarding symptoms and clinical outcome.

**RESULTS:** In all patients with neutropenic enterocolitis, the ileocecal region was involved with wall thickening >10 mm. A transmural inflammatory pattern, hypervascularity of the thickened bowel wall and free abdominal fluid were the common findings. The sonographically revealed thickness of the bowel wall was associated with lethal outcome ( $P < 0.03$ ). In the 11 surviving patients, the improvement of clinical symptoms was accompanied by progressive reduction of intestinal wall thickness.

**CONCLUSION:** High-end sonography of the bowel is a helpful tool for diagnosis, assessment of prognosis and follow-up of patients with neutropenic enterocolitis. The ultrasonographically revealed bowel thickness reflects the severity and the course of the disease, and seems to be predictive for the clinical outcome.

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**Key words:** Neutropenia; Bowel wall thickness; Ultrasonography

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### INTRODUCTION

Neutropenic colitis, also termed necrotizing enterocolitis or neutropenic typhlitis (Greek: *typhlon* = cecum), was first described by Cooke in 1930<sup>[1,2]</sup>. It is a necrotizing inflammatory disease of the ileocecal region. The pathogenesis is not entirely known, although bacterial infection of damaged mucosa, often with superinfection, e.g., *clostridia* (especially *Clostridium septicum*) and other bacteria, seems to play an important role<sup>[3-7]</sup>.

Neutropenic colitis is a complication of severe neutropenia, often in patients after (high-dose) chemotherapy. Although most reported cases occurs in patients, who received chemotherapy for leukemia or solid tumors, it has been seen in a variety of other conditions, e.g. aplastic anemia, benign cyclic neutropenia, AIDS and allergic or toxic agranulocytosis as well<sup>[8,9]</sup>.

Neutropenic colitis has a wide spectrum of severity, ranging from mild gastrointestinal symptoms to peritonism and sepsis with lethal outcome. As abdominal discomfort and diarrhea are common in patients receiving chemotherapy, the prevalence of this condition is not well known. The finding of thickened bowel wall, in association with a clinical syndrome characterized by fever, diarrhea, and abdominal pain, confirms the clinical diagnosis of neutropenic enterocolitis in neutropenic patients who have completed intensive chemotherapy.

A Recent report<sup>[10]</sup> has shown that sonographic findings might be helpful in this condition and can be easily repeated in these severely ill patients. Herein we report on 14 neutropenic patients with sonographic features of neutropenic colitis, evaluating the clinical findings, sonographic features and outcome of these patients and reviewing of the literature regarding this condition.

### MATERIALS AND METHODS

#### Patients

We reviewed the clinical records of 14 neutropenic patients (absolute neutrophil count  $< 500/\text{mm}^3$ ) with sonographic signs of neutropenic colitis who presented at the Department of Gastroenterology for sonography during a period of three years. The patients consisted of 8 men and 6 women [age = 48 (22-66) years; body mass index = 23.5 (17.8-28.2)  $\text{kg}/\text{m}^2$ ; weight loss = 3.5 (0-14) kg]. Neutropenia occurred due to intensive chemotherapy in 13 patients (six patients with non-Hodgkin lymphoma, four patients with acute lymphatic leukemia, two patients with acute lymphoblastic leukemia, and one patient with chronic myeloid leukemia). One patient had allopurinol-in-

**Table 1** Frequency of clinical symptoms, laboratory, and microbiological findings in 14 patients with neutropenic enterocolitis.

Clinical symptoms	Frequency
Abdominal pain	14 (100%)
Fever	14 (100%)
Diarrhea	10 (71.4%)
Hypotension	3 (21.4%)
Right lower quadrant pain	10 (71.4%)
Peritonism	6 (42.9%)
Abdominal distension	10 (71.4%)
Vomiting	9 (64.3%)
Bloody diarrhea	6 (42.9%)
Ileus	6 (42.9%)
Reduced clinical condition	12 (85.7%)
Palpable resistance	7 (50%)
Daily bowel movements	4 (1-7)
Laboratory findings	
C-reactive protein [mg/dL]	26.3 (6.6-64.0)
Haemoglobin [g/dL]	9.1 (6.9-11.4)
Haematocrit [%]	25.8 (21.1-33.9)
Platelets [/nL]	33 (19-43)
Microbiological findings	6 patients with negative cultures 3 patients with <i>Streptococcus epidermidis</i> in blood culture 2 patients with <i>Enterococcus</i> in blood culture 1 patient with <i>Pseudomonas aeruginosa</i> in blood culture 1 patient with <i>Streptococcus</i> , <i>Enterobacteriaceae</i> , <i>Enterococcus</i> , and <i>Escherichia coli</i> in blood culture 1 patient <sup>1</sup> with <i>Candida albicans</i> in bronchio-alveolar lavage, <i>Candida glabrata</i> and <i>Enterococcus faecium</i> in blood culture, <i>Pseudomonas aeruginosa</i> and <i>Candida albicans</i> in urine culture

<sup>1</sup>Patients did not survive.

duced severe neutropenia. All patients were monitored by performing blood and feces cultures. In addition, sputum, nasopharynx, oropharynx, and external-genital cultures were performed when appropriate. Clinical symptoms, chemotherapeutic and antibiotic agents, and microbiological findings were documented and evaluated in relation to sonographic results and outcome.

### Examination technique

Real-time ultrasound scanning of the bowel wall was performed using a 7 MHz linear transducer (Siemens Elegra, Erlangen, Germany or Acuson Sequoia, Siemens Erlangen, Germany). Bowel wall thickness (outer wall to luminal surface) was measured at terminal ileum, cecum, sigmoid colon, and small intestine by high resolution sonography with moderate pressure as previously described<sup>[11,12]</sup>. A thickness of less than 2 mm was considered normal, more than 2 mm and less than 5 mm was considered unspecific bowel wall thickening, and a thickness of more than 5 mm was considered abnormal confirming the diagnosis of neutropenic enterocolitis. The morphology and the five layers of ileum and colon were evaluated assessing a mucosal or transmural pattern of inflammation. Bowel wall vascularity was examined by color Doppler imaging and graded as

ischemic (no flow pattern), normal or hypervascular<sup>[12,13]</sup> as recently shown for graft *versus* host disease (GvHD) as a prognostic factor.

### Statistical analysis

Data were expressed as median and range.  $\chi^2$  test was used to evaluate differences in sonographic findings (ascites, bowel wall vascularity, extension of inflammation), symptom presentation and death rate. Differences in bowel thickness and laboratory data between surviving and non-surviving patients were analyzed using the nonparametric Wilcoxon rank sum two-tailed test. 95% confidence intervals were calculated.  $P < 0.05$  was considered statistically significant.

## RESULTS

The clinical symptoms and laboratory findings of the 14 neutropenic patients with sonographic signs of neutropenic enterocolitis are mentioned in Table 1.

In all 14 patients, treatment consisted of multiple antibiotic therapy. The antibiotic treatment usually started using beta-lactamic combined with aminoglycoside. Vancomycin was added if the fever persisted. In 9 cases, antimycotic agents were administered due to suspected invasive fungaemia.

G-CSF was given in 8 patients to shorten the time of neutropenia. Supportive treatment consisted of bowel wall rest and total parenteral nutrition. Packed RBC's, platelets, and albumin were infused when appropriate.

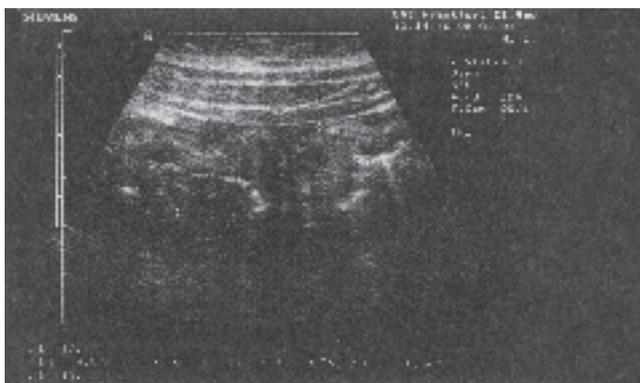
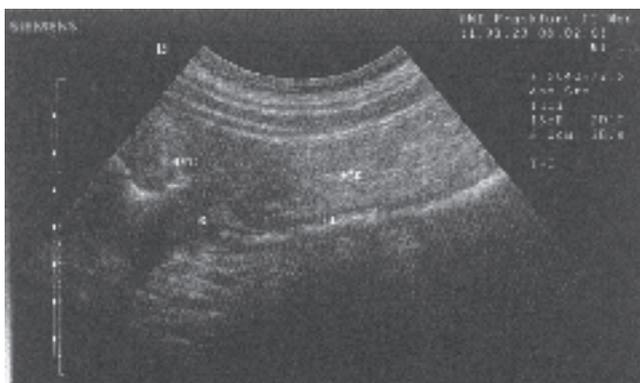
Intensive chemotherapies, according to the protocols for the underlying malignant diseases, preceded in 13 patients with the onset of symptoms. The chemotherapies were intended to induce (first) complete remission. In all protocols, drugs were administered in daily doses which are known to be toxic for the gastrointestinal mucosa (500 to 3 000 mg/m<sup>2</sup> high dose cytarabine instead of the standard dose of 100 to 200 mg/m<sup>2</sup>, 100 to 200 mg/m<sup>2</sup> etoposide, 10 to 12 mg/m<sup>2</sup> idarubicin, 10 mg/m<sup>2</sup> mitoxantrone, 60 mg/m<sup>2</sup> daunorubicin, 50 mg/m<sup>2</sup> doxorubicin, or 500 to 3 000 mg/m<sup>2</sup> methotrexate).

Three patients died due to sepsis with multiorgan failure. High C-reactive protein ( $P < 0.001$ ) and the sonographically revealed significantly thickened bowel wall ( $P < 0.03$ ) were associated with the lethal outcome.

The surviving 11 patients recovered from neutropenic enterocolitis. The reduction of abdominal symptoms was accompanied by progressive decrease in intestinal mural thickening in follow-up ultrasound examinations. The sonographic findings in 14 patients with neutropenic colitis are summarized in Table 2. Nearly all patients with neutropenic enterocolitis (92.9%, 13/14) presented a transmural inflammatory pattern of the thickened bowel wall. In all patients, the ileocecal region was involved. The thickness of the inflamed bowel section was at least 10 mm. Hypervascularity on color Doppler imaging and the detection of small amounts of free fluid in the abdomen were documented in the majority of patients with neutropenic enterocolitis. Free abdominal air, fistula or abscesses were not observed in our collective. Typical sonographic charac-

**Table 2** Sonographic findings in 14 patients with neutropenic enterocolitis (frequency of findings or median and ranges are given)

Localisation of inflammation	13 in ileocecal region 1 in ileocecal region and colon transversum
Pattern of inflammation	10 transmural 4 mural
Longitudinal extension of inflammation	5-15 cm in all 14 patients
Bowel wall thickening (mm)	12 (10-20)
Ascites	11 of 14
Hypervascularisation	84.61% (13/14)
Fistula	None
Abscess	None

**Figure 1** Characteristic sonographic findings in neutropenic enterocolitis showing asymmetric, echogenic (between markers) and inhomogeneous bowel wall thickening with areas of hypoechoogenicity (between markers).**Figure 2** Asymmetric and inhomogeneous wall thickening, transmural inflammatory reaction in a patient with neutropenic enterocolitis (NPC). The ileocecal valve of Bauhin (B) and the terminal ileum (not affected, TI) are also indicated. Typically, the surrounding omentum shows echogenic reaction (UGR).

teristics in neutropenic enterocolitis are depicted in Figures 1 and 2.

## DISCUSSION

### Epidemiology

The incidence of neutropenic colitis in cytopenia patients ranges from 2.6<sup>[14]</sup> to 33%<sup>[15]</sup> with a pooled incidence rate from 21 studies of 5.3%<sup>[16]</sup>. With the use of more intensive

chemotherapy regimens, especially after autologous and allogeneic stem-cell transplantations, a higher incidence of neutropenic colitis should be expected. The tendency to relapse has been reported to range from 27% to 83%<sup>[17]</sup>.

### Etiology and pathogenesis

Various factors are in discussion to play a role in the pathogenesis of neutropenic colitis. Apart from direct damage to the mucosa by leukemic or lymphatic infiltrates, toxic effects of chemotherapeutic agents contribute to the pathogenesis. The first step is the severe initial damage to the mucosa caused by release of pro-inflammatory cytokines from macrophages and monocytes, followed by a near complete arrest of the cell cycle, inhibition of mechanisms of repair and finally apoptosis. Several cytotoxic agents and combinations of chemotherapeutic agents, depending on their dose, have a high toxic potential<sup>[11,17-19]</sup>.

According to the literature, neutropenic colitis is mainly localized in the ileocecal region, although other parts of the bowel can be affected as well. The high concentration of lymphatic tissue in this area and the special anatomy of the terminal branches of the superior mesenteric artery with consecutive less vascular perfusion may contribute to ischemia. The cecum represents an area of relative stasis of bowel content and is easily distensible, causing a high intramural pressure and insufficient blood supply<sup>[7]</sup>.

The role of bacteria and viruses in the pathogenesis of neutropenic colitis has been discussed controversially in the literature. Infection is thought to be largely secondary (e.g., Clostridial bacteria, especially *Clostridium septicum*). Abnormal bacterial colonisation in connection with the neurotoxic effects of vincristine is thought to contribute to the pathomechanism<sup>[20]</sup>. Although *Clostridium septicum* is found in stool cultures of healthy persons only in 2%, it is detectable in a higher percentage in the ileocecal region, especially in the healthy appendix (63%)<sup>[2]</sup>. Clostridia produce a number of tissue degrading enzymes, which may play a significant role in the development of mucosal injury. In the absence of neutrophil granulocytes which produce toxin degrading proteases, an important defence mechanism is missing. Similar pathomechanisms have been described for other Clostridial species (e.g., *Clostridium perfringens*, *paraperfringens* and *Clostridium tertium*).

### Symptoms

The initial symptoms are not specific and usually occur during the nadir with rapid improvement after neutrophil recovery. The symptoms very often consist of a combination of crampy abdominal pain (subileus symptoms), a palpable mass and tenderness in the right lower quadrant with rebound tenderness (a sign of peritonism) and fever. Diarrhea, occasionally bloody diarrhea, may be present, but the leading symptom is abdominal pain in the right lower quadrant. Sepsis and signs of perforation with peritonism, as well as profuse bleeding are life-threatening complications.

A localized tenderness with rebound tenderness above the affected area is very often the only clinical sign in these severely ill patients. Recurrent abdominal pain, caused by mechanical obstruction of the ileocecal area, indicates

Table 3 Clinical features of neutropenic colitis (review of the literature)

Abdominal pain	Fever	Diarrhea	Peritonism	Bloody diarrhea	Number of patients	References
+	+	+			3	Abbasoglu <i>et al.</i> [27]
+	+	+			3	Alexander <i>et al.</i> [22]
+					2	Alt <i>et al.</i> [7]
+			+		2	Avigan <i>et al.</i> [5]
+		+	+		6	Benz <i>et al.</i> [17]
+	+	+		(+)	3	Boggio <i>et al.</i> [29]
+	+	+			1	Capria <i>et al.</i> [30]
+	+	+	(+)	(+)	44	Cartoni <i>et al.</i> [10]
+		+		+	1	Coleman <i>et al.</i> [31]
+		+			1	Dudiak <i>et al.</i> [9]
+	+				4	Frick <i>et al.</i> [23]
			+		1	Frankel <i>et al.</i> [32]
+	+	+		+	2	Furonaka <i>et al.</i> [19]
+		+			2	Gandy <i>et al.</i> [25]
+	+	+		+	1	Glass-Royal <i>et al.</i> [33]
+	+	+	(+)	(+)	18	Gomez <i>et al.</i> [34]
+	+		+		3	Hammerstrom <i>et al.</i> [35]
+	+				1	Hopkins <i>et al.</i> [36]
+	+	+			9	Hsu <i>et al.</i> [37]
+	(+)	(+)	(+)	(+)	11	Jain <i>et al.</i> [38]
+	+				3	Koea <i>et al.</i> [26]
+	+	+	+	+	5	Koroussis <i>et al.</i> [18]
+	+	+			1	Kronawitter <i>et al.</i> [39]
+	+				2	Lev <i>et al.</i> [20]
+	+	+			4	Mulholland <i>et al.</i> [40]
	+				2	Newbold <i>et al.</i> [6]
+	+	+	+		1	Rexroth <i>et al.</i> [2]
+	+				1	Rodgers <i>et al.</i> [41]
+	+	(+)	(+)	(+)	25	Shamberger <i>et al.</i> [15]
+	+				1	Shandera <i>et al.</i> [42]
+					14	Song <i>et al.</i> [43]
+	+	+	+		1	Thaler <i>et al.</i> [44]
+	+	+			1	Verbeeck <i>et al.</i> [45]
+	+	+	(+)	(+)	6	Wach <i>et al.</i> [28]
+	+		(+)		22	Wade <i>et al.</i> [46]
+	+		+		2	Weinberger <i>et al.</i> [47]

symptoms of ileus with dilatation of the bowel loops of the small intestine. Other more unspecific symptoms like abdominal distension, nausea, vomiting and meteorism *etc.* have also been described in the literature. Table 3 summarizes the symptoms mentioned in 36 case reports (including 209 patients overall). Abdominal pain was described in nearly all patients (98%), followed by fever in 87%, diarrhea in 61%, and peritonism in 30% of the patients with neutropenic enterocolitis (Table 3).

### Differential diagnosis

Appendicitis is very often the main differential diagnosis. Because of the high perioperative mortality in these patients, the operative approach should be avoided. The perioperative mortality rate in the literature varies widely and ranges between 0%-100%, depending on the case reports or the studies<sup>[1]</sup>. Besides appendicitis, other acute or chronic inflammatory diseases of the ileocecal area, e.g., bacterial ileocecalitis, cytomegalovirus (CMV) infection, Crohn's disease, pseudomembranous and ischemic colitis, should be taken into account. In patients after allogeneic stem-cell transplantation, one has to think of graft *versus* host disease, although this usually occurs after engraftment.

A neoplastic (lymphocytic leukemia) infiltration of the ileocecal region must be excluded especially in case of a

palpable mass in this area. In pancytopenic patients, one has also to think of an acute hemorrhage into the mucosal wall.

### Diagnosis

Besides the routine laboratory and microbiological tests for bacteria (e.g., *Clostridium difficile* and toxin) viruses and parasites, one should perform the CMV PCR- and CMV early (pp65) antigen-test. The endoscopic approach during pancytopenia is relatively contraindicated, although the definitive diagnosis of CMV-colitis, leukemic or neoplastic infiltrates can be definitively diagnosed only by histological examination.

**High resolution sonography** The characteristic sonographic features of neutropenic colitis are echogenic, asymmetric thickening of the mucosal wall<sup>[10,21,22]</sup> with transmural inflammatory reaction and areas of different echogenicity caused by edema, necrosis and/or circumscribed hemorrhages. Intramural air suggests an infection with anaerobic bacteria. Pericolonic fluid is a sign of a (possible) perforation.

Sonography may demonstrate free abdominal air which is usually right sided, e.g. perihepatic. In advanced disease with catastrophic prognosis, air bubbles in the vena porta may be demonstrated, as seen after application of contrast enhancing agents. Another feature may be pneumatosis cystoides intestinalis, as seen in premature infants with

necrotizing enterocolitis. It is mentionable that in these patients, the hydrogen content of the expiration air is massively increased.

**Computed tomography** Although most authors favor the computed tomography as the most sensitive diagnostic tool to diagnose neutropenic colitis<sup>[23,24]</sup>, high resolution sonography is of advantage. In contrast to CT, sonography can be easily performed and repeated (e.g., at the bedside) even in severely ill patients in intensive care or transplantation units.

**Abdominal X-ray** The findings on abdominal X-ray are often nonspecific and may show small bowel ileus, an ill-defined soft tissue density in the region of the cecum, thickened air-filled loops of bowel or signs of pneumatosis intestinalis.

**Barium enema** As barium enema should not be performed, when perforation is expected, and as it increases the pressure in the ileocecal area and therefore may produce ischemia, this diagnostic tool is relatively contraindicated to diagnose neutropenic colitis.

**Enteroclysis** The oral application of radiopaque medium, such as the barium enema, is not without risk, as large amounts of contrast medium increase the pressure and the risk of perforation. This method is, therefore, also relatively contraindicated.

**Other methods** Other methods, such as gallium-scintigraphy, or indium-labeled granulocytes, are not routinely used in clinical practice. In certain circumstances, they might give additional informations<sup>[25]</sup>.

**Histopathology** The macroscopic findings are dilated, edematous thickened bowel wall with areas of hemorrhage and necrosis. The characteristic histological lesions are mucosal ulceration without accompanying inflammatory response, which might progress to gangrene. Often thrombosis of intestinal veins and extensive macroscopic thrombosis of adjacent mesenteric veins in some cases are present, which are probably caused by endotoxins. The main histologic features of neutropenic colitis are edema, hemorrhage and necrosis. Inflammatory, fungal, leukemic or neoplastic infiltrates, as well as frank perforation are occasionally seen.

### Therapy

The conservative approach, total parenteral nutrition, antibiotic and antifungal treatment should be placed in forefront. As neutropenia represents the "sine qua non" of neutropenic colitis, time of neutropenia should be shortened, e.g. with granulocyte-colony-stimulating factors or granulocyte transfusions<sup>[7, 25]</sup>.

As the perioperative mortality in these patients is very high, surgical intervention should be placed into the background. On the other hand, the right time for surgery should not be missed, therefore, a close clinical evaluation of the patient by physicians and surgeons is mandatory. The indications for surgical intervention are the same as in immunocompetent patients: Persistent gastrointestinal bleeding after resolution of neutropenia and thrombocytopenia and correction of clotting abnormalities, evidence of intraperitoneal perforation, clinical deterioration requiring support with vasopressors, or large volumes of fluid, suggesting uncontrolled

sepsis<sup>[7,26]</sup>.

Selective or complete bowel decontamination as well as prophylactic granulocyte transfusions, especially in patients who had previous episodes of neutropenic colitis, are possible preventive measures.

### Prognosis

The prognosis depends on the underlying disease and on the clinical conditions of the patient. The mortality rate in patients with signs of perforation, sepsis and multi-organ failure is higher than 50%<sup>[27]</sup>. The main prognostic factor is neutrophil recovery and overall time of neutropenia, as neutropenia allows continuous bacterial invasion of the bowel, perpetuating the lesion, with possible necrosis and perforation<sup>[28]</sup>.

In our study, we observed an involvement of the ileocecal region in all patients, only one patient showed an additional inflammatory reaction of the transverse colon. The sonographically revealed thickness of the bowel wall was associated with poor prognosis and also proved to be a useful tool for monitoring the clinical follow-up by showing the decreasing bowel wall thickening in responding patients. The results of our study agree with the findings of Carton *et al.*<sup>[10]</sup> who described an increased mortality in patients with bowel thickness of more than 10 mm. However, all of our patients were classified into this group. We also could demonstrate an increased death rate in patients with thicker bowel walls in the sonographic examination. Although nearly all patients showed a transmural pattern of inflammation, fistulas or abscesses were not observed. This might be explained by the neutropenic condition with restricted defense mechanisms. In addition, sonography might indicate complications of the disease by detection of free abdominal air or intramural hemorrhage. These complications, however, did not occur in our patients.

In conclusion, the high-end sonography of the bowel proved to be a helpful tool in diagnosis, prognosis and follow-up of patients with neutropenic enterocolitis. The ultrasonographically revealed bowel thickness reflects the severity and course of the disease, and seems to be predictive for the clinical outcome.

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