

Neutropenic enterocolitis

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Abstract

Neutropenic colitis is a severe condition usually affecting immunocompromised patients. Its exact pathogenesis is not completely understood. The main elements in disease onset appear to be intestinal mucosal injury together with neutropenia and the weakened

immune system of the afflicted patients. These initial conditions lead to intestinal edema, engorged vessels, and a disrupted mucosal surface, which becomes more vulnerable to bacterial intramural invasion. Chemotherapeutic agents can cause direct mucosal injury (mucositis) or can predispose to distension and necrosis, thereby altering intestinal motility. This article aims to review current concepts regarding neutropenic colitis' pathogenesis, diagnosis, and management.

Key words: Neutropenic enterocolitis; Neutropenic colitis; Immunocompromise; Intestinal mucosal injury; Neutropenia; Intestinal edema; Intramural invasion; Pathogenesis

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Core tip: Neutropenic colitis is a severe condition usually affecting immunocompromised patients. Its exact pathogenesis is not completely understood. The main elements in disease onset appear to be intestinal mucosal injury together with neutropenia and the weakened immune system of the afflicted patients. These initial conditions lead to intestinal edema, engorged vessels, and a disrupted mucosal surface, which becomes more vulnerable to bacterial intramural invasion. Chemotherapeutic agents can cause direct mucosal injury or can predispose to distension and necrosis, thereby altering intestinal motility.

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INTRODUCTION

Neutropenic enterocolitis (NE) is also known as typhlitis, ileocecal syndrome, cecitis, or necrotizing enterocolitis. Despite the previous use of the term

"necrotizing enterocolitis" to describe NE cases, necrotizing enterocolitis is a different inflammatory illness seen in newborns and is beyond the scope of this review^[1]. NE is a clinical entity initially described in leukemic pediatric patients. It has also been reported in adults with hematologic malignancies such as leukemia, lymphoma, multiple myeloma, aplastic anemia, and myelodysplastic syndromes, as well as other immunosuppressive causes such as AIDS, therapy for solid tumors, and organ transplant^[2].

The true incidence of NE is unknown^[2]. One systematic review published in 2005 suggested a pooled incidence of 5.6% in hospitalized adults with hematological malignancies, chemotherapy for solid tumors, and aplastic anemia^[3]. The reported mortality also varies with rates as high as 50%^[4].

NE was reported initially after the use of taxane drugs, but more recently an increasing number of chemotherapeutic drugs have been implicated^[5]. Other drugs linked to NE include cytosine arabinoside, gemcitabine, vincristine, doxorubicin, gemcitabine, cyclophosphamide, 5-fluorouracil, leucovorin, and daunorubicin. Immunosuppressive therapy for organ transplant, antibiotics, and sulfasalazine for the treatment of rheumatoid arthritis have also been considered causes of NE^[6,7].

This review aims to assess current concepts regarding the pathogenesis, diagnosis, and management of neutropenic colitis. A search for the terms "neutropenic enterocolitis", "neutropenic colitis", "typhlitis", "ileocecal syndrome", "cecalitis", and "necrotizing enterocolitis" was made in PubMed, exclusive to human studies and with no time limits.

PATHOGENESIS

The exact pathogenesis of NE is not completely understood. The main elements in disease onset appear to be intestinal mucosal injury together with neutropenia and the immunocompromised state of the afflicted patients. These initial conditions lead to intestinal edema, engorged vessels, and a disrupted mucosal surface, which becomes more vulnerable to bacterial intramural invasion. Chemotherapeutic agents can cause direct mucosal injury (mucositis) or can predispose to distension and necrosis, thereby altering intestinal motility^[8,9]. Cytosine arabinoside (cytarabine) is a chemotherapeutic agent used to treat leukemia and lymphoma that is particularly associated with the development of NE. Among its adverse effects, gastrointestinal mucosal toxicity and ileus have been described^[10,11].

Intestinal leukemic infiltration is another potential factor in the pathogenesis of NE, which may explain the presence of acute myelogenous leukemia presenting as NE before the onset of chemotherapy regimens^[12,13]. However, some studies have not reported this leukemic infiltration after histologic

evaluation^[13-15]. Other histologic findings have included mucosal ulcers, intramural hemorrhage (usually associated with thrombocytopenia), and necrosis.

The cecum is always affected by NE and very often extends to the ileum. The ascending and transverse colon may also be involved. A case of diffuse colorectal inflammation following chemotherapy in a pediatric leukemic patient was reported^[16]. This predilection by the cecum may be explained by its distensibility and limited blood supply^[2].

Although a superimposed infection of the damaged mucosa in the neutropenic patient is not universally considered a diagnostic criterion, it definitively plays an important role in the pathogenesis of NE^[3]. Gram-negative rods, gram-positive cocci, enterococci, fungi, and virus have been implicated as causes^[8,17,18]. Bacterial translocation and bacteremia is also frequently seen in these patients. While some authors associate NE with infection by *Clostridium septicum*, this is not always implicated among the pathogens in other studies^[19]. Sloas *et al.*^[20] reported NE in 24 leukemic children and found six different pathogens in eight patients with bacteremia (*Escherichia coli* in 3 patients, *Klebsiella pneumoniae* in 2 patients, *Enterobacter taylorae*, *Morganella morganii*, and a *Streptococcus viridans* in 1 patient each). They also found *Clostridium difficile* toxin in the stool of three of the 16 patients who were tested. Immunosuppression and the frequent use of antimicrobials in NE can alter normal flora and facilitate infection by less common agents^[17]. Fungal infections can play an important role in NE. One systematic review of published case studies found a significantly lower mortality rate in patients receiving antifungal agents for the treatment of NE^[21].

CLINICAL PRESENTATION

Patients with neutrophil counts < 500/ μ L are at increased risk for developing NE. Reports of neutrophil counts < 1000/ μ L have also been published^[22]. The most common symptoms of NE are abdominal pain, diarrhea, and fever^[23-25]. Nausea, vomiting, and abdominal distension are also common symptoms. Abdominal pain can be localized in the lower right quadrant or can be more diffuse. Tenderness can be found on palpation. Abdominal compartment syndrome has been reported in a patient with NE presenting with abdominal distension and ascites^[26].

Melena or hematochezia are generally less common forms of presentation^[27]. One autopsy series reported a 35% lower gastrointestinal bleeding rate in pediatric patients and considered this to precede a terminal event^[8]. Severe hemorrhage with hemodynamic instability have also been reported and these patients should undergo immediate interventional radiologic procedures (*i.e.*, angiography with embolization) in an attempt to avoid surgery^[28,29]. Peritoneal signs, shock, and rapid clinical deterioration can be suggestive of

necrosis and bowel perforation.

Symptoms often appear within two weeks following the completion of chemotherapy and coincide with the low leukocyte count following chemotherapy^[30]. Shamberger *et al*^[31] found that NE occurred after induction chemotherapy in the majority of their patients (19/25 pediatric patients with NE). Wade *et al*^[32] reported that the 22 patients in their study had been leukopenic for > 1 wk before the onset of abdominal pain and that all patients had an absolute count of < 500 cells/ μ L at some point during the leukopenia. Leukocyte count recovery after the onset of NE seems to be associated with survival^[33]. Regarding NE after hematopoietic stem cell transplantation in children, Lee *et al*^[34] considered NE to be a pre-engraftment phase complication (occurring before 30 days following transplantation) in their study of hematopoietic stem cell transplantation in children. Specifically, this is the period of marrow aplasia and pancytopenia. Recurrence can occur after resolution of the first episode.

DIAGNOSIS

Due to its nonspecific presentation, NE can mimic many other diagnoses. Differential diagnoses include pseudomembranous colitis, inflammatory bowel disease, appendicitis, ischemic colitis, and other infectious colitides.

Diagnosis generally involves the findings of fever, abdominal pain, neutropenia, and thickening of the abdominal wall (usually the cecum and ascending colon)^[21,35]. In a study that included 40 pediatric patients, the clinical triad (fever, abdominal pain, and neutropenia) was present in 31 patients (78%). The remaining 9 patients (22%) had their diagnosis made after imaging exams (US/CT) in addition to 2/3 clinical features^[36].

Abdominal plain X-rays can show a dilated atonic cecum and ascending colon filled with liquid or gas, signs of intramural gas, and small bowel dilation. However, this simple imaging technique has limited value due to its poor sensitivity and specificity^[20,35]. Radiographic imaging can also show pneumoperitoneum in patients with suspected bowel perforation^[37]. Ultrasonic examination is still an important tool in pediatric patients because it is inexpensive, readily available, and avoids radiation or radiopharmaceuticals^[35]. Computed tomography (CT) is an attractive non-invasive option for diagnosis, with higher accuracy compared to plain radiography and ultrasound^[20,38]. CT can delineate bowel wall thickening, a dilated cecum or other colonic segment, an inflammatory mass, pericolonic inflammation, and pneumatosis intestinalis. It can also help visualize other organs and make differential diagnosis. Colonic wall thickening may suggest the need for surgical treatment and affect prognosis^[21]. A study by Cartoni

et al^[35] reported a mortality rate of 60% due to NE in patients with colonic wall thickness of 10 mm compared to a mortality rate of 4.2% in patients with mural thickness of < 10 mm, seen on ultrasound.

Other imaging methods can be applied in the evaluation of NE. Barium enema is useful in showing torsion and edema of the cecum, but may potentially cause colonic perforation and septicemia^[39-42]. Scintigraphic studies have shown uptake of radiopharmaceuticals in the lower right quadrant and suggest a diagnosis of NE^[43]. Colonoscopy is rarely indicated in suspected NE because of cytopenia and the risk of perforation^[2,36].

Laboratory findings are often nonspecific. Neutropenia and thrombocytopenia are frequent alterations and have a role in the pathogenesis of NE itself. Electrolyte imbalance and albumin loss is a frequent finding in patients receiving chemotherapy with cytosine-arabinoside. Fecal examination suggests that these patients have significant loss of potassium in the stool^[10]. Blood and stool cultures can guide the therapy to specific agents.

MANAGEMENT

The lack of high-quality studies looking at therapeutic strategies makes it impossible for standardized recommendations in the management of patients with NE^[2,3]. Initial reports of NE showed a preference for surgical treatment as the high mortality associated with NE led to a more aggressive treatment regimen^[44]. A better understanding of the disease and higher success rates of conservative management have contributed to reserving surgery for complicated and more severe cases^[44,45].

Conservative management consists of aggressive fluid resuscitation, correction of electrolyte imbalance, bowel rest, abdominal decompression, and broad-spectrum antibiotics. Correction of thrombocytopenia and clotting abnormalities can require blood component transfusion.

Patients who present with a recovery in the leukocyte count tend to have better outcomes^[46]. Leukocyte transfusions and granulocyte-colony stimulation factors (G-CSF) have been applied to treat these patients. Although there are no randomized controlled studies regarding the use of G-CSF in neutropenic colitis, guidelines with recommendations have been proposed^[47,48]. Patient-related factors such as profound neutropenia (absolute neutrophil < 100/mL), uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction, and invasive fungal infection are possible indications for the use of G-CSF in NE^[3].

Bowel rest is commonly used in cases of NE^[2,3,20,24]. Parenteral nutrition can be used to maintain a nutritional source in patients who are at nutritional risk. Bowel rest can also mean intestinal villous atrophy and

Table 1 Antibiotics and dosages for empiric treatment of neutropenic enterocolitis

Antibiotics	Dosages
Adults with NE	
Monotherapy	
Piperacillin-tazobactam	3.375 g IV every 6 h
Imipenem-cillastin	500 mg IV every 6 h or 1 g IV every 6-8 h
Duotherapy	
Ceftazidime	1 g IV every 8-12 h
OR	OR
Cefepime	1 g IV every 8 h
Plus Metronidazole	1 g IV every 6 h
Children (1-12 yr of age) with NE	
Monotherapy	
Piperacillin-tazobactam	(> 9 mo and < 40 kg) 300 mg/kg per day IV divided every 8 h
Imipenem-cillastin	(> 3 mo) 60-100 mg/kg per day IV divided every 6 h maximum 2-4 g/d
Duotherapy	
Ceftazidime	90-150 mg/kg per day IV divided every 8 h - maximum 6 g/d or
OR	50 mg/kg IV every 8 h - maximum: 2 g/dose
Cefepime	
Plus Metronidazole	30 mg/kg per day IV divided every 6 h - maximum 4 g/d

Modified from Cloutier *et al*^[44]. IV: Intravenous; NE: Neutropenic enterocolitis.

mucosal integrity breaching. Some authors consider the possibility of continuing gastrointestinal tract use (oral or enteral) in selected patients^[3,14]. The use of glutamine as an immunonutrient is being studied in other patients receiving parenteral nutrition and the results may suggest its potential use in NE patients.

Prompt administration of antibiotics is essential in the treatment of NE patients. Antibiotics should cover gram-positive, gram-negative, and anaerobic pathogens. Coverage against enterococci should be added in the most critically ill patients. Specific local epidemiology and resistance patterns should guide the choice of antimicrobial agents.

An antibiotic treatment regimen usually starts with β -lactamic monotherapy or combined with aminoglycoside^[44]. Other monotherapy agents such as cefepime, imipenem, and meropenem can be also used. In cases of patients with known or suspected resistant pathogens, combination regimens are preferred. Duotherapy, combining ceftazidime or cefepime with metronidazole is also an option^[44]. For patients in which *Clostridium difficile* cannot be excluded, metronidazole or vancomycin should be added to the regimen^[1]. Recommended drugs for adults and children are summarized in Table 1. Initial empiric coverage for fungal agents is not routinely recommended, but can be considered if the initial therapy does not show good response after 72 h^[1].

Current indications for surgery in NE are evidence of intraperitoneal bowel perforation, uncontrolled bleeding after correction of cytopenia and clotting

abnormalities, and the development of other surgical conditions (abscess, appendicitis). Perforated or necrotic bowel should be resected. Primary anastomosis is not recommended due to the impaired healing and immunosuppression in these patients. Drainage of the necrotic region without resection seems to be insufficient^[13,46].

CONCLUSION

NE should always be considered as a possible diagnosis in immunosuppressed patients, especially those receiving chemotherapy. NE is a life threatening condition and prompt aggressive treatment is warranted in these patients. Resolution of the disease will depend on recovery of leukocyte count and infection control. Conservative treatment is the recommended first step in treatment, with close monitoring of the patient in the event that surgical intervention is required.

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