



Current Approach to Neutropenic Enterocolitis

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Neutropenic enterocolitis (NEC) is a life-threatening clinical condition characterized by fever, abdominal pain, and thickening of the bowel wall. NEC is also known as “typhlitis” because of the involvement of the ileocecal region most often. Nonetheless, it can affect any part of the small or large intestine (1).

The pathogenesis is related to reduced host defense mechanism, mucosal damage caused by cancer therapies like high-dose chemotherapy that involve alkylating agents (cyclophosphamide, ifosfamide, busulfan, melphalan, etc.) and antimetabolites (methotrexate, 5-fluorouracil, cytarabine, capecitabine, etc.), and infiltration of the bowel walls by microorganisms (2–4).

Histopathological examination typically reveals bacterial and fungal infiltration, ulcerated mucosal lesions, necrosis, edema, hemorrhage, and thickened bowel wall. Polymicrobial etiology is commonly observed, and include *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella spp.*, viridans streptococci, enterococci, *Bacteroides spp.*, and *Candida spp.* (1, 3).

Nevertheless, the true incidence of NEC is unclear. Its incidence rate has been estimated to be between 0.8% and 26% per some reports, although this rate is probably an underestimation (5). Several clinical conditions have an associated risk of developing NEC, such as aplastic anemia, agranulocytosis, acquired immunodeficiency syndrome, solid organ transplantation, and history of *Clostridioides difficile* (formerly *Clostridium difficile*) infection. However, a vast majority of cases are related to hematologic malignancies, especially acute leukemia treated with intensive chemotherapy or hematopoietic stem cell transplantation (6).

The primary symptoms of NEC are fever and abdominal pain, especially among patients with neutropenia. The location of abdominal pain depends on the area involved, most frequently the right lower quadrant that can mimic appendicitis. In addition, abdominal distension, nausea, vomiting, diarrhea (with or without blood), and hematochezia can be observed. Peritonitis signs may be present in the case of perforation (2, 3). Plain radiograph, ultrasound, and computed tomography can be used as the imaging modality, which have false-negative diagnosis rates of 48%, 23%, and 15%, respectively (7). Plain X-ray film findings are nonspecific generally, but it can be useful in detecting free air in the abdomen. Notably, barium enema and colonoscopy are relatively contraindicated because of the perforation risk. Ultrasonography typically reveals bowel wall thickening, pericecal fluid, transmural inflammation, and ascites (8). Nonetheless, CT is a preferable technique with findings that include bowel wall thickening (>4 mm on the transverse scan or thickening in any segment of the bowel for at least 30 mm length longitudinal scan), pericecal fluid, bowel dilatation, mucosal enhancement, and pneumatosis (3). In addition to radiological imaging, blood cultures, stool toxin assays, or polymerase chain reaction test for *C. difficile* and gastrointestinal viral panel by using PCR should be obtained. The entities to be considered for differential diagnoses are appendicitis, *C. difficile* colitis, graft-versus-host disease, cytomegalovirus colitis, norovirus infection, ischemic colitis, cholangitis, cholecystitis, colonic pseudo-obstruction, and enteric involvement by neoplastic cells (5).

The recommended treatment for NEC currently includes intravenous antibiotics, adequate intravenous fluid replacement with rigorous follow-up electrolytes, bowel rest with nasogastric suction, total parenteral nutrition, and blood product infusion as needed. Surgical intervention is warranted in cases complicated with necrosis, perforation, and persistent bleeding (9).

Antibiotic treatment should cover possible causative agents, including *P. aeruginosa*, enteric gram-negative bacilli, enterococci, and anaerobes. The treatment should be tailored as per local epidemiologic data and previous bacterial colonization. Piperacillin-tazobactam, cefepime plus metronidazole, imipenem-cilastatin, or meropenem

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can be chosen. Combined antibiotic usage is preferred mostly because of the increased incidence of multidrug-resistant microorganisms (10). When pseudomembranous colitis is not ruled out, *C. difficile* should be covered. NEC is a substantial risk factor for invasive fungal infection, especially the candida species. Empirical anticandidal treatment might be considered owing to the high mortality rate (10).

Anti-motility agents should not be used as they may exacerbate ileus. Granulocyte colony-stimulating factor (G-CSF) can be used to accelerate neutrophil recovery based on the underlying disorder. However, the usage of G-CSF is controversial because increasing the inflammatory response may potentially deteriorate the clinical condition (3). Moreover, the next chemotherapy cycle should be postponed until full recovery. Patients should be monitored closely for late complications after their recovery from neutropenia (e.g., abscess, bleeding, perforation) (11).

The mortality rate was 50%–100% per some reports because of complications, such as sepsis, perforation, or uncontrolled bleeding. Nevertheless, this high mortality rate has decreased with early diagnosis, as well as prompt and optimal management (11). New studies have demonstrated the role of biomarkers, such as 1,3- β -D-glucan, in predicting mucosal damage, thereby facilitating early diagnosis (12).

In conclusion, clinical findings like abdominal pain and fever in patients with neutropenia can be crucial clues for physicians to consider the possibility of typhlitis. Prompt diagnosis and early start of appropriate treatment can be lifesaving and improve the prognosis. Nonetheless, supportive therapy is still the mainstay of treatment, although some cases may need surgical intervention. The pathogenesis of NEC is still ambiguous, and further studies are warranted to delineate the pathogenesis and prevent the disease.

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