Neutropenic Enterocolitis, a Growing Concern in the Era of Widespread Use of Aggressive Chemotherapy

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Neutropenic enterocolitis (NEC) is a life-threatening disease with substantial morbidity and mortality, seen primarily in patients with hematologic malignancies. The frequency of NEC has increased with the widespread use of chemotherapeutic agents such as the taxanes, which cause severe gastrointestinal mucositis. Neutropenic patients with fever and abdominal symptoms (cramping, pain, distention, diarrhea, GI bleeding), should undergo evaluation of the abdomen for bowel wall thickening of >4 mm, the hallmark of NEC. *Clostridium difficile* infection should be ruled out, as well as other etiologies such as graft-versus-host disease. Complications include bacteremia, which is often polymicrobial, hemorrhage, and bowel wall perforation/abscess formation. Management includes bowel rest, correction of cytopathies and coagulopathies, and broad spectrum antibiotics and antifungal agents. Surgical intervention may be necessary to manage complications such as hemorrhage and perforation and should be delayed, if possible, until recovery from neutropenia.

*Keywords.* enterocolitis neutropic enterocolitis; taxanes.

The intestinal tract is a common site of infection in patients with cancer, especially during episodes of neutropenia. Several well-recognized entities cause distinct clinical syndromes in this setting, including cholecystitis, cholangitis, appendicitis, *Clostridium difficile* associated colitis, *Cytomegalovirus* colitis, neutropenic enterocolitis (NEC) and graft-versus-host disease (GVHD) [1, 2]. The clinical manifestations associated with most of these syndromes are similar and include fever, abdominal cramping, tenderness, pain or distention, diarrhea, and intestinal bleeding. These manifestations are not pathognomonic of any single entity and are often blunted in patients with immunosuppression and/or severe neutropenia. Consequently, a combination of clinical features, radiographic findings, microbiologic, serologic, and histopathologic data is often required to make a specific diagnosis [1, 2].

Neutropenic enterocolitis, referred to as “NEC,” but often confused with necrotizing enterocolitis which is an acute inflammatory syndrome seen in the newborn, is also known as typhlitis (typhlon or caecum, from the Greek word typhlos meaning blind or closed), or ileoceleal syndrome, is a life-threatening condition due to inflammatory/hemorrhagic/necrotizing involvement of the lower intestinal tract [3, 4]. NEC is a relatively common explanation for the persistent neutropenic fever and recrudescent neutropenic fever syndromes [5]. Patients may remain febrile until myeloid reconstitution independent of antimicrobial therapy. This, in turn, may lead to increased prescription of antimicrobial medications, increased toxicities, use of resources, and selection for resistant microorganisms. According to one study [6], the expected onset of the syndrome occurs during the third week of chemotherapy (median, 17 days) coinciding with mucosal barrier damage induced by cytotoxic therapy. Other reports suggest earlier or later onset or even...
continuing after resolution of the neutropenia [7–9]. Over the years, NEC has been the subject of vigorous debate, and some authors have even questioned its existence as a separate and distinct clinical entity [10]. One of the fundamental issues of this debate has been the lack of a clear and universally acceptable definition of NEC, because clinical features such as fever and abdominal pain and tenderness are common to most other abdominal syndromes as well. Most reports describing NEC have been single case reports or retrospective reports with a handful of cases. In 2005, a systematic analysis of the quality of evidence regarding NEC in adults was performed, in an attempt to improve our understanding of this entity [11]. This study found 145 relevant reports but found no randomized controlled trials, no high-quality cohort studies, and no case control studies regarding therapeutic interventions. Since then, only a small number of case reports, small series, opinions, and discussions have been published. The authors of this analysis attempted to resolve the debate by proposing a definition that combined common clinical features with radiographic findings, which provided a definition with objective, reproducible, and easily measurable criteria, and has generally been accepted, although it may undergo further refinement in the future [11]. The true incidence of NEC is unknown with reports ranging between 0.8% and 26% [3, 4]. Autopsy studies in children have reported incidence rates as high as 46% [12]. A review of the literature indicates a 5.3% pooled incidence rate in adults hospitalized for the treatment of hematologic malignancies or solid tumors, although this figure is probably an underestimate [11]. NEC is the most common intestinal affliction in patients with neutropenia, fever, and abdominal pain following antineoplastic chemotherapy, affecting as much as 50% of this patient population [2, 13]. NEC was originally thought to involve only the ileocecal area due to poor vascularity of that region; however, it has subsequently been shown to also involve most other regions of the colon. A recent study that correlated computerized tomography (CT) imaging with histopathology and clinical information demonstrated that NEC was limited to the cecum in only 28% of cases, with more extensive colonic involvement in as many as 75% of cases [1]. This study even demonstrated abnormalities in the small bowel in 66% of cases. The mortality rate associated with NEC is relatively high, 50%–100% in some reports [14, 15], with most deaths due to complications such as bowel perforation, uncontrolled bleeding, or overwhelming sepsis. This is likely to improve with increased awareness, early recognition and better medical and surgical management of NEC.

**RISK FACTORS AND EPIDEMIOLOGY**

Chemotherapy associated NEC (typhlitis) was originally described in 24 children treated for various malignancies including acute leukemia [16, 17]. The study criteria specified the presence of fever, abdominal pain, and tenderness, with radiological evidence of right-sided colonic inflammation. While originally, NEC was most common in patients treated for acute leukemia, since then NEC has been reported primarily in adults with leukemia, especially those receiving intensive cytotoxic chemotherapy, such as cytosine arabinoside and idarubicin. NEC has also been reported in patients with other neoplastic disorders including lymphoma and solid tumors, in patients with AIDS, and may also occur in patients with aplastic anemia or cyclic neutropenia who have not received cytotoxic agents. Recent reports have documented an association between NEC and taxanes (docetaxel, paclitaxel) and vinorelbine, which are used for treatment of a variety of solid tumors including breast, lung, and ovarian cancers [11, 17–20]. Consequently, it became important for clinicians to consider NEC when neutropenic patients develop abdominal manifestations following the administration of these agents. Other agents commonly used in patients with solid tumors that have been associated with NEC include 5-fluorouracil, capetcitabine (a pro-drug of 5 FU), cyclophosphamide, ifosfamide, cisplatin, and carboplatin [21–24]. These reports support the concept that intensive, mucositis producing chemotherapy could be associated with the development of NEC. Preexisting bowel abnormalities such as diverticulitis, tumor infiltration, and previous surgery may also increase the risk of development of NEC following chemotherapy.

**PATHOPHYSIOLOGY AND MICROBIOLOGY**

The pathogenesis of NEC is poorly understood and is probably multifactorial [9, 18, 25]. Neutropenia itself is a significant contributing factor as it reduces the immune response against invasion of local tissue by intestinal microbes [18]. Additional factors include direct mucosal injury and destruction of normal mucosal architecture due to cytotoxic chemotherapy and/or radiation; leukemic or lymphomatous infiltration of the bowel; intramural hemorrhage due to severe thrombocytopenia; and a shift in the intestinal microflora from normal commensals to more opportunistic organisms particularly in hospitalized patients, and patients recently treated with antimicrobial or antifungal agents [18]. The interaction of proinflammatory mediators from the intestinal lumen with the components of innate immunity in the submucosal tissues plays an important role in the genesis of the clinical syndrome. This includes sequence of activation of nuclear factor-kB, release of proinflammatory cytokines, epithelial cell apoptosis, and increased mucosal permeability [26, 27]. Some authors have described the predictive value of surrogate markers such as C-reactive protein and interleukin 8 in this syndrome [28]. On direct visualization during surgery or at
autopsy, the bowel appears to be thickened and edematous with varying degrees of ulceration, ecchymosis, and hemorrhage. Exudates consisting of cellular debris and fibrin may cover areas of severe ulceration. Perforation is seen in 5%–10% of cases. The most prominent microscopic findings include mucosal and submucosal edema, hemorrhage, and necrosis, with very little inflammatory exudation due to the presence of severe neutropenia. The predilection for involvement of the cecum might be related to its ability to distend and to the diminished vascularity of this area relative to the rest of the colon. As with other abdominal infections, NEC is frequently polymicrobial with multiple bacterial species and occasionally fungi having a pathogenic role. Studies have found infiltration of the bowel wall or the peritoneal fluid with gram negative bacilli, gram positive cocci, anaerobes, and Candida species. Bacteremia occurs in <50% of patients, with enteric organisms such as Pseudomonas aeruginosa, Escherichia coli, Klebsiella species, viridans group streptococci, the enterococci, and anaerobes such as Bacteroides species and Clostridium species being isolated most frequently [17, 25, 29–31]. One report emphasized the importance of Clostridium septicum in this setting and suggested that fulminant sepsis and death were more common when this organism was isolated from patients with NEC [32]. Fungemia is much less common than bacteremia, with Candida species being the most often recovered fungus. C. albicans isolates account for the majority of episodes of fungemia, although in recent studies other Candida species (C. glabrata, C. tropicalis, C. krusei, C. guilliermondii), or fungi such as Aspergillus species, and Trichosporon beigelli have also been reported [33].

CLINICAL MANIFESTATIONS AND IMAGING CHARACTERISTICS

As mentioned, clinical findings commonly encountered in patients with NEC include fever, abdominal cramping, abdominal distention, pain and/or tenderness, diarrhea, and intestinal bleeding. Paralytic ileus may develop occasionally but is relatively uncommon. These clinical manifestations are non-specific, and could be associated with other abdominal conditions. Fever may occasionally be absent, especially in severely immunocompromized patients and those receiving corticosteroids or other immunosuppressive agents. Nevertheless, fever is common in the majority of patients. Abdominal pain is almost always present, but its distribution can be variable. Most patients have diffuse abdominal pain or tenderness, but these findings might be localized to specific quadrants depending on the location and extent of bowel involvement. Abdominal distention may be found in up to 66% of patients. Abdominal findings may be minimal in a few patients or may evolve over time. Occasionally, clinical findings may appear to worsen as recovery from neutropenia occurs due to the restoration of the inflammatory response. Patients need to be carefully monitored even after recovery from neutropenia, as late complications such as bleeding, perforation, or abscess formation may occur. Careful monitoring during subsequent courses of chemotherapy is essential as the risk of relapse or recurrence is substantial.

Radiographic imaging studies are the most reliable diagnostic tools and have been shown to be predictive of prognosis as well. Findings on plain abdominal films often show a lack of bowel gas particularly in the right lower quadrant; diluted or atomic fluid filled ascending colon; gaseous dilatation or intramural gas in the cecum or other areas of the colon; or small bowel obstruction [34–36]. Plain films are considered to be of limited value due to poor sensitivity and nonspecific findings [1, 8, 37]. They do reveal the presence of free air in the abdomen in patients with bowel perforation. Ultrasonography has wider applications and has been successfully used for the study of bowel abnormalities in intestinal tract disorders such as Crohn’s disease or ulcerative colitis, and for the evaluation of abdominal complications in neutropenic patients [8, 38–40]. Ultrasound findings include the demonstration of bowel wall thickening or the presence of a rounded mass with dense central echoes and a wide hypo-echoic periphery [41]. Ultrasound imaging has also been found to be useful in monitoring the clinical course of NEC by demonstrating measurable reduction in bowel wall thickening in patients who are responding to therapy [8]. Bedside ultrasound imaging may be preferred in patients who cannot easily be transported to the radiology facilities for various reasons, or when exposure to ionizing radiation is of concern. However, ultrasound has some disadvantages when compared to computerized tomography (CT); these include limited resolution especially in certain body habitus types, operator dependency, and lower sensitivity. Although there are no known comparative studies, we believe that CT, when available, is the imaging option of choice for the rapid diagnosis of intestinal pathologies in most patients, including neutropenic patients. CT is useful in differentiating the various causes of abdominal pain in neutropenic patients including appendicitis and cholecystitis, as well as other indications for abdominal surgery [2, 42]. Kirkpatrick et al [1] described specific patterns of bowel wall thickening that may be useful in differentiating between various bowel wall pathologies, suggesting that prominent bowel wall thickening (>12 mm) with wall nodularity is significantly more common in Clostridium associated colitis. Minimal wall thickening (<5 mm) with significant mucosal enhancement is more common in GVHD, whereas the thickness of the bowel wall in NEC is usually around 7 mm (range, 4–15). The imaging characteristics have been incorporated into the definition of NEC. Additionally, an important prognostic finding of Kirkpatrick et al’s study was that bowel wall thickening of > 10 mm was
associated with more severe disease and poorer outcomes [8]. Patients with this degree of bowel wall thickening might benefit from early and aggressive surgical intervention.

**DIAGNOSIS**

Until recently, establishing a diagnosis of NEC has been quite challenging, even controversial, in part due to the lack of a clear definition of the syndrome, as well as of specific diagnostic criteria. With the widespread availability of CT and a growing body of information on the disease and its radiographic characteristics, more definitive and standardized diagnostic criteria have been established [Table 1]. These include the presence of neutropenia (ANC < 500 × 10^6 cells/L), bowel wall thickening of >4 mm on radiographic imaging, and the exclusion of other diagnoses such as *C. difficile* associated colitis, GVHD, or other abdominal syndromes. General laboratory evaluation includes a complete blood count to establish the presence and degree of neutropenia, thrombocytopenia, and anemia; coagulation studies; and chemical analysis, including tests for renal and hepatic function and blood cultures. *C. difficile* toxin assay and/or polymerase chain reaction (PCR) testing should be performed in all patients. CT is preferred over plain abdominal films and ultrasonography and should be performed if available, on all patients with severe neutropenia, fever, and abdominal pain [1, 8, 37]. Barium enema is hazardous in the presence of potentially necrotic bowel as it may lead to perforation or hemorrhage and should be avoided. Similarly, colonoscopy is contraindicated as air inflations and manipulation of the instrument may result in perforation.

**MANAGEMENT**

The management of NEC has evolved over the years as clinical experience with the syndrome has grown, and substantial improvements in general supportive care developed. NEC was initially thought to be a terminal complication in patients with leukemia with very high rates of morbidity and mortality [17, 29]. In 1979, Varki et al [43] reported success with surgical intervention (right hemicolectomy and iliocolic anastomosis) in a patient with acute lymphoblastic leukemia who developed NEC. The authors attributed the patient’s survival to prompt surgical intervention leading to complete remission following maintenance chemotherapy. This and other similar reports led some clinicians to advocate early and aggressive surgical intervention in all patients with NEC, based on the concept that most patients would progress to full thickness colonic involvement with ensuing hemorrhage, necrosis, and perforation, particularly involving the cecum. With improvements in general supportive care, recent studies have reported the success of conservative, nonsurgical management in most patients diagnosed with NEC. Surgical intervention is now generally reserved for selected cases of NEC based on criteria first proposed by Shamberger et al [44]. These include (a) the persistence of gastrointestinal bleeding despite correction of coagulopathies, thrombocytopenia, and neutropenia; (b) free air in the intraperitoneal cavity indicative of bowel perforation; (c) clinical deterioration despite optimal medical management, and (d) the development of other indications for surgery, such as appendicitis [44]. Conservative management is recommended initially when these criteria are absent. In a recent study, Badgwell et al [2] suggested better outcomes if it was possible to delay surgery until recovery from neutropenia had occurred.

General supportive measures include bowel rest with nasogastric suction, parenteral nutrition if necessary, and intravenous fluid support. Platelet transfusions may be necessary in patients with severe thrombocytopenia. Coagulopathies need to be corrected in patients who develop them. The use of granulocyte colony stimulating factor (G-CSF) hastens neutrophil

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<th>Type of Criteria</th>
<th>Finding</th>
<th>Remarks</th>
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<td>Major Neutropenia</td>
<td>ANC &lt; 500 × 10^6 cells/L</td>
<td>Anemia; Bowel wall thickening on CT exam or US exam &gt; 4 mm (transverse scan) thickening in any segment of the bowel for at least 30 mm length (longitudinal scan)</td>
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<td>Minor/nonspecific</td>
<td>Abdominal pain</td>
<td>&gt; 3 on a visual analog scale (1–10)</td>
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<td>Abdominal distension</td>
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Abbreviations: ANC, absolute neutrophil count; CT, computerized tomography; GI, gastrointestinal; US, ultrasound.

* Adapted from Gorschluter et al [11].

Fever may be absent in a minority of patients and some may even be hypothermic.
recovery and may be beneficial in some patients [45]. The role of granulocyte transfusions and hematopoietic growth factors has not been adequately studied and remains controversial as it potentially may have a negative impact on the integrity of the bowel wall involved in the setting of augmented inflammatory response associated with myeloid reconstitution. Granulocyte transfusions may be of benefit in selected patients with prolonged and profound neutropenia but cannot be routinely recommended. The prompt administration of broad-spectrum antibiotic therapy is essential in all patients with NEC. The choice of specific agents will depend on local epidemiology, local susceptibility or resistance patterns, and on previous antimicrobial exposure but must include coverage against enteric gram-negative pathogens such as *P. aeruginosa* and

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Figure 1. Suggested algorithm for the evaluation and treatment of patients with suspected neutropenic enterocolitis. See Table 1 and text for details. Abbreviations: ANC, absolute neutrophil count; CT, computerized tomography; G-CSF, granulocyte colony stimulating factor; GVHD, graft-versus-host disease; PCR, polymerase chain reaction; tpn, total parenteral nutrition; US, ultrasound.
E. coli, anaerobes, and the enterococci [46, 47]. Although monotherapy with agents such as imipenem, meropenem, and piperacillin/tazobactam may be adequate in some patients, combination regimens are preferable particularly in patients known to be colonized with, or suspected of having an infection with, a resistant pathogen (eg, extended-spectrum β-lactamase producing gram-negative bacilli, vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus, or a multi-drug-resistant organism). Initial empiric antifungal coverage is not routinely recommended as the frequency of invasive fungal NEC is only about 5%. It is reasonable to add antifungal coverage if 72–96 hours of potent antibacterial therapy failed to produce signs of clinical improvement (Figure 1). It is also reasonable to add treatment for C. difficile when the latter cannot be excluded. Blood cultures may be positive in 18%–44% of cases and may be used to guide therapy [18]. Supportive measures and antimicrobial therapy should be continued until full resolution of clinical and laboratory manifestations, including normalization of body temperature, recovery from neutropenia and thrombocytopenia, return of normal gastrointestinal function, and resolution of bacteremia, if initially present. Patients should be carefully monitored using repeat imaging to assess bowel wall thickness in addition to clinical response through the course of the disease and for some time thereafter, as relapses, albeit uncommon, do occur [9]. Consideration should be given to delaying antineoplastic therapy until full recovery from NEC has occurred. If the episode of NEC was precipitated by a specific agent or regimen, subsequent courses of chemotherapy might require a change of the offending agent/regimen. An algorithm for the management of patients with NEC is proposed in Figure 1.

SUMMARY

In the past, neutropenic enterocolitis was primarily observed in patients with hematologic malignancies following the administration of antineoplastic therapy, which produced high grade intestinal mucositis. With the increased use of aggressive chemotherapy (eg, the taxanes and vinorelbine) for many solid tumors, and the development of an acceptable definition, NEC is being reported with greater frequency in this subset of cancer patients. Consequently, clinicians caring for patients with solid tumors who receive these and other mucositis producing agents should consider NEC in their differential diagnosis when the patients present with neutropenia and abdominal complaints. Early recognition of NEC based on CT imaging is the diagnostic procedure of choice. Conservative medical management including general supportive care, bowel rest, and broad-spectrum antimicrobial therapy is the current standard of care for most patients. Surgical intervention is usually necessary only when complications such as hemorrhage or bowel perforation develop. Agents that reduce the frequency and/or intensity of chemotherapy associated mucositis represent an unmet need and are the focus of ongoing research.

Notes

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