Diagnosis and Management of Typhlitis and Neutropenic Enterocolitis in Children with Cancer

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Neutropenic enterocolitis (NE) is a common and serious condition affecting adults and children with neutropenia. It mostly affects children receiving myelotoxic therapy for cancer or receiving hematopoietic stem cell transplantation (HCT).[1–3] Although sometimes called 'typhlitis' when limited to the cecum, NE is preferred because it can affect the entire colon, small bowel or rectum.[3] NE is important because it can delay chemotherapy, affect nutrition, require prolonged hospitalization or surgery, and has other life-threatening complications.

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PATHOPHYSIOLOGY AND EPIDEMIOLOGY

The proposed pathophysiology of NE is a vicious cycle initiated by gut mucosal injury from chemotherapy (eg, antimetabolites, alkylating agents, anthracyclines and taxanes), malignant infiltration, radiation therapy, graft vs. host disease or infection. Colonizing gastrointestinal flora, including bacteria and sometimes *Candida spp.*, then enter the damaged gut wall and, without neutrophil clearance, cause further mucosal damage.[4] Gram-negative, Gram-positive and anaerobic bacteria and *Candida*, cytomegalovirus (CMV), adenovirus, rotavirus, norovirus, astrovirus, *Clostridioides difficile* and other enteric pathogens have all been identified in association with NE.[4] Other contributing factors include microbiome disruption, intramural bleeding and other immune dysfunction.[4] NE affects ~2%–10% of children receiving chemotherapy or HCT in contemporary studies.[1,3,5] Risk factors include older age, abdominal radiotherapy, HCT and specific malignancies, such as acute myeloid leukemia, non-Hodgkin's lymphoma and neuroblastoma.[2,3,5]

DIAGNOSIS AND EVALUATION

Clinical Presentation

Clinical presentation of NE is typically with fever, abdominal pain and neutropenia 1–3 weeks after cytotoxic chemotherapy or HCT conditioning.[2,3] The pain is often crampy, periumbilical or generalized, and may peak before a bowel movement. More constant or focal pain and tenderness, especially in the right lower quadrant, is seen in ~25%.[1] Nausea, vomiting, diarrhea, decreased bowel sounds, abdominal distension and palpable bowel mass are also common but frank gastrointestinal bleeding is rare.[1–3,5]

The diagnosis is based on clinical presentation in an appropriate host.[2,3] Imaging and laboratory tests can support the diagnosis or identify alternative diagnoses and can identify specific infections, complications or prognostic factors.

Differential Diagnosis

The differential diagnosis for abdominal pain in an immunocompromised child includes appendicitis, ischemic colitis, chemotherapy-associated mucositis, veno-occlusive disease, medication-induced ileus or pancreatitis and infectious syndromes such as infectious gastroenteritis due to norovirus, adenovirus, rotavirus, intestinal parasites, *C. difficile*, nontyphoidal *Salmonella spp.*, enteropathogenic *Escherichia coli, Yersinia enterocolitica, Shigella spp.,* and *Campylobacter spp.*, ascending cholangitis, cholecystitis and mesenteric adenitis.[1]

Imaging Studies

Ultrasound is preferred to computed tomography (CT) for evaluation of NE because of safety and diagnostic accuracy.[3,6] Ultrasound typically shows colonic wall thickening (≥3–4 mm).[3,5,6] A maximal measurement of 0.9 mm is associated with longer clinical illness and with mortality.[3,6] If

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the diagnosis is unclear, ultrasound can also evaluate the liver, spleen, gallbladder, kidneys, appendix and retroperitoneum. However, image quality is operator-dependent and bowel evaluation must be specifically requested. Although serial ultrasound is sometimes used to evaluate response to therapy, there is insufficient evidence to modify therapy for increasing wall-thickness alone.

Abdominal CT with intravenous contrast is also often used to assess NE; however, wall-thickness-measurement can be challenging in the nondistended colon, and ionizing radiation and intravenous contrast have potential toxicity.[3,6] CT is therefore preferred only in patients with large body habitus or who require concurrent evaluation for chest pathology, suspected perforation or intraabdominal complications, and in centers with limited ultrasound expertise.[3,6] CT can show bowel wall thickening, intramural pneumatosis, pneumoperitoneum and pericolic fluid collections or mesenteric stranding,[3,6] and can also evaluate other alternative or concurrent intraabdominal pathology.

Plain radiographs may show extraintestinal free air as a sign of perforation, cecal dilatation, decreased right lower quadrant air, air-fluid levels in ascending colon, pneumatosis intestinalis and small bowel dilatation, but are not routinely indicated because of poor sensitivity and specificity. Gastrointestinal endoscopy is usually contraindicated because of perforation-risk but may be considered if initial therapy fails, or for diagnosis of graft vs. host disease, CMV colitis or fungal infection.

Laboratory Tests

Blood culture, with added anaerobic culture, should be performed at diagnosis and with any clinical deterioration. This can identify bloodstream infection (BSI) from translocation of gut flora and can guide more specific therapy.[2] If all cultures are negative and there is no clinical deterioration, repeating blood cultures >48 hours has little utility, even with persistent symptoms. Other microbiological testing may be considered to identify alternative etiologies for gastrointestinal pathology. If diarrhea is prominent, stool testing for *C. difficile*, norovirus, adenovirus, rotavirus, intestinal parasites and pathogenic bacteria should be considered. Molecular testing for CMV from blood is reasonable but is negative in ~50% of biopsy-proven cases. Inflammatory markers such as C-reactive protein, Interleukin-8, erythrocyte sedimentation rate and procalcitonin are usually elevated and levels may be associated with the severity of illness or prognosis.

COMPLICATIONS OF NEUTROPENIC ENTEROCOLITIS

Outcomes of NE in children appear to be superior to adults. Adult mortality is 20%–50%, whereas recent pediatric studies report mortality rates <3%.[1,3,5,7,8] Older adolescents (>14 years) appear to be at higher risk than younger children. Other important complications of NE include BSI, sepsis, mechanical complications requiring surgery and gastrointestinal mucormycosis.

Bloodstream Infection

The most common microbiologically-proven complication of NE is BSI, especially due to *E. coli*, viridans group streptococci, *Pseudomonas aeruginosa, Klebsiella spp.* or *Enterococcus spp.*[2,9] Other important pathogens include *Clostridium spp., Pasturella haemolytica*, *Acinetobacter baumanii*, *Aspergillus spp.* and *Candida spp.* Children with NE have lower BSI rates (~25%) than adults (~40%).

Sepsis

Death from pediatric NE is most frequently associated with sepsis, a dysregulated response to infection leading to organ dysfunction.[1,5] Although severe sepsis requiring intensive care is rare, mild organ dysfunction is common with hypotension reportedly occurring in ~40% of cases.[5,7] Early recognition and management of sepsis likely contribute to low mortality rates in recent studies.

MANAGEMENT

Empiric Antibiotic Therapy

Prompt administration of broad-spectrum empiric antibiotics is critical to prevent progressive disease and severe sepsis. (Table 1) Empiric therapy guided by clinical severity usually includes coverage for aerobic Gram-negative and anaerobic bacteria, and may also include coverage for intestinal Gram-positive aerobes or *Candida spp*.[2,3,5,7] The backbone of therapy is usually piperacillin-tazobactam or cefepime plus metronidazole, and some authors have even recommended routine empiric use of carbapenems.[3]

Broader-spectrum Antimicrobial Therapy

Expanded empiric coverage is necessary in select cases. Patients with more severe NE and history of multidrug-resistant Gram-negative infection or colonization may have initial therapy tailored to resistant organisms; options to broaden Gram-negative coverage include adding an aminoglycoside or switching to a carbapenem. Expanded upfront therapy should also be considered in patients requiring critical care support (eg, vasopressor therapy, ventilatory support or severe metabolic acidosis), with signs of peritonitis or an abdominal mass or bowel wall thickening on ultrasound ≥0.9 cm.[2,3] In these cases, broader empiric coverage for Gram-positive bacteria, with vancomycin or linezolid, double Gram-negative coverage with an aminoglycoside, and antifungal coverage with fluconazole or an echinocandin should be considered.

Indications for Escalation or De-escalation of Antibiotic Therapy

Empiric antibiotic therapy should be adjusted as new information becomes available. Patients with documented infection should have antimicrobials tailored to susceptibilities, but broad-spectrum antimicrobials should also be continued because polymicrobial infection of the gut wall is presumed. Patients showing clinical improvement should be considered for de-escalation of therapy after 24–48h, including discontinuation of aminoglycosides, and switching empiric carbapenems to cefepime or piperacillin-tazobactam. Oral metronidazole plus ciprofloxacin can be considered for outpatient management in patients showing clinical improvement and tolerating oral intake.

Indications for empiric escalation of therapy include worsening of gastrointestinal symptoms or signs, increasing bowel wall-thickness, sepsis or positive culture with a resistant organism. In these cases, depending on clinical stability, either stepwise escalation of therapy while monitoring for clinical response, or broad escalation with subsequent rationalization can be considered. Ongoing mild-moderate symptoms or fever usually do not require escalation, since they can persist until neutrophil count recovery even with optimal therapy.

Duration of Antibiotic Therapy

The duration of antibiotic therapy for NE is controversial. Although prolonged therapy after resolution of neutropenia and symptoms has been recommended for adults with uncomplicated NE, our practice is to discontinue antibiotic therapy after count recovery (absolute neutrophil count >500) plus the resolution of symptoms, unless a longer course is indicated for BSI, *C. difficile infection*, peritonitis or intraabdominal abscess.[10] In certain diseases (eg, acute myeloid leukemia or relapsed leukemia), count recovery may be very delayed, and clinicians must balance the risk of continued NE therapy (eg, antibiotic resistance and metronidazole-neurotoxicity) against the benefits.

Surgical Management

Because mechanical complications, including obstruction, intussusception, perforation and fistulization are rarely described in pediatric NE in the current era,[1,5] >90% of pediatric NE cases can be treated conservatively.[1,2,5,8] Also, surgery is technically challenging due to friable

TABLE 1. A risk-stratified approach to management of neutropenic enterocolitis in children

Patient Characteristics	Recommended Empiric Therapy
Neutropenic patients with mild abdominal pain and fever	Consider treating as per standard fever and neutropenia guidelines Abdominal imaging to identify patients with enterocolitis
Neutropenic patients with fever plus any of the following: Moderate-severe abdominal pain Focal abdominal tenderness Diarrhea Bowel wall thickening between ≥0.3 cm and <0.9 cm PLUS clinical symptoms	Metronidazole IV/PO plus Cefepime IV Or Piperacillin-Tazobactam IV
Neutropenic patients with moderate-severe abdominal pain plus any of the following: Toxic appearance Rebound tenderness New abdominal mass or local 'fullness' on examination Frank or macroscopic blood in stool Bowel wall thickening ≥0.9 cm on ultrasound imaging	Metronidazole IV/PO plus Cefepime (or Piperacillin-Tazobactam IV) plus an Aminoglycoside IV Consider addition of fluconazole or micafungin
Neutropenic patients with abdominal pain plus: Past colonization or infection with Gram-negative bacteria resistant to cefepime *and* aminoglycoside *AND* any of the following: Toxic appearance Rebound tenderness New abdominal mass or local 'fullness' on examination Frank or macroscopic blood in stool Bowel wall thickening ≥0.9 cm on ultrasound imaging	Consider tailoring empiric therapy to include coverage for resistant bacteria
Neutropenic patients with severe abdominal pain plus: Sepsis requiring ICU-level care	Meropenem IV plus Aminoglycoside IV plus Vancomycin IV plus Fluconazole or Micafungin IV

IV indicates intravenous.

bowel, surrounding inflammation, impaired healing and bleeding diatheses. Potential indications for surgery include persistent bleeding after correcting thrombocytopenia and coagulopathy, intestinal perforation, intraabdominal abscess or compartment syndrome, and rapid clinical deterioration despite medical management. Clinical signs of perforation include acute sepsis, or the development of focal abdominal pain, tenderness and peritonism. Persistent abdominal pain or fever alone typically does not necessitate surgery.

Other Supportive Care

Complete 'bowel-rest', restricting all oral intake, has often been recommended for NE.[2,3,8] However, no controlled trials evaluated this, and many patients are empirically managed with a limited plain diet.[7] Indications for bowel rest include impending surgery, suspected perforation, peritonitis or bowel obstruction, severe abdominal pain or nausea and uncontrolled gastrointestinal bleeding. If bowel rest is required, attention to fluid and electrolyte supplementation is important (potassium depletion may occur from large volume diarrhea), and parenteral nutrition should be considered. Neutrophil recovery is required for resolution of NE, so support with granulocyte colony-stimulating factor (G-CSF) is often considered, despite absent high-quality evidence.[8] If not contraindicated, we use G-CSF if likely to speed neutrophil recovery without marked leukocytosis. Pain control is also an important component of management.

CONCLUSIONS

NE is a potentially life-threatening condition affecting neutropenic patients of all ages. Early recognition and appropriate risk-stratified management can prevent surgery, complications, unnecessary antibiotics and mortality. Abdominal ultrasound with colonic wall measurements and other simple investigations can confirm the diagnosis and exclude common differentials. The central pillars of treatment are empiric antibiotic therapy and supportive care, with surgery reserved for intestinal perforation, severe bleeding or fulminant disease. Close monitoring for improvement, deterioration, or development of intraabdominal complications can guide subsequent management. Outcomes are usually good, with rapid resolution after neutrophil recovery. Important future research directions include evaluation of empiric antibiotic approaches, duration of therapy and indications for escalation or de-escalation of empiric antimicrobial treatment.

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