Enteric Infections

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Abstract

Cancer patients, particularly those with neutropenia, are at risk for enteric and intra-abdominal infections. Specific infections and infectious syndromes in this setting include neutropenic enterocolitis, bacterial infections such as *Clostridium difficile* infection (CDI), viral infections such as CMV colitis, and parasitic infections such as strongyloidiasis. Diagnosing and gauging the severity of CDI presents challenges, as chemotherapy may produce symptoms that mimic CDI and laboratory findings such as leukocytosis are not reliable in this population. Treatment for enteric infections should be pathogen specific, although broad-spectrum antibiotics are often required as initial empiric therapy in patients with neutropenia.

Keywords

Intra-abdominal infections · Neutropenic enterocolitis · *Clostridium difficile*

Contents

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1 Introduction

Treatment for cancer often involves potent chemotherapeutic agents with resultant neutropenia for which prophylactic antibiotics are often prescribed [1, 2]. These chemotherapeutic regimens may result in abdominal complications, many of which are infectious in nature [1]. Abdominal infections in the setting of neutropenia carry significant mortality risks, particularly in hematologic malignancies, and 72–92 % of these neutropenia-associated infections occur in patients with hematologic malignancies [1, 3].

The differential diagnosis for cancer-related abdominal infection is broad and includes entities that also occur in patients without cancer. Non-infectious etiologies that may mimic abdominal infections include small bowel obstruction, cholecystitis, colonic pseudo-obstruction, and splenic rupture [3]. Infections not unique to cancer patients, but which are common in this setting, include appendicitis, diverticulitis, and *Clostridium difficile* infection (CDI). Enteritis due to Salmonella, Shigella, Yersinia, and Campylobacter are rare in the cancer population [4]. These pathogens are normally contracted via contaminated food products and are uncommon in hospitals. The enteric infectious syndrome most directly related to malignancy is neutropenic enterocolitis [1].

2 Neutropenic Enterocolitis

Neutropenic enterocolitis is a life-threatening complication of chemotherapy in patients with leukemia or solid tumors [5, 6]. It also occurs in individuals with aplastic anemia or cyclic neutropenia who have not received cytotoxic therapies. However, neutropenic enterocolitis most frequently occurs after intensive chemotherapy for leukemia [7]. The reported incidence of neutropenic enterocolitis varies from 0.8 to 26 %. Pooled data from 21 studies gave an incidence of 5.3 % in patients hospitalized for hematologic malignancies, high-dose chemotherapy in solid tumors, and aplastic anemia [7].

Currently, there is no standard clinical definition for neutropenic enterocolitis [7]. The traditional clinical triad includes fever, abdominal pain, and diarrhea [5, 7, 8]. Ultrasound and computed tomography (CT) have been established as useful diagnostic tools [5, 7, 9]. Bowel wall thickening has been proposed as an indicator of neutropenic enterocolitis, but there is no agreement to the degree of thickness

required for this diagnosis. One study proposed a cutoff of 4 mm as suggestive of the diagnosis [7], whereas another study proposed mural thickening of 10 mm as indicative of a poorer outcome [9]. Neutropenic enterocolitis usually involves the cecum and has also been referred to as typhilitis [10]. In addition, neutropenic enterocolitis is frequently complicated by bacteremia or fungemia [5, 11]. Fungemia, bacteremia, and hypotension are all associated with increased morbidity and mortality [11].

Clinically distinguishing neutropenic enterocolitis from CDI may be difficult [12]. Pathological findings in neutropenic enterocolitis include diffuse dilatation and edema of the bowel wall, prominently involving the cecum and ascending colon. There may be different degrees of mucosal and submucosal necrosis, hemorrhage, and ulceration [5]. Obtaining a pathologic diagnosis may be difficult, especially given patients' degrees of neutropenia and thrombocytopenia. In addition, similar pathologic and radiographic findings are seen in CDI and CDI may be limited to the ascending colon as well [13]. Pseudomembranes suggest CDI. Bloody stools, often seen in neutropenic enterocolitis, are not characteristic of CDI. A positive stool *C. difficile* toxin assay is usually present in CDI.

There is no universal consensus regarding specific treatment for neutropenic enterocolitis, but antibiotic treatment should target the likely pathogens involved in the disease. Commonly implicated organisms include *Enterococcus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Bacteroides fragilis*, viridans group *Streptococcus*, and alpha-hemolytic *Streptococcus* [5, 11]. The guidelines from the Infectious Disease Society of America (IDSA) for treatment for neutropenic fever suggest a carbapenem, such as imipenem or meropenem, or ceftazidime or cefepime [14]. An antipseudomonal beta-lactam antibiotic may also be combined with an aminoglycoside as dual therapy [7, 14]. However, cefepime and ceftazidime as monotherapy may not provide adequate anaerobic coverage. In this instance, metronidazole should be added [7]. The IDSA guidelines for treatment for intra-abdominal infections also include meropenem or imipenem or cephalosporins plus metronidazole [15]. In the case of cephalopsorins, an antipseudomonal agent such as ceftazidime or cefepime would be consistent with neutropenic fever guidelines. Other acceptable regimens may include piperacillin/tazobactam or aztreonam plus metronidazole [15].

The role of antifungal therapy for neutropenic enterocolitis has not been firmly established, but pooled data from one meta-analysis reported the frequency of fungal involvement of 6.2 % [16]. *Candida* species are most frequently implicated, including *C. albicans, C. glabrata*, and *C. krusei* [5, 16]. There is currently no consensus on the choice of antifungal agents. Fluconazole may be considered in select patients, particularly those with *C. albicans* and those not previously on fluconazole prophylaxis. Other therapeutic options include caspofungin, voriconazole, and amphotericin B [16, 17]. Fungemia and fungal infections in neutropenic enterocolitis carry a high mortality, ranging from 81.8–100 % [3, 5, 11]. The decision to include antifungal therapy must be made on an individual basis.

Surgical therapy for neutropenic enterocolitis carries significant morbidity and mortality. Abdominal surgery in neutropenic patients carries a 30-day and 90-day mortality risk of 30 and 52 %, respectively [3]. If possible, conservative management is preferable [1, 3, 5], with surgery delayed until after recovery of neutrophil counts [3]. Surgery should be considered in those cases with perforation [6]. Non-surgical management options that may be helpful include bowel rest, bowel decompression, antibiotics, and nutritional support [1].

3 *Clostridium Difficile* Infection

Clostridium difficile is the most common infectious cause of hospital-acquired diarrhea and colitis in general and the most common cause among cancer patients as well [18, 19]. The major risk factors for CDI overall, antibiotics, hospitalization, and advanced age [20] are also common among cancer patients. Cancer patients have additional factors, which may increase their risk of CDI. In particular, neutropenia secondary to hematologic malignancy or chemotherapeutic agents appears to increase CDI risk [19, 21]. CDI occurred at a median of 10 days of neutropenia and was complicated by bacteremia due to other enteric organisms in 21 % of the neutropenic episodes in one study of patients on a leukemia ward with CDI [19]. Other potential risk factors in cancer patients include hypoalbuminemia, treatment with proton pump inhibitors, histamine-2 blockers, intravenous vancomycin, fluoroquinolones, and cephalosporins [21]. Antibiotic use is of particular concern in this patient population. Antibiotics often have profound effects on the indigenous bowel flora, which normally provide resistance to infection with *C. difficile*. In addition, some antibiotics may select for specific antibiotic-resistant *C. difficile* strains [22]. Antibiotic duration is also an important factor as evidenced by one case–control study of outpatients at a cancer hospital where case patients that developed CDI received longer courses of antibiotics than control patients [23]. Historically, cephalosporins and clindamycin have carried the highest risk for CDI [24]. However, fluoroquinolones have been increasingly associated with CDI [24–27] and this class of antibiotics is often used for prophylaxis in patients with hematologic malignancies and neutropenia [2]. Fluoroquinolones have been implicated in the recent North American epidemic of CDI due the BI/NAP1/027 strain of *C. difficile*, which has developed high-level fluoroquinolone resistance [18]. During this epidemic in Quebec, fluoroquinolones were the single biggest risk factor for developing CDI [25]. Other outbreaks have implicated levofloxacin [26] or a formulary switch from levofloxacin to gatifloxacin [28].

Chemotherapy may also be an inciting agent for CDI, even in the absence of antibiotics. One potential explanation for this finding is chemotherapy-induced alteration of bowel flora [29]. Regimens containing high-dose paclitaxel had a rate of CDI as high as 20 %, compared with standard regimens with an incidence of 2 % [30]. Similarly, a study of ovarian cancer patients reported a CDI rate of 6.4 % in those receiving cisplatin-based regimens [31]. Other chemotherapy

agents that have been implicated include methotrexate, bleomycin, vinblastine, 5-FU, cyclophosphamide, doxorubicin, and cytarabine [32]. Unfortunately, gastrointestinal side effects, including nausea, vomiting, and diarrhea, are commonly associated with chemotherapy, particularly platinum-based regimens, and these side effects may be difficult to differentiate from CDI [30].

Diagnosis of CDI among cancer patients can be challenging because of the frequency of diarrhea and other gastrointestinal symptoms in this population as well as the high rate of asymptomatic carriage of *C. difficile* in the hospital setting. The stool cytotoxicity cell assay using tissue culture has traditionally been used for diagnosis [33]. However, toxin testing has been replaced in most clinical laboratories by enzyme immunoassays (EIA) for toxin A and toxin B [33–35]. This assay has a quick turnaround time and is reasonably specific, but it has an estimated sensitivity of ~80 % [34]. The lack of sensitivity is not overcome by repeating EIA testing [33–35], and in general, the test should not be repeated within a seven-day period [33–35]. However, with the understanding that *C. difficile* is primarily acquired in the hospital setting, repeating the toxin assay days or weeks later in patients with prolonged hospital stays who have new or additional gastrointestinal symptoms is appropriate. Culture has high sensitivity, but has a three- to four-day reporting delay and is not widely available [33]. Newer testing strategies include screening with a test for glutamate dehydrogenase (GDH) followed by toxin assay for GDH-positive specimens and PCR [36, 37], but stool toxin testing remains the most widely used strategy at the present time.

Other laboratory findings that may suggest CDI include leukocytosis, elevated serum creatinine, and hypoalbuminemia. Leukocytosis may not be as useful in this population, given the frequency of neutropenia [38]. Radiographically, bowel wall thickening on CT scan may be useful, although this test is relatively insensitive [13, 33]. Pseudomembranous colitis demonstrated by endoscopy is specific, but it is also not a sensitive test for the diagnosis and endoscopy may not be practical or advisable in the setting of neutropenia [33].

Given the increasing severity of CDI, treatment regimens have been increasingly scrutinized. Prior recommendations have included metronidazole as first-line therapy for all patients with CDI. However, several recent studies have documented increased rates of treatment failure with metronidazole [39, 40]. There is now good evidence supporting improved outcomes of treatment for severe CDI with oral vancomycin over treatment with metronidazole [41]. However, mild to moderate CDI usually responds to treatment with metronidazole [41] and metronidazole has been effective for CDI in the setting of chemotherapy-induced neutropenia [19]. Appropriate regimens with these agents include metronidazole 500 mg orally three times daily for 10–14 days or vancomycin 125 mg orally four times daily for 10–14 days [42]. In addition, fidaxomicin, a non-absorbed macrocyclic agent, has also been approved for treatment for CDI [43]. Fidaxomicin 200 mg twice daily for 10 days was not inferior to vancomycin for cure and was superior for sustained response at 25 days after treatment completion.

Recurrent CDI has been increasingly problematic and may occur in one-third of all cases after successful recovery from the first episode [44]. First recurrences can be treated with the same agent used in the initial treatment regimen [42, 44]. However, if a relapse is noted to be severe, then oral vancomycin should be used. In addition, repeated or prolonged metronidazole courses should be avoided because of the risk of neurotoxicity. For patients with multiple recurrences, vancomycin in tapered and pulsed dose regimens is often effective in stopping subsequent recurrences [42]. There has been limited experience with other regimens for managing recurrent CDI, including vancomycin plus *Saccharomyces boulardii* [45], a post-vancomycin chaser regimen of rifaximin for 2 weeks [46], nitazoxanide [47], intravenous immunoglobulin [42], and fecal transplantation [48]. However, caution is advised in immunocompromised patients as cases of fungemia secondary to saccharomyces containing probiotics have been reported [49]. There are no data on stool transplants in immunocompromised patients, and they are not recommended in this setting [48].

4 Other Bacterial Infections

4.1 *Clostridium* Infections Other than CDI

Clostridium species, particularly bacteremia, have been associated with occult malignancy, most commonly a gastrointestinal source [50, 51]. One of these studies documented malignancy in 48 % of clostridial bacteremia, while another documented a relative risk of 40 for malignancy in patients with clostridial bacteremia. The *Clostridium* species most commonly associated with malignancy is *Clostridium septicum* [51, 52].

C. septicum has a particularly high association with hematologic malignancies and colon cancer. Approximately 24 % of patients with *C. septicum* infection will have hematologic malignancies and 75 % will have colon cancer [53]. *C. septicum* can be found in the gastrointestinal tract in humans [53]. It is possible that the acidic and hypoxic environment provided by anaerobic glycolysis of the tumor results in spore germination [52]. In the absence of a hematologic malignancy, a screening colonoscopy should strongly be considered [52].

Clinical syndromes seen with *C. septicum* infection include gas gangrene, myonecrosis, and septicemia. In distinction to disease associated with *C. perfringens*, gas gangrene associated with *C. septicum* typically develops in the absence of trauma and is spread hematogenously [54]. The α-toxin produced by *C. septicum* can induce hemolysis and cause tissue necrosis and is likely a key virulence factor of the organism [50–53]. Clinically, lesions may begin innocuously, but may evolve into overt gas gangrene within hours. Systemic toxicity then ensues with tachycardia, fever, diaphoresis, shock, and multiple organ failure [54].

In general, clostridial infections carry a high mortality [50–53] and often require surgical debridement [50, 53]. Effective treatment regimens include

penicillin plus clindamycin, although tetracycline and chloramphenicol have also been used effectively [54].

4.2 *Streptococcus bovis* Infection

Streptococcus bovis is classified as a non-enterococcal group D Streptococcus and is found among the normal flora of the human intestinal tract in 5–16 % of adults. As with *C. septicum*, *S. bovis* bacteremia carries a high association with colorectal cancer [55–57]. It is hypothesized that *S. bovis* may stimulate an overexpression of cyclo-oxygenase-2 (COX-2), which is also overexpressed in human colorectal cancers. COX-2 can inhibit apoptosis or stimulate angiogenesis, which may promote a carcinogenic process [56]. There is also considerable debate whether *S. bovis* is specifically involved in the pathogenesis of colon cancer or whether ulcerating colorectal carcinomas allow for increased growth of *S. bovis* with subsequent bacteremia [56].

Patients with *S. bovis* infection often present with bacteremia or endocarditis. *S. bovis* endocarditis was first discovered in 1951, but at the time, it was not distinguished from enterococcal endocarditis [55–57]. A review of studies among patients with *S. bovis* bacteremia demonstrated colon cancer incidences ranging from 6 to 71 % [57, 58]. Thus, colorectal screening is recommended in patients with *S. bovis* bacteremia or endocarditis [55–57].

5 Parasitic Infections

5.1 *Cryptosporidium* Infection

Cryptosporidium (*C. parvum* or *C. hominis*) is an intestinal protozoan parasite that is recognized as a cause of sporadic, self-limiting diarrhea in normal individuals. However, in immunocompromised patients, it may be associated with prolonged or life-threatening gastroenteritis [58]. While patients with AIDS are the most common immunocompromised risk group, cancer patients may also be at increased risk. While patients with solid tumors receiving chemotherapy are at risk for *Cryptosporidium* infection, those with hematologic malignancies such as acute leukemia are at considerably higher risk [58, 59]. Although not frequently diagnosed in immunocompetent patients in the United States, there have been outbreaks of cryptosporidiosis related to contaminated drinking water [59].

The clinical course of cryptosporidiosis can range from asymptomatic to severe or mild diarrhea. Gastroenteritis is characterized by watery diarrhea and malabsorption. Fever is also commonly present. Ingested oocysts release sporozoites, which attach to intestinal epithelium [60]. Extraintestinal disease, including pulmonary cryptosporidiosis, has rarely been reported in hematologic malignancy.

Biliary tract involvement has been reported in AIDS patients, but not in cancer patients [61].

Diagnosis of cryptosporidiosis first requires consideration of the pathogen when ordering diagnostic testing. Specimens should be sent specifically for microscopic examination of *Cryptosporidium* oocysts. The most commonly employed methods for detection include modified acid fast staining and direct fluorescent antibody staining [61, 62]. These tests must be specifically ordered because they are not part of the routine ova and parasite screening in most clinical laboratories. ELISA kits for antigen detection are also increasingly available [60].

Treatment options currently include supportive therapy and possibly antiparasitic therapy [58, 59]. Most cases, particularly in immunocompetent persons, are self-limiting [60]. Nitazoxanide 500 mg orally every 12 h has been shown to be efficacious in resolution of cryptosporidiosis in immunocompetent and moderately immunocompromised patients [63]. Treatment for three to seven days is recommended for immunocompetent adults with prolonged diarrhea or for pediatric patients. A longer course is typically recommended for AIDS patients or for patients with hematologic malignancies, although prior studies have had mixed results [64]. In addition, paromomycin is also noted to have in vitro activity and may have some clinical usefulness [64]. Correcting the underlying immune dysfunction is critical to eradicating the illness in HIV-infected patients [61, 64].

5.2 *Strongyloides* Infection

Strongyloides stercoralis is an intestinal helminth that is endemic in many developing countries, particularly tropical and subtropical regions, and in some parts of Europe and the southern United States [65–67]. A large number of infections are subclinical, but immunocompromised patients may have potentially fatal infections [65, 66, 68]. In patients with hematologic malignancies [66, 67], use of systemic corticosteroids [66] and allogeneic hematopoietic stem cell transplantation are important risk factors for strongyloidiasis [66]. In addition, prior gastric surgery and gastrointestinal cancer are also reported risk factors [67, 69].

The larvae of *Strongyloides* can penetrate the skin of the human host during the filariform stage. These larvae normally then migrate through circulation to the lungs, airway, and then are swallowed into the intestine [65]. Symptoms can range from asymptomatic to life-threatening hyperinfection [65–69]. Non-disseminated symptoms may include pruritic rash, particularly in the buttocks, groin, and trunk. Abdominal symptoms may include chronic diarrhea, nausea, and abdominal bloating [65, 66]. Pulmonary involvement can present as Loeffler's syndrome (dry cough, dyspnea, and transient pulmonary infiltrates with eosinophils) [66].

Immunocompromised patients may have life-threatening complications of strongyloidiasis, particularly those with impaired cellular immunity [65–67]. This is due to exaggeration of the autoinfection cycle, which occurs when the number of organisms increases rapidly and is present in extraintestinal regions [65].

Pulmonary hyperinfection can result in pneumonia or intra-alveolar hemorrhage. In addition, bacterial infections can result from translocation of gastrointestinal flora from damaged bowel mucosa, resulting in septicemia, pneumonia, meningitis, or disseminated disease [65, 66].

Diagnosis of strongyloidiasis should be considered in patients from endemic areas, even if they moved from the endemic region many years ago. The diagnosis is most frequently made on microscopic examination of stool for larvae [65]. Bronchial specimens may also be diagnostic in pulmonary disease [66]. Peripheral eosinophilia may or may not be present in strongyloidiasis [65, 66]. Pulmonary infiltrates on chest radiographs may also vary, including alveolar or interstitial, diffuse or local, unilateral or bilateral [65]. Ivermectin is currently first-line therapy for chronic strongyloidiasis. It is given orally at 200 μg/kg daily for 2 days, with consideration of repeat dosing after 2 weeks. Alternative regimens include albendazole 400 mg twice a day for 3 days. Longer courses may be necessary for disseminated strongyloidiasis or hyperinfection syndrome [70]. Screening for asymptomatic strongyloidiasis should be strongly considered in high-risk patients from endemic areas who are diagnosed with hematologic malignancies or who are to receive steroid or stem cell transplantation [66, 69].

5.3 Cytomegalovirus Infection

Cytomegalovirus (CMV) colitis is common in immunocompromised patients, particularly those with AIDS, solid organ transplants, and bone marrow allogeneic transplants. Bone marrow patients may be susceptible due to T-cell immunodeficiency, particularly during episodes of graft-versus-host disease (GVHD) [71]. Infections can be asymptomatic or cause disease in the gastrointestinal tract, liver, lungs, or eyes [72]. CMV can present as enterocolitis, specifically in those who have impaired T-cell function [73]. CMV colitis may follow administration of standard chemotherapy regimens [73–75]. Cases have been reported following administration of cisplatin and etoposide for lung cancer [75], docetaxel, 5-FU, and cisplatin for hypopharyngeal cancer [74], and a regimen of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone) for non-Hodgkin's lymphoma [67].

CMV gastrointestinal disease has been increasing in frequency among patients with hematologic malignancy over the last several decades following conventional chemotherapy, aggressive therapy, and bone marrow transplantation [76, 77]. Gastrointestinal manifestations may include anorexia, nausea, vomiting, and diarrhea [77]. CMV risk appears to increase with the use of T-cell-depleting agents and aggressive chemotherapy [72]. Re-activation of CMV disease has occurred with the use of the immunomodulating antibody, rituximab [78], and CMV colitis has been reported with alemtuzumab [79].

Nucleic acid-based assays and antigen assays have been employed for the detection of CMV [80–82]. These assays allow both the diagnosis of active

infections and surveillance for incipient clinical disease in patients at risk. The CMV pp65 antigenemia assay is an indirect immunofluorescence stain with monoclonal antibodies to the CMV protein pp65 [81]. However, this test has been reported to be labor-intensive and subjective, particularly to less fresh specimens [80]. Other assays to detect CMV have included CMV DNA PCR and mRNA pp67 assays [80]. More recently, a real-time CMV PCR assay has been developed to diagnose and monitor CMV infections [82]. In a trial of HIV patients, break points of 3.0×10^3 copies/mL in whole blood had a sensitivity of 93 % and specificity of 86 %, while 1.0×10^3 copies/mL in plasma had a sensitivity of 89 % and specificity of 85 % [82]. The advantages of real-time PCR include improved accuracy and speed, and they are less time-consuming than traditional PCR [82]. CMV colitis is also diagnosed by intestinal biopsy and identification of cells with typical cytomegalic inclusions. However, sampling error may result in false-negative biopsies [83]. Stool PCR has also been proposed as a test for CMV colitis [83, 84]. However, studies supporting this method were small studies and need to be further evaluated on a larger scale.

Treatment for CMV infections includes ganciclovir, foscarnet, and/or cidofovir [76]. Intravenous (IV) ganciclovir has been considered first-line therapy, but CMV resistance has been reported. Ganciclovir treatment recommendations in patients with normal renal function normally include an induction dose, 5 mg/kg every 12 h, followed by a maintenance dose of 5 mg/kg daily, intravenously. Oral ganciclovir, however, may not be clinically efficacious because of poor absorption [72]. Intravenous foscarnet or cidofovir may be considered for treatment for infection with ganciclovir-resistant isolates [76, 84]. Foscarnet has been associated with renal and neural toxicity. Cidofovir has previously been used for treatment for CMV retinitis and also can be nephrotoxic [84]. CMV hyperimmunoglobulin (CMVIG) may also have benefit, but appears to more beneficial for CMV pneumonia rather than CMV colitis [76]. Treatment efficacy may be monitored by serial antigen or nucleic acid assays.

Prophylaxis of CMV may be beneficial in stem cell transplant patients. Ganciclovir or foscarnet are administered at induction doses for 1–2 weeks or until CMV load and/or antigenemia decreases [85]. Maintenance dosing may then commence for a total of 6 weeks to 3 months, or when immunosuppression resolves [71, 85]. An oral agent, oral valganciclovir, may be given for prophylaxis or preemptive therapy. It is dosed 900 mg every 12 h for induction, and 900 mg daily for maintenance [84]. Late CMV infection, or cases presenting after 100 days, may be associated with prior CMV antigenemia, graft-versus-host disease, CD4 cell counts of <50 cells/mm^3, or post-engraftment absolute lymphopenia of <100 lymphocytes/mm^3 [71]. These findings may support long-term prophylaxis of at-risk stem cell transplant patients.

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Note of added proof: CDI severity criteria based on WBC count and creatinine level may not be applicable to patients with hematologic malignancies.