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Gastrointestinal Surgical Emergencies in the Neutropenic Immunocompromised Patient

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Abstract

Surgeons encounter neutropenic patients through elective or emergency consultation with increasing regularity. As medical management continues to extend the lives of patients with benign hematologic diseases, hematologic malignancies, solid malignancies, or iatrogenic neutropenia, more patients are presenting with infectious complications caused and/or complicated by their neutropenia. This leaves surgeons in the difficult position of managing medically fragile patients with unusual presentations of common disease processes. These patients often fall outside of classical guidelines and treatment pathways. Many studies addressing these issues are retrospective and non-randomized. Here, we review common emergency gastrointestinal surgery scenarios and their management in the setting of a neutropenic patient. While biliary disease, appendicitis, anorectal disease, and perforations will be covered in detail, an extensive appreciation of a patient's medical or oncologic disease course and appropriate utilization of consultants such as interventional radiology, gastroenterology, and hematology is often necessary.

Keywords

Neutropenia; Pneumoperitoneum; Abscess

Introduction

The frequency with which surgeons encounter neutropenic patients varies greatly based on their practice setting. While neutropenic patients represent a substantial proportion of patients treated at cancer centers or tertiary referral academic centers, they are less common in community settings. Nevertheless, as the treatment of both liquid and solid malignancies

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continues to evolve, management of these patients will become more commonplace across healthcare settings.

Neutropenia is frequently defined as having a plasma absolute neutrophil count (ANC) less than 1500 per microliter[1]. A neutropenic state can be multifactorial in etiology but is commonly caused by cytotoxic chemotherapeutic agents, myelosuppression secondary to systemic inflammation, and/or primary hematopoietic malignancies. Hereditary causes of asymptomatic chronic neutropenia are not associated with increased infectious risk, such as benign ethnic neutropenia, and are less commonly encountered in inpatient situations warranting surgical consultation.

Significant comorbid conditions occur frequently in this patient population. Additionally, secondary to an inherently dysregulated immune system, the presentation of a patient's disease process will often be atypical. This is exemplified in a retrospective study of patients evaluated for abdominal pain and neutropenia at a single institution. Their diagnosis, as determined via laparotomy or autopsy, only confirmed the preoperative diagnosis in 19 of 36 patients studied (53%)[2]. Similarly, no clear diagnosis was rendered in 35% of patients in a second series of 60 neutropenic patients who presented with abdominal pain[3]. These findings underscore how a variety of these pathologies will present in an atypical nature in patients with neutropenia.

When diagnosing and managing morbid disease processes with atypical presentations in medically fragile patients, realistic expectations should be discussed with the patient, their family, and referring or co-managing physicians at the onset of their care. Moreover, minimizing invasive interventions in these patients or utilizing temporizing measures to allow a patient's neutropenia to recover may often be the most prudent path. For example, a report of neutropenic patients treated at a quaternary cancer center demonstrated 30% in-hospital mortality and 52% 90-day survival, with a median overall survival of 2.9 months. The most common causes of death in this cohort were sepsis and cancer progression[3]. In the following manuscript, we discuss the management of specific disease processes in the setting of this patient population.

Intra-abdominal Processes

Infectious complications are unfortunately common in neutropenic patients. In patients with hematologic malignancies, approximately 30% of these infections stem from the gastrointestinal tract[4]. These infections are difficult to diagnose, and prompt management is necessary to optimize patient outcomes. In a series of neutropenic cancer patients with abdominal pain, the most common diagnosis prompting surgical consultation was neutropenic enterocolitis (28%) followed by small bowel obstruction (12%), *Clostridium difficile* infection (7%), diverticulitis (5%), appendicitis (5%), cholecystitis (3%), pseudo-obstruction (3%), splenic rupture (2%), and an unclear diagnosis (35%). Multidisciplinary care with close communication among providers optimizes the prompt thoughtful evaluation, accurate diagnosis, and consideration of surgical and medical options necessary to provide the best outcome[5]. This includes seeking input from hematologists or oncologists regarding the patient's underlying pathology as well as their assistance in

managing coagulation profiles for those patients with concurrent thrombocytopenia and/or pancytopenia. Finally, it is our practice to have a low-threshold for the use of broad spectrum antibiotics and anti-fungals, often with the assistance of an infectious disease consultation. Given the difficulty inherent in conducting stringent studies, multi-disciplinary care and input from trusted consultants is crucial.

Biliary Pathology

Biliary pathology in the Western population is common, with cholecystectomy being the most common surgical procedure performed by general surgeons in the United States[6]. Cholecystitis in neutropenic patients, however, is relatively uncommon, with an incidence of 0.4%[7]. Nevertheless, neutropenic patients are at particularly high risk for developing acalculous cholecystitis (66% of cholecystitis cases in neutropenic patients) as compared to the general population with cholecystitis (5%). As acalculous cholecystitis is a common marker of critical illness, it is not surprising that mortality associated with this diagnosis in a small systematic review of neutropenic patients is 44%. None of these deaths (n=4), however, were associated with the gallbladder disease directly. Instead, the patients died from progressive leukemia (n=1), pneumonia (n=2), or sepsis (n=1)[7].

Cholecystitis in the neutropenic patient should be promptly diagnosed and confirmed with classic findings on right upper quadrant ultrasound. Intravenous antibiotics should be initiated followed by surgical evaluation. Given the almost inherently tenuous nature of these patients, interventional radiology should be routinely engaged for consideration of percutaneous drainage[8]. Temporizing these patients with medical management (antibiotics, with consideration for growth factor support, such as granulocyte colony stimulating factor, GCSF) and decompression via cholecystostomy tube can help effectively mitigate any acute processes. Patients are then allowed to medically recover while their neutropenia improves. At that point elective cholecystectomy can be planned to minimize interruption of their chemotherapy and/or optimize their underlying medical state[9, 8].

While gallbladder disease is uncommon in the neutropenic population, cholangitis or other more complex biliary pathologies are similarly uncommon. It is worth mentioning, however, that biliary obstruction is a common complication of patients with neutropenia induced by chemotherapy for management of their biliary, liver, duodenal, or pancreatic malignancy. Palliation and management of these patients should ideally be managed by the surgical oncologist caring for the patient longitudinally as these decisions may impact future operative interventions. Biliary obstruction and associated cholangitis can be decompressed through endoscopic or percutaneous means. While little data exists specifically in the neutropenic patient population, endoscopic drainage is generally preferred[10, 11]. Surgical decompression offers lower risks of recurrence and decreased hospitalization; however, these endeavors should be considered once the patient’s counts have recovered and in the context of their overall care and treatment course[12].

Appendicitis

As appendicitis occurs at all ages, it will inevitably occur during episodes of neutropenia. While debate exists in a general patient population between medical and surgical

management of patients with uncomplicated appendicitis, the risk/benefit equation for neutropenic patients is weighted toward medical management. In a series of cancer patients, many of whom were neutropenic at presentation, the majority (62.5%) were treated with antibiotics alone, 25% went straight to appendectomy, and 12.5% required drainage by interventional radiology and antibiotic treatment[13]. No patients treated in this series required conversion to appendectomy at their index admission, while one of four patients in the IR drainage group required an appendectomy after failed drainage. Six of the twenty patients treated with observation required an interval appendectomy, three electively, and three after readmission for failed medical management. In a hemodynamically stable patient, antibiotics, bowel rest, and consideration of interventional radiology consultation and/or growth factor support should be the first line of management of these patients. Although small series have demonstrated success in treating neutropenic pediatric patients with appendectomy, expeditious source control whether through drainage of associated abscesses or parenteral antibiotics in the neutropenic patient should be the primary goal of care[14]. This is especially true given the inherently emergent setting when treating appendicitis. For neutropenic patients undergoing abdominal operations, the rate of mortality for urgent operations has been shown to be 16.4% as compared to 1.4% in elective procedures, a discrepancy largely driven by the severe nature of intra-abdominal complications (such as a non-resolving small bowel obstruction or perforated viscous) in urgent cases[15].

Enterocolitis and Pneumatosis

Neutropenic enterocolitis (NE) is a common complication of cytotoxic chemotherapy[16]. Although its overall incidence is unknown, 5.6% of hospitalized neutropenic patients with aplastic anemia or undergoing treatment for hematologic or solid malignancies may develop NE during their care. This clinical condition is difficult to diagnose given the broad differential diagnosis of abdominal pain in a neutropenic patient. The current definition of NE is <500 cells/L, fever > 38.3 C, and abdominal pain along with cross sectional imaging demonstrating >4 mm bowel wall thickness in a >3 cm length of bowel. Of note, fever may be absent in patients with NE and occurs both in the treatment of liquid and solid malignancies[17-20]. Despite advanced medical care, mortality is significant and upwards of 50%[21, 22]. C. difficile infection and graft-versus-host disease, for those with a prior allogenic stem cell transplantation, should be ruled out. Initial management should involve peripheral blood cultures, bowel rest, and broad-spectrum IV antibiotics. Antifungal coverage should be added if clinical improvement is not noted in 72-96 hours[17]. Growth factor support should also be strongly considered but has not been systematically studied in this population[16]. Nasogastric (NGT) decompression is oftentimes used, although its efficacy in improving outcomes has not been established. We typically reserve NGT use for patients with significant nausea or emesis. While some have studied the use of continuous feeding and/or glutamine supplementation to prevent villous atrophy and maintain mucosal integrity, conservative courses should still involve NPO status and consideration for parenteral nutrition with divergent courses reserved for extenuating circumstances or clinical research protocols[16, 23].

While historical studies describe right hemicolectomy being offered to these patients, and an association with improved outcomes, surgical management is most often not the initial

modality of treatment for NE in the modern setting[24]. Given improvements in supportive care and treatment with GCSF in recent decades, most patients are now able to be safely managed non-operatively[3, 25-27]. Of note, GCSF is often used prophylactically in patients who are neutropenic or anticipated to experience neutropenia. However, patients with active febrile neutropenia and who did not previously receive GCSF may be considered for GCSF treatment; its use remains controversial and under-studied in this subset of patients. Surgical intervention is reserved for patients who develop complications necessitating an operation: persistent GI bleeding, pneumoperitoneum, and/or frank clinical deterioration[28]. When comparing complication rates, there is no benefit to early surgical intervention, even in historic literature[16,29]. In these patients who oftentimes require further medical therapy and management, minimization of interventions and their associated morbidity may optimize overall outcomes. It is important for surgeons to be familiar with this disease process, not only in managing its complications, but, as a consideration when building a differential diagnosis for a neutropenic patient with abdominal pain and knowing when not to operate as well as when to operate.

Pneumoperitoneum will mandate an emergent exploratory laparotomy in nearly all patients. This is not the case, however, in neutropenic patients who may have impaired ability to recover or respond to an infectious complication. Evaluation of these patients will need to be expedited, but the decision regarding surgical exploration in the neutropenic patient should be approached cautiously and with shared decision making[24]. This is especially true in the setting of patients with advanced malignancies, where discussion of patient goals and an in-depth understanding of the underlying disease processes is of paramount importance[30]. It is our practice and teaching to utilize the "Best Case/Worst Case" model, especially when broaching these topics at the time of initial consultation for previously unknown patients[31]. This tool has undergone significant study in the geriatric surgical population, ensures key information is covered in any discussion, and provides an excellent framework for both patients and clinicians of all levels of training.

In a retrospective study of patients presenting with free air and a concomitant cancer diagnosis, there was not a statistically significant difference in survival between the operative and non-operative group on Kaplan-Meier analysis[23]. In the cancer patient, pneumoperitoneum can be induced by obstruction, tumor invasion into a hollow viscus, or cancer-directed therapy. It is important, however, to be cognizant of the associated risk with a wide variety of agents including many new or novel medications[32, 33]. Many of these therapies block pathways associated with tumor growth as well as with wound healing, thereby increasing rates of perioperative complications. Although data is limited, immune checkpoint blockade, one of the most frequently-used novel medication, has not been shown to affect wound healing or perioperative complications[34].

At the completion of any operation involving a neutropenic patient, care should be taken to consider the closure method. Unfortunately, a paucity of data in this space exists as these procedures are historically rare, often emergent, and do not lend themselves to a controlled study. Moreover, these patients are typically excluded from trials of wound closure methods and thus subset analyses or controlled series are not available for study. We advocate for conservative closure methods in keeping with the operative surgeon’s standard practice. It

is our practice to close fascia with large looped non-absorbable monofilament suture to minimize evisceration and to approximate the skin with staples and a low-threshold for removal and packing should any signs of infection develop. Finally, for those patients with or who are prone to ascites, an abdominal drain can be considered to optimize midline wound healing. This should be placed however, with a clear plan for removal and with plans to closely monitor the patient's volume status post-operatively.

While review of each medication and their respective pathways is outside of the scope of this review, this effect is most commonly noted in vascular endothelial growth factor (VEGF) inhibition with bevacizumab[35]. The intended effect of bevacizumab is to inhibit vascular growth and remodeling associated with tumor progression. In the case of wound healing, however, this impedance creates disordered wound vascular growth within the wound bed and is associated with a significant increase in wound healing complications (meta-analysis OR 2.32 95% CI [1.43-3.75])[36]. Surgical exploration, therefore, should be undertaken with great trepidation in patients on bevacizumab, with the medication ideally being held for at least 8 weeks prior to elective surgery. The minimal timeline between bevacizumab exposure and more emergent surgery is not well established or studied; therefore, the risks and benefits of urgent and emergent surgery in the setting of recent bevacizumab exposure must be carefully discussed with the patient and/or their appointed surrogate decision makers[37]. It should be underlined that classical management of many of acute processes cannot be safely undertaken and that minimal intervention, including diversion or wide drainage, can allow for supportive therapy until safe definitive care. Ultimately, if the underlying process is not survivable, early involvement of palliative care (preferably prior to any acute event), a goals of care discussion, and palliation should be undertaken.

Perianal disease

Anorectal infections are a complication of the neutropenic patient with rates reported to be between 5% and 9% in patients with hematologic malignancies[38]. Although the rates in solid malignancies or benign neutropenia are unknown, they are suspected to be lower, as patients with hematologic malignancy typically are treated with myelosuppressive regimens, especially in the context of bone marrow transplantation[38-41]. As neutrophils are critical in the formation of an abscess, these patients may often times present atypically with physical exam findings discordant to the extent of their disease[5]. Rectal exams should be undertaken with caution and only if necessary in these patients who can classically have their disease well evaluated using cross-sectional imaging[42]. If a clear collection is seen on exam or cross-sectional imaging, consideration should be given to open drainage, especially in the setting of a superficial abscess. This is oftentimes the most conservative course from a surgical perspective and in keeping with current practice guidelines[43]. Open drainage procedures, however, must be weighed against wound healing issues and potential delays in oncologic or hematologic treatments. In this setting consideration can be given for medical management with close observation, percutaneous aspiration with antibiotics, or percutaneous drain placement with antibiotics. This should be considered, however, with the knowledge that a complex fistula may likely form in the case of drain placement and that failure of management may ultimately act to delay eventual open drainage.

Surgical management should be reserved for patients with undrained collections, large collections, or those not amenable to percutaneous drainage[40]. Operative intervention, however, can be performed safely with appropriate patient selection and when improvement is not noted with medical measures[44, 39]. It is not uncommon for these patients to develop abscesses as their counts recover. As such, surgical intervention may be required at a later date for more definitive drainage. Definitive management of fistulae should be deferred and done as elective procedures once the peri-rectal inflammation has resolved.

Graft Versus Host Disease

GVHD is a complication of allogenic stem cell transplantation. Although incompletely understood, GVHD development involves alloreactive donor T-cells activating against host tissue. This process can occur throughout the body. GVHD can present with a number of life-threatening complications. In the case of the gastrointestinal tract, gut microbial dysbiosis has been suggested in gastrointestinal GVHD. This can lead to breakdown of the mucosal barrier and diarrhea associated with poor absorption[45]. Gastrointestinal GVHD can present in both an acute or chronic form and is confirmed with histologic examination[46].

Acute disease will typically present 3 or more weeks after transplant as a maculopapular rash and hyperbilirubinemia as a result of damage to terminal branches of bile ducts. Abdominal pain, diarrhea, nausea, and vomiting are common with this presentation. Surgical intervention is not a part of the treatment of GVHD. It is, however, essential for surgeons caring for the allogenic stem cell transplant patient to be aware of GVHD and its downstream effects given the potential for the need for surgical intervention in the rare instance a patient with GVHD develops an associated surgical problem. Surgical consultation is warranted in instances of gastrointestinal bleeding or bowel obstruction[47]. Small series describing surgical intervention in these patients, however, report significantly high rates of peri-operative mortality (31-33%), even in the pediatric patient population[48, 47]. Although a diagnosis of GVHD is made histologically, it should remain on the differential of physicians treating a patient following allogenic stem cell transplantation to avoid confusion, misdiagnosis, or mistreatment. While various treatment modalities exist to manage GVHD, it is frequently incurable and difficult to manage.

Conclusion

Here we outline guidance and data behind the surgical management of a variety of abdominal and perineal disease processes in the neutropenic patient. While varying levels of data and understanding exist for each disease, there are some important global guiding principles. It is of paramount importance to obtain a full understanding of a patient's disease status, prognosis, and the impact their acute disease is expected to have on their treatment plan. Neutropenia should be defined as transient or permanent, inciting factors identified, along with their risk for severe neutropenia and its expected duration when developing a definitive care plan. This will likely involve discussion with other treating medical teams and a frank discussion with the patient about the current status of their care and the effect this acute process will have on those expectations.

While we reviewed a variety of work suggesting that classic treatment algorithms that may involve early operative intervention should be questioned in the treatment of a neutropenic patient, a number of these referenced works demonstrated improved survival with operative intervention. It is notable that the work cited here represents retrospective studies at high volume centers regularly treating neutropenic patients. Any change in survival with or without operative intervention will clearly be largely a reflection of patient selection by an experienced surgical consultant.

For many neutropenic patients, a surgical consultation will require the expertise to recommend against an operative intervention. As such, an intimate understanding of supportive care and adjunctive procedures such as those offered by interventional radiology, gastroenterology, and hematology are critical. Surgeons should remain engaged in these patients' care longitudinally as well for eventual definitive management as indicated or to be available should non-operative means fail. In many cases these events can be terminal ones for patients or preclude them from continuing or initiating further management of their underlying disease process. In an acute setting it may fall to the consulting surgeon to discuss these goals, ideally with the input and in collaboration with their treating medical oncologist[49, 50]. These often-difficult conversations can be well directed for both familiar and unfamiliar practitioners with the implementation of a best case/worst case framework as outlined by Kruser et al[31].

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