Neutropenic Fever in the Intensive Care Unit

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Contents

Abstract

Neutropenic fever is a common and potentially life-threatening condition in patients treated for cancer. Rapid initiation of appropriate antimicrobial therapy is necessary to decrease the risk of mortality. Most infections are due to gram-positive organisms, but the mortality rate is higher for gram-negative infections. Multidrug-resistant organisms are an emerging threat to neutropenic patients. Increasing data suggest that the pathophysiology of neutropenic fever and neutropenic sepsis is substantially different from non-neutropenic fever and sepsis. Additional research is needed to both further elucidate the pathogenesis of neutropenic fever and to develop additional effective antimicrobials.

Keywords

Neutropenia · Neutropenic · Fever · Sepsis · Gram negative · Gram positive · Fungal

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Introduction

Neutropenic fever is one of the defining conditions of oncologic critical care. Neutropenic fever is defined as a single temperature higher than 38.3 °C or a sustained temperature greater than 38.0 °C for more than 1 h, in the presence of an absolute neutrophil count [ANC]) less than 1500 cells/mm^3, though many centers and guidelines use an ANC cutoff of less than 500 cells/mm^3 [28, 33]. Exceedingly common in patients receiving cytotoxic chemotherapy, neutropenic fever is a medical emergency which requires urgent initiation of broad-spectrum antibiotics. Any oncologic patient receiving myelosuppressive chemotherapy is at risk of developing neutropenia and opportunistic infections, but profound neutropenia with life-threatening infectious complications is most commonly seen in patients with hematologic malignancies. This can occur during aplasia and before engraftment in patients receiving hematopoietic stem cell transplant (HSCT) or from disease-related or treatment-induced cytopenias in other hematologic malignancy patients.

Etiology

While there are many potential causes of fevers in neutropenic hosts, both infectious and noninfectious, fevers must be presumed to be infectious in origin. Potential infectious agents and sources of infection are legion and include viruses, bacteria, and fungus. Viral pathogens include respiratory viruses (e.g., respiratory syncytial virus, rhinovirus, adenovirus, coronavirus, influenza, parainfluenza), reactivated or de novo herpes viruses (e.g., herpes simplex, cytomegalovirus, Epstein-Barr virus), and many other potential candidates. Bacterial infections may arise from gut translocation, oral mucosal translocation, infection of indwelling vascular catheters, skin and soft tissue infections, pneumonias, and urinary sources. Fungal infections typically arise from gut translocation, fungal pneumonias (e.g., aspergillosis), and vascular catheters. Drug fevers or "tumor fevers" are the most common example of noninfectious fevers, but these are diagnoses of exclusion.

Epidemiology

Neutropenic Fever

Neutropenic fever occurs in up to 50% of patients with solid tumors receiving cytotoxic chemotherapy and in more than 80% of patients receiving chemotherapy for hematologic malignancies or undergoing HSCT [28]. In 2012, more than 90,000 adults were hospitalized for cancer-related neutropenia, with a total cost of $2.3 billion [75]. In-hospital mortality for all patients admitted with neutropenic fever is nearly 10%; this increases to a hospital mortality rate of more than 15% for patients with leukemia admitted for neutropenic fever [37].

Bacteremia is documented in up to 25% of neutropenic fever patients [28]. Whereas in the past gram-negative organisms were commonly cultured, gram-positive organisms, including staphylococci, enterococci, and streptococci, are currently the most commonly isolated bacteria [28, 50] (Table 1). This shift is presumably due to the increased use of long-term indwelling vascular catheters and may also be affected by increased use of prophylaxis against gram-

Table 1 Typical pathogens during bacterial sepsis in neutropenic patients

Origin	Frequent pathogens
Unknown	*Coagulase-negative Staphylococci*, *Escherichia coli*, *Enterococcus* species
Lung	*Pseudomonas aeruginosa*, *Streptococcus pneumonia*, *Viridans streptococci*, *Acinetobacter* species
Abdomen	*Escherichia coli*, *Pseudomonas aeruginosa*, *Clostridium* species, *Enterococcus species*, *Klebsiella* species
Urogenital	*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* species
Soft tissue	*Staphylococcus aureus*, alpha-hemolytic *streptococci*
Central venous catheter	*Coagulase-negative Staphylococci*, *Coryneform bacteria*, *Propionibacterium* species, *Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Stenotrophomonas maltophilia*

Modified from [57] (Springer)

negative organisms [50, 59]. Though gram-positive infections are more common, gram-negative infections confer a higher risk of mortality [77]. Fungal infections, particularly *Candida* and *Aspergillus*, are also frequent, especially in patients with prolonged or profound neutropenia [33]. Respiratory viruses can be isolated in approximately 20% of patients [34]. Despite best efforts, no causative organism can be identified in about 50% of cases of neutropenic fever [28, 33].

Neutropenic Sepsis

Sepsis has been most recently defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [70]. A premium is placed on identification of organ dysfunction using either the Sequential Organ Failure Assessment (SOFA) score or the Quick SOFA (qSOFA) score; the presence of organ dysfunction in the setting of a suspected or proven infection is sufficient to diagnose sepsis (Tables 2 and 3). Septic shock is defined by the need for vasopressors to maintain a mean arterial pressure (MAP) ≥65 mmHg or a serum lactate >2 mmol/L despite adequate volume resuscitation.

There is no specific consensus definition for neutropenic sepsis, other than sepsis occurring in the presence of neutropenia. Any evidence of organ dysfunction, including an elevated lactate, in the presence of neutropenia should be treated as a potential indicator of sepsis. There are few reliable data on the incidence of neutropenic sepsis or neutropenic septic shock. It has been estimated that 50% of patients with neutropenic fever will develop sepsis, and up to 10% of patients with neutropenic fever will progress to septic shock [33]. Among neutropenic allogeneic HSCT patients, approximately 10% will develop severe sepsis during the engraftment period [38].

Pathophysiology

Cytotoxic chemotherapy or cytotoxic radiation, whether given as an antitumor agent or conditioning regimen for HSCT, induces neutropenia by injuring or destroying hematopoietic precursor cells within the bone marrow as well as injuring the bone marrow structure itself [44]. Circulating

Table 2 Sequential organ failure assessment score

	Score				
System	0	1	2	3	4
Respiration: PaO_2/FiO_2, mmHg	≥400	<400	<300	<200[a]	<100[a]
Coagulation: platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver: bilirubin, mg/dL	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12
Cardiovascular	MAP ≥70 mmHg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine
CNS: GCS	15	13–14	10–12	6–9	<6
Renal:					
Creatinine (mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output (ml/day)				<500	<200

Modified from Vincent et al. [79]
CNS central nervous system, *GCS* Glasgow Coma Scale
[a]With respiratory support, catecholamine doses given as mcg/kg/min

Table 3 Quick SOFA criteria (qSOFA)

Respiratory rate ≥22/min
Altered mentation
Systolic blood pressure ≤100 mm Hg

Modified from [70]

leukocytes are not replaced as they reach the end of their life span, and neutropenia ensues. Circulating neutrophils have a short life span in the peripheral blood [43], so neutropenia develops rapidly after myelosuppressive therapy. Depending on the chemotherapy employed, circulating neutrophils and other white blood cells may also be damaged or destroyed, causing a more rapid leukopenia than regimens which only affect the marrow. Some agents will injure progenitor cells but not primitive stem cells (which re-populate the progenitor cells), whereas other agents will injure all cells in the marrow [44].

In the normal patient with a localized infection, neutrophils are rapidly recruited at the onset of focal infection and are essential to microbial killing and infection control [40, 45]. Neutropenic fever and neutropenic sepsis have historically been thought of as variants of non-neutropenic fever and sepsis, just without an intact immune system, akin to a "fire without firefighters." However, increasing data suggest that the pathophysiology of neutropenic patients is much more complicated than simply an uncontrolled infection [36]. In addition to their key role in the response to localized infections (e.g., pneumonia), in sepsis neutrophils are rapidly recruited to organs (lungs, kidneys, liver) and are thought to contribute to tissue damage and organ dysfunction [45]. Neutrophils also contribute to resolution of injury and tissue repair [36], as well as regulation of the adaptive immune response [40, 76]. Thus neutropenic patients are not only deficient in the immediate response to infection but also have an altered physiology regarding the development of systemic inflammation and sepsis and in the regulation of the immune response to injury and tissue repair. It is increasingly unclear whether neutropenic sepsis (and the organ damage sequelae) is the same disease as non-neutropenic sepsis.

Because cytotoxic chemotherapy is not selective, neutropenic patients are also lymphopenic, thrombocytopenic, and anemic. Lymphocytes, including T cells, B cells, and natural killer (NK) cells, have protean roles in the immune system and a broad effect on the response to infection and septic physiology [20, 43]. These cells are also drastically reduced after cytotoxic chemotherapy, and lymphopenia has been associated with an increased risk of death [67, 71]. Adding to the complexity, the kinetics of count recovery and engraftment vary, and reconstitution of all cell lines does not happen simultaneously [11]. Though the total effect of lymphopenia on the pathophysiology of neutropenic fever and infection remains to be fully determined, patients with neutropenic sepsis have different cytokine profiles than patients with non-neutropenic sepsis: neutropenic patients have higher levels of IL-6, IL-8, and G-CSF than non-neutropenic patients [60]. Monocytes are also dysfunctional in neutropenic sepsis, with evidence not only of deactivation of monocytes in peripheral blood but also of deactivation of differentiated pulmonary macrophages in patients with neutropenic sepsis [48, 49].

The implications of pancytopenia for the response to infection extend beyond white blood cells. Most neutropenic patients are thrombocytopenic, and platelets are increasingly recognized to play an important role in the immune response [23, 74]. Thrombocytopenia is associated with poor outcomes in critical illness, including in sepsis [18]. In addition to secreting mediators and regulators of inflammation, platelets interact with neutrophils and monocytes and play a vital role in the defense against bacterial, viral, and fungal infections via the formation of neutrophil extracellular traps (NETs) [16, 21, 23]. Platelets also play roles in the development and resolution of organ failure in inflammatory states, including sepsis. In particular, thrombocytopenia has been demonstrated to potentiate lung injury [46, 86], and platelets may play a role in the pathophysiology of acute kidney injury [23]. While the role of thrombocytopenia in infection remains incompletely elucidated, it seems clear that

thrombocytopenia is an important factor in the pathophysiology of neutropenic infection.

Other organ systems with relevance to neutropenic infections are also affected by cytotoxic chemotherapy. The most important of these is injury to the mucosal barrier of the intestinal tract [13, 14, 78]. Disruption of this barrier, which can occur throughout the gastrointestinal (GI) tract, creates portals through which enteric pathogens, including bacteria and yeast, can enter the bloodstream. This is an important source of gram-positive, gram-negative, and fungal infections in neutropenic patients. The respiratory system is also affected in neutropenia. Not only are pulmonary macrophages known to be qualitatively dysfunctional in neutropenic sepsis [48, 49], but quantitative cell counts of alveolar macrophages, lymphocytes, and neutrophils are decreased during neutropenia [19]. Neutropenia also appears to adversely affect lung repair after injury [12]. Taken together, these data strongly support the hypothesis that neutropenic sepsis has a significantly different pathophysiology than non-neutropenic sepsis.

Clinical Features

As defined above, the diagnosis of neutropenic fever requires a single temperature higher than 38.3 °C or a sustained temperature greater than 38.0 °C for more than 1 h in the presence of neutropenia [28, 33]. While some patients are asymptomatic in the presence of neutropenic fever, many describe non-specific symptoms (e.g., cough, anorexia, nausea, fatigue, dizziness, myalgias, confusion, behavioral changes). Patients may also present with respiratory symptoms (cough, shortness of breath, sinus pain or drainage) or abdominal symptoms such as pain or diarrhea. Fewer than half of patients will feel feverish, shiver, or have rigors [17]. Presentation to the hospital can be delayed, with one study suggesting a mean delay in presentation of 11 h and nearly 40% of patients delaying presentation for more than 12 h [17]. Though neutropenic patients have higher fevers than non-neutropenic patients, there is no association between peak temperature and mortality. Hypothermia during neutropenic sepsis is associated with worse outcomes [84].

Neutropenic patients with septic shock tend to have more frequently positive blood cultures, more fungal infections, more multidrug-resistant bacterial infections, and higher mortality rates than immunocompetent patients. Compared to non-neutropenic patients, patients with neutropenic sepsis have higher rates of shock and are at higher risk to sustain acute kidney injury [60].

Diagnosis

Early recognition of neutropenic fever is essential. Regardless of whether neutropenic patients are hospitalized or not, frequent temperature checks are essential to detect fever; outpatients must particularly be educated on the importance of monitoring temperature. Similarly, interventions that might mask fevers (e.g., antipyretics such as acetaminophen) should generally be avoided in neutropenic patients, and clinicians should be aware of other interventions (e.g., steroids, continuous renal replacement therapy) which may suppress fevers. Once a fever is detected, blood cultures should be obtained without delay, and antibiotics initiated as quickly as possible. Diagnostic measures must not interfere with the timely administration of antibiotics. A comprehensive physical exam should be performed and may uncover potential sources of infection (e.g., mouth sores, skin lesions, pulmonary findings, abdominal tenderness or pain).

Blood cultures are essential to the evaluation of neutropenic patients with fever. A minimum of two sets of blood cultures should be drawn upon presentation. Current recommendations suggest obtaining two sets of cultures, including both peripheral blood cultures and cultures from a central venous catheter, if present [28, 33]. Additional laboratory studies at presentation should include complete blood count with differential, electrolytes, and markers of renal and hepatic function (creatinine, blood urea nitrogen, transaminases).

Depending on the clinical scenario, strong consideration should be given to obtaining an arterial blood gas, coagulation studies, and lactate level [33]. Lactate is of particular potential interest, as an elevated level may help detect early evidence of sepsis-induced malperfusion [33, 70]. Other microbiologic studies can be targeted toward patient-specific indicators. For example, urinary symptoms or an abnormal urinalysis should prompt urine cultures. Diarrhea, especially in a patient treated with antibiotics, should prompt evaluation for *Clostridium difficile* colitis. Fungal markers such as galactomannan or beta-D-glucan may be useful in some patients [33]. Respiratory symptoms or abnormalities on chest imaging should be evaluated with testing for respiratory viruses and sputum culture [28].

Symptom-guided imaging studies comprise an important part of the evaluation of neutropenic fever. Chest computed tomography (CT) scanning should be performed in patients with respiratory symptoms, and potentially asymptomatic patients with cryptic fevers [33]. Plain chest radiographs are of limited utility in this population and should not be routinely obtained in lieu of CT scans [87]. Sinus, head, and abdominal imaging should be performed as indicated [28, 33]. The use of nuclear medicine techniques such as FDG-PET/CT to identify foci of infections in febrile neutropenia has been described, but the utility of these techniques has not yet been proven, and remains impractical for current clinical use [80].

As noted above, respiratory symptoms and/or the presence of abnormalities on chest imaging should prompt evaluation for a respiratory infection. In most cases, this can be done noninvasively [6, 8, 10]. Bronchoscopy may be indicated in some patients, but the benefits of potential diagnosis must be weighed against the risk of requiring endotracheal intubation during bronchoscopy. Abdominal symptoms (pain, diarrhea) should lead to consideration of neutropenic enterocolitis, also known as typhlitis, which is an incompletely understood condition of ileocolonic inflammation which can lead to intestinal necrosis and perforation and is associated with a high mortality rate [63, 64]. Diagnosis requires the presence of neutropenia, bowel wall thickening >4 mm over a >30 mm longitudinal distance, fever >38 °C, and abdominal pain [31, 51, 63]. Specific diagnosis is elusive in many patients, and diagnostic steps should be repeated if no source is found and fevers persist for 72–96 h. Repeat blood cultures and repeat or expanded imaging studies may provide additional diagnostic information.

Risk stratification is an essential part of diagnosis, as it informs immediate management. The Multinational Association of Supportive Care in Cancer (MASCC) score (Table 4) [35] was developed to predict which patients with neutropenic fever may be safely treated as outpatients. A score ≥21 identifies a standard risk patient, whereas a score <21 indicates a high-risk patient. Additional criteria for outpatient treatment have been enumerated by Heinz et al. [33]; these focus on signs of clinical and social stability, with particular emphasis placed on expected good adherence to oral medications, adequate social support (the patient does not live alone), and the ability to present to the hospital within 60 min. It should be noted that the MASCC score has limited utility in predicting either the risk of critical illness or ICU outcomes. Other factors which influence risk stratification include the depth and duration of neutropenia, with an ANC ≤100 cells/mm^3 and >7 days duration, respectively, being markers of a high-risk patient [28]. Accordingly, neutropenic

Table 4 MASCC score

Characteristic	Weight
Burden of febrile neutropenia	5 (no symptoms); 3 (mod symptoms); 0 (moribund)
No hypotension (SBP >90 mmHg)	5
No COPD	4
Solid tumor *or* heme malignancy with no prior fungal infection	4
No dehydration requiring IV fluids	3
Outpatient status	3
Age <60 years	2

Modified from [35]

patients with a hematologic malignancy or status post HSCT are almost always higher risk than patients who become neutropenic during the course of cyclic treatment for a solid malignancy. Comorbid conditions should also be integrated into any clinical risk assessment.

Management

Pharmacologic

Prophylaxis in Neutropenic Patients Before Neutropenic Fever Develops

Due to the high risk of infection in neutropenia, many centers provide routine antimicrobial prophylaxis to patients deemed to be at high risk for infection and who are expected to have prolonged periods of profound neutropenia (e.g., ANC $\leq$500 cells/mm^3 for $>$7 days). The rationale for antibacterial prophylaxis is to reduce the risk of gram-negative infections and streptococcal infection from oral mucositis. In high-risk patients, current guidelines suggest antibacterial prophylaxis with a fluoroquinolone such as ciprofloxacin or levofloxacin, with the latter preferred if severe mucositis is anticipated [29, 30]. Antifungal prophylaxis against yeast is recommended in high-risk patients (HSCT, chemotherapy for leukemia) with fluconazole, itraconazole, voriconazole, posaconazole, or an echinocandin (caspofungin or micafungin). Anti-mold (*Aspergillus*) prophylaxis (with voriconazole or posaconazole) is recommended in patients undergoing chemotherapy for leukemia or patients with anticipated very prolonged neutropenia or prior invasive mold infection [28]. Antiviral prophylaxis acyclovir or valacyclovir is recommended for patients who are seropositive for herpes simplex virus (HSV) and for varicella zoster virus (VZV)-seropositive HSCT patients. Finally, leukemia and HSCT patients should receive prophylaxis against *Pneumocystis jirovecii* pneumonia. These prophylactic antimicrobials may lessen, but do not eliminate the risk infections while neutropenic; thus, patients and caregivers must remain vigilant for the development of fever. Moreover, attention must be paid to the prophylactic regimen, as it will affect the choice of empiric antibiotics for neutropenic fever.

Antimicrobial Therapy in Neutropenic Fever and Sepsis

Neutropenic fever is a medical emergency, and appropriate empiric antibiotics must be started without delay: within 60 min of presentation [28, 33, 57]. Some data suggest that even delays in antibiotic administration beyond 30 min are associated with increased mortality [62]. As noted above, it is desirable to obtain blood cultures if possible before antibiotic initiation, so long as this does not delay antibiotic administration. No other diagnostic maneuvers should be attempted before antibiotic initiation. Empiric antibiotics must cover the common organisms discussed above (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcal* species) and should also be tailored according to prior patient-specific culture data and institutional epidemiology [28, 33]. Appropriate empiric antibiotics include an antipseudomonal penicillin (e.g., piperacillin/tazobactam), or antipseudomonal cephalosporin (e.g., cefepime), or a carbapenem (imipenem, meropenem) [28, 33]. Some data suggest improved outcomes with prolonged antibiotic infusion times [58] though these data require confirmation. Fluoroquinolones, which are frequently used as prophylactic therapy in neutropenia, should not be used as empiric monotherapy in neutropenic fever due to the possibility of resistance. Though gram-positive organisms are common causes of neutropenic fever, vancomycin is not routinely indicated, but should be added in the presence of suspected catheter-related infection, soft tissue infection, oral mucositis, radiographically proven pneumonia, known colonization with resistant gram-positive organisms (e.g., methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus*), or hemodynamic instability [28, 33, 57].

The use of combination antibiotic regimens (defined as dual gram-negative coverage with an antipseudomonal beta-lactam and an aminoglycoside) in neutropenic fever is controversial. Though some studies have suggested a mortality benefit to combination antibiotics [39],

this has not been a consistent finding, and 2 meta-analyses have shown no benefit to the addition of an aminoglycoside to a beta-lactam and a higher risk of renal failure with combination therapy [55, 56]. Accordingly, current guidelines for the management of neutropenic fever and sepsis recommend monotherapy with an antipseudomonal beta-lactam unless otherwise dictated by circumstances such as patient allergies, the presence of resistant organisms, or refractory hemodynamic instability [28, 57, 61]. It should be noted, however, that this recommendation does not preclude the use of vancomycin or antifungals; it is only directed at combination therapy targeted against gram-negative bacteria.

Even with appropriate antibiotics, fever in neutropenic patients typically persists for a median of 5 days; thus, ongoing fevers, unless accompanied by clinical instability, should not necessarily be viewed as evidence of failure of antibiotic therapy [73]. In patients with persistent or recurrent fevers after 3–5 days, a modification of antibiotic regimen is reasonable, especially if guided by new or changing clinical data. Earlier antibiotic escalation is necessary in some patients, most commonly in patients with hemodynamic instability. In the face of hemodynamic instability, vancomycin should be added if not already part of the regimen. Additionally, antipseudomonal cephalosporins or penicillins should be escalated to a carbapenem (e.g., meropenem), and strong consideration should be given to the addition of an aminoglycoside, fluoroquinolone, or aztreonam [28, 33, 57, 61].

Drug-resistant and multidrug-resistant (MDR) organisms are an increasing problem in neutropenic infections [26, 29, 50]. Vancomycin-resistant enterococcus (VRE) bacteremia affects a substantial portion (10–35%) of patients during induction therapy for leukemia or after HSCT and is associated with significantly worse outcomes [3, 53, 85]. Early treatment with agents active against VRE such as linezolid or daptomycin may improve outcomes. Predictive models are being developed to assist with early identification of patients who might benefit from early initiation of antibiotics active against VRE [83]. Similarly, MDR gram-negative infections, particularly carbapenem-resistant *Enterobacteriaceae*, are associated with high mortality rates, especially among allogeneic HSCT patients [66]. Successful treatment of these infections requires early use of multidrug antibiotic regimens, typically including aminoglycosides, carbapenems, and polymyxins. The use of surveillance rectal cultures, performed pre-transplant and then weekly after HSCT, to identify patients with MDR infections and allow immediate initiation of antibiotic therapy targeted against MDR organisms may result in better outcomes [26].

Fungal pathogens are a constant threat in neutropenic patients, and consideration must be given to the use of antifungal agents in all patients with neutropenic fever. In general, antifungal therapy should be initiated in the setting of persistent fever after 5–7 days of appropriate antibacterials [28, 33]. Appropriate antifungals should have activity against molds, especially aspergillosis; examples include liposomal amphotericin, caspofungin, and voriconazole, though the data are more robust in favor of the former two [33, 81, 82]. Fluconazole should not be used as empiric therapy. An increasing number of neutropenic patients are on antifungal prophylaxis with voriconazole prior to developing fever; the utility of changing antifungal agents upon fever development in this setting is unclear. Antifungals should be strongly considered as early therapy in all patients who are hemodynamically unstable [28, 33].

With the advent of multidrug-resistant organisms, antibiotic stewardship is increasingly important, even in neutropenic patients. The optimum duration of antimicrobial therapy in the neutropenic patient and whether antimicrobials may be safely de-escalated in the face of clinical stability are ongoing areas of investigation. One randomized controlled trial suggests that empiric antibiotics may be safely discontinued after a patient has defervesced and remained afebrile for 72 h, regardless of whether neutrophil recovery has occurred [2]. Another recent paper suggested that it is safe to withhold antibacterial therapy in children with neutropenic fever in whom infection with a respiratory virus has been proven [65]. Neither of these tactics has become standard of care, but both highlight the increasingly realized

importance of antibiotic stewardship, even in neutropenic patients.

Hematopoietic Growth Factors

Hematopoietic growth factors may be considered in select cases of neutropenic fever, as they have been shown to shorten the duration of neutropenia, but do not impact mortality [22]. According, due to a lack of proven mortality benefit, current guidelines recommend against the routine use of hematopoietic growth factors in neutropenic fever or neutropenic sepsis [29, 72].

Granulocyte Transfusions

Granulocyte transfusions have been used to support patients with neutropenia, both to prevent infections and to help treat established infections. Very few studies have been performed to evaluate this intervention, and those studies that are available are small. Two recent Cochrane meta-analyses have examined the use of granulocyte transfusions in neutropenic patients to prevent and treat infections, respectively. Both concluded that there was insufficient evidence to determine whether granulocyte transfusions conferred any mortality benefit [24, 25].

Non-pharmacologic

Early and appropriate administration of antimicrobials is essential to preventing death from neutropenic fever and neutropenic sepsis. Good outcomes also depend on successfully managing the hemodynamic derangements and organ failure of sepsis. The intensive care unit (ICU) is the best-suited location to care for neutropenic patients with sepsis and septic shock, and earlier ICU admission has been associated with improved survival rates [7, 9].

Recent guidelines have been published for the management of sepsis and septic shock [61]; these guidelines are also applicable to the management of neutropenic sepsis. Key points include initial resuscitation with at least 30 ml/kg of intravenous crystalloid with additional fluid resuscitation as indicated and using norepinephrine as a first-line vasopressor to target a mean arterial pressure $\geq$65 mm Hg. Either vasopressin or epinephrine may be added if the response to norepinephrine is inadequate. There may be benefit to using balanced crystalloid solutions such as lactated Ringer's or PlasmaLyte rather than normal saline [68, 69]. Source control should be obtained if possible. Though occasionally an abscess may be present and feasible to drain, most commonly, an indwelling central venous catheter is the only addressable source of infection. In the hemodynamically unstable patient with a suspected catheter infection, early catheter removal is associated with improved survival [39]; accordingly, infected or potentially infected catheters should be removed without delay.

Patients with neutropenia and sepsis are at high risk of developing multi-organ failure, particularly the acute respiratory distress syndrome (ARDS) [4, 5]. The use of noninvasive ventilation in immunosuppressed patients with hypoxemic respiratory failure is increasingly controversial, and heated humidified high-flow oxygen may be a better option [5, 15, 27, 41, 42, 52]. Once patients are intubated, low tidal volume ventilation should be used to maximize lung protection and minimize ventilator-induced lung injury [1]. Adjuncts such as neuromuscular blockade and prone positioning should be used in patients with moderate to severe ARDS (PaO2: FiO2 $<$ 150) [32, 54]. Mortality for patients who develop ARDS in this context remains high, but outcomes are improving. Attention to best practices for mechanical ventilation is essential.

Management Algorithm

An algorithm for the empiric management of neutropenic fever can be found in Fig. 1.

Prognosis

The risk of neutropenic fever and neutropenic sepsis resolves once the bone marrow recovers and neutrophil counts return to normal. If treated appropriately, neutropenic fever is a common, predictable, and manageable complication of

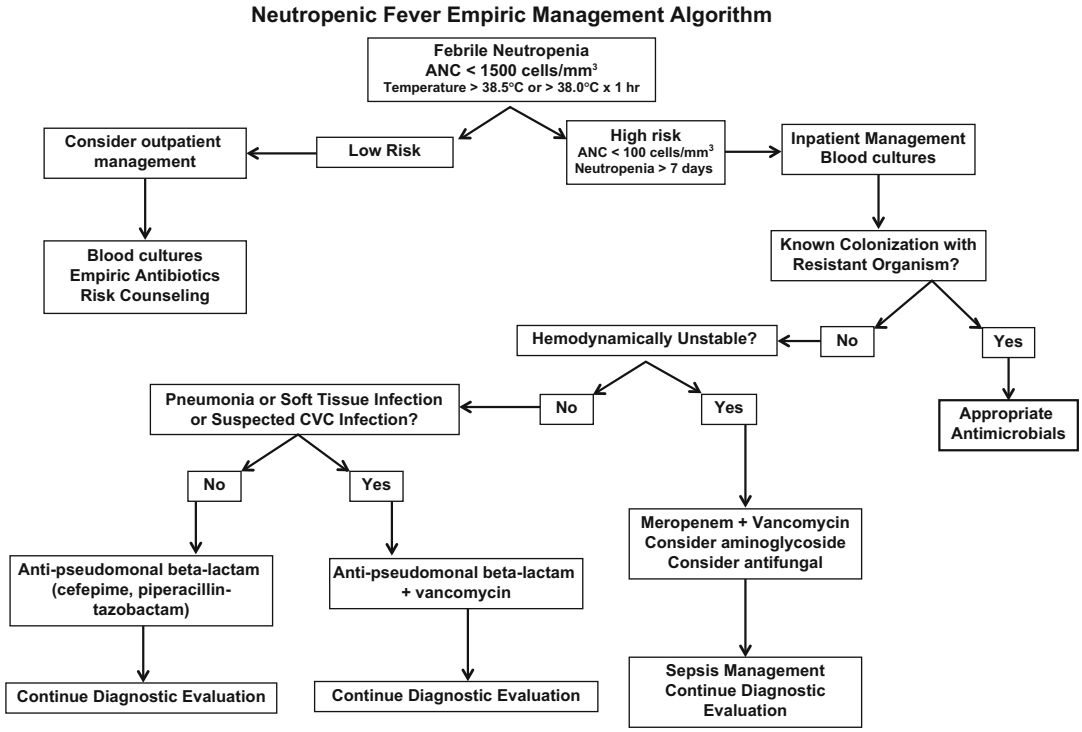

Fig. 1 Empiric Management of Neutropenic Fever

cytotoxic therapy or HSCT. Neutropenic sepsis continues to confer a poor prognosis, with recent data suggesting an approximate 46% mortality rate in patients with hematologic malignancies who develop septic shock [7, 39, 47]. Predictors of mortality include sepsis after allogeneic HSCT, the presence of graft vs host disease, respiratory failure requiring mechanical ventilation, positive blood cultures, cardiac failure, renal failure, and hepatic failure [38, 47]. Younger age (<70 years) and the presence of neutropenic enterocolitis are associated with improved survival [47].

Conclusion and Summary

Encouragingly, survival in neutropenic sepsis and septic shock appears to be improving but is still worse than in non-neutropenic septic patients [9, 10, 39]. The emergence of multidrug-resistant organisms is a major concern, and there is an urgent need for novel antibiotics to address this threat. Along these lines, additional work needs to be done to identify patients in whom antibiotic therapy can be safely de-escalated. The pathophysiology of neutropenic sepsis requires further study and efforts made to facilitate earlier diagnosis and identification of pathogens in neutropenic patients. Finally, neutropenic sepsis should be studied as a specific and separate entity from "normal" sepsis, and efficacy of interventions confirmed in this specific population.

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