

Febrile Neutropenia in Intensive Care Unit

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ABSTRACT

Febrile neutropenia is a serious complication of cancer treatment and causes significant morbidity and mortality, especially when these patients present with sepsis or septic shock requiring intensive care unit admission. Careful assessment and evaluation of these patients and appropriate empiric antibiotics can reduce mortality. Current guidelines recommend antipseudomonal antibiotics as empiric treatment; combination therapy is recommended in hemodynamic unstable patients. Granulocyte colony-stimulating factor does not improve survival but decreases length of stay in cancer patients with febrile neutropenia. Antifungals drugs are recommended in patients with prolonged, unexplained fever. Sepsis has a high mortality rate in these patients even with rapid and appropriate empiric antibiotic coverage. More studies on treatment and outcome in patients with febrile neutropenia are needed.

Key words: Febrile neutropenia, cancer, critical care

INTRODUCTION

Hospitalization for febrile neutropenia from chemotherapy has significant morbidity, mortality, and cost in cancer treatment. Febrile neutropenia accounts for approximately 40% to 50% of the total cost of hospitalization in cancer care and results in mortality rates between 3% and 20%.^{1, 2} Patients at high risk for complications are those with anticipated prolonged (more than 7 days duration) and profound neutropenia (absolute neutrophil count [ANC] <100 cells/mm³ following cytotoxic chemotherapy) and/or significant medical co-morbid conditions.³ An initial presentation of sepsis with septic shock that re-

quires intensive care unit (ICU) admission or transfer to ICU during hospitalization in cancer patients has increased mortality rates up to 50%.^{4, 5}

WHAT IS FEBRILE NEUTROPENIA?

The definitions of fever and neutropenia are uniform in The Infectious Disease Society of America (IDSA) and The National Clinical Practice Guidelines in Oncology (NCCN) Guidelines. Fever in neutropenic patients is defined by a single oral temperature more than 38.3°C or 101°F or a temperature more than 38.0°C or 100.4°F over one hour. Neutropenia is defined as either: 1) an absolute neutrophil count (ANC) less than 500 neutrophils/μL; or 2) an ANC less than 1000 neutrophils/μL and a predicted decline to 500 neutrophils/μL or less over the next 48 hours.^{3, 6}

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Cytotoxic antineoplastic therapy damages the mucosal linings of the GI, sinopulmonary, and genitourinary tracts by initiating an inflammatory cascade and release of proinflammatory cytokines causing increased mucosal permeability and translocation of microflora bacteria and fungi colonizing the mucosal or skin surfaces damaged by cytotoxic therapy.

WHO QUALIFIES FOR ICU ADMISSION?

Respiratory complications requiring ventilator support and hemodynamic compromise requiring fluid and vasopressor resuscitation for sepsis syndromes are the most common reasons for ICU admission or referral in cancer patients, followed by gastrointestinal bleeding, fungal infection, other organ damage, and surgical emergencies.⁷ In the past, neutropenia was a contraindication for ICU admission due to high hospital mortality rate and the patients were “too ill” to benefit from critical care.⁸ However, in a study of cancer patients admitted to the ICU with septic shock, mortality was not different in cancer patients compared to mixed populations, and neutropenia was not associated with increased mortality.⁹ High risk patients, including patients with profound neutropenia and prolonged duration which happens more in patients with hematological malignancies and patient who underwent hematopoietic stem cell transplant, are more likely to develop complications that require ICU admission.^{7,10} Other factors associated with complications are comorbidities, liver or renal dysfunction,

and a Multinational Association for Supportive Care in Cancer (MASCC) risk index score of <21.¹¹ (Table 1)

ASSESSMENT AND DIAGNOSIS

The neutropenic state can mask normal inflammatory responses to infection. For example, physical findings, such as exudates, fluctuance, erythema, or swelling, might not be prominent in these patients.¹² Fever is present but can also be marker for a non-infectious process, such as drug fever, venous thromboembolism, or blood product transfusion reactions.⁸ A careful physical exam is important to help localize the site of infection and potentially tailor the initial treatment. This includes examination of the skin and oral cavity for mucositis, examination of intravenous catheters, and perianal inspection. Initial laboratory work-up should include complete blood counts with a leukocyte differential, serum electrolytes, blood urea nitrogen, serum creatinine, serum transaminase, and total bilirubin and urine analysis.⁶ At least 2 sets of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing central venous catheter (CVC), if present, and from a peripheral vein site; two blood culture sets from separate venipunctures should be sent if no central catheter is present.³

Initial imaging studies are based on the clinical picture and physical examination findings. Chest x-ray is usually done as part of the initial work up with

Table 1 MASCC index score

Category	Weight
Burden of illness: no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous invasive fungal infection	4
Outpatient status	3
Burden of disease: moderate symptoms	3
No dehydration	3
Aged <60 years	2

Abbreviation: MASCC=Multinational Association of Supportive Care in Cancer.

The maximum theoretical score is 26. A MASCC score ≥ 21 identifies low-risk patients with a positive predictive value of 91%, specificity of 68% and sensitivity of 71%.¹¹

the caveat that it might be normal in neutropenic patients with lung infection.

MANAGEMENT

Initiation of antibiotics in a timely manner is essential in febrile neutropenic patients. This should be guided by the clinical picture and localizing symptoms if any. Since most patients will not have localizing signs and symptoms, broad-spectrum antipseudomonal monotherapy agents are class IA recommendation in febrile neutropenia patients, including cephalosporins (cefepime), carbapenems (meropenem or imipenem-cilastatin) or beta-lactamase inhibitors (piperacillin-tazobactam).³ The choice among these varies depending on institutional antibiograms and the patients' allergy profile. Penicillin-allergic patients with a history of hypersensitivity reaction (hives and bronchospasm) should avoid beta-lactams and carbapenems. Aztreonam may be an acceptable option in these patients despite its narrow spectrum. It had successful clinical outcomes in a retrospective, single institution study as both monotherapy and combined therapy in neutropenic patients with a history of beta-lactam hypersensitivity or as a transitional therapy following an adverse reaction with a beta-lactam.¹³

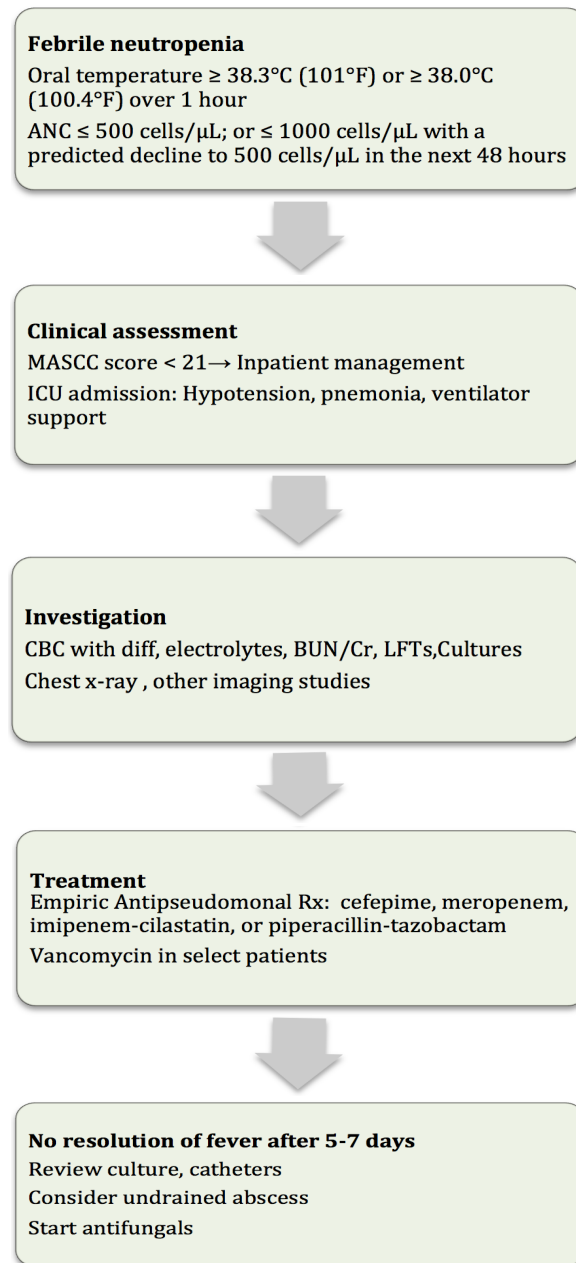
A combination of antibiotics is not routinely recommended. However, it should be considered if resistance is suspected, especially in unstable patients. Patients at risk of antibiotic resistance include those with previous infections or colonization with these organisms or those on prolonged prophylactic antibiotics, which are usually used in hematologic malignancies and hematopoietic stem cell, transplant patients.³ A single institution retrospective study reported a 15% resistance rate to piperacillin-tazobactam in febrile neutropenic patients with Gram-negative bacilli positive cultures, which was also associated with a higher 30-day all-cause mortality rate (29% vs 11%, $P=0.024$). Multivariate analysis revealed that risk factors for antibiotics resistance were ICU status, previous prolonged (>14 days) antibiotic exposure in the last 90 days, and a respiratory source of infection. All resistant organisms were sensitive to amikacin, and 88% were sensitive to meropenem.¹⁴ The addition of amikacin, therefore, can be considered if antibiotic re-

sistance is suspected or proven.

The addition of vancomycin is not routinely recommended, as most Gram-positive isolation in this population is coagulase-negative staphylococci, which may be contaminants. The addition of vancomycin as initial therapy is recommended in patients with hypotension, pneumonia, severe mucositis, patients with clinically suspected central venous catheter infection, and those who are colonized with methicillin resistant *Staphylococcus aureus* (MRSA).¹⁵ A meta-analysis comparing vancomycin to other available antibiotics for patients with Gram positive infection, showed that vancomycin is as effective as other antibiotics with no difference of outcomes in febrile neutropenia subgroup.¹⁵ If vancomycin was used initially, it can be stopped after two days if there is no evidence of Gram-positive infection.^{6,15} Further adjustment of initial antibiotics is based on the clinical and microbiology culture results. Empiric antifungal agent is recommended when there is no resolution or recurrence of fever after 4-7 days of antibiotic treatment without evidence of infection.^{3,6,15} Fluconazole has been used in patients not receiving prophylactic antifungal therapy, which is effective against invasive candidiasis but not molds. Invasive mold infections occur in high-risk patients such as those with profound neutropenia (<100 cells/mm³) lasting longer than 10–15 days most commonly occurring in patients with acute leukemia and HSCT patients. Prophylactic antifungal therapy is recommended in these patients.³ There are no adequate data to recommend therapy used in patients on prophylactic antifungals. This depends on the clinical information, including newer assays for fungal antigens. NCCN and IDSA guidelines endorse different approaches. One is to switch to echinocandin, voriconazole, or amphotericin B empirically. The other is pre-emptive targeted treatment after performing chest and sinus computed tomography (CT) scans looking for lesions suspicious for invasive fungal infections.^{3,6}

Both IDSA and NCCN guidelines recommend continuing antibiotics until ANC recovers to 500 neutrophils/ μ L or greater³, and for the duration recommended for the specific infection in general if isolated.⁶ Most patients will have no infectious etiology

Figure 1 Algorithm of Management for Febrile Neutropenia



Abbreviation: ANC=Absolute neutrophil count, MASCC=Multinational Association of Supportive Care in Cancer. CBC with diff=complete blood counts with differential, BUN=blood urea nitrogen, Cr=serum creatinine, LFT=Liver function test (serum transaminase, total bilirubin and alkaline phosphatase).

documented. Clinically documented infections occur in 20%–30% of febrile episodes; common sites of tissue-based infection include the intestinal tract, lung, and skin.³

Granulocyte colony-stimulating factors (G-CSF) does not change hospital mortality rate.^{5,16} However, G-CSF with antibiotics did significantly decrease hospital length of stay and promote faster recovery from the neutropenic phase.¹⁶

OUTCOME

Legrand et al conduct a 10-year retrospective study from 1998-2008 to determine the mortality risk in febrile neutropenic patients with sepsis or septic shock. Noninfectious condition, such as cardiovascular events, neurologic complications, tumor lysis syndrome, venous thromboembolism, bleeding complications from thrombocytopenia, and life-threatening side effects of chemotherapeutic agents, were associated with increased mortality in neutropenic cancer patients in critical care units.⁵ In one retrospective study, factors potentially improving survival included the initial administration of aminoglycoside in antibiotic combination, early removal of indwelling catheters, and ICU admission after 2004.⁵ Another study showed that sepsis itself carries more than 50% mortality rate regardless of neutropenic status.⁹ Mechanical ventilation and liver dysfunction are independent predictors of mortality,^{9,17} and HSCT patients with mechanical ventilation have the highest mortality rate (80%).¹⁰

SUMMARY

Febrile neutropenia is a life-threatening complication of cancer therapy. Hemodynamically unstable patients and those who develop respiratory and other organ dysfunction are at increased risk for complications and require ICU admission with higher mortality. Careful assessment and prompt initiation of appropriate broad-spectrum antimicrobial therapy is critical. More studies on treatment outcomes in these patients in critical care setting are needed.

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