

Neutropenic Fever



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Abstract Neutropenia is defined as an abnormally low absolute neutrophil count (ANC) and can be further delineated as severe or profound (see below). Recipients of chemotherapy will often have a decreased ANC leading to an increased risk of infections specifically from bacterial sources. Neutropenia traditionally is risk stratified based on duration and depth of neutropenia. Recipients of chemotherapy for acute myelogenous leukemia (AML) and stem cell transplants (SCTs) often are deemed as having high risk neutropenia due to significant depth and duration of neutropenia. The mortality associated with febrile neutropenia is up to 11%, and can be as high as 50% in the setting of severe sepsis or septic shock. By risk stratifying neutropenia and the resultant neutropenic fever, the goal is to decrease the resultant morbidity and mortality (Taplitz et al., J Clin Oncol 36:3043–3054).

Keywords Neutrophil count (ANC) · Severe neutropenia · Profound neutropenia · Neutropenic fever · Drug fever · Chemotherapy induced mucositis · Tumor fever · Transfusion related fever · Graft-versus-host disease · Growth factor · Myeloid reconstitution syndrome · Engraftment syndrome

Background Definitions [1]

- Neutropenia is defined as an absolute neutrophil count (ANC) $<1000 \mu\text{L}$ (equivalent to $<1.0 \times 10^9 /\text{L}$)
- Severe neutropenia is an ANC $<500/\mu\text{L}$ (equivalent to $<0.5 \times 10^9/\text{L}$)
- Profound neutropenia is an ANC $<100/\mu\text{L}$ (equivalent to $<0.1 \times 10^9/\text{L}$)
- High risk neutropenia is neutropenia lasting ≥ 7 days

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- Fever in neutropenic patients is defined as a single oral temperature of ≥ 38.3 °C (101 °F) or a temperature of ≥ 38.0 °C (100.4 °F) sustained over a 1 h period.

Neutropenic Fever (NPF)

Two categories of neutropenic fevers have been described. Microbiologically-based NPF infection is defined when the cultures isolate an organism. On the other hand clinically documented NPF is present when there is a high clinical suspicion for infection based on physical examination findings or radiological testing but there is a negative microbiologic work up. During the work up of NPF, an infectious origin can be identified either microbiologically and/or clinically in only 30–50% of the cases [2]. This is often related to an incomplete medical exam or untimely collection of specimens such as biopsies or aspirations due to concomitant thrombocytopenia. These patients tend to improve after empiric antibiotic therapy which suggests an occult infection. However other non-infectious causes of fever such as chemotherapy induced mucositis, tumor fever, transfusion related fever, drug fever, or graft-versus-host disease should also be considered as potential causes of unexplained fever [3]. Tumor fever is in part thought to be related to cytokine release by the cancer cells, and it is usually a diagnosis of exclusion. Drug fever is not uncommon particularly from certain chemotherapies or growth factors. A thorough detail orientated history, medication reconciliation and physical exam is important in identifying patterns between medications and fever curves. Drug fever should be suspected in the presence of rash, peripheral eosinophilia and increasing transaminases. These associated symptoms are not always present.

Mucositis is a common cause of neutropenic fever. It often develops when there is an ongoing mucosal barrier injury that results from the toxic effects of chemotherapy allowing for either micro- or macro-translocation of bacterial organisms from the GI tract into the systemic system. Micro-translocation leads mainly to an inflammatory syndrome with negative blood cultures but punctuated with NPF whereas macro-translocation presents with positive blood cultures. Chemotherapy induced mucositis and less frequently radiation induced mucositis can involve the entire gastrointestinal tract including the oral cavity. Studies have shown that it may be more important as a cause of infection than neutropenia itself in cancer patients [4].

Other noninfectious causes of fever not to be overlooked include venous thromboembolism, pulmonary emboli, adrenal insufficiency and stroke. Microbiologically documented infections include catheter associated bacteremia, bacterial translocation from the gastrointestinal, genitourinary or respiratory tract, or from skin and soft tissue infections [2].

When evaluating a patient with neutropenic fever, myeloid reconstitution syndrome and engraftment syndrome are two other phenomena that should be taken into consideration. Myeloid reconstitution syndrome is similar to immune reconsti-

tution syndrome seen in HIV patients after initiation of antiretroviral therapy (ART). With the addition of ART, there is a shift from an immunosuppressed state to a pro-inflammatory state. In the setting of hematological malignancies, it occurs within 15 days of neutrophil recovery and manifests as fevers. Superinfection needs to be ruled out in these circumstances prior to considering discontinuing antimicrobials [5]. Engraftment syndrome, more commonly seen in patients undergoing autologous stem cell transplants than SCT, develop fevers, rash and pulmonary infiltrates at the beginning of engraftment; i.e. neutrophil recovery. If the patient has an aggressive and symptomatic engraftment syndrome, steroids can be considered. Patients with breast cancer, previous monotherapy and recent use of G-CSF appear to have higher risk for this syndrome [6].

Microbiology

The causes of bloodstream infection causing neutropenic fever have changed with the use of indwelling catheters and the evolution of chemotherapy modalities. There has been an increased frequency in bacteremias with gram-negative organisms compared to gram positive, with *Enterobacteriaceae* sp. being more predominant, followed by *P. aeruginosa* and other gram negatives. Unfortunately, the use of prophylactic antibiotics has led to an increase in frequency of resistant pathogens such as extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* and carbapenem resistant pathogens. Gram positive bacteria continue to be an important cause of bacteremia. *Staphylococcus aureus* including Methicillin resistant *Staphylococcus aureus* (MRSA), coagulase negative staphylococcus, viridans group streptococcus and *Enterococci*, especially vancomycin resistant *Enterococcus* (VRE) are particularly concerning [2]. Anaerobic bacteria are not as common but have been associated with a polymicrobial bacteremia and in those patients undergoing abdominal surgery. Fungal infections are less common compared to bacterial infections as the cause of fever early in the course of neutropenia. When they are identified, *Aspergillus* sp. and *Candida* sp. are the most common. Non *C. albicans* strains are increasing in frequency due to selective pressure from the ongoing use of prophylactic fluconazole [2]. The greatest risk factor for mold infection is profound and prolonged neutropenia (i.e. 14 days or more with ANC < 100).

Management

Management for neutropenic fever first starts with a discussion of appropriate prophylaxis which has been risk stratified on the basis of the anticipated duration of neutropenia [1]. The optimal time to choose a patient's regimen for a future neutropenic fever is during the initial consult by an infectious diseases consultant after discussing all of the risk stratifying past medical issues for a particular patient

including but not limited to previous infections especially while neutropenic. In addition, prophylaxis against *Pseudomonas* and other Enterobacteriaceae are of utmost importance in this population. Unfortunately, *Pseudomonas* continues to be a significant cause for neutropenic fever. Other enteric gram-negative rods (GNRs) are important sources of bacteremia after chemotherapy induced mucosal damage resulting in mucositis/enteritis and bacterial translocation [2].

Risk Factors for Febrile Neutropenia

The risk of febrile neutropenia not only depends on the duration and degree of neutropenia but also on other factors related to the demographics of the patient, for example the malignancy in question or the treatment regimen being delivered [1]. The highest risk for NPF is in patients with profound and protracted neutropenia after induction chemotherapy for acute leukemia and in the pre-engraftment stage following SCT infusion Table 1. Summarizes key risk factors.

Primary Prophylaxis

In terms of antimicrobial prophylaxis there is a three-pronged approach. The first prong is antibacterial. The second is antifungal and the third is antiviral [1]. Traditionally antibacterial prophylaxis is utilized to prevent first and foremost an invasive *Pseudomonas* (PSA) infection, thus the use of ciprofloxacin or levofloxacin.

Table 1 Common Risk Factors for Neutropenic Fever

Factors related to	Higher risk
Patient factors/ characteristics	Advanced age
	Low performance status
	Low albumin
	Prior episode of neutropenia
	Presence of comorbidities
Malignancy	Acute leukemia
	Myelodysplastic syndrome (MDS)
	High grade lymphoma
	Soft tissue sarcoma
	Non Hodgkin Lymphoma (NHL)/myeloma
	Increased risk if advanced stage or not in remission or if in relapse
Treatment regimen	High doses of anthracyclines, cisplatin, ifosfamide, cyclophosphamide, etoposide or cytarabine
	Remission-induction and rescue chemotherapy
	Duration and degree of GI/oral mucositis

Levofloxacin is the best choice if there is a concomitant need for viridans group streptococcus (VGS) due to dental or gingival issues. If a patient has prolonged QT corrected or is intolerant of a fluoroquinolone, the alternative option for antibacterial prophylaxis is cefdinir or cefpodoxime [1]. Unfortunately, with this approach, there is an increased risk for pseudomonas bacteremia due to the lack of coverage with oral cephalosporins. Primary prophylaxis is recommended for patients who are at high risk for febrile neutropenia or with profound and protracted neutropenia (ANC ≤ 100 for >7 days), such as patients with AML/MDS or SCT treated with myeloablative conditioning regimens. Current guidelines do not recommend routine prophylaxis in patients with low risk neutropenia such as those with solid tumors [1, 7]. Due to the increase of multidrug resistant organisms (MDROs) there are regions of the world including the northeast of the US where the rates are higher for drug resistance for PSA as well as other gram-negative rods (GNRs) making the use of antibacterial prophylaxis useless and only increases the risk of *Clostridium difficile* infection (CDI) (Tables 2 and 3).

For primary antifungal prophylaxis, the drug of choice depends on the total assessment of the patient's current situation (disease status, chemotherapy present and past, if there is a history of fungal infections, and potential lifetime exposures). It is important to risk stratify to adequately estimate the pre-test probability of invasive yeast infection versus mold infection in neutropenic patients. For example, an acute myelogenous leukemia (AML) undergoing induction chemotherapy would be a candidate for voriconazole primary prophylaxis due to the risk of neutropenia in a patient expecting neutropenic longer than 14 days (a known risk factor for invasive mold infection). Prophylaxis against invasive *Aspergillus* sp. infections with posaconazole is considered for patients ≥ 13 years of age, and undergoing intense chemotherapy for AML or MDS [1]. On the other hand, an impending neutropenic patient for SCT may have duration of neutropenia less than 14 days thus fluconazole or an echinocandin would be sufficient for prophylaxis against *Candida* sp. Antifungal prophylaxis is recommended for patients expected to have profound, protracted neutropenia such as patients with AML/MDS or SCT patients [1]. Similar

Table 2 Non-infectious causes of fever in cancer patients

Mucositis
Graft versus host disease (GVHD)
Myeloid reconstitution syndrome
Pre-engraftment syndrome
Drug fever
Tumor fever
Deep venous thrombosis (DVTs), thromboembolism
Stroke
Transfusion-related fevers
Fever secondary to G-CSF/ GM-CSF
Radiation-related fevers

Table 3 Microbiology of infections in febrile neutropenia

Bacterial	Gram negative pathogens (blood stream infections)
	Enterobacteriaceae, 24%
	<i>P. aeruginosa</i> , 10%
	<i>Acinetobacter</i> , 2%
	Other gram negatives, 3%
	Gram positive pathogens (blood stream infections)
	<i>S. aureus</i> , 6%
	Coagulase-negative staphylococci, 25%
	Viridans group streptococci, 5%
	<i>Enterococci</i> , 5%
	Other gram positives, 6%
	<i>Clostridium difficile</i> (GI infections)
	<i>Helicobacter pylori</i> (GI infections)
	<i>Salmonella</i> and <i>Shigella</i> (rare)
	<i>Mycoplasma pneumoniae</i> (pulmonary infections)
<i>Chlamydia pneumoniae</i> (pulmonary infections)	
Tuberculosis	
Fungal	<i>Candida</i> spp.
	<i>P. jirovecii</i>
	Cryptococci
	<i>Aspergillus</i> spp.
	Mucorales
	<i>Fusarium</i>
	<i>Scedosporium</i>
Viral	Herpes simplex virus (reactivation in 60% HSV sero-positive)
	Hepatitis B virus and hepatitis C virus reactivation)
	Cytomegalovirus (CMV)
	Respiratory syncytial virus (RSV)
	Influenza A or B
	Parainfluenza 1–4
	Metapneumovirus
	Adenoviruses
	Coronaviruses
	Rhinoviruses/Enterovirus
	Norovirus
Other Pathogens	Strongyloidiasis
	Leishmaniasis, trypanosomiasis, malaria

to antibacterial prophylaxis, anti-mold prophylaxis is not recommended for solid tumors. Regimens associated with an increased risk of infection by *Pneumocystis jirovecii* such as those patients on purine analogues or those on ≥ 20 mg of prednisone for more than 1 month should receive trimethoprim-sulfamethoxazole ideally in daily dosing to increase compliance. If intolerant or allergic to trimethoprim-

Table 4 MASCC scoring system to identify patients with cancer and FN at low risk of medical complications

Burden of FN with no or mild symptoms	5
No hypotension	5
No COPD	4
Solid tumor or hematological malignancy with no previous fungal infection	4
No dehydration requiring IV fluids	3
Burden of FN with moderate symptoms	3
Outpatient status	3
Age < 60	2
Maximum score is 26, ≥ 21 low risk	

Table 5 The clinical index of stable febrile neutropenia (CISNE)

Explanatory Variable	
Eastern Cooperative Oncology Group performance status ≥ 2	2
COPD	1
Chronic cardiovascular disease	1
National Cancer Institute common toxicity criteria mucositis of grade ≥ 2	1
Monocytes <200 μL	1
Stress-induced hyperglycemia	2

0–8 score. Low risk (zero points), intermediate risk (1–2 points), high risk (≥ 3 points)

sulfamethoxazole then alternatives such as dapsone, atovaquone or aerosolized pentamidine can be considered [1]. Prior to utilizing dapsone, ensuring the patient has a sufficient level of G6PD is recommended.

As far as antiviral prophylaxis, HSV seropositive patients undergoing leukemia induction therapy or SCT should receive prophylaxis. In terms of primary herpes simplex or varicella prophylaxis, traditionally acyclovir at either 400 mg BID by mouth or 800 mg BID by mouth is utilized. Per specific indications like previous breakthrough infections while on acyclovir, a patient may be considered a candidate for a pro-drug such as famciclovir or valacyclovir for prophylaxis while neutropenic. Tenofovir or entecavir is recommended for patients whom are at risk of hepatitis B reactivation while on chemotherapy or immunotherapy that is B-cell depleting [1, 2] (Tables 4 and 5).

Secondary Prophylaxis

When evaluating the patient for impending neutropenia, the infectious diseases (ID) team needs to review the patient's medical history. In general if a particular infection develops while neutropenic, there is a concern that the patient will be at risk for

reactivation/recurrence of the same infection when creating the same situation again i.e. a new episode of neutropenia. The drug(s) that was (were) used to treat the original infection should be re-considered as the ideal drug to resume when the patient becomes neutropenic during subsequent episodes. By creating the same milieu that lead to the infection in the first place, the patient is now at risk for that infection to recur. For example, if voriconazole was used to treat a fungal pneumonia during induction chemotherapy, one should consider restarting voriconazole for secondary prophylaxis for the impending neutropenia expected during SCT [1, 8].

Other Considerations

The role of granulocyte colony stimulating factor (G-CSF) in prophylaxis is at times controversial. G-CSF has shown to decrease length and degree of neutropenia and reduce the risk of febrile neutropenia in solid tumors however it has not shown to decrease the risk of febrile neutropenia or reduce mortality in hematological malignancies. The recommendation overall is to give G-CSF in patients who are on chemotherapy regimens known to have a 20% increase risk of febrile neutropenia or in presence of comorbidities but lower risk [7].

Hand hygiene, diet and other environmental factors are also to be considered. It is recommended to avoid undercooked meats, unpasteurized milk, unpasteurized cheese or unpeeled fruits and vegetables unless washed properly at home [1, 2]. Also, neutropenic patients in an outpatient setting should avoid contact with environments that have high concentrations of airborne fungal spores such as construction/renovation sites, intense gardening and digging [1, 2]. In the same line of thinking of minimizing exposure to plant matter, it is not recommended for neutropenic or impending neutropenic patients to utilize tobacco products or marijuana products due to the theoretical risk of fungal pneumonia.

Outpatient Versus Inpatient Therapy

The management of neutropenic patients who present with fever can be divided into inpatient versus outpatient management. It is also important to identify patients presenting to the outpatient setting who will require inpatient referral [1] (Tables 6 and 7).

When a cancer patient with fever and neutropenia comes to an emergency room for evaluation, it should be assumed that there is an infectious cause until proven otherwise. Per the 2010 IDSA clinical guidelines, an assessment should be done within 15 min of being seen in triage. A complete history and physical as well as appropriate lab work including a complete blood count (CBC), renal function test, lactic acid level, and liver function test should be performed. Blood cultures should

Table 6 Talcott's rules

Group	Characteristic
I	Inpatients (at time of fever onset)
II	Outpatients with acute comorbidity requiring hospitalization
III	Outpatients without comorbidity but with no uncontrolled cancer
IV	Outpatients with controlled cancer and without comorbidity

Group IV is low risk

Table 7 Spectrum of antimicrobial activity in neutropenic fever

	Pseudomonas coverage	Anaerobic coverage	Enterococcal coverage	ESBL coverage
Anti-Pseudomonal cephalosporin (i.e. cefepime)	+	–	–	–
Pip-tazo	+	+	++	±
Anti-Pseudomonal carbapenem (i.e. meropenem)	+	+	+	+

be collected from different sites including a peripheral stick as well as a culture from each of the lumens of a patient's central catheter if present. Other cultures such as urine, CSF and imaging such as a chest x-ray are obtained as clinically indicated. Patients with influenza-like symptoms should be tested for influenza ideally via polymerase chain reactions (PCR). Empiric antimicrobial therapy should be administered within 1 h from presentation to the ER [1]. Either an antipseudomonal B-lactam or a carbapenem should be given empirically for NPF. Additional gram-positive coverage is recommended only when there is suspicion of a gram-positive producing infection such as line infection or soft tissue infection where the addition of IV vancomycin is indicated [1]. Empiric NPF regimens are designed to be adjusted based on patient risk factors i.e. known ESBL colonization and the need for empiric meropenem. Traditionally if the patient is colonized with MRSA, there is the consideration of empiric 48 h use of IV vancomycin, linezolid or daptomycin. If the patient is colonized with vancomycin resistant enterococcus (VRE) then there is a consideration of 48 h of empiric daptomycin or linezolid use for NPF. Carbapenamase producing organisms in a patient's history would lead the ID team to consider the early use of prolonged infusion meropenem and polymyxin-colistin or ceftazidime avibactam if sensitive in the past. Anaerobic coverage is added as clinically indicated [10].

If a NPF develops on the outpatient service, the decision algorithm has to assess the need for inpatient versus outpatient care. Febrile neutropenia in patients who are expected to be neutropenic for more than 7 days and have profound neutropenia and/or have significant comorbidities is deemed high risk. These patients are then candidates for inpatient therapy [1]. On the other hand, patients with febrile neutro-

penia who are expected to have a short duration of neutropenia and none/few comorbidities would therefore be considered low risk. Low risk patients are then considered candidates for outpatient therapy. There are several tools that have been validated to supplement clinical decision making: MASCC index, Talcott's rules or CISNE (specifically for solid tumors presenting with NPF). These tools are designed to augment clinical decision making but if the patient is deemed unstable for discharge by a treating physician from an emergency room then regardless of the score, the patient would need admission to the hospital [8]. Also those patients infected with a resistant pathogen will have a higher pretest probability of admission due to the difficulty in organizing intravenous antimicrobials from an emergency room setting. Afebrile patients who have new signs or symptoms suggestive of an infection that are considered high-risk would automatically be candidates for inpatient therapy [2, 7].

If the patient is determined to be stable for outpatient management, after also taking into consideration logistic factors such as ease of follow up visits, and transportation, among others then they can be discharged after 4 h of the initial hospital, ER or clinic assessment. Empiric therapy for NPF on the outpatient service would be an oral fluoroquinolone plus amoxicillin-clavulanate acid or clindamycin (if the patient was penicillin allergic) [1]. If these patients were previously on an oral fluoroquinolone for prophylaxis then they should not be given empiric therapy with a fluoroquinolone. Prior prophylaxis with a fluoroquinolone followed by NPF is an indication to be admitted to an inpatient unit until a resistant bacterial infection is ruled out. If a patient fails to defervesce after 2–3 days or he/she develops a new NPF, new infection or if initial blood cultures become positive or intolerance to oral therapy develops, then reevaluation and hospital admission is indicated [1, 7].

Tailoring therapy depends on the individual's clinical course. Patients with unexplained fevers but who are stable would be continued on the initial therapy for up to 5 days prior to consideration for either a lateral change (possible drug fever) versus escalation (concern for inadequate coverage) \pm CT chest without contrast to rule out an occult mold infection. If the patient has a documented infection then the antimicrobial regimen should be adjusted to reflect the positive cultures. Those patients who are on IV therapy can also be switched at that point to oral therapy if GI absorption is deemed adequate and they are clinically stable. Those patients who become unstable or hypotensive, should have their regimen broadened to cover for resistant pathogens [1, 7]. With persistent NPF beyond 5 days, the consideration needs to be made for empirically adjusting antifungal coverage to include anti-mold therapy. Antiviral therapy is indicated in febrile neutropenia only if there is strong clinical or laboratory evidence of a viral infection. If there is an ongoing community-based outbreak of influenza A or B, then a febrile neutropenic patient presenting with influenza-like symptoms should be treated empirically with neuraminidase inhibitors [1, 7].

When to De-escalate Therapy?

This topic used to be controversial when it comes to NPF but there is an increasing breadth of knowledge and guidelines to support de-escalation under the auspices of antimicrobial stewardship. Per 2010 IDSA clinical guidelines, it depends on the duration of neutropenia as well as having a clinically or microbiologically documented infection [1]. In the setting of an unexplained fever, the initial therapy should be continued until there is marrow recovery i.e. ANC >500. In the case of a documented infection, therapy depends on the site of infection and or organism isolated. Antibiotics (whether prophylaxis or treatment) are continued until the ANC > 500 or if they received an appropriate duration of therapy for that particular infection, then they can be switched to prophylactic antibiotics for the remaining duration of neutropenia [1]. However there have been an increasing collection of studies and the European Guidelines that recommend early de-escalation of antibiotics back to prophylaxis in cases of resolved unexplained fever. When considering this option, patients should be afebrile at least for >48 h, clinically stable, and without signs or symptoms of new infection [9].

Pathogen Based Treatment Algorithms

With the advent of multiplex polymerase chain reactions (PCRs), the paradigm of treating neutropenic fever is slowly but steadily changing. Multiple microbiology labs have invested into an array of platforms that help facilitate the rapid diagnosis of bacteremias. The previous paradigm was monitoring blood cultures continuously for up to 5 days or at least until they turned positive. Once the blood culture turned positive, an initial sample was assessed via a gram stain. Simultaneously the sample is plated with the goal of growing a pure colony to run through a VITEK II allowing for the assessment of antimicrobial sensitivities as well as placing a sample in one of many types of PCR platforms. Based on the example of the BioFire®, the turn-around time for the blood culture identification (BCID) panel is approximately 1 h. after only 5 min of hands on time. This allows for the identification of the organism but unfortunately for sensitivities, one still has to wait for the pure culture to be selected out and run through the VITEK II [11]. The integration of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has further changed the face of microbiology by utilizing protein fingerprinting to diagnose organisms by use of referencing them against a database and various algorithms [12].

Key Points

- Neutropenic fever among cancer patients may be associated with significant morbidity and mortality.
- Prophylaxis is indicated for patients with profound, protracted neutropenia to reduce the risk of febrile episodes related to infection.
- All cancer patients who are neutropenic, presenting with fever should be evaluated for infection while also ruling out other non-infectious causes of fever.
- Thorough evaluation augmented by clinical judgment and if needed specific scoring tools should be implemented to identify those patients with febrile neutropenia who require inpatient management.
- Empiric antimicrobial therapy involves the use of antibiotics with anti-pseudomonal coverage, with the addition of gram-positive coverage depending on the clinical scenario.
- Antifungal coverage and the evaluation of fungal infections in high risk patients should be considered with profound neutropenia with persistent fevers.
- Timing of de-escalation of therapy is still debatable however for stable patients with resolved, unexplained fevers after 48 h of therapy can be de-escalated back to prophylaxis and followed closely if clinically stable.

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