# Neutropenic fever syndrome

- INTRODUCTION
- Cancer patients receiving cytotoxic antineoplastic therapy sufficient to adversely affect myelopoiesis and the developmental integrity of the gastrointestinal mucosa are at risk for invasive infection due to colonizing bacteria and/or fungi that translocate across intestinal mucosal surfaces

- Since the magnitude of the neutrophil-mediated component of the inflammatory response may be muted in neutropenic patients [1], a fever may be the earliest and only sign of infection.
- It is critical to recognize neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly to avoid progression to a sepsis syndrome and possibly death.

- Guidelines have been developed for the evaluation and management of fever in neutropenic patients with cancer [2-4].
- The recommendations below are generally in keeping with the 2010 Infectious Diseases Society of America (IDSA) guidelines and the 2018 American Society of Clinical Oncology/IDSA guidelines [2,4].

- DEFINITIONS
- The Infectious Diseases Society of America defines fever in neutropenic patients as a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a one-hour period [2].
- We agree with using this definition of fever in neutropenic patients. Similar definitions have been provided from South America, Europe, and Asia

- It is known from animal models that glucocorticoids may have a mitigating effect on the development of fever due to bacterial or endogenous pyrogens [13].
- The antipyretic effect of concomitant use of glucocorticoids in neutropenic patients may confound the recognition of an infection [14].
- The presence of signs of systemic inflammatory response syndrome, including tachycardia, tachypnea, or hypotension in an afebrile neutropenic patient who is receiving concomitant glucocorticoids, should raise the suspicion of infection.

- Neutropenia :
- The definition of neutropenia may vary from institution to institution, but neutropenia is usually defined as an absolute neutrophil count (ANC) <1500 or 1000 cells/microL, severe neutropenia as an ANC <500 cells/microL or an ANC that is expected to decrease to <500 cells/microL over the next 48 hours, and profound neutropenia as an ANC <100 cells/microL [2].
- The risk of clinically important infection rises as the neutrophil count falls below 500 cells/microL and is higher in those with a prolonged duration of neutropenia (>7 days). Further, the risk for bacteremic infection increases as the ANC decreases below 100 cells/microL. For the purposes of this discussion, we are defining severe neutropenia as an ANC <500 cells/microL (<0.5 x 109/L).

- Neutropenic fever syndromes
- A number of neutropenic fever syndromes have been described [15,16]. The International Immunocompromised Host Society has classified initial neutropenic fever syndromes into the following three categories [15]:
- Microbiologically documented infection – Neutropenic fever with a clinical focus of infection and an associated pathogen
- Clinically documented infection – Neutropenic fever with a clinical focus (eg, cellulitis, pneumonia) but without the isolation of an associated pathogen
- Unexplained fever – Neutropenic fever with neither a clinical focus of infection nor an identified pathogen

- The myeloid reconstitution syndrome is defined by fever and a new inflammatory focus or progression of a pre-existing inflammatory focus in temporal relationship to neutrophil recovery from aplasia.
- This syndrome is similar to the immune reconstitution inflammatory syndrome that can follow the initiation of antiretroviral therapy in patients with human immunodeficiency virus (HIV) infection

- RISK OF SERIOUS COMPLICATIONS :
- The initial clinical evaluation focuses on assessing the risk for serious complications.
- This risk assessment dictates the approach to therapy, including the need for inpatient admission, intravenous antibiotics, and prolonged hospitalization

- Validated scoring systems used to estimate the risk for medical complications include the Talcott rules [17],
- the Multinational Association for Supportive Care in Cancer (MASCC) score (calculator 2) [18],
- and the Clinical Index of Stable Febrile Neutropenia (CISNE) score [19].
- These scoring systems assume the states of neutropenia and fever for a given patient and do not focus upon either the degree or duration of neutropenia as predictors of the likelihood of medical complications that require or prolong hospitalization

- Low-risk patients are those who are expected to be severely neutropenic (absolute neutrophil count [ANC] <500 cells/microL) for ≤7 days, have an MASCC score ≥21 or a CISNE score of 0 at the time of assessment, and who have no comorbidities or evidence of significant hepatic or renal dysfunction.
- This group of patients has been well studied in randomized trials and has been shown to be at low risk for serious complications [2].
- Most patients receiving chemotherapy for solid tumors are considered to be low risk for complications requiring hospitalization or prolonging hospitalization.

- High-risk patients are those who are expected to be severely neutropenic (ANC <500 cells/microL) for >7 days and who have an MASCC score <21 or a CISNE score of ≥3 at the time of assessment.
- Intermediate CISNE scores (1 or 2) may require clinicians to judge the relative safety of outpatient oral therapy versus hospitalization for parenteral antibacterial therapy.
- Patients with neutropenic fever who have ongoing comorbidities or evidence of significant hepatic or renal dysfunction are also considered to be high risk for medical complications, regardless of the duration of neutropenia

- Some experts have defined high-risk patients as those expected to have profound neutropenia (ANC ≤100 cells/microL) for >7 days based on experience that such patients are the most likely to have life-threatening complications

- Profound prolonged neutropenia (ie, ANC ≤100 cells/microL expected to last >7 days) is most likely to occur in the pre-engraftment phase of hematopoietic cell transplantation (particularly allogeneic) and in patients undergoing induction chemotherapy for acute leukemia.

- In general, neutropenic fevers develop in approximately 5 to 10 percent of solid tumor patients receiving cytotoxic therapy and who are at low risk for medical complications [21],
- compared with 20 to 25 percent of non-leukemic hematologic malignancy patients and 85 to 95 percent of acute leukemia patients .

- APPROACHES TO MANAGEMENT
- Approaches to the management of infection in patients at risk for neutropenic fever include primary prophylaxis, secondary prophylaxis, empiric therapy, and pre-emptive therapy.

- Primary prophylaxis :
- Primary prophylaxis involves the administration of an antimicrobial drug to prevent infection in patients at increased risk.

- Secondary prophylaxis:
- Secondary prophylaxis involves the administration of prophylactic doses of an antimicrobial drug to prevent recurrent infection

- Empiric therapy :
- In patients with chemotherapy-induced neutropenia, empiric therapy involves the initiation of therapy at the time of the onset of neutropenic fever but before a firm diagnosis of infection has been established.
- Empiric antimicrobial therapy is a standard part of the management of neutropenic fever.

- Pre-emptive therapy :
- Pre-emptive therapy involves the initiation of therapy based upon screening with a sensitive microbiology assay (eg, antigen detection or molecular assays) in an attempt to detect the presence of a putative pathogen or early subclinical infection.
- Patients whose infections are detected using a pre-emptive approach are treated to avoid progression to invasive disease.
- A pre-emptive approach is sometimes used for antifungal therapy

- TEMPERATURE MEASUREMENT
- An elevated body temperature is the trigger for initiating an aggressive protocol of neutropenic fever management

- We favor oral thermometry in patients without oral mucositis, and tympanic membrane thermometry or axillary thermometry in patients with oral mucositis.
- Each of these methods has shortcomings, and the use of each method requires that proper technique be used to obtain accurate results [7].
- Peripheral methods of monitoring temperature (tympanic membrane, temporal artery, axillary, and oral thermometry) do not accurately reflect core body temperature as measured by central methods (pulmonary artery catheter, urinary bladder, esophageal, and rectal thermometry) and are less sensitive [25]; however, central methods are not practical or safe in neutropenic patients.

- Rectal thermometry is not recommended in neutropenic or thrombocytopenic patients because it may increase the risk for local mucosal trauma-induced bacteremia and bleeding.

- PATHOGENESIS :
- Contributory factors to the pathogenesis of neutropenic fever include [2]:
- The direct effects of chemotherapy on mucosal barriers and the immune system
- Breeches in host defenses related to the underlying malignancy
- Chemotherapy-induced mucositis occurs throughout the alimentary system, and seeding of the bloodstream from endogenous flora in the gastrointestinal tract is believed to cause the majority of episodes of neutropenic fever

- Obstruction of lymphatic channels, the biliary tract, and/or bronchial, gastrointestinal, or urinary systems by tumor(s) or as a result of surgical procedures are also common causes of infection.
- Immune defects related to underlying hematologic disorders, in addition to the immunosuppressive effects of chemotherapy, also place patients at higher risk for infection

- Risk of infection based on type of malignancy:
- The risk for specific types of infections is influenced by the nature of the underlying malignancy and its associated humoral or cellular immune deficits:

- Abnormal antibody production or clearing of immune complexes in multiple myeloma, chronic lymphocytic leukemia, and splenectomized (including functional asplenia) patients results in an increased risk of sepsis from encapsulated organisms, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*, as well as from *Capnocytophaga canimorsus* and *Babesia* spp.

- The T cell defects associated with lymphoma result in an increased risk of infection with intracellular pathogens, such as *Listeria monocytogenes*, *Salmonella* spp, *Cryptococcus neoformans*, and *Mycobacterium tuberculosis*.
- Patients with acute lymphocytic leukemia, central nervous system tumors, and other cancer patients receiving high-dose glucocorticoids are at increased risk for *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia.

- EPIDEMIOLOGY:
- An infectious source is identified in approximately 20 to 30 percent of febrile neutropenic episodes [2,35].
- Often the only evidence of infection is bacteremia, which is documented in 10 to 25 percent of patients [2].
- Approximately 80 percent of identified infections are believed to arise from the patient's endogenous flora [36].

- Bacterial pathogens :
- Gram-negative bacilli, particularly *Pseudomonas aeruginosa*, were the most commonly identified pathogens in neutropenic patients until the 1980s [37].
- Subsequently, gram-positive bacteria have become the most common pathogens [38,39].
- Common gram-positive cocci include *Staphylococcus epidermidis* (by far the most common), *Staphylococcus aureus*, and streptococci; less common gram-positive organisms include *Corynebacterium jeikeium*, *Bacillus* spp, *Leuconostoc* spp, *Lactobacillus* spp, *Cutibacterium* (formerly *Propionibacterium*) *acnes*, and *Rhodococcus* spp

- The following observations have been made about bacterial infections in neutropenic patients:
- Bacteria are the most frequent infectious causes of neutropenic fever [48].
- Gram-negative bacteria (eg, *P. aeruginosa*) are generally associated with the most serious infections.
- *S. epidermidis* is the most common gram-positive pathogen, accounting for approximately one-half of all infections due to gram-positive infections. It is much less virulent than other bacterial pathogens

- Among gram-positive bacteria, *S. aureus* (particularly methicillin-resistant strains), some viridans streptococci, and enterococci (particularly vancomycin-resistant strains) can cause serious infections [39]. In some European cancer centers, methicillin resistance has dominated among *S. aureus* bloodstream isolates [49].
- Although anaerobic bacteria are abundant in the alimentary tract, they are infrequent pathogens isolated from patients with neutropenic fever.
- However, they can contribute to the pathogenesis of necrotizing mucositis, sinusitis, periodontal cellulitis, perirectal cellulitis, intra-abdominal or pelvic infection, and neutropenic enterocolitis (typhlitis) and can cause anaerobic bacteremia.
- Polymicrobial infections are infrequent, but their frequency appears to be rising [48].

- Fungal pathogens :
- Fungal pathogens are common in high-risk patients with neutropenic fever (table 1) but are uncommon in low-risk patients.
- The risk for invasive fungal infections increases with the duration and severity of neutropenia, prolonged antibiotic use, and number of chemotherapy cycles. Fungi are rarely the cause of the first febrile episode in neutropenic patients [50].
- More commonly, invasive fungal infections occur later as a cause of persistent or recurrent neutropenic fever. However, fungal infections can occasionally present early or even prior to initial chemotherapy.

- Fungi are rarely identified as the cause of initial fever during neutropenia. More commonly, they are identified as causes of persistent or recurrent fever beyond the first week of neutropenia.
- *Candida* spp and *Aspergillus* spp account for most invasive fungal infections during neutropenia.
- The former are acquired through gastrointestinal tract colonization and translocation across damaged intestinal epithelial surface.
- The latter are acquired by inhalation of airborne spores (conidia) into the upper and lower respiratory tract followed by germination and invasive hyphal growth.

- Fever is often the sole manifestation of candidemia.
- Erythematous macronodular skin nodules may occur in some patients with candidemia.
- Among patients who develop disseminated candidiasis following chemotherapy, hepatosplenic involvement is common; signs and symptoms are often not present until the neutropenia resolves.
- The reported median time to a diagnosis of hepatosplenic involvement after AML induction therapy has been 26 days (range 19 to 31 days) from the first day of the cytotoxic regimen

- *Candida albicans* accounts for the majority of candidemias; *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* are the most common non-albicans *Candida* spp isolated in candidemia and invasive candidiasis.
- A higher proportion of candidemias are due to non-albicans *Candida* species when fluconazole prophylaxis has been administered.
- *Candida* spp are common fungal causes of central venous catheter-associated infections and can cause disseminated candidiasis

- *Aspergillus* spp is a common fungal pathogen in immunocompromised hosts, and infection follows the inhalation of airborne conidia (spores);
- manifestations primarily affect the lower respiratory tract (pneumonia) and upper respiratory tract (sinusitis) but may also involve the central nervous system, bones, and skin.

- The agents of mucormycosis can cause life-threatening rhino-orbital-cerebral, pulmonary, and disseminated infections in immunocompromised hosts, particularly those with uncontrolled hyperglycemia due to pre-existing diabetes mellitus or administration of glucocorticoids.

- Viral pathogens :
- Viral infections, especially human herpesviruses, are common in high-risk patients with chemotherapy-induced neutropenia (table 1) and are effectively prevented with antiviral prophylaxis

- Most herpes simplex virus (HSV)-1 and -2 infections in adults are due to reactivation of latent infections in seropositive patients.
- The likelihood of reactivation is influenced by the intensity of the chemotherapy regimen and by the relative impact upon virus-specific cytotoxic T-lymphocyte-mediated host defenses

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- Ulcerations of the oral or esophageal mucosa and ulcers or vesicles of lips, genitalia, skin, or perianal areas are the most common manifestations.
- HSV can cause a wide variety of syndromes, including encephalitis, meningitis, myelitis, esophagitis, pneumonia, hepatitis, erythema multiforme, and ocular disease.

- Herpes zoster, which is caused by varicella-zoster virus (human herpesvirus 3), often presents in an atypical disseminated pattern involving multiple dermatomes or widespread skin dissemination in immunocompromised hosts

- Infections caused by community-acquired respiratory viruses (CARVs) are a significant threat to patients with hematologic malignancies and stem cell transplantation [56-58].
- CARVs have been documented with increasing frequency and occur commonly in neutropenic patients; these include influenza virus, respiratory syncytial virus, parainfluenza viruses types I to IV, human adenovirus, human rhinoviruses, human coronaviruses, and human metapneumovirus

- Although information on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), in cancer patients and organ transplant recipients is limited, reports suggest that the severity of the infection may be greater.

- Other :
- Reactivation of tuberculosis should be considered in patients with epidemiologic risk factors, especially in those with prolonged glucocorticoid use or other forms of immunosuppression that increase the risk (eg, a tumor necrosis factor-alpha inhibitor).

- MANAGEMENT :
- It is critical to recognize neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly to avoid progression to a sepsis syndrome and possibly death.
- In all cancer patients presenting with neutropenic fever, empiric antibacterial therapy should be initiated immediately after blood cultures have been obtained and before any other investigations have been completed.

- Initial assessment :
- A reliable method for obtaining body temperature must be used and a mechanism for estimating the absolute neutrophil count (ANC) is mandatory (see 'Temperature measurement' above and 'Neutropenia' above).
- The risk of neutropenia, the risk of complications from neutropenic fever, and the risk of sepsis must be assessed quickly.

- Timing of antibiotics:
- Antibiotics should be given as early as possible.
- The guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Oncology and the Northern Ireland Cancer Network recommend that empiric broad-spectrum antibacterial therapy be initiated immediately after blood cultures have been obtained and before any other investigations have been completed in all patients with neutropenic fever [11,64].
- International guidelines advocate the administration of empiric antibacterial therapy within 60 minutes of presentation in all patients presenting with a neutropenic fever

- The successful management of neutropenic fever and sepsis syndromes is a time-dependent process analogous to acute stroke or ST-segment elevation myocardial infarction syndromes

- Diagnostic evaluation:
- Once empiric antibacterial therapy has been started, all patients should have a thorough history and detailed physical examination as well as laboratory, microbiology, and imaging studies

- Treatment regimens :
- The aim of empiric therapy is to cover the most likely and most virulent pathogens that may rapidly cause serious or life-threatening infection in neutropenic patients (table 3) [2].
- Although antimicrobial agents are usually administered empirically, they should always include appropriate coverage for suspected or known infections.
- Even when the pathogen is known, the regimen should provide broad-spectrum empiric coverage for the possibility of other pathogens, unlike the treatment strategy adopted in many immunocompetent hosts.

- Initial regimen:
- Monotherapy or compound therapy
- Addition of gram-positive coverage
- Addition of an antifungal agent

- Monotherapy with an antipseudomonal agent:
- Cefepime
- Meropenem
- Imipenem
- Piperacillin-tazobactam
- ceftazidime

- Addition of gram-positive coverage:
- Hemodynamic instability or other signs of severe sepsis
- Pneumonia
- Positive blood culture for gram-positive bacteria
- Catheter infection
- Skin or soft tissue infection
- Severe mucositis

- Addition of an antifungal agent:
- Amphotericin B deoxycholate
- Caspofungin
- Voriconazole
- itraconazole

- Duration of treatment
- G-CSF effect and absolute indication

Thank you for attention