Febrile Neutropenia

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Definition:

An absolute neutrophil count (ANC) of less than 1000* cells/microliter with either
(1) A single oral temperature greater than or equal to 101ºF for at least an hour *or*
(2) a temperature greater than or equal to 100.4ºF for at least an hour.

Severe neutropenia: ANC is less than 500 or ANC is expected to decrease below 500 in the next 48 hours.
Profound neutropenia: ANC less than 100
Profound prolonged neutropenia: ANC less than 100 for >7 days
**ANC definition of neutropenia may vary from institution to institution or in different guidelines*

How to calculate ANC:

$$\frac{\text{WBC x total neutrophils [segmented neutrophil \% + segmented bands \%]}}{100}$$

Etiology:

- Most commonly unknown cause; 10-25% documented bacteremia
- Infections are the primary cause of morbidity and mortality in patients with cancer who present with fever and neutropenia.
- Most often bacterial infections, can also be viral or fungal
    - Commonly due to staphylococcus, streptococcus, and enterococcus species.
    - Gram negative bacteria cause more severe infections Can also be due to drug-resistant organisms such as (*Pseudomonas aeruginosa*, Acinetobacter species, *Stenotrophomonas maltophilia* as well as *E. coli*, Klebsiella species
- Most common and serious complication associated with hematopoietic cancers or with patients receiving chemotherapy
- Fever during chemotherapy-induced neutropenia may be the only sign of a severe underlying infection

History and Physical

- Detailed history (chemo regimen, medications, hx of previous infections, hx bacterial resistant organisms, allergies)
- Signs of infection (pain, dysuria, cough, diarrhea, abdominal pain, thorough ROS).
- Risk factors: older age, comorbidities, certain cancers, type and number of myelosuppressive chemotherapy agents in use
- Pay attention to the skin (rashes, indwelling lines, bone marrow biopsy sites), GI tract (mucositis, intestines, perirectal area), and lungs.
- Avoid digital rectal exam

Evaluation:

- CBC w/differential, UA, lactate, BMP, LFTs,
- Blood cultures (2 sets) before starting abx from peripheral and any venous catheter
- +/- CXR, urine, stool, throat and viral studies based on clinical suspicion and symptoms
    - Pyuria may be absent in the neutropenic patient.
- **Scores: MASCC and CISN to risk stratify into high and low risk**
    - **MASCC-** assesses risk of serious complications in patients with neutropenic fever. Score >21 = low risk, < 21 = high risk. All patients with score < 21 or high risk by clinical criteria should be initially admitted to the hospital for empiric antibiotics.
    - **CISNE -** for low-risk patients, useful in ED, takes functional status into account.

Treatment

- Considered an oncologic emergency

- **Low-risk patients**, outpatient: empiric oral fluoroquinolone + amoxicillin/clavulanate
    - If penicillin allergy → clindamycin
    - If remains febrile for 48-72 hours → hospital admission
- **High-risk patients:** IV antibiotics within 1 hour after triage and monitored for at least 4 hours. IDSA recommends: antipseudomonal beta-lactam (cefepime, carbapenems, or piperacillin/ tazobactam).
    - Empiric antifungal coverage can be added after prolonged (>4 to 7 days) neutropenic fever with expected neutropenia of >7 days
    - Consider vancomycin if suspecting catheter-related infection, skin or soft tissue infections, pneumonia, or hemodynamic instability.
    - If no response, broaden to include resistant species: MRSA (vancomycin, linezolid, or daptomycin), VRE (linezolid or daptomycin), ESBL (carbapenems), Klebsiella (carbapenems, polymyxin, colistin, or tigecycline)
- **Add anti-fungal coverage?** More likely to be fungal infections after prolonged neutropenia (>7 days) and/or prolonged antibiotic use.
    - Add when fever persists or recurs after 4-7 days of empiric antibiotics, positive serum fungal markers, imaging evidence of fungal infection, or positive fungal cultures
        - Amphotericin B (gold standard), echinocandins, or azoles (e.g. voriconazole).
- G-CSF - can be given as prophylaxis with chemotherapy to prevent /shorten duration of neutropenia. It is NOT recommended during an episode of febrile neutropenia.
- Duration: can consider stopping antibiotics/fungals once febrile symptoms resolve, ANC > 500, and after treatment of any identified infections.

Prognosis:

- Most important determining factor of patient outcomes = **timing of IV antibiotic administration**
- Early administration IV antibiotics reduces mortality and length of stay
- Poor prognostic signs: expected prolonged (>10 days) and profound neutropenia (ANC <100), age over 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or hospitalization at the time of fever development

Citation:
https://www.ncbi.nlm.nih.gov/books/NBK541102/
https://www.idsociety.org/practice-guideline/neutropenic-patients-with-cancer/
https://thecurbsiders.com/podcast/288
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