## Infection in neutropenic ptn.

- In general what are the risk factors for infection:
  - Neutropenia.
  - Immune system defects (from disease or immunosuppressive drug therapy).
  - Compromise of natural host defenses.
  - Environmental contamination.
  - Changes in the normal flora of the host: Administration of broad-spectrum antimicrobial agents disrupts GIT flora and predisposes patients to infection with more virulent pathogens.
- What is neutopenia ?
  - An absolute neutrophil count (ANC) of less than 1,000 cells/mm3, which increase risk for infection.
  - ANC< 500 = severe neutropenia
  - ANC<100 = profound neutropenia.

- Empirical broad-spectrum antibiotic therapy is effective at reducing early mortality and any delay lead to unacceptable high mortality rate
- Treatment and prophylaxis can be extremly challenging and guidelines remain unclear.
- During periods of neutropenia, patients should continue to receive broad-spectrum therapy even if afebrile.
- Fever in the neutropenic patient should be considered to be due to infection until proven otherwise

### Management of febrile neutropenic ptn:

- **High-dose broad-spectrum-bactericidal, parenteral, empirical antibiotic therapy should be initiated at the onset of fever or at the first signs or symptoms of infection.**
- **Empirical therapy is 70-90% effective ( shouldn't be delayed).**
- **Ptn factors, institution pattern of infections and biogram must be taken into consedration during therapy.**
- **Empirical therapy targets :** P. aeruginosa and other gram- negative bacilli and staphylococci

### Ptn divided into 2 categories:

- **Low-risk patients:**
  - **May be Candidate for IV,oral or outpatient Abx and you can switch to oral after 2 days of IV Abx in ptn who become afebrile.**
  - **Chracteristics:**
    - anticipated duration of neutropenia ≤ 7 days.
    - are clinically stable.
    - have no or few co-morbidities.
    - have no bacterial focus or systemic signs of infection other than fever.
  - **Oral Abx for low risk ptn: Ciprofloxacin or levofloxacin + amoxicillin-clavulanate or clindamycin**

- **High-risk patient:**
  - **Should be hospitalized for IV Abx**
  - **Maintained on IV Abx until neutropneia resolve (ANC>500)**
  - **Chracteristics:**
    - anticipated duration of neutropenia of > 7 days
    - profound neutropenia
    - clinically unstable
    - have comorbid medical problem

## ❖ Treatment :

- optimal antibiotic regimen remains controversial.
- Prrolonged antibiotic use has been associated with superinfections resulting from resistant bacteria and fungi and increased risk of antibiotic-related toxicities.
- empirical regimens must be: carefully monitored and appropriately revised
- A higher rate of adverse effects was observed in **aminoglycoside-containing combination regimens.**
- **Cefepime** and a**ntipseudomonal carbapenems** have good activity against **viridans streptococci and pneumococci** but not all gram positive bacteria.
- ✓ **Recognized antibiotic regimen:**

1. **Monotherapy**:
   - **choose one:**
     - antipseudomonal β- lactam (cefepime or ceftazidime)
     - carbapenem (imipenem–cilastatin or meropenem)
     - piperacillin–tazobactam.
   - **Disadvantage: limited gram positive activity, and high rate of superinfection.**

2. **combination therapy:**
   - Antipseudomonal β-lactam + aminoglycoside: **limited gram positive activity, potential for nephrotoxicity and need of TDM.**
   - Antipseudomonal β-lactam + fluoroquinolone(ciprofloxacin or levofloxacin) : **limited gram positive activity and development of resistance.**

3. **Monotherapy or combination therapy + vancomycin**
   - **Disadvantage: risk of nephrotoxicity and need for TDM.**
   - **I**f vancomycin was included in the initial empirical regimen and the patient **is still febrile after 2 to 3 days** of therapy without isolating a gram-positive pathogen, **discontinue vancomycin .**

- **If fever persist for more than 2 days:**
  - **patients should be evaluated carefully**
  - **Causes:**
    - nonbacterial infection
    - resistant bacterial infection or infection slow to respond to therapy.
    - secondary infection
    - inadequate drug concentrations
    - drug fever
    - infection at a non-vascular site (catheter infection or abscess)
    - noninfectious causes such as: tumors.

- **If febrile or develops new fever despite > 4 - 7 days of broad-spectrum antibiotic therapy**:
  - **indicate the presence of a fungal infection, most commonly Candida or Aspergillus sp.** ( these pathogens should be targeted by empirical therapy )
  - **Ptns are candidates for antifungal therapy and therapy should be started**
  - **significant percentage of febrile patients who die during prolonged neutropenia have evidence of invasive fungal infection on autopsy.**
  - **Blood culture is positive in <50%**

- ✓ **<u>Treatment in this ptn:</u>**
  - **Aspergillus**: **amphotericin** B/ lipid-associated amphotercin B (LAMB) is the preferred agent.
    - common in patients with hematologic malignancies.
  - **Fluconazole** has good activity against C. albicans.
    - Azole compounds are associated with emergence of resistant Candida strains.
  - **Voriconazole** is a preferred agent for invasive aspergillosis (especially pulmonary).
  - **Posaconazole** has extended activity against some Mucorales, in addition to Candida and Aspergillus but **Only approved for prophylaxis .**
  - **The echinocandin antifungals (caspofungin, micafungin, and anidulafungin)** have broad spectrum of antifungal activity and favorable adverse effect profiles.
    - **Caspofungin** is as <u>effective as, and better tolerated than, liposomal amphotericin B for empirical treatment</u> of neutropenic patients with persistent fever. Therefore, it is **considered an appropriate alternative to LAMB and voriconazole.**

LAMB is less toxic, can be used at higher dose compared to amphotericin B, but higher cost

| Posaconazole | Hepatotoxicity, rash; interactions with CYP3A4 |
|---|---|
| Voriconazole | Mental status changes, headache, hallucinations, visual disturbances, hepatotoxicity, QTc prolongation; interactions with CYPs 2C9, 2C19, and 3A4 |

| Drug | Adverse Reaction |
|---|---|
| Amphotericin B (lipid-associated) | Nephrotoxicity, hepatotoxicity, electrolyte disturbances, infusion reactions |

❖ **Initiation of Antiviral Therapy**

- **Febrile neutropenic patients** with **vesicular or ulcerative skin or mucosal lesions** should be evaluated carefully for infection due to **herpes simplex virus (HSV) or varicella-zoster virus (VZV).**
- **Site of ulcers is a portal for 2nd infection.**
- **If viral infection is presumed or documented, neutropenic patients should receive aggressive antiviral therapy.**
- **acyclovir and the newer antivirals valacyclovir and famciclovir may be used.** ( without mucosal lesions not recommended)
- **optimal duration of antimicrobial therapy remains controversial.**
- **Decisions of dicontinuation is harder than initiation of therapy.**
- **Ptns with severe neutropenia (ANC > 100 but < 500 cells/mm3), mucosal lesions, or unstable vital signs or other risk factors should continue to receive antibiotics until ANC becomes ≥ 500 cells/mm3, and the patient is stable clinically.**

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- **Granulocyte-macrophage colony-stimulating Factor (Sargramostim) and Granulocyte colony-stimulating factor (filgrastim**) May be used as adjunct therapy to antimicrobial treatment of febrile neutropenic patient, **why?**
  1. Reduce duration of Abx use
  2. Reduce hospitalization And duration of stay.
  3. Overall mortality or infection-related mortality is NOT decreased.
- **GM-CSF and G-CSF should not be routinely used**
- **To whom we should give CSF: ( أي حدا طابل مثلي و مثلك بنعطيه)**
  - Profound neutropenia (ANC <100 cells/mm3)
  - Expected prolonged period of neutropenia (>10 days)
  - Patient age >65 years
  - Uncontrolled primary disease
  - Sepsis syndrome, or severe infection manifest by hypotension and multiorgan dysfunction
  - Pneumonia
  - Invasive fungal infection
  - Other clinically documented infection
  - Hospitalized at the time of the development of fever
  - Severe complications during previous episode of febrile neutropenia
- **SE of CSF:**
  - Bone pain: because of proliferation of WBCs in bone marrow. Relieved with analgesics.
  - Leukocytosis.
  - Bruises, bleeding gum and nose bleeding: Due to drop in platelet count.
  - Splenomegaly and spleen rupture.