**WHAT IS FEBRILE NEUTROPENIA?**

<table>
<thead>
<tr>
<th>FEVER</th>
<th>General risk factors for infection in cancer patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oral temperature $\geq 38.3^\circ C$</td>
<td>• ANC $\leq 0.5 \times 10^9$/L (500 cells/mm$^3$)</td>
</tr>
<tr>
<td>• Oral temperature $\geq 38^\circ C$ for more than 1 hour</td>
<td>• ANC $\leq 1.0 \times 10^9$/L (1000 cells/mm$^3$) with predicted ↓ to &lt; 0.5 $\times 10^9$/L in the next 24-48 hr</td>
</tr>
<tr>
<td>• Neutropenia = a reduction in the number of circulating granulocytes or neutrophils</td>
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<td>• Degree of neutropenia expressed in terms of absolute neutrophil count (ANC) or total number of granulocytes (PMNs and band forms) present in the circulating pool of WBC's</td>
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<td>• ANC is calculated as the product of the WBC count and the fraction of PMNs and band forms in the differential analysis</td>
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<td>• ANC = WBC (cells/mm$^3$) x percent (PMNs + bands)/100</td>
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</table>

**WHY ARE CANCER PATIENTS A CONCERN?**

- 1960s: ↑ mortality rates in neutropenic patients with gram (-) bacteremia
- Failure to initiate antibiotics for gram (-) bacteremia

**GENERAL RISK FACTORS FOR INFECTION IN CANCER PATIENTS:**

<table>
<thead>
<tr>
<th>NEUTROPENIA</th>
<th>ANC &lt; 500-1000 increases incidence of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe infection</td>
<td>• # of days spent on antibiotics</td>
</tr>
<tr>
<td>• # of days of fever</td>
<td>• Underlying disease:</td>
</tr>
<tr>
<td>• Multiple myeloma &amp; lymphocytic lymphoma/leukemia</td>
<td>• Defects in B-cell number/function ↑ risk of infection with encapsulated bacteria</td>
</tr>
<tr>
<td></td>
<td>o S. pneumonia, H. influenza, N. meningitidis</td>
</tr>
<tr>
<td>• SPECIFIC THERAPY</td>
<td>• Steroids, chemotherapy, radiation</td>
</tr>
<tr>
<td></td>
<td>• Prophylactic antibiotics</td>
</tr>
<tr>
<td></td>
<td>• Long-term indwelling catheters/central lines</td>
</tr>
<tr>
<td></td>
<td>• Hospital pathogens &amp; local antibiotic use</td>
</tr>
</tbody>
</table>

**RISK FACTORS FOR INFECTION IN NEUTROPENIC CANCER PATIENTS:**

**GENERAL**

- Rapid rate of decline and protracted neutropenia are MAJOR risk factors for infection

**PT-RELATED**

- Age ≥ 65 years
- Female gender
- Poor performance status
- Co-morbidities (renal, hepatic, CV disease)
- Low BMI/BSA

**DISEASE-RELATED**

- Tumor-type, advanced disease, genotype in solid tumors
- Type of chemotherapy (myelosuppression, dose intensity)

**NON-CANCER RELATED NEUTROPENIA:**

- ANC not necessarily predictive of pt’s ability to respond to infection
- Infectious risk determined by adequacy of bone marrow neutrophil reserve (i.e. ability of bone marrow to produce neutrophils)

- Lower risk of acute infection likely because mucosal integrity maintained and lack of other risk factors

**MECHANISMS FOR NON-CANCER RELATED NEUTROPENIA:**

- Decreased production from bone marrow
  - Ex/ congenital neutropenia, aplastic anemia
  - Shift of circulating neutrophils to vascular endothelium/tissues
  - “Margination”
  - Ex/ hypersplenism/splenomegaly
  - Immune destruction
  - Ex/ drug reaction or autoimmune disorder

**S/S OF INFECTION IN A NEUTROPENIC PATIENT:**

- Fever (with or without chills/rigors)
  - Single oral temperature of $\geq 38.3^\circ C$ in the absence of obvious environmental causes OR
  - $\geq 38^\circ C$ for $\geq 1$ hour indicates a febrile state
  - Hypotension (especially if patient is on steroids)
  - Blunted inflammatory response at infxn site → lack of typical S/S

**CANCER PATIENTS HAVE AN UNUSUAL PRESENTATION OF INFECTION:**

- Lack of signs or symptoms
  - Ex/ normal CXR with pneumonia
  - Unusual sites of infection
  - Rapid progression of infection
  - Unusual infecting organisms
  - Ex/ low virulence bacteria, fungi

**MOIST COMMON SITES OF INFECTION:**

- GI tract
  - Chemotherapy-induced mucosal damage
  - Colonization of damaged mucosal surface with subsequent translocation and tissue invasion
- Skin
  - Vascular access devices (ex/ Hickman line)
- Sinuses
- Lungs

**PREVENTION OF INFECTION IN A NEUTROPENIC HOST:**

- Hand washing
- Protected environments
  - High-efficiency particulate air (HEPA) filtration
  - No live plants/flowers
- Prophylactic anti-infectives (antifungals, antivirals)

**MOST LIKELY PATHOGENS:**

- Range relatively narrow
- Bacteria from normal microflora most common (translocation)
- Antibiotic-resistant bacteria, fungi (yeast/mold) & certain viruses

<table>
<thead>
<tr>
<th>Gram (+)</th>
<th>CoNS</th>
<th>Enterococci (VRE)</th>
</tr>
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<tbody>
<tr>
<td>60-70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram (-)</td>
<td>Pseudomonas aeruginosa</td>
<td>E. coli</td>
</tr>
<tr>
<td>30%</td>
<td></td>
<td>Klebsiella</td>
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<tr>
<th>Anaerobic (&lt;5%)</th>
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Therapeutics of Febrile Neutropenia in Cancer Patients

Lecture
MONOTHERAPY:

- Lowest all-cause mortality compared to other 1st lines

PIP/TAZO
- Increased resistance against gram (-) and poor activity against gram (+)
- Used in VGH if non-anaphylaxis penicillin allergy

CEFEPIME
- Infection-related mortality, bacterial superinfection and D/C of treatment more common
- Still considered a 1st line empiric abx by IDSA 2010

IMI/MERO- PENEM
- Higher ADR rate with imipenem
- More pseudemembranous colitis (C. difficile colitis)

CAUSES OF LACK OF RESPONSE:
- Even after C&S still need broad-spectrum antibiotic coverage if patient is neutropenic
- Continue antibiotics until ANC > 0.5 x 10⁹/L and rising

CAUSES OF LACK OF RESPONSE:
- Non-bacterial pathogen
- Resistant organism at least in part to abx regimen being used
- New super-infection
- Infection at a difficult to treat site (ex// abscess or catheter)
- Sub-therapeutic serum or tissue antibiotic levels
- Drug fever
- Non-infectious causes (ex// atelectasis, PE, phlebitis)

MONITORING PARAMETERS:
- Vital signs q4-h (temp, BP, HR, RR, O₂ sats)
- CBC + differential, SCr daily
- Radiographic results
- Culture results

TIME TO RESPONSE:
- High-risk patients treated with appropriate antibiotics is 5 days
- Low-risk patients is 2-3 days
- If the patient is clinically stable and no new source of infection is evident on clinical assessment, no change in empiric antibiotics during days 2-4 of treatment

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- Used in VGH if non-anaphylaxis penicillin allergy

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MONOTHERAPY: anti-pseudomonal B-lactams

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MONOTHERAPY VS. COMBINATION THERAPY
- No difference in all-cause mortality
- Nephrotoxicity
- No difference in super-infections
- No clinical benefit associated with synergism
- No antibiotic combination shown to be superior to others

VANCOMYCIN UPFRONT:
- Associated with better treatment success without modification of the initial regimen
  - Overall treatment success not different if glycopeptide was added in the case of continuation of fever ≥ 72 hours after initiation of antibiotics
- No difference in overall mortality
- No difference in time to defervescence
- Increased ADRs and nephrotoxicity

INDICATIONS FOR INITIAL EMP IRIC THERAPY WITH VANCOMYCIN:
- Hemodynamically unstable or evidence of severe sepsis
- Colonization with MRSA
- Positive blood culture for gram (+) bacteria
- Ex// on gram stain before final C&S available
- Clinically suspected serious catheter-related infection
- Skin or soft tissue infection at any site
- Radiographically documented pneumonia
- Severe mucositis, especially if on: 
  - Previous fluoroquinolone prophylaxis
  - Ceftazidime monotherapy for empiric treatment

STopping VANCOMYCIN:
- Vancomycin should be stopped in 48-72 hours if a resistant gram (+) infection is NOT identified

GOALS OF THERAPY:
- Stabilize vitals, defervescence, eliminate symptoms
- Prevent morbidity & mortality
- Minimize ADRs

DECIDING INITIAL ANTIBIOTIC REGIMEN:
- Determine if patient is low or high risk for complications of severe infection
  - If high risk → IV
  - If low risk → IV or PO
- Broad spectrum of activity
- Potential infecting organisms
- Potential site of infection
- Organ dysfunction
- Drug allergy
- Previous antibiotic therapy
- Local susceptibility patterns

MASCC RISK INDEX SCORE:
- Max theoretical score = 26; low-risk cases ≥ 21
- No clear, standardized definition of “burden of febrile neutropenia” and symptoms associated with that burden → difficulties in uniform application of the MASCC tool
- Need to use clinical judgment on how “sick” patient appears

ETIOLOGY OF INFECTION:

LATE 1960s-1980s
- 60-80% aerobic gram (-) bacilli
  - Pseudomonas aeruginosa, Escherichia coli
  - Staph aureus (gram +)

MID 1980s
- Increasing incidence of gram (+) infections
  - Coagulase (-) staphylococcus
  - Staph aureus
- Not absolutely clear – probably multifactorial
  - Aggressive regimens – more severe mucositis, longer durations of neutropenia
  - Long-term indwelling catheters
  - Hi-antagonists, PPIs, antacids
  - Prophylactic antibiotics with relatively weak gram positive coverage (ex// quinolones)

WHY THIS CHANGE IN SPECTRUM
- Not absolutely clear – probably multifactorial
  - Aggressive regimens – more severe mucositis, longer durations of neutropenia
  - Long-term indwelling catheters
  - Hi-antagonists, PPIs, antacids
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EMPIRIC THERAPY:
- Empiric therapy should be administered to all neutropenic cancer patients with fever immediately
  - Decreased mortality rates with prompt initiation of empiric broad-spectrum antibiotics (carbenicillin/gentamycin)
    - 5% overall mortality in solid tumors (1% in low risk)
    - Up to 11% overall mortality in hematologic malignancies
  - 48-60% have an established or occult infection
  - 10-20% with ANC < 0.1 x 10⁹/L will develop a bloodstream infection

MONITORING PARAMETERS:
- CBC + differential, SCr daily
- Radiographic results
- Culture results

GOALS OF THERAPY:
- Stabilize vitals, defervescence, eliminate symptoms
- Prevent morbidity & mortality
- Minimize ADRs

TIME TO RESPONSE:
- High-risk patients treated with appropriate antibiotics is 5 days
- Low-risk patients is 2-3 days
- If the patient is clinically stable and no new source of infection is evident on clinical assessment, no change in empiric antibiotics during days 2-4 of treatment

INFECTION IN NEUTROPENIC PERIOD:

- Direct hematologic system defect
- Herpes Simplex Virus
- Gram negative bacteria
- Staphylococcus epidermidis
- GI Streptococcus sp.
- Candida sp.
- Aspergillus sp.

- Days of neutropenia

MONOTHERAPY:
- No difference in all-cause mortality
- Nephrotoxicity
- No difference in super-infections
- No clinical benefit associated with synergism
- No antibiotic combination shown to be superior to others

EVALUATION OF PATIENT WITH INFECTION:
- Determine if patient is low or high risk for complications of severe infection
  - 60% have an established or occult infection
  - 0% with ANC < 0.1 x 10⁹/L will develop a bloodstream infection
- Local susceptibility patterns
- Drug allergy
- Previous antibiotic therapy
- Local susceptibility patterns
- No clear, standardized definition of “burden of febrile neutropenia” and symptoms associated with that burden → difficulties in uniform application of the MASCC tool
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- Broad spectrum of activity
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- MASCC RISK INDEX SCORE:
EMPIRIC ANTIFUNGAL TREATMENT IN FEBRILE NEUTROPENIA:

- For continued unexplained fever, consider CT scan for fungal infections

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<thead>
<tr>
<th>FEBRILE NEUTROPENIA</th>
<th>PROPHYLAXIS</th>
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<tbody>
<tr>
<td>Liposomal amphotericin B</td>
<td>Micafungin</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Posaconazole</td>
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</table>

VORICONAZOLE = not approved for FN

EMPIRIC TREATMENT WITH ANTIVIRALS:

- Indicated only if clinical or laboratory evidence of viral disease or viral reactivation
- Predominantly herpesviruses and respiratory viruses
  - Herpes simplex virus (HSV)
  - Varicella-zoster virus (VZV)
  - Cytomegalovirus (CMV)
  - Epstein-Barr virus (EBV)
  - Rhinovirus
  - Adenovirus
  - Respiratory syncytial virus
  - Parainfluenza virus
  - Influenza A and B virus
- All herpes viruses can cause fever and sepsis, however, usually:
  - HSV presents as mucositis or vesicular rash
  - VZV as vesicular rash in a dermatomal distribution
  - CMV (in SCT setting) as interstitial pneumonia
- HSV or VZV dissemination
  - Cutaneous lesions
  - Visceral (liver, lung, brain) involvement