Infections in Patients with Cancer

- Infections are a common cause of morbidity and mortality in cancer patients
- Infection-related mortality (autopsy studies)
  - most deaths in acute leukemia
  - half of lymphoma deaths
- Intensive chemotherapy as well as underlying cancers predispose to infection
Risk Factors for Infection: Net State of Immunosuppression

Underlying disease/tumor burden
Cytotoxic chemotherapy: depth & duration of neutropenia
Immunosuppressives: T & B cell suppressants, steroids, alemtuzumab, etc.
Barriers breached: VAD, mucositis, surgery
Radiation therapy
GVHD
COPD
Renal/hepatic insuff.
Performance status
Age >65 yrs
Nutritional status
Controlled cancer (or not)

Higher risk of Infectious Complications
### Disruption of Physical Barriers to Infection in Cancer Tx

<table>
<thead>
<tr>
<th>Defense</th>
<th>Problem</th>
<th>Organism</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Breaks, radiation damage, surgery</td>
<td>Staphylococci, Streptococci</td>
<td>Cellulitis, extensive skin infxn</td>
</tr>
<tr>
<td>Mucosal Lumens</td>
<td>Obstruction, Mucositis</td>
<td>Gram-negative rods (GNR)</td>
<td>Bacteremia, UTI, cholangitis; Overwhelming sepsis</td>
</tr>
<tr>
<td>(intestine, ureters, bile ducts)</td>
<td></td>
<td>Strep viridans</td>
<td></td>
</tr>
<tr>
<td>Lymphatics</td>
<td>Node dissection (breast CA)</td>
<td>Staphylococci, Streptococci</td>
<td>Cellulitis</td>
</tr>
<tr>
<td>Spleen</td>
<td>Splenectomy</td>
<td>S. pneumoniae, H.influenzae, N.meningitidis, Babesia, Capnocytophaga</td>
<td>Rapid, overwhelming sepsis</td>
</tr>
<tr>
<td>Defense</td>
<td>Problem</td>
<td>Causes</td>
<td>Organism</td>
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<td>-------------------------</td>
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<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Phagocytes (Neutrophils)</td>
<td>Neutropenia</td>
<td>Cytotoxic chemotx, acute leukemia</td>
<td>Staphylococci</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Streptococci, Enteric GNR, Fungi</td>
</tr>
<tr>
<td>Humoral Immunity</td>
<td>B cells</td>
<td>Mult. myeloma, Chronic lymphocytic leukemia (CLL)</td>
<td>S. pneumoniae</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>H. influenzae, N. meningitidis</td>
</tr>
<tr>
<td>Cellular Immunity</td>
<td>T cells</td>
<td>Lymphoma (Hodgkins/NHL) Hairy cell leukemia &amp; ALL</td>
<td>MTB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glucocorticoids, monoclonal Abs, fludarabine</td>
<td>Listeria, Herpesviruses, Fungi</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumocystis Strongyloides</td>
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A quick review of neutrophils (polymorphonuclear leukocytes) …

- Terminology note: “granulocytes” are cells with granules= neutrophils, basophils, eosinophils

- Neutrophils make up 60–70% of the blood leukocytes (WBC’s)
  - Lysosomes=granules
  - phagocytes

- Derived from bone marrow stem cells, live ~8hrs in blood then migrate to tissues

- Important phagocytic cells
  - respond to chemotactic stimuli
  - marginate & migrate from blood into the tissues
  - engulf micro-organisms in phagolysosomes
Severe Infections Increase with Decreasing Granulocyte Counts
(Bodey 1966)

Absolute Neutrophil Count (ANC) = total # of neutrophils + band forms

WBC = 1000
40% neutrophils + 2% bands
ANC=420 cells/µL

ANC cells/µL
IMMUNOCOMPROMISED HOSTS:

Decreased inflammatory responses, i.e., no pus or erythema, no infiltrate on CXR, no WBC's in urine, reduced levels of pain.

FEVER is common during neutropenia and may be the only sign of a serious infection.
Etiology of Initial Fever During Neutropenia

- >70% = Unexplained Fever
- 30% = Documented Infections
  - 10-20% bacteremias (bacteria in bloodstream)
  - Oral HSV, respiratory tract infections, skin/soft tissue infections, UTIs

Most infections are due to ENDOGENOUS or colonizing microbes
  - Coagulase negative staph (Staph epidermidis)
  - Staphylococcus aureus
  - Enteric (gut) bacteria (E. coli, Klebsiella; Pseudomonas)
  - HSV reactivations
Bloodstream Pathogens in Neutropenic Patients

**Gram Positive (61%)**
- Coag-negative Staphylococci (32%)
- Staph aureus (12%)
- Alpha (viridans) Streptococci
- Enterococci/VRE
- MRSA
- Strep pneumoniae

**Gram Negative (25%)**
- E. Coli (7%)
- Klebsiella (5%)
- Other LF-GNRs (6%)
- Pseudomonas aeruginosa (4%)
- Resistant GNR’s

**Anaerobes (5%)**

**Candida (9%)** -- rarely with initial fever
A few words about these bacteria...

- Coagulase negative staph (often Staph epidermidis)
  - *common skin contaminant* in blood cultures.
  - Coag neg staph is a WEAK pathogen
  - NO need to put everyone on Vancomycin
    (yes, even if they have a catheter in place--no vanco!)

- Gram negative organisms
  - Can kill you quick, especially if you have no Neutrophils
  - Pseudomonas difficult to treat, very virulent
  - Rising incidence of β-lactamase producing Gm negatives
Pseudomonas Aeruginosa
Gram Stain and Ecchyma gangrenosum

Pseudomonas aeruginosa during neutropenia
- accounts for only 4% of bloodstream isolates
- 48% mortality in neutropenic patients

Why do neutropenic patients require empiric antibiotics at onset of fever?

- Mortality >80% for Gram negative bacteremia if therapy delayed in neutropenic patient

- Impossible to distinguish F&N pts with bacteremia
  - Height of temp, CRP, ESR, etc do not predict

- Empiric antibiotic therapy
  - Start antibiotics at onset of fever during neutropenia
  - Do not wait 24-48hrs for culture results
  - Goal is to treat PRESUMED BACTERIAL infections early
EMPIRIC ANTIBIOTIC THERAPY for FEVER & NEUTROPENIA
Initial Evaluation of Febrile Neutropenic Patient

- History and Physical exam
- CBC + diff, chemistries + LFT’s
- Blood cultures x 2 including sets from indwelling catheters
- Chest x-ray
- Urine culture
- Culture of any site of suspected infection
- Broad-spectrum, bactericidal antibiotic regimen = empiric antibiotic therapy
Indications for Empiric Antibiotic Therapy

- **FEVER**: T ≥ 38.3°C once or T ≥ 38°C sustained over 1 hr.

- **NEUTROPENIA**:
  Absolute neutrophil count (ANC) < 500/mm³ or anticipated to fall < 500/mm³ in 24 - 48 h
  - Example: Total WBC = 12,000 but 2% are neutrophils, 0% bands. The rest are blast cells (leukemia).
  - ANC = 0.02 x 12,000 = 240

- Neutropenic patient with new onset signs or symptoms of infection---even if they are not febrile!
  - e.g. abdominal pain, perirectal pain, infiltrate on CXR

Empiric Antibiotic Regimens for Fever and Neutropenia

- Fear of severe gram negative infections, especially *Pseudomonas aeruginosa* drives antibiotic selection

- **Monotherapy**
  - Cefepime
  - Imipenem or Meropenem
  - Piperacillin-tazobactam (zosyn)
  - Ceftazidime

- **Combination regimens:**
  - One of above *plus* an aminoglycoside
  - Combination above *plus* VANCOMYCIN (selected circumstances)
## Indications for Empiric Vancomycin in Fever and Neutropenia

- Serious catheter-related infection (tunnel/port pocket)
- Severe oral mucositis
- Colonization with methicillin-resistant *Staph aureus* or Penicillin-resistant *Strep pneumoniae*
- Hypotension or shock
Changes in Management of Fever and Neutropenia

- **1960’s - 1990’s**: hospitalized for IV empiric antibiotics
- **1990’s**: Risk stratification -- not all febrile neutropenic patients have same risk for infection
  - Risk assessment strategies developed to distinguish pts at LOW vs HIGH RISK for complications during F&N
  - Medical comorbidity, cancer type (solid tumors vs leukemias or HSCT), expected duration of neutropenia
Not all Cancer Therapy is the Same
Risk of infection is related to the depth and duration of neutropenia

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Incidence of neutropenia</th>
<th>Incidence of fever &amp; neutropenia</th>
<th>Infection risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer standard therapy</td>
<td>Common but very short duration (1-2d)</td>
<td>~3-5%</td>
<td>Low</td>
</tr>
<tr>
<td>Lymphoma therapy</td>
<td>Common, for several days</td>
<td>~20-40%</td>
<td>Moderate-High</td>
</tr>
<tr>
<td>Acute leukemia induction therapy</td>
<td>Very common, for &gt; 3weeks</td>
<td>Close to 100%</td>
<td>Very High; sometimes fatal</td>
</tr>
</tbody>
</table>
RISK Criteria for Fever and Neutropenia

**HIGH**
- Inpatients
- Associated comorbid illness (hypotension, pain, renal/liver insuff., etc.)
- Uncontrolled/progressive cancer
- Prolonged neutropenia (>7 days) anticipated
- Pneumonia
- HSCT, acute leukemic

**LOW**
- Outpatients
- No comorbid illnesses
- Cancer under control
- Less than 7 days neutropenia anticipated
- No pneumonia on CXR
- Age <65 yrs
- NO HSCT, acute leukemia

**IV empiric antibiotic regimen in hospital**

- Oral/outpatient antibiotics (Cipro + Augmentin q 8hr)
- Early discontinuation of IV --> switch to oral/outpatient
Duration of empirical antibiotic therapy

- Until ANC ≥ 500 neutrophils/µL

- **Modify antimicrobial regimen during neutropenia if:**
  - Persistent fever: *Do not* add or juggle around antibiotics in stable pts who just have fever but are stable
  - Clinical evidence of worsening infection
  - Cultures positive for pathogens

- **Persistent or recurrent fever after 7 days of broad spectrum antibiotics**
  - Increased incidence of invasive mold (Aspergillosis)
  - Add a mold-active agent (voriconazole, echinocandin, amphotericin B)
  - ? ☢️ chest CT

Reasons to change antibiotics
INFECTION SYNDROMES & PATHOGENS IN PATIENTS with FEVER & NEUTROPENIA
Catheter Infections

- 10 - 40% long-term tunneled devices become infected; (Hickman or Groshung lines)
- Ports may be less susceptible to infection but harder to clear
- Pathogens
  - Skin flora: Coag neg Staph & Staph aureus
  - Enteric GNR’s, contaminated flush or IV solutions
  - Candida
- Diagnosis of intralumenal catheter infection
  - “Differential time to positivity”: catheter blood cultures becomes + > 120min prior to peripheral blood cultures
  - Coag neg staphylococci are common contaminants!
  - 2 + separate blood cultures required to diagnose CNS catheter infection
Tunneled catheters

Hickman/Broviac
Groshung
Catheter Tunnel Infection

- **Staph aureus** is most common pathogen
- Remove catheter!
- IV antibiotic x 10 days.
Indications for indwelling catheter removal

- Tunnel or port pocket infection
- Hemodynamically unstable pt (hypotensive)
- Positive blood cultures for:
  - Candida
  - *Staph aureus*
  - Gram negative rods (*E.coli, Enterobacter, Klebsiella, Pseudomonas*)
  - Nontuberculous mycobacteria (*M.chelonae, abscessus*)
  - *Corynebacterium jeikeium*
- Persistent bacteremia
  - Repeat blood cx’s still positive despite 48 hrs abx
Herpesvirus Infections

- Enveloped DNA viruses
  - HSV, VZV, CMV, HHV-6,7,8, EBV
- Herpes Simplex (HSV-1 & HSV-2)
  - 1° oral infection usually in childhood
    ---most asymptomatic; gingivostomatitis
  - Lifetime latency in craniospinal ganglia, after primary infection
  - Reactivations periodically: stress, intercurrent infection, sunlight, immunosuppression
    Usually asymptomatic --> cold sore in ~30%
- IC hosts: severe reactivations of oropharyngeal /esophagitis, genital dz
- Acyclovir
Varicella-Zoster virus (VZV)

Primary infection
- Chickenpox
- Lifetime latency in craniospinal ganglia, after primary infection
- Life-threatening complications (dissemination, pneumonia, encephalitis)
  - children undergoing chemotherapy
  - worse in adults, pregnant women

Reactivation
- Herpes zoster ("shingles")
- 10-20% of infected individuals (95% of U.S. adults are seropositive for VZV), usually after age 40, usually only once
- Severe, disseminated disease associated w/lymphomas, HSCT
- Acyclovir (need 2x higher dose than for HSV)
Cytomegalovirus (CMV)

Primary infection

- Primary infection is usually asymptomatic in childhood
- Occasionally an infectious mononucleosis-like illness occurs: “Mono-spot negative”.

 Reactivation

- Reactivations or re-infections are common throughout life and are usually asymptomatic.
- IC hosts: Both primary and recurrent CMV infection may lead to severe symptomatic disease.
CMV: Clinical Manifestations

- Limited almost exclusively to ALLOGENEIC HSCT recipients who are themselves seropositive for CMV
  - Fever, leukopenia, malaise = “CMV syndrome”
  - Pneumonitis
  - Hepatitis
  - Gastrointestinal manifestations eg. colitis
  - Encephalopathy
  - Retinitis
  - Poor graft function

Pneumonitis is the most severe manifestation, and carries a mortality rate of 85% in the absence of treatment.

- Diagnosis by PCR
- Ganciclovir, Foscarnet
### Pulmonary Infections in Cancer Patients: Patterns of Radiographic Infiltrates

<table>
<thead>
<tr>
<th>Infiltrate</th>
<th>Infection</th>
<th>Non-infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>Bacteria, Legionella, Mycobacteria</td>
<td>Localized hemorrhage, emboli, tumor</td>
</tr>
<tr>
<td>Nodular</td>
<td>Fungi (<em>Aspergillus or Zygo</em>, <em>Nocardia</em>, <em>Histoplasma</em>)</td>
<td>Tumor</td>
</tr>
<tr>
<td>Diffuse</td>
<td>Viruses (CMV, resp. viruses), Pneumocystis, Chlamydia, mycoplasma, toxo</td>
<td>CHF, radiation pneumonitis, drug-induced lung injury, diffuse alveolar hemorrhage, bronchiolitis obliterans</td>
</tr>
</tbody>
</table>
DIFFUSE Pulmonary Infiltrates in Cancer Patients

**CMV** (allogeneic BMT pts)

Respiratory viruses

*Pneumocystis jerovicii* (PCP)

*Legionella* spp, *Histoplasma*, *TB*

*Chlamydia*, *Mycoplasma*

(“atypicals”--treat with fluoroquinolones or macrolides)

Non-infectious causes common: pulmonary edema/CHF, radiation pneumonitis, bronchiolitis obliterans
**Pneumocystis jiroveci**
*(Pneumocystis carinii)*

- **Risks:**
  - Acute lymphocytic leukemia, lymphomas, alloBMT but can happen with any cancer
  - STEROIDs being tapered from high dose (ie brain tumor tx)
  - Bacitracin prophylaxis prevents PCP; lack of prophylaxis is risky

- Abrupt onset Fever, SOB, dry cough, hypoxemia

- CXR may be normal initially

- **Dx:** Bronchoalveolar lavage (BAL)---+ silver

- **Tx:** TMP-SMX (Bactrim) high doses IV + steroids for severely low PAo2

*Pneumocystis jiroveci* cysts in bronchoalveolar lavage material; Giemsa stain
Focal pneumonia in neutropenic cancer patients

Patchy infiltrate along right heart border.

Gram negative bacteria common
- *Pseudomonas*
- Enterics: *E. coli*, *Enterobacter*, *Klebsiella*
Fungal Infections in Cancer Patients

- **Candida**
  - Yeast colonizer in oropharynx--> thrush, esophagitis
  - Bloodstream infection:
    - ~9% of BSI in neutropenics; rare w/ fluconazole prophylaxis (high risk pts only)
    - always remove indwelling IV catheters!
    - 40% mortality
  - Very very very rare cause of pneumonia

- **Aspergillus**
  - Mold; soil/environmental
  - Inhaled----> sinus & pulmonary disease
  - RISK factors = STEROIDS for treating GVHD, long durations of neutropenia (ie acute leukemia)
  - High mortality (angioinvasive) > 50% in leukemia, alloHSCT
Dry Cough in a Patient with Graft vs Host Disease

- 43 yr old woman 60 days post allo txplnt, on high dose steroids for GvHD of the gut. ANC=3500
- Mild pleuritic chest pain and dry cough, Tmax 38°C x 3 days
- Exam unremarkable. Looks well.
- CXR: negative; but you are smart and obtain a chest CT scan
- The next day she develops progressive dyspnea, hemoptysis
Early Signs of Invasive Pulmonary Aspergillosis: Macronodules and Halo Signs on CT Scans

Present in 90% of pulmonary aspergillosis at diagnosis

Present in 30% of pulmonary aspergillosis at diagnosis

Aspergillus Pathophysiology

Aspergillus sp. exposure is universal
- Airborne conidia (2.5-3 microns) inhaled
- Lungs, sinuses.
- Hematogenous spread (e.g. brain).
- Blood cultures RARELY +
- Vascular invasion, infarction, hemorrhage, necrosis
Evaluation of Pulmonary Infiltrates in Cancer Patients

**FOCAL**
- Cephalosporin, FQ, + vanco x48 hrs;
- BAL if no response

**CT scan**

**DIFFUSE**
- Empiric TMP/SMX, cephalosporin + FQ
- rapid BAL

**BAL**: > 90% yield for viruses, bacteria, PCP;
~ 50% yield for molds

If no response to broad spectrum abx, add Voriconazole (esp in high risk pt); consider lung biopsy

If no dx or response, consider lung biopsy

CAVEAT: BAL has ~50% diagnostic yield, no effect on mortality.
Abdominal pain in a neutropenic patient

- 19 y/o man with Burkitt’s lymphoma, abdominal debulking surgery followed by intensive chemotx
- Day 8 s/p cycle #2 of chemotherapy
- Awakened from sleep by right side abdominal pain
- Exam: Afebrile
  
  No bowel sounds; rebound tenderness initially in right lower quadrant but later benign

- Absolute neutrophil count = 0
Abdominal Pain in Cancer Patients

- *Clostridium difficile*: COMMON
  - Fever, diarrhea, crampy abdo pain
  - Toxin assay
  - *Flagyl* orally or IV; limit use of oral Vancomycin

- Perforation post-chemotherapy & tumor lysis

- Bowel obstruction

- Abscess

- Typhlitis (neutropenic enterocolitis)
Typhlitis
(Neutropenic enterocolitis)
Typhlitis
(Neutropenic Enterocolitis)

**Risks:**
- Leukemia, aplastic anemia, myelodysplastic syndromes, aggressively rx'd solid tumors
- Cytotoxic (chemothx) damage to bowel mucosa
- Prior antibiotics ----> selects organisms invading bowel wall
  (*Pseudomonas, Clostridium septicum*)
  Prolonged Neutropenia of long duration (usually)

- Right lower quadrant abdominal pain with rebound; hypotension, fever in neutropenic patient
- Mortality >50 %-- sepsis, necrotic bowel
- Tx: bowel rest, broad spectrum antibiotics, fluids
Infection Prevention in Cancer Patients

- No need for “neutropenic isolation” routinely, Positive pressure airflow/HEPA filtered air for alloHSCT
- Prophylactic antibiotics and antifungals
  - NOT routine for all cancer pts
  - allogeneic HSCT or acute leukemias primarily
  - Penicillin for splenectomized pts x at least 3 yrs
- Prophylactic Acyclovir
  - For HSV seropositive HSCT & acute leukemias, or any chemotx pt who has had an outbreak
- Vaccines
  - Influenza seasonally
  - Pneumococcal every 5 yrs
  - Hib, meningococcal, pneumococcal prior to splenectomy
  - 12, 14, & 24 months after alloHSCT: DPT, polio, Hib, Hep B, MMR (24 m only)
  - VZV vaccine contraindicated except in children w/ALL