Bacterial Infections in Neutropenic Patients and HSCT Recipients

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Outline

- Risks: changes in therapy
- Bacterial Infections: update in a select population
  - Overall epidemiology
  - Gram – negative bacteria
  - Gram – positive bacteria
  - Clostridium difficile disease
  - Risks: new developments
- NOT discussed: empirical treatment

Course of BMT

- Conditioning therapy
  - Spectrum: myeloablative to non-myeloablative
    - reduced toxicities
  - Infusion of stem cells
    - Self origin: Autologous
      - Other: Allogeneic
        - HLA match important
        - Source of stem cells
          - Peripheral blood, marrow, cord blood
          - Manipulation of stem cell product:
            - CD34-selected, T cell depleted
- Infection risks
  - Periods of immune impairment:
    - Neutropenia (early)
    - T cell (late)
  - GI tract mucositis
  - GVHD and therapy
  - Intravascular lines
Time line, and incidence of OIs changed with preventative therapy and type of BMT.

Non-myeloablative

- Different conditioning regimens
- Much less neutropenia and early mucositis
- GVHD encouraged (Graft vs. Malignancy effect)
- Infection risks associated with
  - GVHD and therapy
  - Long-term intravascular access
- Infections predominate LATE after BMT


<table>
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<th>Rank</th>
<th>Pathogen</th>
<th>BSU %</th>
<th>% BSI Total (%)</th>
<th>% BSI ICU (%)</th>
<th>% BSI Non-ICU (%)</th>
<th>% Crude Mortality Total (%)</th>
<th>% Crude Mortality ICU (%)</th>
<th>% Crude Mortality Non-ICU (%)</th>
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Bacterial Infections: Hematology

- Population-based studies don’t tell whole story
  - Changes over time
  - Evolving epidemiology based on differences in host, differences in supportive care

- Time-dependent changes:
  - Decrease in gram-negative bacteremias during 1990's
  - Rebound increase in Gram - neg: Resistance
  - Increased problems with gram+

Prophylaxis

- Highly 'pre-treated' population
- Multiple studies have shown better outcomes with some antibacterial prophylaxis
  - β-lactams
  - Quinolones
  - Decreased fever, bacteremias
  - But increased breakthrough resistance

- Practices change epidemiology in institutional-host dependent fashion

Bacteremia

- European Organization for Research and Treatment of Cancer
  - 1970's: gram-negative bacteria caused 70% of bloodstream infections, 40% mortality
  - 1980's: gram positive bacteria caused 70%, gram negative 30% ¹
  - Resistance in Strept: β-lactam, carbapenem
  - Pseudomonas high mortality 40%

- University of Florida: 519 BMT ²
  - 29.5% patients developed bacterial infection
  - Incidence decreased 1991 to 1997
  - Decreased in Streptococci and Staphylococci
  - Resistance in Strept: β-lactam, carbapenem

1 Eur J Cancer 26: 569-74 (1990)
13 centers in Brazil: March – Nov 2004
- Day 0 until engraftment or death
- Resistance to 2 drug classes: MDR
- 411 pts: prophylaxis 34% (β-lactam, quin)
- Bacteremia 91 (27%)
  + 47% gram-positive, 37% gram-negative
  + 37% of gram-negative bacteria MDR
  - K. pneumoniae, P. aeruginosa, Enterobacter spp., E. coli, B. cepacia, S. maltophilia, Acinetobacter spp., C. freundii
- Risks: 3rd generation cephalosporins, clustering in hospitals

Empirical therapy considerations

Most common cause of bacterial pneumonia before day 100

- FHCRC review (1990 – 2001)
  - 95 / 5772 patients (1.65%)
    - 2% allogeneic, 1% autologous
    - 63 days after HCT (5-1435)
    - Bulk during GVHD; 28% during neutropenia
- Copathogens common: 48% (IFI, CMV, polymicrobial bacterial infection)
- 16% developed recurrent disease after 2 weeks of antibiotics (mortality 60%): GVHD
- Longer therapy should be considered
Stenotrophomonas maltophilia

- Resistance to carbapenems
- Bloodstream infection, pneumonia
- Poor outcomes\(^1\)
- Risks in case-control study at Barnes Jewish Hospital \(^2\)
  - Mucositis, diarrhea, metronidazole, many antibiotics used

2 Apisarnthanarak et al. Infect Control and Hosp Epid 2003; 24: 269-74

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Acinetobacter baumannii

- Natural habitat water and soil, hot and humid climates
  - Nosocomial: burns, wounds, pneumonia
  - Outbreaks in hospitals and facilities
  - Multidrug resistance


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Acinetobacter baumannii

- Neutropenia = risk for death
- Not simply related to drug resistance
  - Underlying disease severity, toxicities

Kremery and Kalavsky Emer ID 13(6) 2007
Classically, hospital-associated MRSA relatively low incidence in hematologic population, in absence of outbreak.

- Single UK HCT center: 41/776 (5%); 9% in unrelated donor allogeneic HCT
  - Increased during outbreak in 2004
- Colonization and persistent carriage risk factor for infection

1 Shaw et al. Bone Marrow Transplant 2007; 39: 623-29

1994 – 1996 DUMC

- 430 – MSSA / MRSA bacteremia
  - 122 (28%) cancer
  - 52 non-neutropenic
    * Device-related: 42%
    * Tissue infection: 44%
    * Unidentified focus: 13%
    * IE: 15%
  - MRSA 20 patients (38%)


High-virulence "community-acquired" MRSA causing hospital infection

- Skin, soft tissue infection in healthy people, bloodstream infection, necrotizing pneumonia, abscess formation
- Into the hospital-colonization pre-therapy

Vancomycin Resistant Enterococcus

- 281 HCT recipients at Cleveland Clinic: 1997 - 2003
  - Early VRE infection in 2.6% patients, poor outcomes
- Leukemia / HCT at Barnes Jewish (1996 - 2002)
  - Incidence bloodstream 0.6 - 2.1 / 1000 patient days
  - Dependent on infection control (gowns)
  - 334 patients colonized: 13% BSI
  - 70% infected were colonized prior
  - 78% hospitalized in prior 30 days
  - Survival poor: GVHD, pneumonia, antifungals, high APACHE II

Active surveillance study at University of Chicago HCT unit:
- Sequential cultures upon admission
- Prevalence rate: 11.2% current BMT, 67.3% previous HCT, 24% nontransplant
- Risk for conversion: voriconazole, trimethoprim-sulfamethoxazole, carbapenem, URD HCT

Question

- 42 yr old M with AML 12 days after therapy with mucositis, neutropenia 12 days, fever for 6 days
  - Levofoxacin prophylaxis- ceftaziidime empirically, added vancomycin (1 day)
- Gram-positive coccus in blood culture
- After 24 hours, patient became hypotensive and developed ARDS, and a diffuse erythematous rash
- Which organism is the most likely etiology?
  1. Streptococcus pneumoniae
  2. Coagulase-negative Staphylococcus
  3. Enterococcus faecalis
  4. Streptococcus mitis
  5. Stomatococcus mucilaginosus
**Viridans Streptococci**

- Important cause of bacteremia in neutropenic cancer patients
- Risk factors: severe neutropenia, oral mucositis, high-dose cytosine arabinoside, antimicrobial prophylaxis with TMP-SMX or a fluoroquinolone
- Can present with fever, flushing, chills, stomatitis, pharyngitis
- After 24-48 hours, hypotension in 1/3 of cases
- Rash, shock, ARDS in 1/4 of cases (similar to toxic shock)
- Endocarditis unusual (<10%)
- Mortality high (15-20%)

**Gi Infections**

- Diarrhea is a common complaint
  - Most non-infectious
  - Tips for infections
    - Bloody, fever, abdominal pain
- Colitis
  - Neutropenic enterocolitis
  - *C. difficile* colitis
  - CMV, other Herpes viruses (not common)

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**Streptococci**

- *S. pneumoniae*
  - MD Anderson
    - 1989 – 2005: incidence 7/1000 HCT
    - Late complication: median 443 days
    - Lymphoma, steroids risks
    - 347 / 100,000 person yrs (vs. 11.5 / 100,000 in general population)
    - Serotypes would be protected in vaccine (not given)
    - High rates of Tm/Sf resistance
    - Allogeneic HSCT: timing of vaccination

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2 Youssef et al. Medicine 2007 86(2): 69-77
3 Kumar et al. Bone Marrow Transplant 2008 41: 743-47
**Clostridium difficile disease**

- Little data in HCT or neutropenic population
- 119 patients (auto, allo) – 7 / 109 (6%) CDAD
- Incidence subsequent to toxigenic strain (NAP-1) likely increased
  - Multiple risks predict problem
    - Quinolone resistance
    - Antibiotic-induced changes in flora
    - Low humoral immune response to circulating toxin A (IgG)

1 Tomblyn et al. Bone Marrow Transplant 2002 30: 517-19

**C. difficile disease**

- Risks for CDAD ↑ neutropenia, HSCT
  - Incidence, risks unknown
  - Certain drugs may potentiate risks
- Autologous PBSCT (n=242, 1996-2001)1
  - Incidence 15%
  - Risks: cephs, vanco
  - Paclitaxel with mobilization: lower incidence
- 2003-2004 case-control2
  - Incidence cancer floor 2.4/1,000 pt-days
  - Cases: older; lung cancer (3x) antibiotics 22x higher (cephalosporins); IL-2 7x
- Recent small retrospective study3:
  - 1st allogeneic HSCT 2003-2007 (n=26)
    - 88.5% had diarrhea
    - 30% had CDAD diagnosed (n=7)
    - AML (n=6); imipenem

1 Arango et al. BMT 2006 37, 517-521

**Neutropenic Enterocolitis**

- Neutropenic enterocolitis (typhilitis)
  - Necrotizing inflammation with transmural infection of damaged bowel wall
  - Mixed infection with gram-negative, gram-positive, anaerobic bacteria
  - Can be accompanied by bacteremia
    - Mixed, Anaerobic (C. septicum, C. tertium, B. cereus)
  - Medical and surgical management

Cornely Lancet 358:9296 (2001)
Risks for bacterial infection

- Neutropenia, mucositis, intravascular catheters
  - Different risks associated with conditioning

- Genetic risks
  - HLA-matched siblings (Korea)¹
    - Polymorphism in P2X7 receptor: plasma membrane R for ATP involved in IL-1 processing
    - Associated with survival, bacteremia
  - FHCRC: case-control study alloHCT
    - Polymorphism in LPS binding protein (promoter) associated with gram-negative bacteremia and mortality
    - Paris: non-T depleted (n=192)
      - Polymorphism in PTPN22 gene (protein tyrosine phosphatase): negative regulator of T cell activation
    - Polymorphism 2q21.3 (lactase phlorizin hydrolase) associated with pneumonia, TRM¹

Conclusions

- Epidemiology
  - Always evolving
  - Institutional infection control issues
  - Additional pressures (prevention)

- Issues of great concern
  - Resistance (both gram – and +)
  - Some practices should differ
    - Longer course therapies for *P. aeruginosa* pneumonia
  - CDAD not well understood
    - Risks and outcomes, factors that dictate recurrence

- New understanding of infectious risks

¹ Lee et al. Haematologica 2007; 92(5)
² Chen et al. Blood 2008; 111: 2462-69
³ Azarian et al. Transplantation 2008; 85: 1859-62