

Principles of Management of Infections in Pediatric Oncology/HSCT Patients

What are the Major Arms of Host Defense against Microbial Pathogens?

Innate Phagocytic Host Defense

- Neutrophils
- Monocytes
- Macrophages

Non-phagocytic Innate Host Defense

- NK cells
- Complement
- Antimicrobial peptides
- MBL, collectins
- Cytokines: TNF-alpha, IL-1, IL-6

Adaptive Immunity

- Lymphocytes (CMI)
- Antibody production

What are the Major Populations of Immunocompromised Pediatric Patients?

Neutropenia

- Chemotherapy or radiation-induced
- E.g., Leukemia, lymphoma, neuroblastoma, BMT

- Aplastic anemia

Neutrophil dysfunction

- Inherited immunodeficiency
- E.g., chronic granulomatous disease
- Corticosteroid therapy

What are the Major Populations of Immunocompromised Pediatric Patients?

Impaired CMI:

- Pharmacologically induced
 - Corticosteroids (other effects occur on PMNs, MNCs, and Macrophages)
 - CsA, tacrolimus, fludarabine

Inherited Deficiency in CMI

- SCID, DiGeorge's syndrome,

Acquired Deficiency in CMI

- HIV

Impaired Ab Production

- X-linked hypogammaglobulinemia
- Hypogammaglobulinemia

What are the Risk Factors for Infection in Patients with Cytotoxic Chemotherapy?

- Neutropenia
 - Depth of Nadir
 - Duration of Neutropenia
- Mucosal Disruption/Altered mucocutaneous flora
- Foreign body- CVC

Case #1

- A 14 year old female with newly diagnosed AML is treated with doxorubicin and Ara-C.
- She is discharged and four days later presents to outpatient clinic with new onset of fever (T=38.7°C) and anorexia.
- PE reveals a tired appearing teenager but with no localizing findings.
- Laboratory: ANC <100/ μ l; platelets=16,000; Hgb=9.2 g/dl

Case #1: What are the organisms most likely etiological organisms as the initial cause of fever in profound neutropenia?

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- Coagulase negative *Staphylococcus*
- *Aspergillus fumigatus*

Case #1: What are the organisms most likely etiological organisms as the initial cause of fever in profound neutropenia?

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Case #1: What option do you choose for initial management?

- Return to home for further monitoring (your colleague says that only 5-10% of patients ever develop "real" infections).
- Return to home on oral outpatient therapy (your hospital administrator says that it will save money for the hospital).
- Admit for empirical antibacterial therapy.

Case #1: What option do you choose for initial management?

- Admit for empirical antibacterial therapy.

Case #1: Among the following regimens, what are the appropriate agents for initial management of febrile neutropenic patients?

- Ceftazidime
- Cefepime
- Ciprofloxacin
- Imipenem or meropenem
- Piperacillin-tazobactam +/- aminoglycoside

Case #1: Among the following regimens, what are the appropriate agents for initial management of febrile neutropenic patients?

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- Cefepime
- Imipenem or meropenem
- Piperacillin-tazobactam + aminoglycoside

Case #1: Results of blood cultures, treatment, and outcome

- Ceftazidime
- *E. coli* in 2/2 bottles
- Susceptible to ceftazidime
- Patient's BCs cleared and fever resolved

Case #1: If this patient had a history of anaphylaxis to beta-lactam antibiotics, what would be an appropriate option?

- Aztreonam and vancomycin

What are the appropriate options for initial antibacterial therapy in febrile neutropenic patients?

- Standard choices- well established
- Ceftazidime
 - Imipenem
 - Meropenem
 - Cefepime
 - Extended spectrum penicillin + aminoglycoside

What are the appropriate options for initial antibacterial therapy in febrile neutropenic patients?

UNLESS

1. Hemodynamic Instability
Vancomycin/Aminoglycoside/Ceftazidime, Cefepime, or Carbapenem
2. Site of Catheter Infection
Vancomycin + Ceftazidime, Cefepime, or Carbapenem
3. Severe Perianal/Perirectal/Perioral Infection
Anaerobic Coverage: metronidazole, carbapenem; pip-tazo
4. Severe mucositis

Case #1 (continued)

Day 6 of hospitalization:

Patient's temperature precipitously increased to 39.4°C.
Empirical antifungal therapy with L-AMB was initiated.
BCs: (-) x4
PE: unremarkable
CT scans of chest and abdomen: (-)

Day 7 of hospitalization:

Fever persisted (Tmax=39.7°C).
Systolic BP: 115-120 => 100-105
U.O.: declined over last 12 hrs
What is your next step and what are the likely pathogens?

Case #1 (continued)

Day 8 of hospitalization:

Imipenem, gentamicin, and vancomycin were initiated with increased hydration and ICU monitoring
BCs grew *Enterobacter cloacae*
Resistant to ceftazidime, cefepime, and all other beta-lactams
Susceptible to carbapenems, ciprofloxacin, and TMP/SMX

Day 9 of hospitalization:

Patient's fever resolved
BP, and UO normalized
Transferred to floor

Emerging Bacterial Pathogens and Infections: Gram-negative bacilli

Stably derepressed beta-lactamase producing Enterobacteriaceae

Enterobacter spp., *Citrobacter* spp., *Serratia* spp., *Providencia* spp., *Morganella* spp. and occasionally *P. aeruginosa*

Chromosomally mediated (*Amp C* or Type 1 beta-lactamase): lower probability of transmission of genetic elements (implications for infection control)

Resistance: All beta-lactams, including 3rd and 4th (+/-) generation cephalosporins

Treatment: Carbapenem; fluoroquinolone; TMP-SMX

Emerging Bacterial Pathogens and Infections: Gram-negative bacilli

Extended spectrum beta-lactamase producers

E. coli, *Klebsiella* spp.

Plasmid mediated: point mutations leading to significant a.a. change in TEM-1 (type 2) beta-lactamase (heightened probability of transmissibility within an institution)

Resistance: most beta-lactam agents, including 3rd generation cephalosporins (? 4th generation)

Treatment: Carbapenem; fluoroquinolone

Case #1 (continued)

Day 13 of hospitalization:

New fever 38.8°C on imipenem and L-AMB

Confusion

P=130; R=34; BP = 78/52

No localizing signs

CXR negative

What is the most likely pathogen at this time?

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Stenotrophomonas maltophilia*
- Coagulase negative *Staphylococcus*
- *Candida albicans*

What is the most likely pathogen at this time?

-
-
- *Stenotrophomonas maltophilia*
-

Stenotrophomonas maltophilia

- Emerging cause of fatal bacteremia, sepsis, and pneumonia in immunocompromised patients, particularly those with cancer
- May cause ecthyma like lesions similar to that of *Pseudomonas aeruginosa*
- Indigenous within an institution: water distribution system?
- Multiply resistant

**What is the preferred treatment
for *Stenotrophomonas
maltophilia*?**

TMP-SMX

Case #2

13 year old male with relapsed ALL in remission is receiving a myeloablative BMT.

Receiving prophylactic ciprofloxacin
Grade 3-4 oral mucositis

During the sixth day of profound neutropenia, new fever (T=39.1°C) developed.

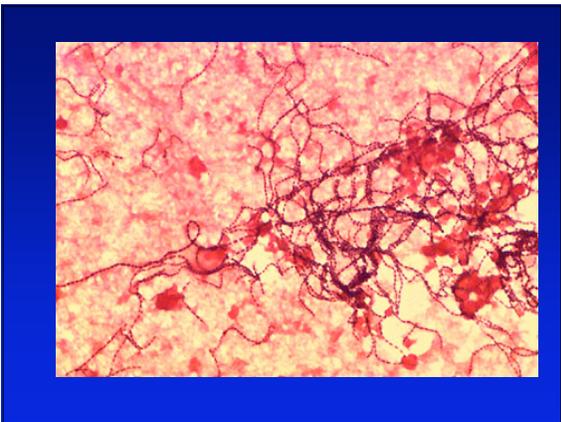
P=128; R=36; BP=82/60

Case #2: What are the organisms most likely etiological organisms as the initial cause of fever in profound neutropenia and severe mucositis?

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- Viridans streptococci
- *Aspergillus fumigatus*

Case #2: What are the organisms most likely etiological organisms as the initial cause of fever in profound neutropenia with severe mucositis?

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- Viridans streptococci



Viridans Streptococci in Oncology-BMT Patients: Microbiology

Microaerophilic streptococci
Viridans streptococci (a-hemolytic streptococci),
Oral commensal organisms.
All viridans streptococci are not the same

Viridans Streptococci in Oncology-BMT Patients: Microbiology

Strep. gingivalis

Strep. salivarius

Strep. oralis

Strep. mitis

Strep. anginosus-constellatus-intermedius

Case #2

Streptococcus mitis

Syndrome of septic shock, ARDS, and rash in high-dose chemotherapy

Treatment: vancomycin (penicillin resistance is now occurring)

Infections due to Viridans Streptococci in Patients with Cancer: Pathogenesis

Antimicrobial selective pressure
(fluroquinolones; TMP-SMX)

Increased burden of mucosal organisms

Mucosal disruption due to cytotoxic
chemotherapy

Permissive effect of neutropenia

Bacteremia

Super antigen activation of cytokine
cascade

Viridans Streptococci in Oncology-BMT Patients: Epidemiology

In the non-immunocompromised population, they are the most common cause of native valve endocarditis, which usually has a sub-acute course.

In neutropenic patients, viridans streptococci are more virulent (permissive effect of neutropenia).

Viridans Streptococci in Oncology-BMT Patients: Clinical Manifestations

Clinical manifestations:

- Neutropenic patients with viridans streptococcal bacteremia may have a 24-48 hour prodrome of low grade fever and facial flushing
- Followed by a high fever and chills
- In approximately 25% of patients, bacteremia is complicated by a shock syndrome



Empirical Vancomycin: Controversies

1. Overuse-> in 95% of pts not indicated
2. Minimal Morbidity and No Mortality
 - With exception of alpha-hemolytic Strep., Gr A Strep, ORSA.
 - Associated with
 - Myeloablative HSCT
 - Ara-c
 - Fluoroquinolone Prophylaxis
 - Soft tissue injuries
3. Cost
4. Monitoring
5. Selection for Resistant Organisms
 - Vancomycin Resistant Enterococci
 - NOT recommended by CDC for routine empirical therapy of F+N

Selecting Appropriate Initial Empiric Therapy: Additional Factors

- Choice of Antibiotic for Empirical Therapy
- Institutional Experience
 - Incidence of Resistant Bacteria
 - Recent Outbreak of Resistant Bacteria
 - Cost/Availability
 - Patient Characteristics
 - Condition of Patient at Diagnosis
 - Presence of Documented Site-Requiring Additional Therapy
 - Allergies
 - Drug Interactions

Management of Invasive Mycoses in Neutropenic and HSCT Recipients

What are the Major Fungal Pathogens in High Risk Patients with Hematological and Neoplastic Disorders?

Most common:

- *Candida* spp.
- *Aspergillus* spp.

Less common:

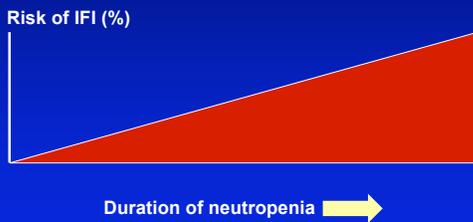
- Yeasts
 - » *Trichosporon* spp.
 - » *Cryptococcus neoformans*
- Filamentous fungi
 - » *Fusarium* spp.
 - » Zygomycetes; e.g., *Rhizopus oryzae*.
 - » *Sceodosporium/Pseudallescheria*
 - » Dematiaceous moulds

Strategies for Preventing the Complications of Invasive Fungal Infections during Neutropenia

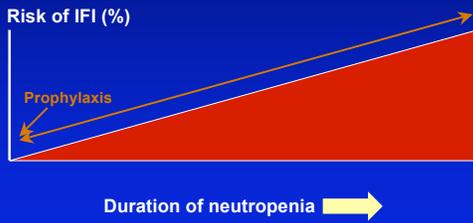
Early initiation of antifungal therapy:

- **Prophylaxis:** chemotherapy initiation at or near time of beginning antineoplastic chemotherapy or HSCT preparative regimen
- **Empirical therapy:** persistent fever and risk-based intervention for patients with persistent fever and neutropenia despite broad spectrum antibiotics and who are at risk for invasive fungal infection
- **Pre-emptive therapy:** with persistent fever and risk-based intervention for patients with persistent fever and neutropenia despite broad spectrum antibiotics PLUS other evidence of invasive fungal infection
 - E.g., positive surveillance culture, sinus opacification, pulmonary infiltrate, or positive GM antigen

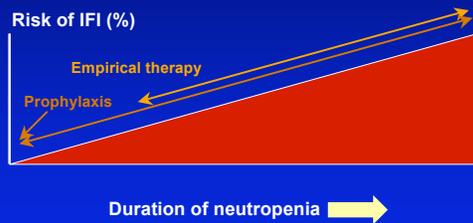
Probability of invasive fungal infection is directly related to duration of neutropenia



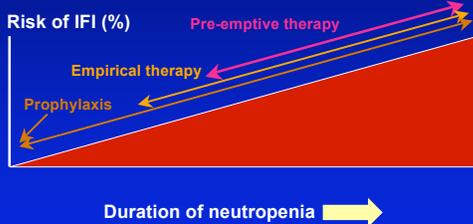
What is the timing of antifungal prophylaxis in neutropenic patients?



What is the timing of empirical antifungal therapy in neutropenic patients?



What is the timing of pre-emptive antifungal therapy in neutropenic patients?



What are the Standards of Therapy for Prophylaxis and Empirical Therapy?

Prophylaxis

- Fluconazole (Goodman *et al* 1992, Slavin *et al* 1995)
- Itraconazole? (Winston *et al* 2002, Marr *et al* 2003)
- Voriconazole? (investigational: NHLBI-CTN)
- Posaconazole (Cornely *et al*, 2007)
- Echinocandins (Micafungin, Van Burik *et al*, MSG-46, 2004)

Empirical Therapy

- Amphotericin B (Pizzo *et al* 1982, EORTC 1984)
- Liposomal amphotericin (Walsh *et al* 1999, Prentice *et al* 1998)
- Itraconazole (Boogaerts *et al*, 2001)
- Voriconazole (Walsh *et al*, MSG-42, 2002)
- Echinocandin (Caspofungin, Walsh *et al*, 2003)

Invasive Candidiasis

All Deeply Invasive Candidiasis is not the Same

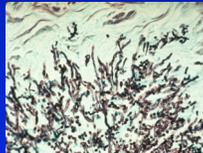
- Candidemia
- Acute Disseminated Candidiasis
- Chronic Disseminated Candidiasis

All Invasive Candidiasis is not the Same

- Candidemia
- Positive blood culture
- Usually signifies deep tissue infection
- Mortality and morbidity is similar to that of bacteremia due to *Staphylococcus aureus*
- All cases require treatment

All Invasive Candidiasis is not the Same

- Acute Disseminated Candidiasis
- Candidemia complicated by clinically overt deep tissue infection
- Hypotension, septic shock, multiorgan dysfunction
- Cutaneous lesions, myalgias

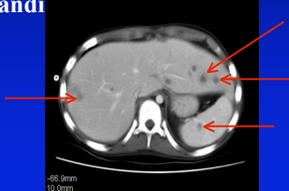


All Invasive Candidiasis is not the Same

- Chronic Disseminated Candidiasis
- Stable ambulatory patient with fever, abdominal pain, elevated alkaline phosphatase
- History of previous neutropenia +/- candidemia
- Th2 dysimmunoregulation
- Protracted therapy usually required

All Invasive Candidiasis is not the Same

Chronic Disseminated Candidiasis



All *Candida* species are not the Same

- *Candida albicans*: most common cause of candidemia (approximately 50%)
- *Candida tropicalis*: highly virulent in neutropenic hosts causing acute disseminated candidiasis (approximately 10-15%)
- *Candida parapsilosis*: adherence to catheters, prosthetic valves, and IV catheters (approximately 10-15%)
- *Candida glabrata*: second most common cause of candidemia (approximately 25%); 10% of these isolates are resistant to azoles and/or amphotericin
- *Candida krusei*: (<5% of blood stream isolates) all are resistant to fluconazole

Selected Medically Important Yeasts Resistant to Amphotericin B

- *Candida lusitanae*
- *Candida guilliermondii*
- *Candida lipolytica*
- Some isolates of *Candida glabrata*, *Candida krusei*, and *Candida tropicalis*
- *Trichosporon* spp.

**Interpretation of
National Committee for Clinical
Laboratory Standards
Breakpoints for Fluconazole**

- Susceptible: $\leq 8 \mu\text{g/ml}$
- Susceptible dose-dependent:
16-32 $\mu\text{g/ml}$
- Resistant: $\geq 64 \mu\text{g/ml}$

**All *Candida* species are not the
Same: Implications for Fluconazole
MICs (Candidemia)**

- *Candida albicans*: $< 8 \mu\text{g/ml}$
- *Candida tropicalis*: $< 8 \mu\text{g/ml}$
- *Candida parapsilosis* $< 32 \mu\text{g/ml}$
- *Candida glabrata* $1- > 64 \mu\text{g/ml}$
- *Candida krusei* $> 64 \mu\text{g/ml}$

**Antifungal Compounds for
Primary Treatment of Candidemia**

- **Polyenes**: amphotericin B (deoxycholate) and lipid formulations of amphotericin B
- **Triazoles**: fluconazole; voriconazole (data from clinical trial in press)
- **Echinocandins**: caspofungin, micafungin, anidulafungin (investigational; study in candidemia completed)

A Rationale for Selection of Primary Therapy for Antifungal Agents in Treatment of Candidemia

- For institutions with low frequency of triazole resistance or for patients not receiving previous antifungal triazoles, start fluconazole
- For institutions with high frequency of triazole resistance or for patients receiving antifungal triazoles, start echinocandin or LFAB
- For patients with hepatotoxicity, start LFAB or echinocandin
- For patients with nephrotoxicity, avoid amphotericin B
- For patients receiving fluconazole prophylaxis (e.g. BMT recipients), start echinocandin or LFAB

What is the Approach to Patients with Positive Blood Cultures for a Yeast-like Organism?

- Remove vascular catheters where feasible
- Perform ophthalmoscopy and abdominal CT scans (if patient is neutropenic, do so upon recovery from neutropenia (R/O HSC))

Remember Drug Interactions

- Nephrotoxicity with AmB
 - Aminoglycosides
 - Acyclovir
 - Foscarnet
 - CSA and tacrolimus
- Myelosuppression with 5-FC
 - Ganciclovir
 - Cancer chemotherapy
- Cytochrome P-450 competitive antagonism
 - Antifungal triazoles (e.g. vincristine)
 - Boxed warning with triazoles: quinidine, cisapride, pimozide, dofetilide

Invasive Aspergillosis

Aspergillosis in Immunocompromised Patients: Epidemiology

- *Aspergillus* species are the most common cause of infectious pneumonic mortality in bone marrow/stem cell transplant recipients and leukemia.
- Important cause of pneumonia in patients with solid organ transplantation

Aspergillosis in High Risk Hematology Patients: Evolving Risk Factors

- Pharmacological Immunosuppression
 - Prolonged neutropenia
 - Repeated cycles of profound neutropenia
 - Corticosteroid therapy
 - Infliximab therapy
- Intrinsic Immune Defects
 - Aplastic anemia
 - Advanced HIV infection (CD4<100/ μ l)
 - Chronic granulomatous disease
 - Job's syndrome

Epidemiology of Aspergillosis in BMT Recipients

- Bimodal Distribution
- Neutropenic phase
 - depth
 - duration
- Post engraftment phase
 - GVHD
 - Corticosteroids
 - Tacrolimus/CsA
 - Mucosal disruption
 - CMV disease

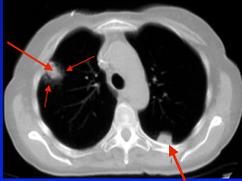
Aspergillosis in Immunocompromised Patients: Clinical Manifestations

- Pneumonia
 - Pleuritic pain
 - Cough
 - Hemoptysis
- Sinusitis
 - Nasal congestion
 - Eschars
 - Epistaxis
 - Palatal hemierythema
 - Disseminated infection (CNS)

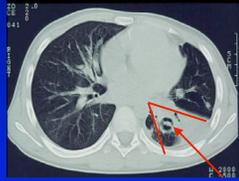
Aspergillosis in Immunocompromised Patients: Radiological Evaluation

- CXR: lacks sensitivity
- CT scan:
 - Bronchopneumonia
 - Nodules
 - Wedge-shaped infiltrates
 - "halo sign,"
 - Cavities

Invasive Aspergillosis: Radiological Evaluation



Halo Sign



Crescent Sign

Invasive Pulmonary Aspergillosis: Laboratory Evaluation

- Diagnostic procedures:
 - BAL
 - Percutaneous needle aspiration
 - Thoracoscopy
 - OLB
- Microbiologic detection:
 - direct exam (calcofluor, cytology, histopathology)
 - culture
- Antigenic and molecular detection
 - Galactomannan: EIA format (recently approved 510K in USA)
 - PCR (investigational)
 - Glucans (*Limulus* or *Tachypleus* assay)

Antifungal Compounds for Treatment of Invasive Aspergillosis

- Polyenes: amphotericin B (deoxycholate) and lipid formulations of amphotericin B
- Triazoles: voriconazole and itraconazole
- Echinocandins: caspofungin, micafungin (investigational)

Guidelines: Treatment of Invasive Pulmonary Aspergillosis

- Assessment for Parenteral vs Oral Therapy
 - Host factors
 - Time factor
 - Bioavailability
- Primary Therapy in most cases: **Voriconazole** improves survival and overall response (>AmB)
- Intolerant of or refractory to conventional therapy -> LFAB or echinocandin

What are the relative indications for surgery for invasive aspergillosis?

- Infected hardware (catheters / implants)
- Infections of skin and soft tissues
- Invasion of chest wall or pericardium
- Proximity to great vessels
- Hemoptysis from a single cavitory lesion
- Intractable pain
- Selected cases of sinusitis
 - minimally invasive for aeration during neutropenia
 - aggressive for disease progression despite medical therapy
- Amenable cerebral lesions
- Other amenable deep tissue lesions
- Endocarditis and osteomyelitis

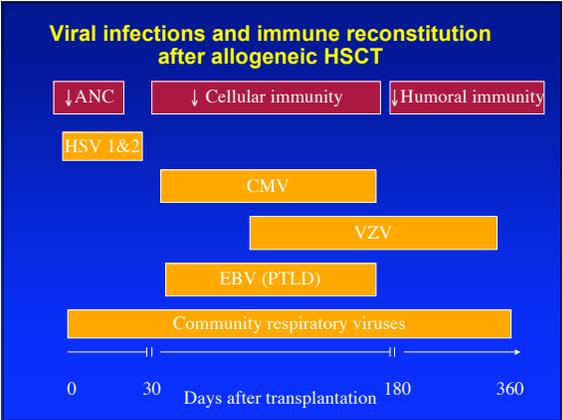
What is the potential impact of surgery in appropriate candidates with invasive aspergillosis?

- Resection may lead to definitive cure
- More rapid reduction of residual fungal burden than can be achieved with medical therapy
- May be life-saving
- Caillot *et al* (1997) found that 15 of 16 patients with hematological malignancies and IPA who underwent lung resection had successful outcome.

Augmentation of Host Response against Invasive Aspergillosis in Pediatric Hematological Malignancies and HSCT

- Discontinue or rapidly taper corticosteroids
- GM-CSF or G-CSF for persistent but reversible neutropenia
- Granulocyte transfusions for patients with
 - refractory infection
 - persistent but reversible neutropenia

Viral Infections

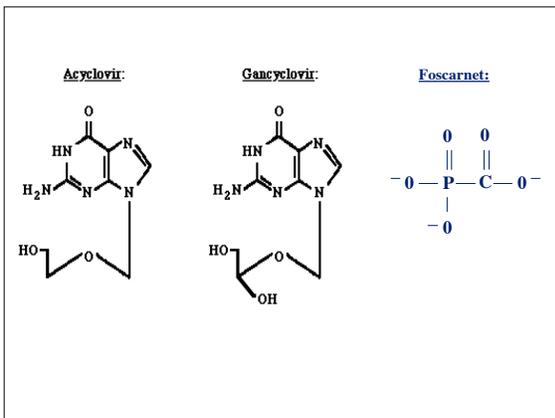


Herpes viruses

- HSV 1 and 2
- CMV
- VZV
- EBV
- HHV-6

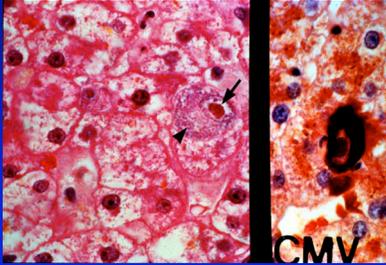
HSV 1 and 2 infection

- Predominantly observed during neutropenia and within day 30 of BM/SCT
- Mucocutaneous (oral/genital), esophageal, disseminated
- Routine use of acyclovir in acute leukemia and BM/SCT has significantly ↓ frequency of HSV disease in HSV-seropositive pts
- Resistance is uncommon
 - TK mutants confer resistance to acyclovir, valacyclovir, famciclovir, and ganciclovir, but not to foscarnet



CMV Disease

- Definitive dx: + histopathology or cytology
- CMV inclusions and immunostaining



CMV Disease

- Definitive dx: + histopath or cytology
- Mostly observed in allogeneic BM/SCT
- Non-transplant patients with acute leukemia also at risk
- Pneumonitis is most common and severe complication
- Other organs: GI tract, liver, adrenals, kidney, CNS, retina
- Graft failure and cytopenias
- Treatment of CMV disease: Ganciclovir or foscarnet + IVIG

CMV Prophylaxis in Allogeneic HSCT

- Ganciclovir administration to all sero-positive patients
- Decreased CMV disease but increased myelosuppression
- Increased frequency of bacterial and fungal infections
- Increased complications of thrombocytopenia
- Concerns for emergence of resistance

pp 65 CMV antigenemia

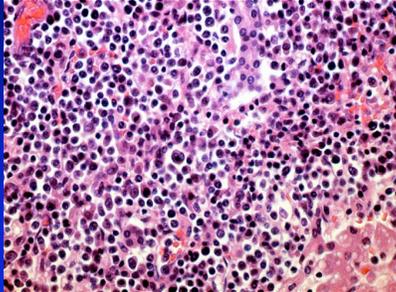


Pre-emptive therapy for CMV

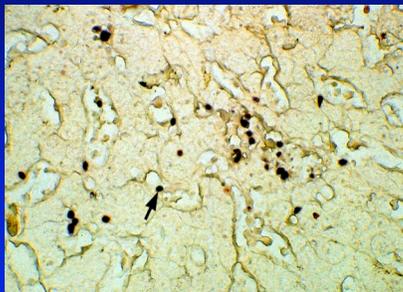
- Methods for detection of CMV:
 - pp65 CMV antigenemia
 - PCR on PBLs
 - plasma PCR (useful for neutropenic pts)
 - viral blood culture (shell vial)
- Preemptive therapy is associated with ↓ transplant-related mortality
- Late CMV disease detected with preemptive tx
- Caveat: considerable inter-lab variability with PCR (improving with standard protocols)

EBV Post-Transplant Lymphoproliferative Disorder: An Emerging Infection

EBV Post-Transplant Lymphoproliferative Disorder



In situ PCR for EBV



Therapy for EBV PTLPD

- ↓ immunosuppression is effective in certain pts (e.g., collagen vascular disease), but usually ineffective in hematopoietic transplant recipients
- Antiviral agents, although active *in vitro*, are typically ineffective
- Donor-derived EBV-specific CTLs useful as prophylaxis and therapy
- Promising data with rituximab
 - Anti-CD20 mAb depletes B-cells, principal reservoirs during EBV reactivation

Varicella

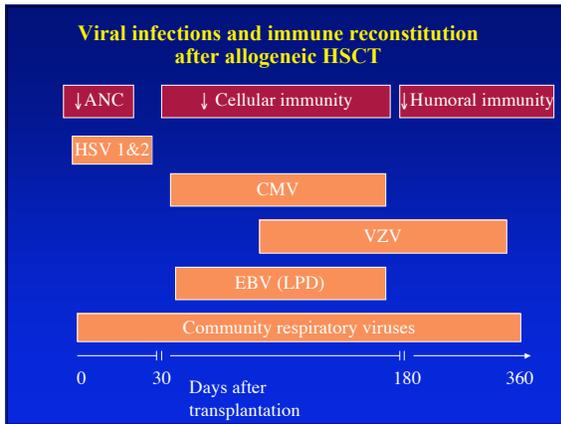
- Primary vs. reactivated
- High mortality rate in disseminated infection
 - High-dose acyclovir (IV 10 mg/kg q8h) warranted
- Often a late complication of HSCT
- Prevention
 - Acyclovir prophylaxis
 - VZIG in seronegative recipients within 96h of exposure
 - Immunization of seronegative household members
 - Contact and respiratory precautions

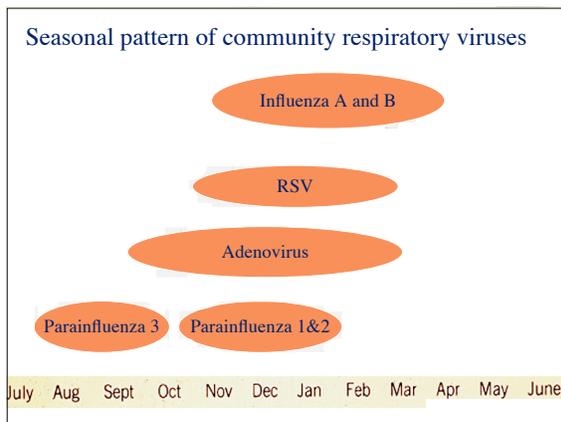
HHV-6: An Emerging Viral Pathogen

- Childhood exanthem (roseola)
- HHV-6 disease due to reactivation occurs principally in allo HSCT
- Most patients seropositive

HHV-6: An Emerging Viral Pathogen

- Diagnosis: clinical presentation and + PCR from an acellular specimen or immunohistochemistry
 - Encephalitis
 - Marrow suppression (graft failure)
 - Pneumonitis
 - ? Role in GVHD
- Antiviral therapy: ganciclovir or foscarnet





- ### Community respiratory viruses
- Important cause of diffuse interstitial infiltrates in allogeneic HSCT and acute leukemia
 - Diff dx: CMV, PCP, LIP, DAH
 - Initially may present as non-specific URI
 - More commonly diagnosed in centers that search for them
 - Frequency parallels prevalence in community
 - Low threshold for nasopharyngeal wash
 - Rapid immunofluorescent detection methods
 - Early initiation of antiviral agents
 - Infection Control precautions
 - Heightened alert for SARS

**Limited Treatment Options of Emerging
Community Respiratory Viruses**

- Influenza A+B: neuraminidase inhibitors (e.g., oseltamivir)
- RSV: ribavirin + Ig
- Adenovirus: Cidofovir
- Others: supportive measures

Thank you!

Questions
