Objectives

- Recognize viral infections that affect patients after hematopoietic cell transplant (HCT)

- Describe the pathophysiology and clinical manifestations of viral infections after HCT

- Identify treatments and different strategies to manage viral infections after HCT
Overview

- Discuss viral infections in HCT patients
  - CMV, EBV, HHV-6, BK-virus, Adenovirus

- Respiratory Viruses:
  - RSV, Rhinovirus, MPV, Parainfluenza, Influenza
Cytomegalovirus (CMV)

Pathophysiology

- Herpes virus family
  - 50-80% of adults are infected by age 40

- Pathogenesis of CMV is complex

- Immune mediated through multiple mechanisms
  - Effects on HLA expressions
  - Cytokine production
  - Expression to adherence molecules
Risk Factors

<table>
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<tr>
<th>Donor CMV IgG Status</th>
<th>Recipient CMV IgG Status</th>
<th>% Reactivation</th>
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<tbody>
<tr>
<td>CMV negative</td>
<td>CMV negative</td>
<td>Low</td>
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<tr>
<td>CMV Positive</td>
<td>CMV negative</td>
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<td>CMV Positive</td>
<td>CMV positive</td>
<td>Controversial</td>
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<tr>
<td>CMV negative</td>
<td>CMV positive</td>
<td>Higher Risk</td>
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Risk Factors

- Level of Immunosuppression
  - Type of HCT
  - GvHD
  - Corticosteroid use
  - Second line systemic IST
Symptoms

- Can be mild (most patients are asymptomatic)
  - Fever, sore throat, malaise, cough
- Viremia detectable by PCR
- Bone marrow suppression
- End organ disease:
  - Lung
  - GI
  - Liver
  - Eyes
  - Brain

Interventions and Therapies

- Prophylaxis Therapy
  - High risk
- Pre-emptive Therapy
  - First line Valganciclovir/Ganciclovir
  - Foscarnet
- Treatment Therapy
  - Requires invasive procedures
  - Prolong therapy
  - Reduction of IST therapy
  - Use of IVIG-controversial
  - Use of growth factor
Nursing Considerations

- CMV PCR monitoring
  - Weekly or bi-weekly starting at day 20 post transplant
  - Blood count monitoring
  - Renal function
  - Fluid status

Epstein Barr Virus (EBV)
Pathophysiology

- Herpes virus family
- Latent infection within the recipient
- Related Diseases:
  - Lymphomas, Lymphoproliferative disorders, hemophagocytic lymphohistiocytosis, solid tumors among other diseases.

EBV latent life cycle.

- Viral entry
- Infection
- Proliferation
- Differentiation
- Persistence

<table>
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<th>Latency type</th>
<th>Type 3</th>
<th>Type 2</th>
<th>Type 0</th>
<th>Type 1</th>
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<td>Default</td>
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<td>Naive B</td>
<td>Germinal center B</td>
<td>Resting memory B</td>
<td>Dividing memory B</td>
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<td>Malignant Counterpart</td>
<td>PTLD</td>
<td>HD, NPC</td>
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<td>BL, Gastrointestinal Ca</td>
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</table>

Helen E. Heslop Blood 2009;114:4002-4008

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EBV-Post-Transplant Lymphoproliferative Disorder (PTLD)

- Adverse Effect of Suppression of T-cell Function
  - Drugs (Anti-Thymoglobulin, Campath)
  - High Risk transplant (Haplo/Cord/second transplant)

- Incidence
  - Cord, Haplo HCT, T-cell Depleted up to 20%
  - MUD/MSD HCT (0.5-1%)

- Risk of PTLD increases from 20-120% compared to the general population based on level of immunosuppression

Diagnosis

<table>
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<tr>
<th>Test</th>
<th>Information Gained</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>EBV viral load</td>
<td>Elevated level supports diagnosis</td>
<td>High sensitivity, specificity varies with clinical scenario</td>
</tr>
<tr>
<td>Imaging</td>
<td>Enlarged lymph nodes or nodules support Differential causes for diagnosis</td>
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<tr>
<td>Biopsy affected organ</td>
<td>Confirm EBV positivity by LMP1 immunostaining and IHCs</td>
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<tr>
<td></td>
<td>Assess histology (high-grade mononuclear lymphoma vs polyclonal lymphoproliferation)</td>
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<tr>
<td></td>
<td>Immunophenotyping (CD20 expression)</td>
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<tr>
<td></td>
<td>Cytogenetics</td>
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</tbody>
</table>
Interventions and Therapies

- Reduce Immunosuppression
- Rituximab
  - Pre-emptive treatment
  - Potential fatal disorder
- Immunotherapy
  - EBV CTL

Maximum-intensity projection 18F-FDG–PET/CT images.

Daan Dierickx et al. Blood 2015;126:2274-2283

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Nursing Considerations

- EBV monitoring post HCT
  - Day 20 post HCT
  - Use of ATG
  - Second line IST
  - Increase risk for other infections

Human Herpes Virus 6 (HHV-6)
Pathophysiology

- HHV-6 Very common - Prevalence is >95%
- Primary infection
  - Viral exanthem; Infant to age 3
- Replicates in salivary glands
  - Latent in lymphocytes and monocytes
  - Persists at low levels in cells and tissues without causing disease in the immunocompetent

Risk Factors

- Reactivation occurs post HCT
- 20-72% of cases
- Associated with HLA mismatch, CBU, MUD, Steroid use
- HHV-6 Viremia is Associated With:
  - Increased subsequent mortality
  - Grade 3-4 GVHD
  - Lower probability of platelet engraftment
Symptoms

- May develop Constitutional symptoms
  - Fever, malaise, URI
  - Body rash
- Bone marrow suppression
- Viremia detectable by PCR
- End organ disease
  - GI
  - Liver
  - CNS
  - Lung

HHV-6
Interventions and Therapies

- Monitor HHV-6 plasma PCR
- Decrease Immunosuppression if possible
- Pre-emptive Treatments:
  - Ganciclovir
  - Foscarnet

Nursing Considerations

- Lab monitoring
  - Weekly plasma HHV-6 PCR
  - Monitor renal function
  - Monitor fluid status
  - Monitor blood counts
  - Monitor for end-organ disease
    - Liver function
    - New onset of respiratory symptoms
    - New onset of altered mental status
    - New onset of nausea, vomiting, diarrhea
**BK Virus**

**Pathophysiology**

- Family of Polyoma virus
- 60-80% prevalence
- Infection occurs early in childhood; asymptomatic
- Reactivates in immunocompromised HCT
  - Seen in as high as 50% of HCT patients
  - Hemorrhagic cystitis in 10-15%
  - Usually occurs within 60 days post HCT
Symptoms and Organ Involvement

- Hematuria, dysuria, urgency
- Bone marrow suppression
- Organ involvement
  - Bladder
  - Kidney

Interventions and Therapies

- Laboratory Tests:
  - Urine and plasma BK PCR
- Supportive Treatments:
  - Hydration
  - Antispasmodics (Levsin, Oxybutin, Phenazopyridine)
  - Bladder irrigation
  - Keep platelets >50K
- Treatments:
  - Ciprofloxacin
  - Cidofovir (IV, Intravesicular)
  - Decrease immunosuppression
Nursing Considerations

- Lab monitoring
  - Weekly plasma and urine BK PCR
  - Monitor renal function
  - Monitor blood counts
- BK monitoring only if receiving active treatment
- Discontinue monitoring with symptom resolution
- Low BK plasma levels

Adenovirus
Pathophysiology

- Common (adult: 9%; pediatric: 20% - 26%)
- Reported mortality: 8% - 26%
- Risk factors for acquisition
  - GVHD, MUD, total body irradiation, presence and severity of T-cell depletion, recent HCT, and T cell suppression following HCT
  - Definitive cure requires adequate immune reconstitution

Symptoms and Organ Involvement

- Enteritis
- Pneumonia
- Hemorrhagic cystitis
- Upper respiratory infection
- Conjunctivitis
- Hepatitis
- Skin rash
- Urethritis
Survival after Adenoviral Infections

Stratified by site of AdV infection and presence of GvHD


Interventions and Therapies

- Reduce Immunosuppression
- Cidofovir + Probenicid
- Immunotherapy
  - Adeno CTLs
Respiratory Viruses

Regular CXR
Influenza, day 1 hospitalization

Day 3, In ICU
Day 4, In ICU

Day 5, one day before death
Pathophysiology

- Upper respiratory infections (URI) involve direct invasion of the mucosa lining the upper airway
- Inflammatory cytokines mediate the immune response
- Immunosuppressed are at increased risk for contracting an URI and increased risk for a severe or prolonged course

Burden of Respiratory Viruses in Transplant Patients

- High frequency of pneumonia an associated mortality
- Co-infections
- High potential for nosocomial acquisition
- Prolonged viral shedding despite treatment
Types of Viruses

- Respiratory syncytial virus (RSV)
- Parainfluenza virus type 1,2,3 or 4
- Influenza A and B
- Metapneumovirus
- Adenovirus
- Rhinovirus
- Coronavirus

Symptoms

- Runny nose
- Watery eyes
- Fever
- Chills
- Cough
- Sore throat
- General aching
- Malaise
Progression to LRI

- Progression rates from URI to lower respiratory tract infection (LRI) vary by virus
- Highest for RSV (30-40% of myeloablative transplant patients)
- Followed by parainfluenza, metapneumo, and influenza virus.
Treatments

- Respiratory Syncytial Virus (RSV)
  - Aerosolized Ribavirin if LRI
  - Oral Ribavirin in no LRI
  - Isolation
- Parainfluenza
  - Decrease immunosuppression if possible
  - Isolation

Treatments

- Influenza viruses
  - Tamiflu
  - Isolation
- Adenovirus
  - Cidofovir
  - Isolation
- Metapneumovirus
  - Isolation
Treatments

- Rhinoviruses
  - Isolation
- Coronaviruses
  - Isolation

Nursing Considerations

- Request RVP nasal wash if symptoms present
- Proper isolation for identified virus
- Thorough screening of visitors for viral symptoms
- Patient education
  - Proper handwashing
  - Neutropenic precautions
  - Wearing a mask when in public
The Economic and Clinical Burden of Respiratory Viral Infections in Hematopoietic Cell Transplant (HCT) Recipients: A Cost Comparison Study Across 19 Major Cancer Centers in the U.S

Shashank S. Ghantoji, Dimpy P. Shah, David R. Lairson, Lynn El Haddad, Joumana Kmeid, Anne K. Park, Roy F. Chemaly

- UHC (University Health Consortium) clinical data base was utilized.
- We compared direct medical costs, including hospitalization and ICU admission costs, associated with RSV, Flu, and PIV from 19 major cancer centers in the U.S. over 44 months (October 2011 to May 2015).
- Hospitalization days: average of 10 d for RSV, 9 d for Flu and 14 d for PIV.
- The average ICU admission rate was 16% for RSV, 15% for Flu and 30% for PIV.
- Overall mortality rate was of 6% (RSV: 7%, Flu: 5%, and PIV: 7%)

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<th>United States Cancer Centers</th>
<th>RSV Cases</th>
<th>RSV Direct Cost ($)</th>
<th>Flu Cases</th>
<th>Flu Direct Cost ($)</th>
<th>PIV Cases</th>
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<td>16,873,034</td>
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<td>6,406,236</td>
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Handwashing!!

Germ Farm

Scrub'em!

www.1st-in-handwashing.com
Handwashing

- Reduces the number of people who get sick with diarrhea by 31%
- Reduces diarrheal illness in people with weakened immune systems by 58%
- Reduces respiratory illnesses, like colds, in the general population by 16-21%

Summary

- Prevention of viral reactivation post HCT remains challenging
- There are still unmet needs for many viruses causing significant morbidity and mortality in the HCT population
- New antiviral agents with less side effects are needed
Questions

References


