Opportunistic infections in the immunocompromised host

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Blood and Marrow Transplant Program
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The Ohio State Comprehensive Cancer Center
Objectives

• Overview of immunity
  – Cellular-mediated immunity: Innate and adaptive immunity
  – Complexity in immune response

• Defining the immunocompromised patient population
  – Primary (congenital) immunodeficiency
  – Secondary (acquired) immunodeficiency
  – An expanding patient population (biologic and cellular therapies)

• Infections in immunocompromised hosts
  – Common themes across patient populations
  – Invasive fungal infection (IFI)
  – Cytomegalovirus (CMV)
  – Respiratory viruses

• Therapy-associated infections
  – Biologic therapies
  – Hematopoietic cell graft manipulation
  – Cell therapies: Chimeric antigen receptor (CAR) T cells

• Antimicrobial cellular therapies
Immunity
Immunity: Functional homeostasis

Hallmarks of functional immune response:
1. Detection
2. Activation
3. Recruitment/Mobilization
4. Redundancy
5. Memory
6. Elimination
7. Regulation

Immune Surveillance

(+) Anti-microbial
(+) Anti-tumor

Immune Tolerance

(-) Auto-immunity
(-) Allo-immunity

Nationwide Children's
The Ohio State University
College of Medicine
Cellular Immunity: Innate and adaptive arms

PAMP = pathogen-associated molecular pattern
TLR = Toll-like receptor  (e.g., PRR = pattern recognition receptor)

NEJM 2000; 343: 338
Cellular Immunity: Innate versus Adaptive

**Innate Immunity**
- Minimal Recruitment/ER hematopoiesis
- Broad specificity
- Germline-conserved
- Rapid, non-specific
- No

**Regulation**
- Amplification
- Receptor specificity
- Receptor origin
- Speed of response
- Memory

**Highly regulated Clonal expansion**
- Narrow specificity
- Random generation
- Slower, Antigen-specific
- Yes

**Adaptive Immunity**

Type 1 and Type 2 Immune Responses

Type 1 immune response
IL-12, IL-17 and IFNγ

Bacteria, viruses and protozoa

Infection

Type 2 immune response
IL-4, IL-5, IL-13 and IL-10

Helminths

Type 1 immunity
Autoimmunity
Metabolic disorders

Type 2 immunity
Fibrosis
Allergy

Simplified concept, but immune response is more complex!

Nat Rev Immunol 2013; 13: 607
# Immunity: A multi-layered social network

<table>
<thead>
<tr>
<th>Network Component</th>
<th>Social Network</th>
<th>Immune System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Actors</strong></td>
<td>Members of society</td>
<td>Immune-cell types</td>
</tr>
<tr>
<td><strong>Roles</strong></td>
<td>Same profession; similar age; shared interests</td>
<td>Shared function—e.g., early defense mechanisms; humoral immunity</td>
</tr>
<tr>
<td><strong>Context</strong></td>
<td>Family; professional; spare time</td>
<td>Organ; tissue; activation status</td>
</tr>
<tr>
<td><strong>Intra-layer communication</strong></td>
<td>Personal communication; e-mails; phone calls</td>
<td>Direct cell–cell interactions; receptor–ligand interactions</td>
</tr>
<tr>
<td><strong>Inter-layer communication</strong></td>
<td>Similar to intra-layer communication</td>
<td>Signaling across organs, tissues</td>
</tr>
</tbody>
</table>

*Nature Immunol 2017; 18: 481*
Importance of immune regulation: Stop inflammation

Pro-inflammatory vs. immunomodulatory response

Pathogen burden

Antimicrobial immunity

Blood 2012; 119: 1801
Who is immunocompromised?
Primary immunodeficiency (PID)

- **Primary (congenital) immunodeficiency**
  - Phagocyte disorders
  - Humoral (B-cell differentiation and antibody production)
  - T-cell and mixed (combined B and T-cell disorders)
  - Complement deficiency

STRIDE (Study Targeting Recognition of Immune Deficiency and Evaluation) >1000 adult and pediatric patients
91 total pediatric patients: 61 (67%) Ab deficiency

Figure 1. Relative incidence of different primary immunodeficiency disorders diagnosed in patients seen during an 8-year period in a pediatric tertiary hospital.

Ann Allergy Asthma Immunol 2000; 84: 25
PID is not just a pediatric diagnosis!

Patient age at PID diagnosis

- 65+ 3%
- 45-64 23%
- 30-44 25%
- 18-29 9%
- 13-17 4%
- 7-12 9%
- 0 to 6 27%

Q9. At what age (in years) was that person first diagnosed with a primary immunodeficiency disease? (N=1,330 – excludes missing data)

Hem/Bone Marrow - 94%
Autoimmune - 6%

Red flags for potential PID

10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

Is it just an infection?

You should be suspicious if you have an infection that is...

- **Severe**: requires hospitalization or intravenous antibiotics
- **Persistent**: won’t completely clear up or clear very slowly
- **Unusual**: caused by an uncommon organism
- **Recurrent**: keeps coming back

If any of the words describe your infection, the Immune Deficiency Foundation (IDF) recommends that you ask your physician to check for the possibility of a primary Immunodeficiency disease. These diseases are caused by genetic defects and can affect anyone, regardless of age or gender. People with primary immunodeficiencies are more susceptible to infections and health problems that lead to serious and debilitating diseases. It is critical to get an early diagnosis and proper medical care.

As the national patient organization dedicated to persons living with primary Immunodeficiency diseases, IDF says THINK IMMUNE.

In medical school, many doctors learn the saying, “when you hear hoofbeats think horses, not zebras” and are taught to focus on the limited possibilities when making a diagnosis, not the unusual ones. However, sometimes physicians need to think for a zebra. Patients with primary Immunodeficiency diseases are the zebras of the medical world.

If you have an infection and any of these characteristics, ask your physician to THINK IMMUNE.
Defining immunodeficiencies

• Secondary (acquired) immunodeficiency
  – HIV
  – Cancer
  – Transplant: Hematopoietic cell and solid organ
  – Age: premature versus elderly
  – Malnutrition: Protein-losing enteropathy
  – Autoimmunity: Lupus, diabetes mellitus
  – Therapies: Procedures, monoclonal antibodies
  – Sepsis

How many Americans are immunocompromised?

No one knows!

In 2002 study, 10 million people were immunocompromised, but authors counted only “recipients of organ transplants, individuals with diagnosed and undiagnosed HIV infection or AIDS, and patients with cancer.”

American Cancer Society 2016 Report

1,685,210 new cancer cases in 2016

Effective Clin Pract 2002; 5: 84
An increasing patient population…

- Cross-sectional analysis of non-institutionalized adults (>18y) using 2013 National Health Interview Survey
- 34,426 participants
- “Immunosuppressed” if answered “yes” to:
  - Q1 (n=2148) + Q2 AND Q3 or Q4 OR
  - Had hematologic cancer within last 2 years (Q7 & Q8)

2.7 per 100 people in US (2017 325M) → 8.8M
Autoimmune Disease

Apoptosis
- Low affinity
- High affinity

Anergy
Deletion
Exhaustion
Suppression

Thymic deletion

Peripheral deletion

Tolerance Lost

- Wrong environment
- Tolerance fails
- Wrong genes

Autoimmune disease

Wrong environment
Tolerance fails
Wrong genes

Global (present)
Therapies
Selective (new)
Autoimmune disease

Autoimmune Diseases Disproportionately Affecting Women

- Hashimoto's thyroiditis
- Systemic lupus erythematosus
- Sjogren's syndrome
- Primary biliary cirrhosis
- Scleroderma
- Rheumatoid arthritis
- Multiple sclerosis

Autoimmune diseases represent:³
- The fourth largest cause of disability among women in the U.S.
- The eighth leading cause of death for women between the ages of 15 and 64.

10 Warning Signs of an Autoimmune Disease

1. Feeling fatigued or tired
2. Difficulty concentrating or focusing
3. Weakness or pain or tremors in the muscles/joints
4. Hair loss
5. Dry eyes, mouth or skin
6. Unexplained weight gain or loss
7. Numbness or tingling in the hands or feet
8. Abdominal pain, blood in urine or stool, diarrhea
9. Rashes, hives, or photosensitivity
10. Multiple miscarriages or blood clots

To learn more about autoimmune diseases, please visit:
http://www.mollysfund.org/autoimmune-diseases

It takes most autoimmune patients up to five years and nearly five doctors before receiving a proper autoimmune disease diagnosis.³

www.operationshootingstar.com
Gender differences in immune response

- **Autoimmune diseases**
  - Graves disease
  - Hashimoto thyroiditis
  - Multiple sclerosis
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Type 1 diabetes

- **Infectious diseases**
  - HIV
  - Influenza
  - Toxoplasmosis
  - Legionella
  - Malaria
  - Zika

- **Non-reproductive cancers**
  - Ebola
  - MERS
  - Hepatitis B
  - Tuberculosis
  - Leptospirosis
  - Campylobacter
  - Schistosomiasis
  - Amebiasis
  - Aspergillosis

**Females:**
- ↑ B-cells and Antibody
- ↑ CD4+ cells

*Nat Rev Immunol* 2016; 16: 626
Infections in immunocompromised patients

- **Common themes across immunocompromised patients**
- Invasive fungal infection (IFI)
- DNA viruses: Cytomegalovirus (CMV)
- Respiratory viruses
Theme #1: Common infections are common, infection-related mortality is high
Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study

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1University of Pennsylvania, Philadelphia; 2Centers for Disease Control and Prevention, Atlanta, Georgia; 3Washington University, St. Louis, Missouri; 4VA Medical Center, University of Michigan, Ann Arbor; 5Johns Hopkins University, Baltimore, Maryland; 6University of Toronto, Canada; 7University of Queensland, Brisbane, Australia; 8University of Pittsburgh, Pennsylvania; and 9University of Alabama at Birmingham

- Prospective, multicenter cohort study (2006-2011)
- 4 US transplant centers, 444 allogeneic HCT recipients
- Standardized data prospectively collected until 30 mos post-HCT
- No standardized antifungal or antiviral prophylaxis across centers
- GvHD requiring treatment occurred in 336 (76%) patients
- Infection occurred in 410 (92%) patients, 415 (93%) transplants
- 471 total infections: BSI (56%, 231), viral (46%, 187), fungal (11%, 53)
- 231 total deaths: 49 (21%) infection-related
Bloodstream infection (BSI)

- **Most common infection (N=231)**
  - 56% (231/410) patients with infection
- Median time to first BSI: 48d
- **Most prevalent isolates**
  - Gram-positive (GP): 244 (56%)
    - CoNS, Enterococci
  - Gram-negative (GN): 93 (21%)
    - Pseudomonas aeruginosa
  - Polymicrobial: 50 (12%)
- **Mortality within 7d of BSI**
  - GN (45%) vs. GP (13%), p=0.02

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>(Percent or Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive</td>
<td>244</td>
<td>(56)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>126</td>
<td>(31)</td>
</tr>
<tr>
<td>Vancomycin-resistant Enterococcus</td>
<td>41</td>
<td>(17)</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>31</td>
<td>(13)</td>
</tr>
<tr>
<td>Methicillin-susceptible Staphylococcus aureus</td>
<td>17</td>
<td>(7)</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>8</td>
<td>(3)</td>
</tr>
<tr>
<td>Methicillin-resistant S aureus</td>
<td>7</td>
<td>(3)</td>
</tr>
<tr>
<td>β-hemolytic streptococci</td>
<td>8</td>
<td>(2)</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>(3)</td>
</tr>
<tr>
<td>Gram negative</td>
<td>93</td>
<td>(21)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>24</td>
<td>(26)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>20</td>
<td>(22)</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>20</td>
<td>(22)</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>6</td>
<td>(7)</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>5</td>
<td>(5)</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>5</td>
<td>(5)</td>
</tr>
<tr>
<td>Acinetobacter baumanii complex</td>
<td>3</td>
<td>(3)</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>2</td>
<td>(2)</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>(9)</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>50</td>
<td>(12)</td>
</tr>
</tbody>
</table>
Invasive fungal (IFI) and viral infections

Table 4. Proven and Probable Invasive Fungal Infections in 444 Hematopoietic Cell Transplant Recipients

<table>
<thead>
<tr>
<th>Fungal Organisms</th>
<th>N=53</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>18</td>
<td>(34)</td>
<td></td>
</tr>
<tr>
<td>Aspergillus</td>
<td>17</td>
<td>(32)</td>
<td></td>
</tr>
<tr>
<td>Mucorales</td>
<td>7</td>
<td>(13)</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis jiuroveci</td>
<td>3</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>Exophiala</td>
<td>2</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>Alternaria</td>
<td>1</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>53</td>
</tr>
</tbody>
</table>

Table 5. Viral Infections in 444 Hematopoietic Cell Transplant Recipients (n = 187)

<table>
<thead>
<tr>
<th>Virus</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus infection</td>
<td>154</td>
<td>(82)</td>
</tr>
<tr>
<td>Viremia only</td>
<td>148</td>
<td>(86)</td>
</tr>
<tr>
<td>Human herpes virus-6</td>
<td>21</td>
<td>(11)</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>18</td>
<td>(10)</td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>13</td>
<td>(7)</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>13</td>
<td>(7)</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>12</td>
<td>(6)</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>10</td>
<td>(5)</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>8</td>
<td>(4)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>6</td>
<td>(3)</td>
</tr>
<tr>
<td>Influenza B virus</td>
<td>3</td>
<td>(2)</td>
</tr>
</tbody>
</table>

• CMV most common virus (35%, 154 patients)
  ➢ Viral DNAemia (96%)
• Respiratory viruses (11%, 49)
  ➢ Of 49 RSV+ patients, 6 (12%) died
• VZV (3%, 13 patients)

53 IFI (18 probable, 35 proven) in 48 (11%) pts
• Median time for IFI = 167d
• Isolates: 18 (yeast), 32 (mold), 3 (PJP)
• Median time from Dx IFI to death = 29d
Patient outcomes

Table 6. Outcomes in 444 Hematopoietic Cell Transplant Recipients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to engraftment, days</td>
<td>12</td>
<td>(0–101)</td>
</tr>
<tr>
<td>Graft-versus-host disease requiring treatment</td>
<td>336</td>
<td>(76)</td>
</tr>
<tr>
<td>Death</td>
<td>231</td>
<td>(52)</td>
</tr>
<tr>
<td>Death from underlying disease</td>
<td>102</td>
<td>(44)</td>
</tr>
<tr>
<td>Death from infection</td>
<td>49</td>
<td>(21)</td>
</tr>
<tr>
<td>Autopsy performed</td>
<td>24</td>
<td>(5)</td>
</tr>
<tr>
<td>Autopsy evidence of fungal infection</td>
<td>4</td>
<td>(1)</td>
</tr>
</tbody>
</table>

- Transfer to ICU (32%, 162 pts)
  - 122 pts (75%) ultimately died
- 86% patients requiring ventilation died
- 69% patients requiring dialysis died

↑↑ Infection-related morbidity & mortality!

Clin Infect Dis 2017; 44: 457
Theme #2: Net immunosuppression

- Net state of immunosuppression affects infection risk
  - Immunosuppressive therapy (IST)
    • Type, dose, duration
  - Presence or absence of leukopenia
    • Neutropenia, lymphopenia
  - Amount and type of previous therapy
    • Chemotherapy, antimicrobial agents
  - Mucocutaneous-barrier integrity
    • CVL, urinary catheters, drains
  - Underlying host factors
    • Disease
    • Immunodeficiency (acquired or inherited)
    • Metabolic conditions (malnutrition, hyperglycemia)
    • Alterations to the microbiome
  - Presence of immunomodulatory pathogens
    • Example: CMV, EBV
Theme #3: Opportunistic infections are fairly predictable in transplant patients
Solid Organ Transplantation (SOT)

Sources of infection

- Donor-Derived
- Recipient-Derived

NOSOCOMIAL TECHNICAL DONOR/RECIPIENT

Activation of Latent Infections, Relapsed, Residual, Opportunistic Infections

COMMUNITY ACQUIRED

TRANSPLANTATION

DYNAMIC ASSESSMENT OF INFECTIOUS RISK

<4 WEEKS

1-6 MONTHS

>6 MONTHS

Common Infections in Solid Organ Transplantation Recipients

- Antimicrobial-resistant species:
  - MRSA
  - VRE
  - Candida species (non-albicans)
  - Aspiration
  - Line infection
  - Wound infection
  - Anastomotic leaks/ischemia
  - C. difficile colitis

- Donor-Derived (Uncommon):
  - HSV, LCMV, rabies, West Nile

- Recipient-Derived (colonization):
  - Aspergillus, Pseudomonas

- With PCP and antiviral (CMV, HBV) Prophylaxis:
  - BK Polyomavirus
  - Nephropathy
  - C. difficile colitis
  - Hepatitis C virus
  - Adenovirus, influenza
  - Cryptococcus neoformans
  - M. tuberculosis

- Anastomotic complications

- Without Prophylaxis Add:
  - Pneumocystis
  - Herpesviruses (HSV, VZV, CMV, EBV)
  - Hepatitis B virus
  - Listeria, Nocardia, Toxoplasma
  - Strongyloides, Leishmania, T. cruzi

- Community Acquired Pneumonia
  - Urinary Tract Infection
    - Aspergillus, Atypical mycobacteria, Nocardia
    - Late Viral:
      - CMV (Colitis/Retinitis)
      - Hepatitis (HBV, HCV)
      - HSU encephalitis
    - Community acquired (SARS, West Nile)
    - JC polyomavirus (PML)
    - Skin Cancer, Lymphoma (PTLD)

Allogeneic Hematopoietic Cell Transplantation

Phase I: Pre-engraftment
- Graft-versus-host-disease: Acute
- Neutropenia, barrier breakdown (mucositis, central venous access devices)

Phase II: Post-engraftment
- Impaired cellular and humoral immunity; NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire

Phase III: Late Phase
- Impaired cellular and humoral immunity; B cell & CD4 T cell numbers recover slowly and repertoire diversifies

Bacterial
- Gram negative bacilli
- Gram positive organisms
- Gastrointestinal Streptococci species
- Encapsulated bacteria

Viral
- Herpes simplex virus
- Respiratory and enteric viruses
- Cytomegalovirus (Seasonal/intermittent)
- Varicella Zoster virus
- Other viruses eg. HHV
- EBV PTLD

Fungal
- Aspergillus species
- Candida species
- Aspergillus species
- Pneumocystis

Day 0
Day 15–45
Day 100
Day 365 and beyond

More common
Less common

Bone Marrow Transplant 2009; 44: 457
Infections in immunocompromised patients

- Common themes across immunocompromised patients
- **Invasive fungal infection (IFI)**
- DNA viruses: Cytomegalovirus (CMV)
- Respiratory viruses
Invasive fungal infection (IFI)

Aspergillus fumigatus

Mucor
Host immune response against *Aspergillus*
Host immune recovery is needed to ensure best patient outcomes

84 hematologic malignancy patients with *Fusarium*

Cancer 2003; 98: 315
Combination antifungal therapy does not significantly improve patient outcomes!

<table>
<thead>
<tr>
<th>Antifungal Agents</th>
<th>Triazoles’ Alone (n = 252)</th>
<th>Amphotericin B* Alone (n = 8)</th>
<th>Echinocandins’ Alone (n = 34)</th>
<th>Two or More Antifungal Agents (n = 220)</th>
<th>Total (n = 514)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFD diagnosis level at initiation of therapy</td>
<td>3 (1.2)</td>
<td>0</td>
<td>0</td>
<td>5 (2.3)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Proven</td>
<td>17 (6.7)</td>
<td>3 (37.5)</td>
<td>2 (5.9)</td>
<td>49 (22.3)</td>
<td>71 (13.8)</td>
</tr>
<tr>
<td>Probable</td>
<td>84 (33.3)</td>
<td>4 (50.0)</td>
<td>10 (29.4)</td>
<td>74 (33.6)</td>
<td>172 (33.5)</td>
</tr>
<tr>
<td>Possible</td>
<td>148 (58.7)</td>
<td>1 (12.5)</td>
<td>22 (64.7)</td>
<td>97 (41.8)</td>
<td>263 (51.2)</td>
</tr>
<tr>
<td>Suspected</td>
<td>33 (13.1)</td>
<td>0</td>
<td>5 (14.7)</td>
<td>60 (27.3)</td>
<td>98 (19.1)</td>
</tr>
</tbody>
</table>

Data are n (%).
* Fluconazole, itraconazole, voriconazole.
† Amphotericin B, liposomal amphotericin B.
‡ Caspofungin, micafungin
Infections in immunocompromised patients

• Common themes across immunocompromised patients
• Invasive fungal infection (IFI)
• **DNA viruses: Cytomegalovirus (CMV)**
• Respiratory viruses
CMV during allogeneic HCT

- Reactivation (DNAemia) → Infection
- Primary (or secondary) infection
  - Pneumonitis, cystitis, enteritis, hepatitis
  - Chorioretinitis, meningoencephalitis
- Immunomodulation
  - Graft failure or rejection
  - Bacterial and fungal superinfection
  - Co-viral infection (ADV, EBV, HHV-6)
  - EBV+ PTLD
  - GvHD
- Organ dysfunction
  - Direct viral organ involvement
  - Secondary to anti-viral therapy (GCV, CDV, FOS)

**Rate of increase in CMV load for 18 allogeneic BMT recipients**

![Graph showing rate of increase in CMV load over time.](image)

Cancer Letters 2014; 342 : 1
BMT 2010; 16: 1309
J Infect Dis 2002; 185: 273
Immune response to CMV
**Risk factors**

- D/R seropositivity
- D/R HLA mismatch
- Ex vivo T-cell depletion
- Serotherapy (ATG, αCD52)
- Aberrant / absent immune reconstitution
- Lymphopenia
- Co-DNA virus
- Acute rejection
- Acute GvHD
- Chronic GvHD
- Immunosuppression (T-cell directed)

**Clinical Manifestations**

- Meningoencephalitis
- Stomatitis/Eosophagitis
- Pneumonitis
- Hepatitis
- Cystitis/Nephritis
- Myocarditis
- BM Suppression
- Colitis/Enteritis
- DNAemia
- Rash
- Retinitis

**Post-transplant outcomes**

- (+) Graft failure
- (+) GvHD
- (-) Immune Reconstitution
- (+) Post-transplant lymphoproliferation

↑ Transplant-related morbidity

↑ Transplant-related mortality

↓ Overall Survival

*Blood* 2015;126: 2274
*Cancer Letters* 2014; 342 : 1
*Curr Opin Infect Dis* 2017; 30: 377
Efficacy of pre-emptive therapy in the transplant setting

↑ Asymptomatic infection
↓ CMV disease
↓ CMV-associated death

Figure 1. Rate, morbidity and mortality of HCMV infection in solid organ transplant recipients (SOTR) and hematopoietic stem cell transplant recipients (HSCTR) before and after introduction of pre-emptive therapy.

*Historical data [4,6,130,131,132,133,134].

†Data from patients (272 SOTR and 325 adult and pediatric HSCTR, excluding donor seronegative/recipient seronegative patients) transplanted at our institution in the period 2003–2014 undergoing DNAemia-guided pre-emptive therapy [7,50,65,135,136].
# Systemic antiviral therapies: A limited armamentarium

<table>
<thead>
<tr>
<th>Property</th>
<th>Acyclovir (ACV)</th>
<th>Ganciclovir (GCV)</th>
<th>Foscarnet (FOS)</th>
<th>Cidofovir (CDV)</th>
<th>Brincidofovir (CMX-001)</th>
<th>Other Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activity:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ADV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>+</td>
</tr>
<tr>
<td>- BK</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>+</td>
</tr>
<tr>
<td>- CMV</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>- EBV</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>- HHV6</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>- HSV / VZV</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>IV/PO</td>
<td>IV/PO</td>
<td>IV</td>
<td>IV</td>
<td>IV/PO</td>
<td>IV/PO</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>DNA polymerase inhibition (nucleoside analogues except FOS)</td>
<td>Variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CNS penetration</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Renal</td>
<td>BM&gt;&gt;Renal</td>
<td>Renal</td>
<td>Renal</td>
<td>Hepatic, GI</td>
<td>Variable</td>
</tr>
</tbody>
</table>

**Efficacy** ~ 40%

**Toxicity** ~ 60%

**Resistance!**

LRV = Letermovir
MBV = Maribavir
Ritux = Rituximab

*J Pharmaceut Biopharm Analysis* 2018; 147: 400
Infections in immunocompromised patients

• Common themes across immunocompromised patients
• Invasive fungal infection (IFI)
• DNA viruses: Cytomegalovirus (CMV)
• **Respiratory viruses**
Respiratory: AdV, CorV, Flu, MPV, PIV, RhV, RSV

Risk factors
URTI → LRTI

Older age
Co-morbidity score
HLA mismatch
UCB > BM > PB
Myeloablation
Pre-engraftment
Neutro / lymphopenia
GvHD
Steroids
Pulmonary co-infections
Oxygen requirement at Dx

Respiratory viruses
CorV = Corona
MPV = Metapneumo
PIV = Parainfluenza
RhV = Rhino

Post-Transplant Outcomes

↑ TRM (Lung injury)
-- Alveolar damage
-- ARDS / BOOP
-- Respiratory failure

↑ TRM (Infection)
-- Bacterial superinfection

↓ Overall survival
Anti-respiratory viral Rx: Limited drugs, poor efficacy

VIRUS

- Viral attachment and entry
- Fusion and penetration
- Uncapping
- Early protein synthesis
- Nucleic acid synthesis
- Late protein synthesis and processing
- Packaging and assembly
- Viral release

HUMAN CELL

- Blocked by palivizumab (RSV)
- Blocked by M2 inhibitors (Influenza)
- Blocked by ribavirin (RSV)
- Blocked by neuraminidase inhibitors (Influenza)

This diagram illustrates the various stages of viral infection and the mechanisms by which anti-respiratory viral drugs act. The drugs mentioned include:

- Oseltamivir
- Zanamivir
- Amantadine
- Ribavirin
- Palivizumab
- DAS181

The table provides a more detailed view of the drugs in development across different phases:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Drug Name</th>
<th>Phase</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>GS-5806 (Prasatovir)</td>
<td>GILEAD</td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>ALS-8176</td>
<td>ALIOS</td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td>ALN-RSV01</td>
<td>ALNYLAM</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>MED8897 mAb</td>
<td>MEDIMMUNE</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>DAS181 (Fludase)</td>
<td>ANSUN</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Zanamivir</td>
<td>GlaxoSmithKline</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Favipiravir</td>
<td>TOYOMA CHEMICAL</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Nitazoxanide</td>
<td>ROMARK</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Hyperimmune Immunoglobulin</td>
<td>NIH</td>
<td></td>
</tr>
<tr>
<td>Anti-Influenza</td>
<td>Immune Plasma</td>
<td>NIH</td>
<td></td>
</tr>
<tr>
<td>Laninamivir</td>
<td>BIOTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS181</td>
<td>(Fludase)</td>
<td>ANSUN</td>
<td></td>
</tr>
<tr>
<td>MHAA4549A mAb</td>
<td>GENENTECH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR6261 mAb</td>
<td>JANSSEN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MED18852 mAb</td>
<td>MEDIMMUNE</td>
<td></td>
<td></td>
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<tr>
<td>TCN-032 mAb</td>
<td>THERAQUENCE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vapendavir</td>
<td>BIOTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omalizumab (Xolair)</td>
<td>GENENTECH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References:
- Blood 2016; 127: 2682
Therapy-associated infections

- **Biologic therapies**
  - Hematopoietic cell graft manipulation
  - Cell therapies: Chimeric antigen receptor (CAR) T cells
Biologic Rx: Mechanisms of action

- Anti-TNF
- Anti-IL-12/23 (anti-p40)
- Abatacept
- Anti-IL-17

TNF

Mononuclear phagocytes such as DCs

IL-23
IL-6

CD28

IL23R-expressing cells (e.g., CD4+)

Stabilized T\textsubscript{H}17 cells

IL-17
IFN-γ

Neutrophilia
Tissue repair
Antimicrobial defense
Other functions

- Anti-CD20

CD20

B cell
Plasma cell
Autoantibody synthesis

Nat Med 2015; 21: 730
Consideration #1: Context is everything

- Despite its defined mechanism of action, a biologic therapy may have different effects depending upon the clinical context that it is being used
Consideration #2: Exchanging problems

Inhibitory receptors involved in “T-cell exhaustion”

Programmed cell death protein 1 (PD-1) immunologic checkpoint

Cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) immunologic checkpoint

Inhibitory receptors involved in “T-cell exhaustion”

Programmed cell death protein 1 (PD-1) immunologic checkpoint

Cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) immunologic checkpoint
Check-point blockade: Immune-related AEs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iplimunab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high micro-satellite instability or mismatch-repair deficiency</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high micro-satellite instability or mismatch-repair deficiency</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Non–small-cell lung cancer, urothelial carcinoma</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Merkel-cell carcinoma, urothelial carcinoma</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>Urothelial carcinoma</td>
</tr>
</tbody>
</table>

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.
### Serious infection rates* for RA patients Rx biologics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Serious infection incidence rate: patients with events per 100 patient-years (95% CI)</th>
<th>Number of trials</th>
<th>Number of patients</th>
<th>Cumulative exposure (patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab</td>
<td>5.45</td>
<td>13</td>
<td>5,547</td>
<td>4,522</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>5.04</td>
<td>18</td>
<td>6,570</td>
<td>7,095</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>7.59</td>
<td>5</td>
<td>3,212</td>
<td>1,339</td>
</tr>
<tr>
<td>Etanercept</td>
<td>4.06</td>
<td>17</td>
<td>7,141</td>
<td>13,037</td>
</tr>
<tr>
<td>Infliximab</td>
<td>6.11</td>
<td>11</td>
<td>4,592</td>
<td>3,555</td>
</tr>
<tr>
<td>Golimumab</td>
<td>5.31</td>
<td>6</td>
<td>2,820</td>
<td>1,648</td>
</tr>
<tr>
<td>All TNF inhibitors</td>
<td>4.90</td>
<td>57</td>
<td>26,492</td>
<td>29,429</td>
</tr>
<tr>
<td>Abatacept</td>
<td>3.04</td>
<td>11</td>
<td>5,953</td>
<td>6,070</td>
</tr>
<tr>
<td>Rituximab</td>
<td>3.72</td>
<td>8</td>
<td>2,926</td>
<td>2,687</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>2.93</td>
<td>14</td>
<td>5,671</td>
<td>12,664</td>
</tr>
</tbody>
</table>

*number of unique patients with events per 100 patient-years exposure

*Nat Rev Rheumatol 2017; 13: 399*
### Biologic Rx: Infectious sequelae

Not enough published experience!

Therapies are being applied clinically faster than published experience on their associated infection risk!

---

**Table 1**

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Pediatric Indications</th>
<th>Associated Infections in Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>—</td>
<td>—</td>
<td>URI, pneumonia, abscesses, varicella zoster, histoplasmosis</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>CD, UC</td>
<td>Listeria meningitis, cutaneous blastomycosis, <em>Mycobacterium avium</em></td>
</tr>
<tr>
<td></td>
<td>Adalimumab</td>
<td>JIA, CD, UC</td>
<td>Purpura fulminans</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>Polyarticular JIA, psoriasis</td>
<td></td>
</tr>
<tr>
<td>IL-1</td>
<td>Anakinra</td>
<td>NOMID and CAPS, systemic JIA</td>
<td>Visceral leishmaniasis, varicella, labial herpes, URI</td>
</tr>
<tr>
<td></td>
<td>Canakinumab</td>
<td>JIA, FMF, hyperimmunoglobulin D, TRAPS</td>
<td>URI, nasopharyngitis</td>
</tr>
<tr>
<td>IL-2</td>
<td>Basiliximab</td>
<td>Organ transplant rejection prophylaxis</td>
<td>—</td>
</tr>
<tr>
<td>IL-6</td>
<td>Tocilizumab</td>
<td>Polyarticular and systemic JIA</td>
<td>URI, pneumonia, bronchitis, cellulitis, varicella</td>
</tr>
<tr>
<td>IL-12/23</td>
<td>Ustekinumab</td>
<td>UC</td>
<td>—</td>
</tr>
<tr>
<td>CD28</td>
<td>Abatacept</td>
<td>JIA</td>
<td>—</td>
</tr>
<tr>
<td>a-4 integrin</td>
<td>Vedolizumab</td>
<td>Off-label: refractory inflammatory bowel disease</td>
<td>URI, cellulitis</td>
</tr>
<tr>
<td>JAK</td>
<td>Tofacitinib</td>
<td>Off-label: GVHD, JAK/STAT pathway mutations, alopecia areata</td>
<td>Viral infection (BK, CMV, adenovirus), bacterial infection</td>
</tr>
<tr>
<td>CD20</td>
<td>Rituximab</td>
<td>Off-label: PTLD, EBV-related HLH, glomerular diseases, CNS-inflammmatory diseases, Burkitt lymphoma</td>
<td>Viral infection (varicella, CMV, adenovirus), pneumonia, empyema, mastoiditis, <em>Salmonella enteritis</em>, candidiasis</td>
</tr>
</tbody>
</table>

*Infect Dis Clin N Am 2018: 32; 225*
Therapy-associated infections

- Biologic therapies
- **Hematopoietic cell graft manipulation**
- Cell therapies: Chimeric antigen receptor (CAR) T cells
Stem Cell Mobilization

Graft Content Matters!

Post-transplant Outcomes

Donor

Recipient

Graft failure
Acute GvHD
Chronic GvHD
Immune Reconstitution
Infection
Overall Survival
Disease-free Survival

HLA matching

Nationwide Children's
When your child needs a hospital, everything matters.

The Ohio State University
College of Medicine
Haploidentical Donor

Mobilization

Selection/Depletion

"Depletion" -Selection

―Magnetic labeling

―Magnetic separation

―Elution of the labeled cells

"Enrichment" +Selection

MACS® MicroBeads

Recipient

HLA matching

CD34 CD45RA γδT /NK αβT /CD19 CD3/CD19

Selection Depletion Selection Depletion Depletion

CliniMACS Prodigy®

TCD45RA+ αβT γδT NK Mo/φ CD19 DC Pro CD34
Implications of graft manipulation

Manipulation | Graft Content | Post-transplant Outcomes
--- | --- | ---
None | | Engraftment
Naïve CD45RA⁺ T cell depletion | | GvHD
| + Reduce immunosuppression + Reduce side effects
αβT- and B-cell depletion | | GvL
| + Reduce disease relapse
CD3⁺ and CD19⁺ depletion | | Immune reconstitution
| + DC recovery + NK recovery + δγT recovery
CD34⁺ selection | | Infection + Antiviral host defense
Immune reconstitution
| Post-transplant lymphoproliferative disease (PTLD)
αβT and B-cell (CD19) depletion

Current immune cell depletion strategies

- Depletion of CD19 and TCR-αβ T cells
- Depletion of naive T cells
- Depletion of committed progenitors

αβT-cell and CD19-cell depletion

No post-transplant immunosuppression!
Haploidentical PBSC $\alpha\beta$T-cell and CD19 depletion

**Key Points**
- Children with AL given haplo-HSCT after $\alpha\beta$ T- and B-cell depletion are exposed to a low risk of acute and chronic GVHD and NRM.
- The leukemia-free, GVHD-free survival of patients given this type of allograft is comparable to that of HLA-matched donor HSCT recipients.

N=80 (2 PGF)
30% CI Gr 1 skin aGvHD
5y GRFS=71%

N=23 (4 PGF, rescued)
3 Gr 1 skin aGvHD
No liver/GI aGvHD, no cGvHD

**Transplantation**

**Outcome of children with acute leukemia given HLA-haploidentical HSCT after $\alpha\beta$ T-cell and B-cell depletion**

Franco Locatelli,1,2 Pietro Merli,1 Daria Pagliara,1 Giuseppina Li Pira,1 Michela Falco,2 Daniela Pende,4 Roberto Rondelli,5 Barbarella Lucarelli,1 Letizia Pomponia Brescia,1 Riccardo Masetti,6 Giuseppe Maria Milano,7 Valentina Bertaina,1 Mattia Algeri,1 Rita Maria Pinto,1 Luisa Strocchio,1 Raffaella Mezza,4 Lavinia Grapulin,6 Rupert Handgretinger,7 Alessandro Moretta,8 Alice Bertaina,1,4 and Lorenzo Moretta5,9

1Department of Pediatric Hematology and Oncology, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Bambino Gesù, Rome, Italy; 2Department of Pediatric Science, Università di Pavia, Pavia, Italy; 3Dipartimento di Ricerca e Diagnosi, UOC Immunologia Clinica e Sperimentale, Istituto di Ricovero e Cura a Carattere Scientifico Spallanzani, Rome, Italy; 4UOC Immunologia, Ospedale Policlinico San Martino, Genoa, Italy; 5Department of Pediatrics, Sant’Orsola Hospital, University of Bologna, Bologna, Italy; 6Department of Radiotherapy, Policlinico Umberto I, Rome, Italy; 7Department of Pediatric Hematology and Oncology, Children’s University Hospital, University of Tuebingen, Tuebingen, Germany; 8Dipartimento di Medicina Sperimentale e Centro di Eccellenza per la Ricerca Biomedica, Università di Genova, Genova, Italy; and 9Immunology Research Area, IRCCS Ospedale Bambino Gesù, Rome, Italy

**CI** = cumulative incidence, **PGF** = primary graft failure

**GRFS = cGvHD-free, relapse-free survival**

**Blood 2017; 130: 677**

**HLA-haploidentical stem cell transplantation after removal of $\alpha\beta$+ T and B cells in children with nonmalignant disorders**

Alice Bertaina,1 Pietro Merli,1 Sergio Rutella,1,2 Daria Pagliara,1 Maria Ester Bernardo,1 Riccardo Masetti,3 Daniela Pende,4 Michela Falco,5 Rupert Handgretinger,7 Francesca Moretta,1 Barbarella Lucarelli,1 Letizia P. Brescia,1 Giuseppina Li Pira,1 Manuela Testi,7 Caterina Cancrini,8 Nabil Kabbara,9 Rita Carsetti,1 Andrea Finocchi,8 Alessandro Moretta,1,9 Lorenzo Moretta,5 and Franco Locatelli1,11

1Department of Pediatric Hematology and Oncology, Istituto di Ricovero e Cura a CarattereScientifico Bambino Gesù Children’s Hospital, Rome, Italy; 2Department of Medical Sciences, Catholic University Medical School, Rome, Italy; 3Department of Pediatrics, Sant’Orsola Hospital, University of Bologna, Bologna, Italy; 4Istituto di Ricovero e Cura a CarattereScientifico Università San Martino-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy; 5Istituto di Ricovero e Cura a CarattereScientifico Gianna Gaslini, Genoa, Italy; 6Children’s University Hospital, University of Tuebingen, Tuebingen, Germany; 7Laboratory of Immunogenetics and Transplant Biology, Istituto Mediterraneo di Ematologia Foundation at Tor Vergata University, Rome, Italy; 8University Department of Pediatrics, Istituto di Ricovero e Cura a CarattereScientifico Bambino Gesù Children’s Hospital, University of Rome Tor Vergata, Rome, Italy; 9Pediatric Hematology Oncology Division, Rafic Hariri University Hospital, Beirut, Lebanon; 10Dipartimento di Medicina Sperimentale e Centro di Eccellenza per la Ricerca Biomedica, Università di Genova, Genova, Italy; and 11Department of Pediatrics, University of Pavia, Pavia, Italy

**Blood 2014; 124: 822**
182 patients with malignant (n=114) or nonmalignant (n=68) diseases transplanted using either matched unrelated (n=124) or haploidentical (n=58) donors

Cumulative incidence of CMV and EBV viremia: 51% and 33%, respectively

CMV risk: Acute GvHD grades II-IV, D−/R+ serology, and malignant disease
  - CMV disease: 6%

EBV risk: Acute GvHD grades II-IV
  - EBV disease: 0.5%

TCRα/β and CD19 depletion associates with significant CMV and EBV viremia, which don’t affect survival
High Incidence of Early Human Herpesvirus-6 Infection in Children Undergoing Haploidentical Manipulated Stem Cell Transplantation for Hematologic Malignancies

Katia Perruccio¹,⁴, Luisa Sisinni², Antonio Perez-Martinez³, Jaime Valentin³, Ilaria Capolsini¹, Maria Speranza Massei¹, Maurizio Caniglia¹, Simone Cesaro⁴

- **38 pediatric patients received myeloablative conditioning regimens and 2 different types of ex vivo graft manipulation:**
  - CD34+ selection and regulatory T cell/conventional T cell infusion (n=13) and CD45RA T cell depletion (n=25)

- **Antiviral prophylaxis:** ACV (n=33) and foscarnet (n=5)

- All patients experienced early post-transplant HHV6-emia
  - **9 patients (24%) developed symptomatic limbic encephalitis**
  - All patients responded to antiviral treatment, and none died of infection, although 2 experienced long term neurologic sequelae (22%)
Therapy-associated infections

- Biologic therapies
- Stem cell graft manipulation
- **Cell therapies: Chimeric antigen receptor (CAR) T cells**
Infectious complications of CD19-targeted chimeric antigen receptor–modified T-cell immunotherapy

Joshua A. Hill,1,2 Daniel Li,3 Kevin A. Hay,4,5 Margaret L. Green,1,2 Sindhu Cherian,6 Xueyan Chen,6 Stanley R. Riddell,1,4 David G. Maloney,1,4 Michael Hoeckh,1,2 and Cameron J. Turtle1,4

1Department of Medicine, University of Washington, Seattle, WA; 2Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA; 3Juno Therapeutics, Seattle, WA; 4Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; 5Department of Medicine, University of British Columbia, Vancouver, BC, Canada; and 6Department of Laboratory Medicine, University of Washington, Seattle, WA

CD19 CAR T cell therapy for relapsed refractory B-cell malignancies

• Infections within first 90 days post-CAR T cell therapy
• 133 patients (median 54y, 20-73y): ALL (47), CLL (24), NCH (62)
• 50 (38%) prior autologous or allogeneic HCT
• 43 infections (30 pts, 23%) within 28d post CART (median 6d to infx)
• Infx density (infections/100d at risk): 1.19 (D0-28) vs. 0.67 (D29-90)
• ↑D28 ID risk: ALL, ≥4 regimens, higher CART dose (2x10⁷ cells/kg)
• IFI (6 pts, 5%) and life-threatening (5 pts, 4%)
• MVA ↑ Infection risk: Severity of cytokine release syndrome (CRS)

Blood 2018; 131: 121
Anti-microbial cellular therapies

• Virus-specific T cells (VSTs)
Virus-specific T lymphocytes (VSTs)

**A** DIRECT SELECTION
Capture antibodies/multimers bind and select out T cells recognizing relevant antigen

**B** EX VIVO EXPANSION
APC only stimulates T-cell recognizing antigen

**C** GENETIC MODIFICATION
Virus-containing chimeric antigen receptor transgene transduces cells, redirecting their activity

SFCs = IFN-γ-producing spot-forming cells

**LEGEND**
- γTCR
- CAR
- IFN-γ capture antibody
- Multimer
- EBV
- ADV

*Blood* 2016; 127: 3331

*Sci Transl Med* 2014; 6: 242ra83
Multi-virus specific T-cells (VSTs)

Off-the-Shelf Virus-Specific T Cells to Treat BK Virus, Human Herpesvirus 6, Cytomegalovirus, Epstein-Barr Virus, and Adenovirus Infections After Allogeneic Hematopoietic Stem-Cell Transplantation


- **38 patients with 45 infections** [Rx single infusion of VSTs in a phase II clinical trial]
  - **Cumulative complete/partial response (CR/PR) rate = 92%** (95% CI, 78.1-98.3%)
    - By virus: 100% BKV (n=16), 94% CMV (n=17), 71% ADV (n=7), 100% EBV (n=2), and 67% HHV-6 (n=3)
  
- **Clinical benefit:** 31 patients single viral infection, 7 patients multiple viral infections
- **Safety:** 2 occurrences de novo Gr 1 GvHD

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**J Clin Oncol 2017; 35: 3547**
CMV-specific VSTs: Recouping cost?

D28 VSTs prevented CMV DNAemia, were safe (no GvHD), and ↓ need for antiviral therapy

TRANSPLANTATION

Donor-derived CMV-specific T cells reduce the requirement for CMV-directed pharmacotherapy after allogeneic stem cell transplantation

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Key Points

• Infusion of CMV-specific T cells early posttransplant does not increase acute or chronic graft-versus-host disease.
• CMV-specific T cells early posttransplant reduce the need for pharmacotherapy without increased rates of CMV-related organ damage.

We investigated the use of adoptively transferred donor-derived cytomegalovirus (CMV) specific cytotoxic T lymphocytes (CTL) as immune reconstitution postallogeneic transplant in a phase 2 study. Fifty patients were infused with a single dose of 2 × 10⁸ cells/m² after day 28 post-transplant. Twenty-six patients reactivated CMV posttransplant (only 5 post-CTL infusion) and 9 required therapy with ganciclovir or foscarin (only 1 post-CTL infusion). There was 1 case of fatal CMV disease, attributable to high levels of antithymocyte globulin at the time of T cell infusion. We compared the patients in the phase 2 study with a group of contemporaneous controls also treated at the trial centers. There was no increase in acute or chronic graft-versus-host disease attributable to CTL infusion; overall and progression-free survival were similar in both groups. There was a reduction in the percentage of patients who required CMV directed antiviral therapy (17% vs 36%, P = .01) and in the total number of treatment days in the cohort receiving CTL (3.4 days vs 8.9 days, P = .03) without a reduction in CMV reactivation rates. We postulate that adoptively transferred cells are able to expand in response to viral antigen, limit viral replication, and prevent progression to tissue infection. This study was registered on the Australian Clinical Trial Registry as #ACTRN12605000213640 and #ACTRN12607000224426. (Blood. 2013;121(18):3745-3758)
Will Post-Transplantation Cell Therapies for Pediatric Patients Become Standard of Care?

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YES

Biol Blood Marrow Transplant
2015; 21: 402
Summary

- The incidence of immunocompromised patients continues to increase, namely due to the rise in autoimmune diseases and their associated biologic therapies.

- Opportunistic infections are the hallmark infection in the immunocompromised patient. However, they are uncommon relative to other more common infections.

- Novel therapies, including cell therapy, can potentially transform the immunocompromised landscape by potentially treating underlying immunodeficiencies and by decreasing transplant-related morbidity and mortality.
Questions

THANK YOU!