Opportunistic infections in the immunocompromised host

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Host Defense Program

Blood and Marrow Transplant Program

Hematology/Oncology/BMT and Infectious Diseases

Nationwide Children's Hospital

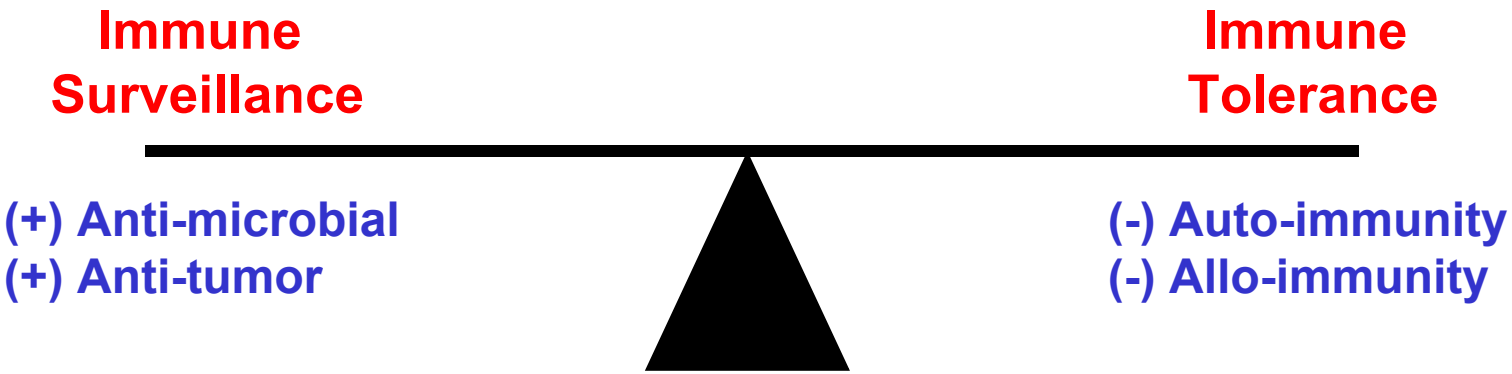
The Ohio State Comprehensive Cancer Center

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

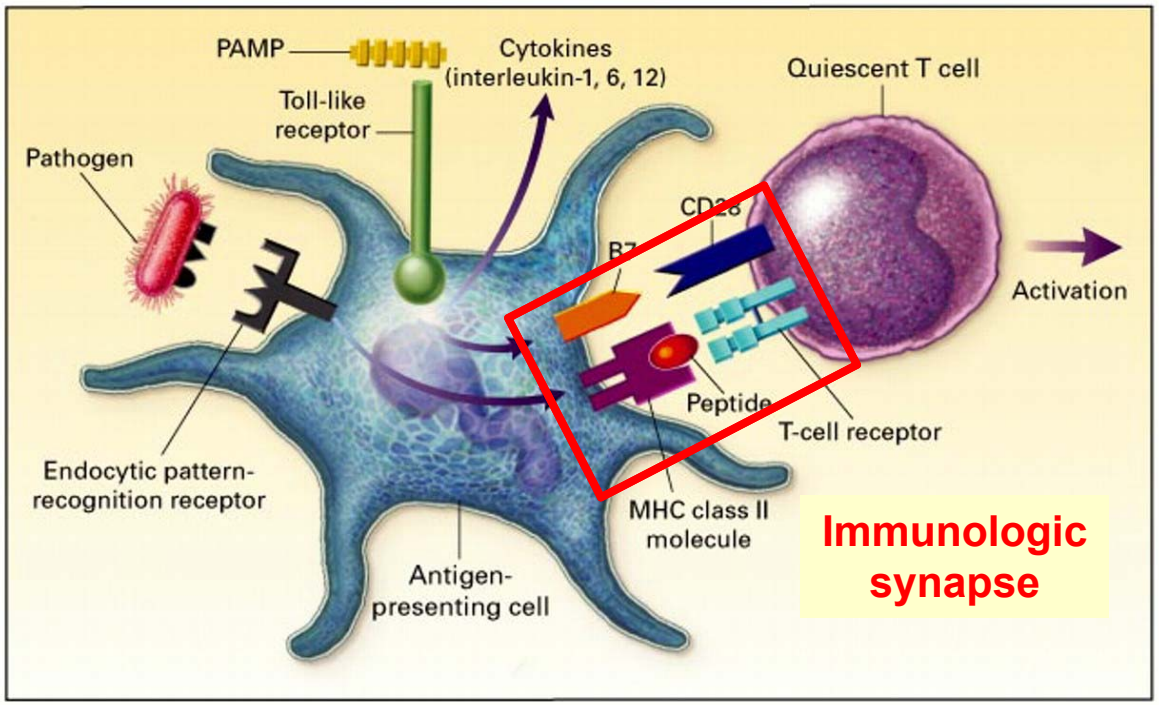
Immunity: Functional homeostasis



Hallmarks of functional immune response:

1. Detection
2. Activation
3. Recruitment/Mobilization
4. Redundancy
5. Memory
6. Elimination
7. Regulation

Cellular Immunity: Innate and adaptive arms

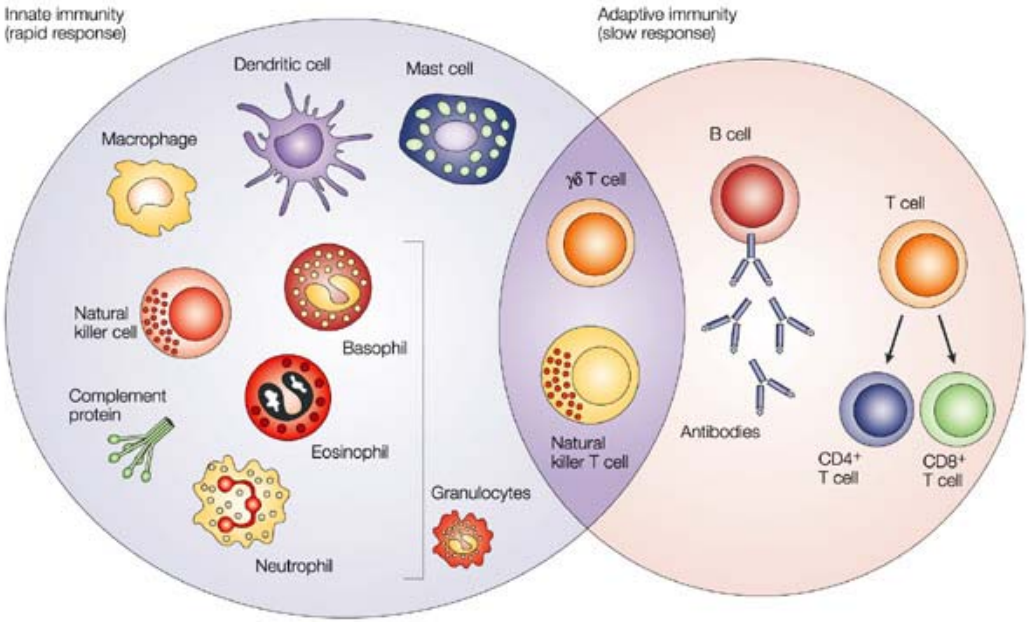


PAMP = pathogen-associated molecular pattern
TLR = Toll-like receptor (e.g., PRR = pattern recognition receptor)

NEJM 2000; 343: 338

Cellular Immunity: Innate versus Adaptive

Innate Immunity

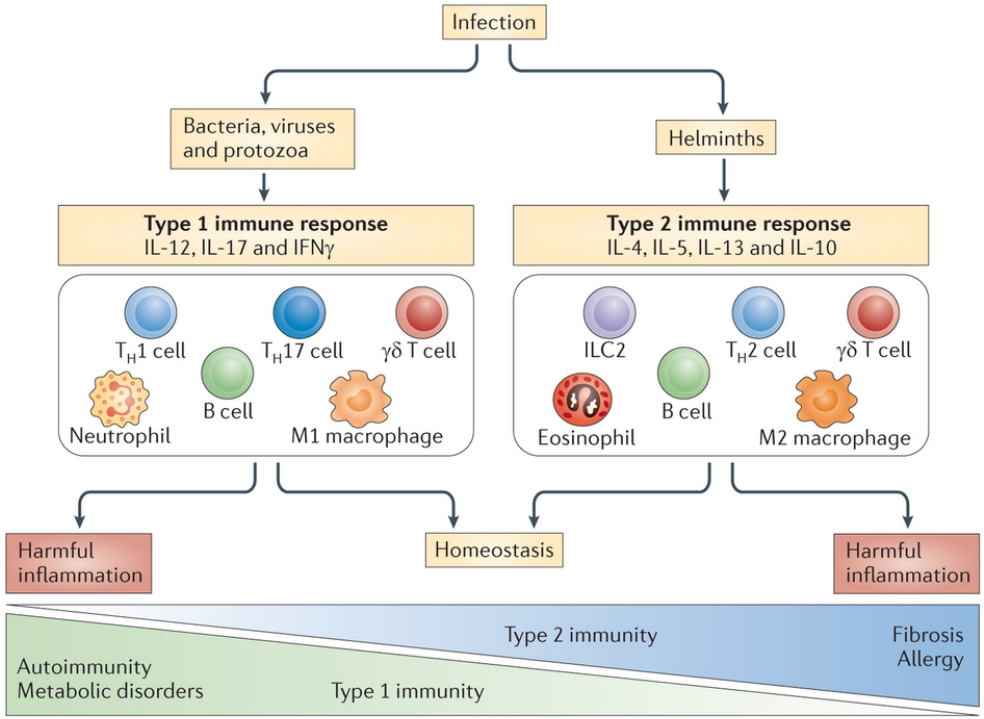


Adaptive Immunity

Minimal	Regulation	Highly regulated
Recruitment/ ER hematopoiesis	Amplification	Clonal expansion
Broad specificity	Receptor specificity	Narrow specificity
Germline-conserved	Receptor origin	Random generation
Rapid, non-specific	Speed of response	Slower, Antigen-specific
No	Memory	Yes

Nature Rev Cancer 2004; 4: 11

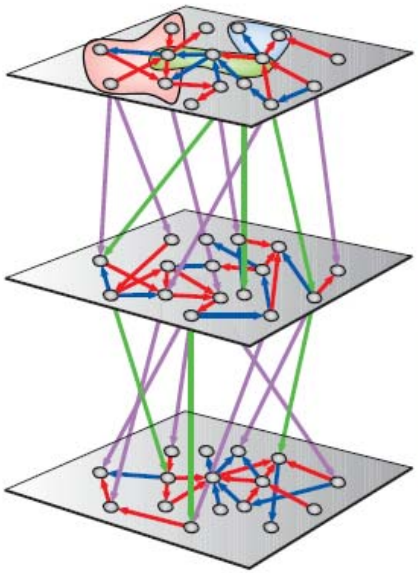
Type 1 and Type 2 Immune Responses



Simplified concept, but immune response is more complex!

Nat Rev Immunol **2013; 13: 607**

Immunity: A multi-layered social network



Network component	Social network	Immune system
Actors	Members of society	Immune-cell types
Roles	Same profession; similar age; shared interests	Shared function—e.g., early defense mechanisms; humoral immunity
Context	Family; professional; spare time	Organ; tissue; activation status
Intra-layer communication	Personal communication; e-mails; phone calls	Direct cell–cell interactions; receptor–ligand interactions
Inter-layer communication	Similar to intra-layer communication	Signaling across organs, tissues

Nature Immunol **2017; 18: 481**

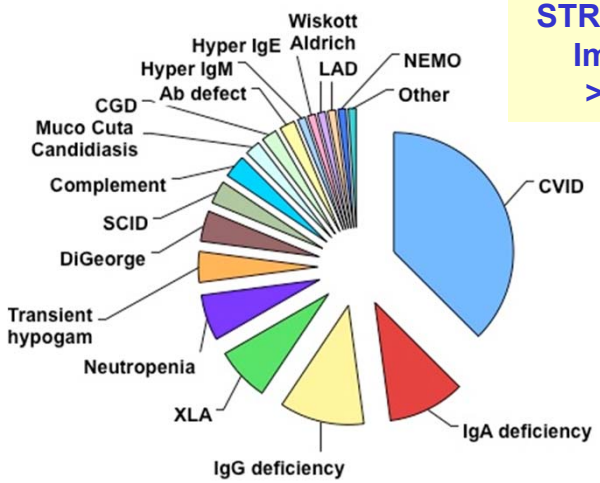
Importance of immune regulation:
Stop inflammation

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

Immune Deficiency Foundation

THINK ZEBRA! Immune Deficiency Foundation

Icahn School of Medicine at Mount Sinai

Jeffrey Modell Foundation
Curing PI. Worldwide.

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PIDs: How common are they?

- **91 total pediatric patients: 61 (67%) Ab deficiency**

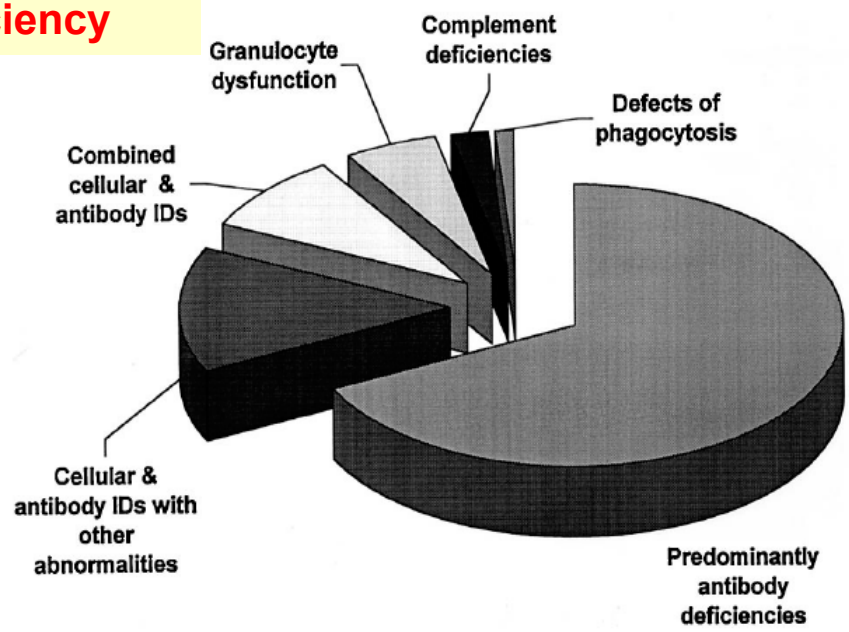

Figure 1. Relative incidence of different primary immunodeficiency disorders diagnosed in patients seen during an 8-year period in a pediatric tertiary hospital.

***Ann Allergy Asthma Immunol* 2000; 84: 25**

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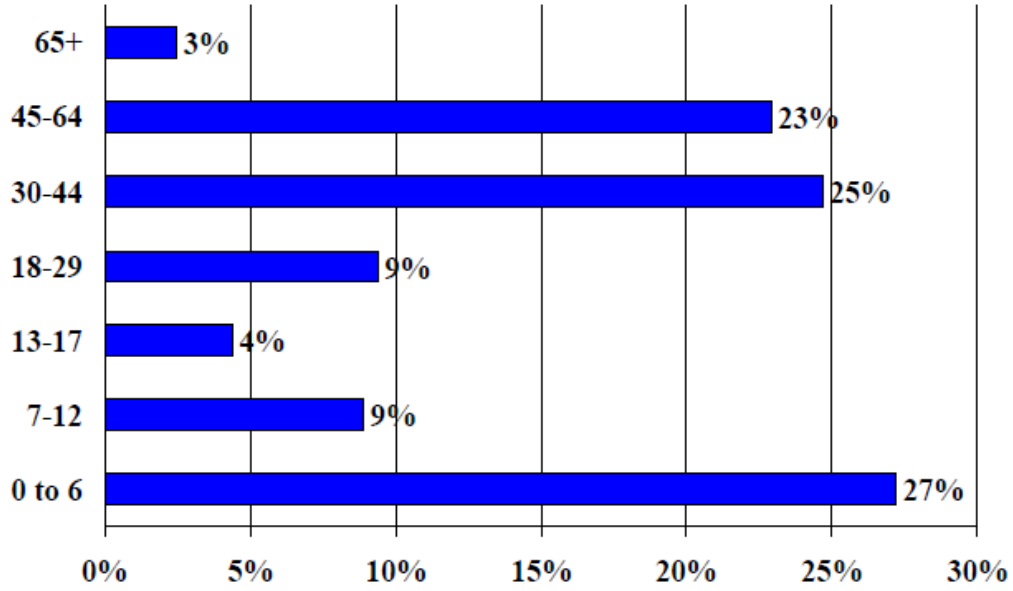
PID is not just a pediatric diagnosis!

Patient age at PID diagnosis



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

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Red flags for potential PID

Immune Deficiency Foundation

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 clears very slowly

Unusual
caused by an uncommon organism

Recurrent
keeps coming back

or if it

Runs in the Family
others in your family have had a similar susceptibility to infection

If any of these 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 ZEBRA!

In medical school, many doctors learn the saying, "when you hear hoof beats, think horses, not zebras" and are taught to focus on the likeliest possibilities when making a diagnosis, not the unusual ones. However, sometimes physicians need to look for a zebra. Patients with primary immunodeficiency diseases are the zebras of the medical world.

If you have an infection with any of these characteristics, ask your physician to THINK ZEBRA!

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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**

1,685,210 new cancer cases in 2016

American Cancer Society 2016 Report

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."

***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

Box. National Health Interview Survey Questions on Immunosuppression, 2013

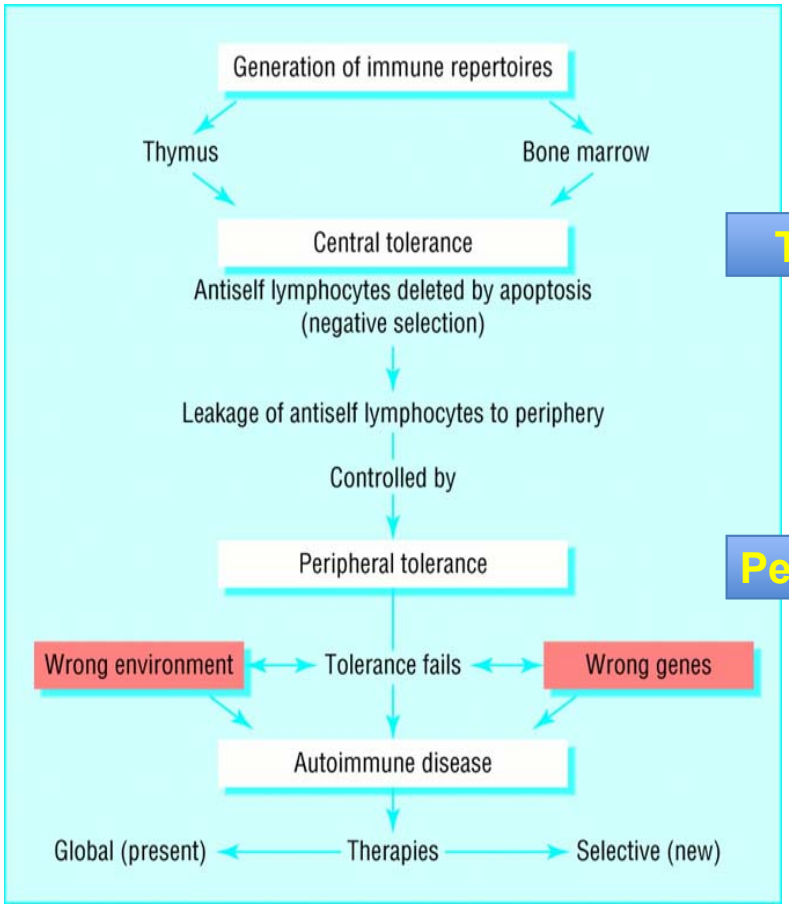
1. Have you ever been told by a doctor or other health professional that your immune system is weakened?
2. Based on what a doctor or other health professional told you, do you still have a weakened immune system?
3. During the past 6 months, have you taken prescription medication or had any medical treatments that a doctor or other health professional told you would weaken your immune system?
4. Do you currently have a health condition that a doctor or other health professional told you weakens the immune system, even without related medications or treatments?
5. Has a doctor or other health professional ever told you that your immune system is weakened because you have kidney disease, lung disease, liver disease, diabetes, poor nutrition, or general frailty?
6. Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?
7. What kind of cancer was it?
8. How old were you when your cancer was first diagnosed?
9. Earlier you said you had cancer. Did a doctor or other health professional ever tell you that your immune system is weakened because of this cancer/these cancers?
10. Has a doctor or other health professional ever told you that your immune system is weakened because you seem to get many infections and colds or that you can't seem to get over them?

Table. Self-reported Immunosuppressed Status

	No. (%) (n = 951)	Prevalence per 100 US Population, % (95% CI)
Currently immunosuppressed	951 (2.8)[a]	2.7 (2.4-2.9)
Sex		
Male	298 (31.3)	1.8 (1.5-2.1)
Female	653 (68.7)	3.5 (3.1-3.9)
Race/ethnicity[b]		
Hispanic	128 (13.5)	1.6 (1.2-1.9)
Non-Hispanic		
White	641 (67.4)	3.0 (2.7-3.4)
Black	122 (12.8)	2.3 (1.8-2.8)
Asian	29 (3.0)	1.7 (0.8-2.7)
Other	31 (3.3)	3.9 (2.0-5.9)
Age group, y (n = 951)		
18-39	182 (19.1)	1.6 (1.3-1.9)
40-49	136 (14.3)	2.3 (1.8-2.8)
50-59	281 (29.5)	4.4 (3.7-5.1)
60-69	213 (22.4)	3.9 (3.2-4.5)
70-79	101 (10.6)	3.1 (2.4-3.8)
≥80	38 (4.0)	2.5 (1.4-3.5)

***JAMA* 2016; 316: 2547**

Autoimmune Disease



Thymic deletion

Apoptosis
- **Low affinity**
- **High affinity**

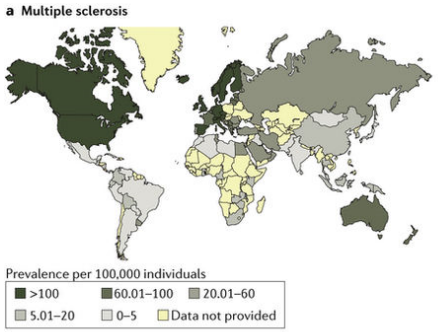
Peripheral deletion

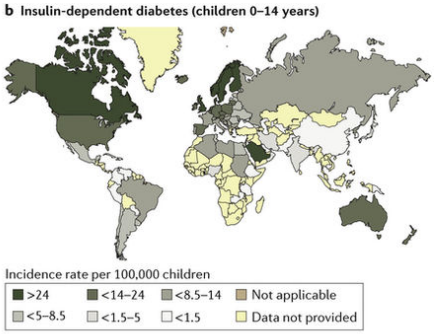
Anergy
Deletion
Exhaustion
Suppression

Tolerance Lost

***BMJ* 2000; 321: 93**

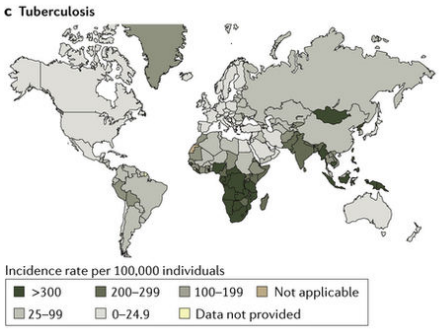
Multiple sclerosis

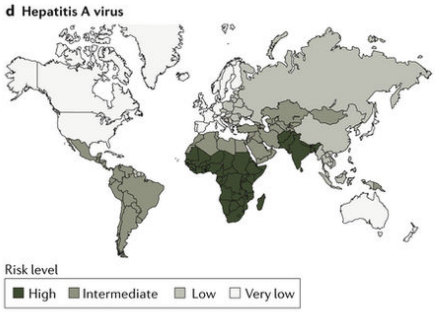




IDDM

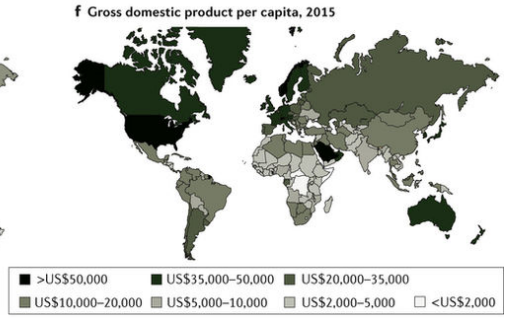
TB





Hepatitis A

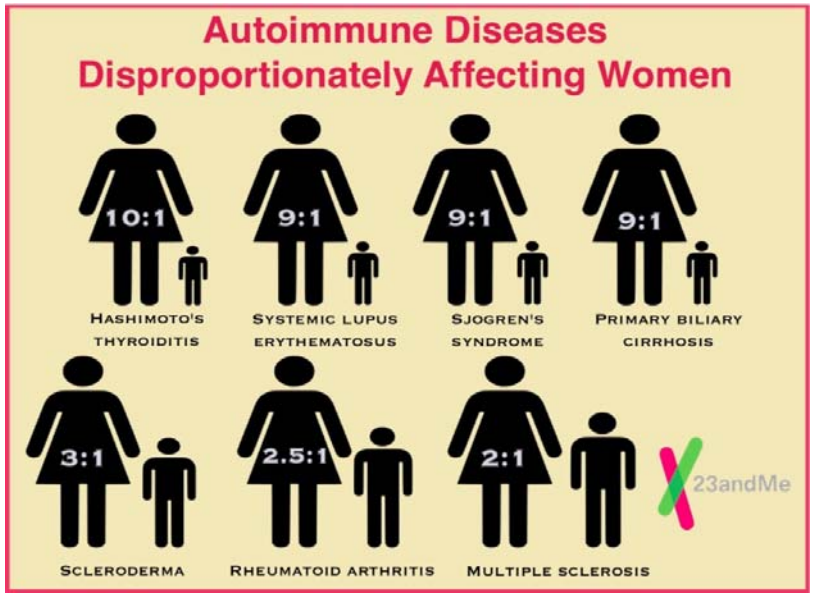
Traveler's Diarrhea

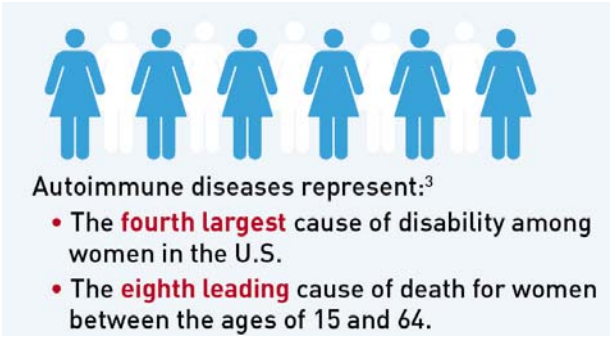


GDP per capita

Nat Rev Immunol
2018; 18: 105

Autoimmune disease





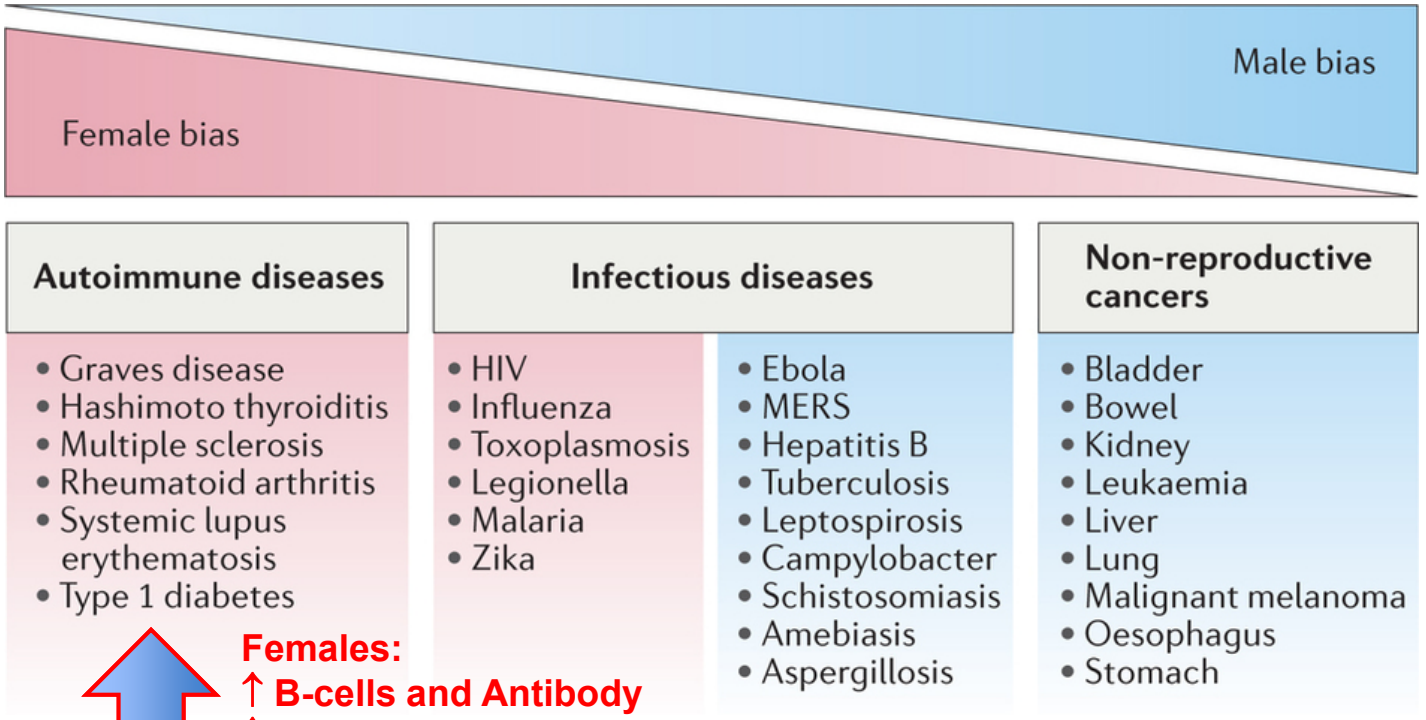
Autoimmune diseases represent:[3]

- 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.

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



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

***Nat Rev Immunol* 2016; 16: 626**

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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

Open Forum Infectious Diseases

MAJOR ARTICLE

Infections in Hematopoietic Cell Transplant Recipients: Results From the Organ Transplant Infection Project, a Multicenter, Prospective, Cohort Study

Mindy G. Schuster,[1] Angela A. Cleveland,[2] Erik R. Dubberke,[3] Carol A. Kauffman,[4] Robin K. Avery,[5] Shahid Husain,[6] David L. Paterson,[7] Fernanda P. Silveira,[8] Tom M. Chiller,[2] Kaitlin Benedict,[2] Kathleen Murphy,[1] and Peter G. Pappas[9]

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

***Clin Infect Dis* 2017; 44: 457**

Bloodstream infection (BSI)

Table 3. Bacterial Bloodstream Infections in 444 Hematopoietic Cell Transplant Recipients

Characteristic	*N*	(Percent or Range)
Gram positive	244	(56)
Coagulase-negative staphylococci	125	(51)
Vancomycin-resistant *Enterococcus*	41	(17)
Enterococcus faecium	31	(13)
Methicillin-susceptible *Staphylococcus aureus*	17	(7)
Enterococcus faecalis	8	(3)
Methicillin-resistant *S aureus*	7	(3)
β-hemolytic streptococci	4	(2)
Other	8	(3)
Gram negative	93	(21)
Pseudomonas aeruginosa	24	(26)
Escherichia coli	20	(22)
Klebsiella pneumonia	20	(22)
Stenotrophomonas maltophilia	6	(7)
Citrobacter freundii	5	(5)
Enterobacter cloacae	5	(5)
Acinetobacter baumanii complex	3	(3)
Burkholderia cepacia	2	(2)
Other	8	(9)
Polymicrobial[b]	50	(12)

- **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

***Clin Infect Dis* 2017; 44: 457**

Invasive fungal (IFI) and viral infections

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

Fungal Organisms **N=53**	*n*	(%)
Candida	18	(34)
Aspergillus	17	(32)
Mucorales	7	(13)
Pneumocystis jiroveci	3	(6)
Exophiala	2	(4)
Alternaria	1	(2)
Mixed	3	(6)
Syndrome		
Pneumonia	26	(49)
Bloodstream infection	18	(34)
Sinusitis	4	(8)
Disseminated	4	(8)
Central nervous system	1	(2)

[a]Fifty-three infections among 48 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**

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

Virus **N=187**	*N*	(%)
Cytomegalovirus infection	154	(82)
Viremia only	148	(96)
Organ involvement[a]	6	(4)
Human herpes virus-6	21	(11)
Parainfluenza virus	18	(10)
Varicella zoster virus	13	(7)
Respiratory syncytial virus	13	(7)
Influenza A virus	12	(6)
Epstein-Barr virus	10	(5)
Herpes simplex virus	8	(4)
Adenovirus	6	(3)
Influenza B virus	3	(2)

[a]One hepatitis, 1 pneumonia, 4 enteritis.

- **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)

***Clin Infect Dis* 2017; 44: 457**

Patient outcomes

Table 6. Outcomes in 444 Hematopoietic Cell Transplant Recipients

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

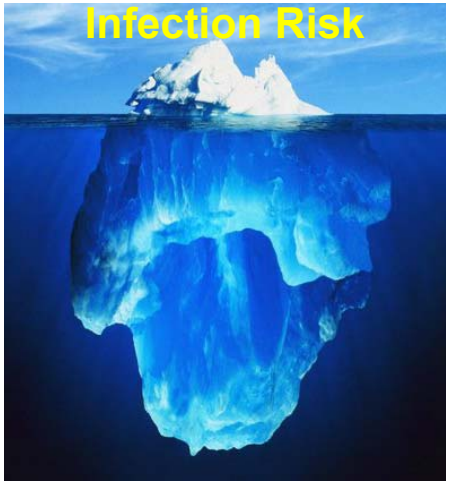
- Transfer to ICU (32%, 162 pts)
  - 122 pts (75%) ultimately died
- **86% patients requiring ventilation died**
- **69% patients requiring dialysis died**

↑↑ Infection-related morbidity & mortality!

Clin Infect Dis **2017; 44: 457**

Theme #2: Net immunosuppression

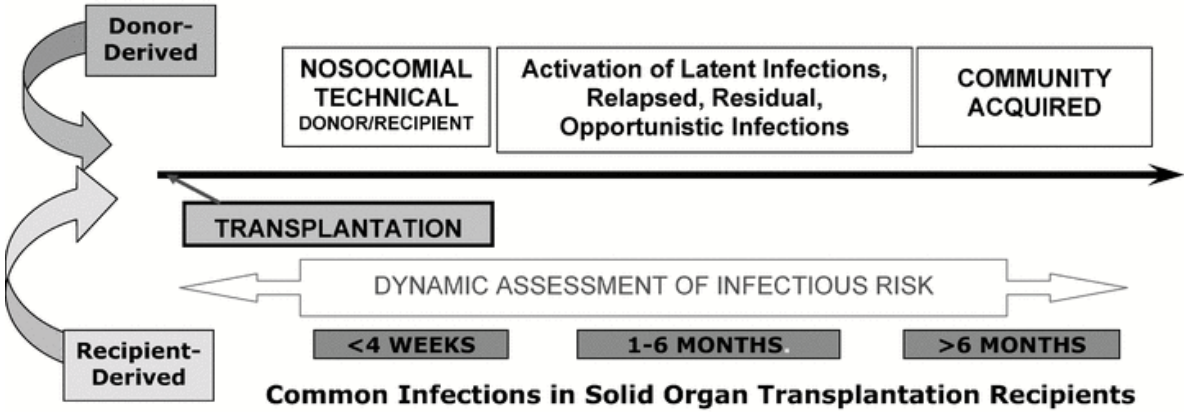
- **Net state of immunosuppression affects infection risk**
  - **Immunosuppressive therapy (IST)**
    - Type, dose, duration
  - **Presence or absence of leukopenia**
    - Neutropenia, lymphopenia
  - **Amount and type of previous therapy**
    - Chemotherapy, antimicrobial agents
  - **Mucocutaneous-barrier 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

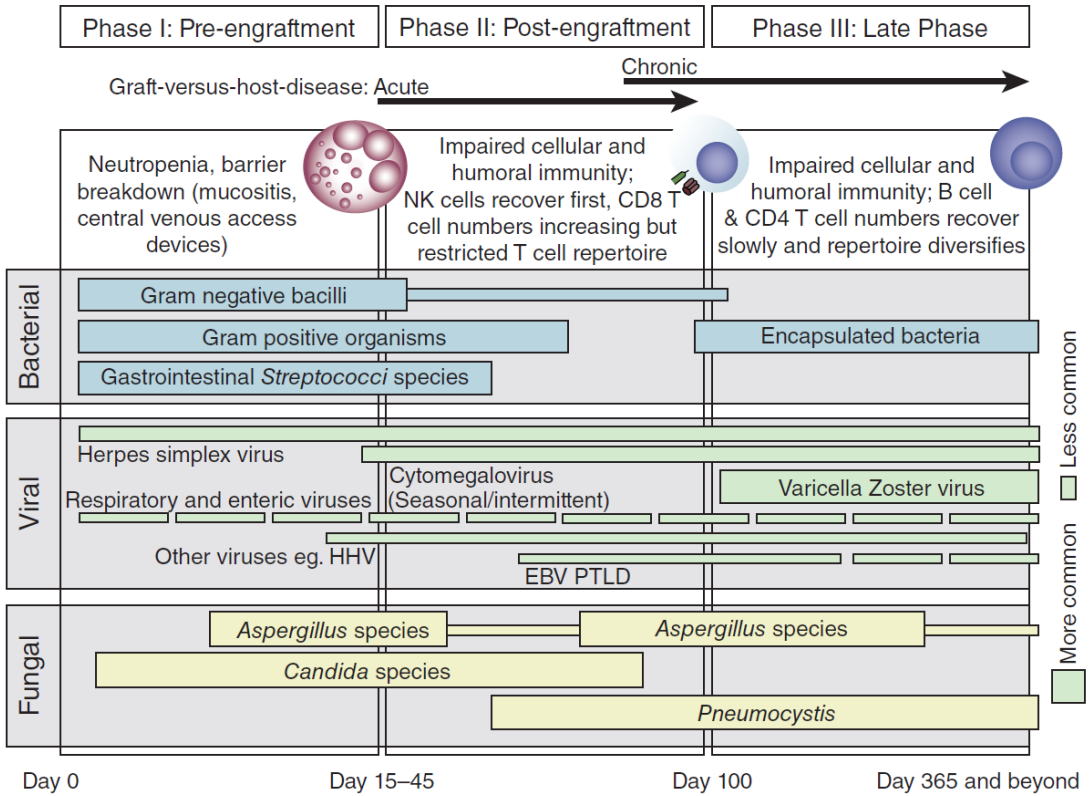


Common Infections in Solid Organ Transplantation Recipients

<4 WEEKS	1-6 MONTHS	>6 MONTHS
Antimicrobial-resistant species: • MRSA • VRE • Candida species (non-albicans) Aspiration Line Infection Wound Infection Anastamotic 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* **Anastamotic 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 moulds, *Mucor* species *Nocardia, Rhodococcus* species Late Viral: • CMV (Colitis/Retinitis) • Hepatitis (HBV, HCV) • HSV encephalitis • Community acquired (SARS, West Nile) • JC polyomavirus (PML) Skin Cancer, Lymphoma (PTLD)

***Am J Transplant* 2009; 9(Suppl 4): S7**

Allogeneic Hematopoietic Cell Transplantation

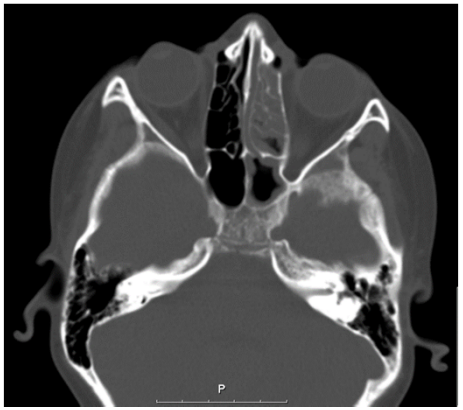


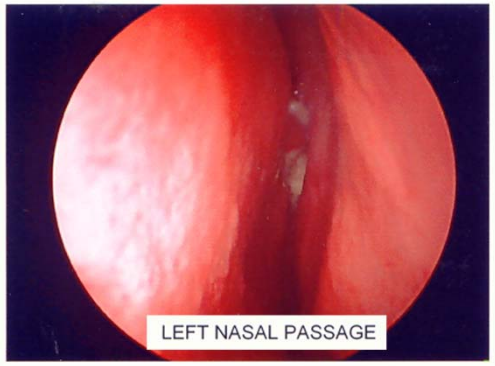
***Bone Marrow Transplant* 2009; 44: 457**

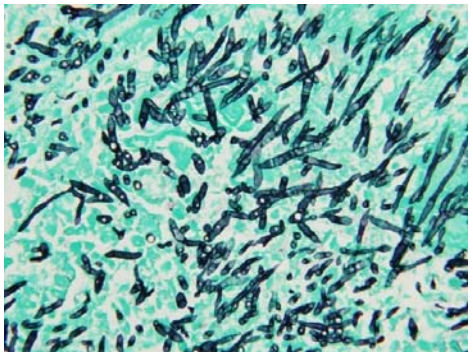
Infections in immunocompromised patients

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

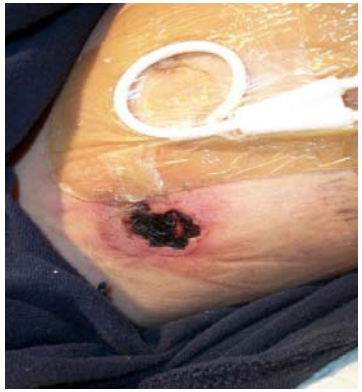
Invasive fungal infection (IFI)

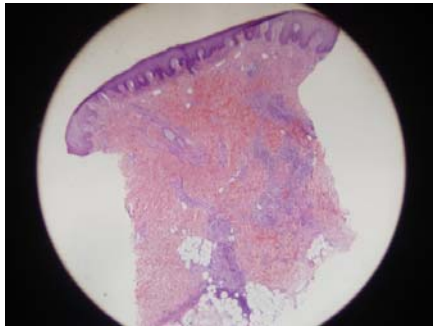


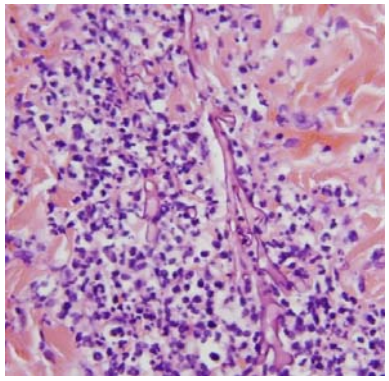




Aspergillus fumigatus

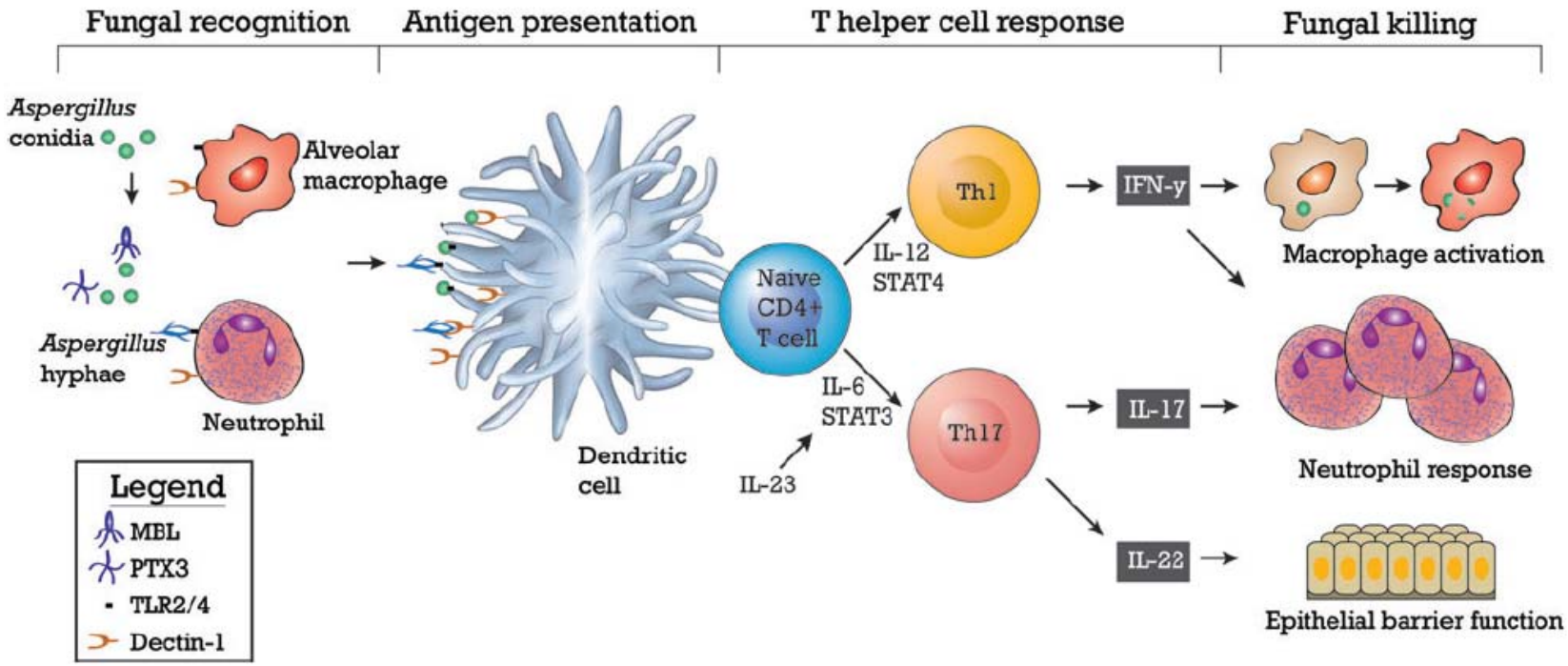






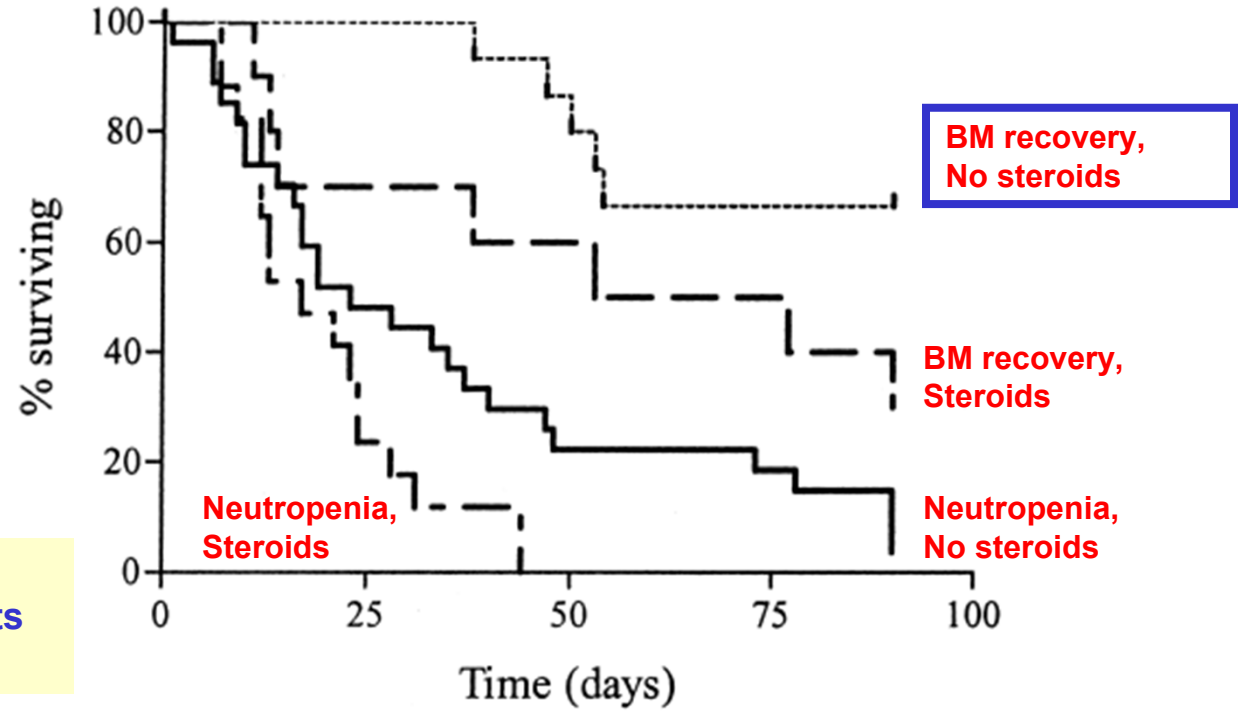
Mucor

Host immune response against *Aspergillus*



Clin Infect Dis 2014; 59: 569

Host immune recovery is needed to ensure best patient outcomes



84 hematologic malignancy patients with *Fusarium*

Cancer 2003; 98: 315

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Combination antifungal therapy

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clinical Research: Supportive Care

Epidemiology, Management, and Outcome of Invasive Fungal Disease in Patients Undergoing Hematopoietic Stem Cell Transplantation in China: A Multicenter Prospective Observational Study

Antifungal Treatment and Mortality among 514 Hospitalized Patients with Hematological Malignancy Receiving HSCT at the Time Antifungal Therapy for IFD was Initiated

	Antifungal Agents				
	Triazoles* Alone (n = 252)	Amphotericin B† Alone (n = 8)	Echinocandins‡ Alone (n = 34)	Two or More Antifungal Agents (n = 220)	Total (n = 514)
IFD diagnosis level at initiation of therapy					
Proven	3 (1.2)	0	0	5 (2.3)	8 (1.6)
Probable	17 (6.7)	3 (37.5)	2 (5.9)	49 (22.3)	71 (13.8)
Possible	84 (33.3)	4 (50.0)	10 (29.4)	74 (33.6)	172 (33.5)
Suspected	148 (58.7)	1 (12.5)	22 (64.7)	92 (41.8)	263 (51.2)
Death	33 (13.1)	0	5 (14.7)	60 (27.3)	98 (19.1)

Data are n (%).

* Fluconazole, itraconazole, voriconazole.

† Amphotericin B, liposomal amphotericin B.

‡ Caspofungin, micafungin

Combination antifungal therapy does not significantly improve patient outcomes!

Biol Blood Marrow Transplant
2015; 21: 1117

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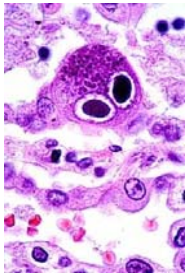
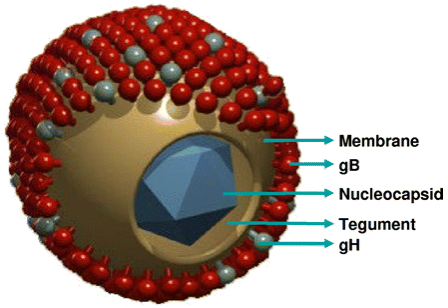
Infections in immunocompromised patients

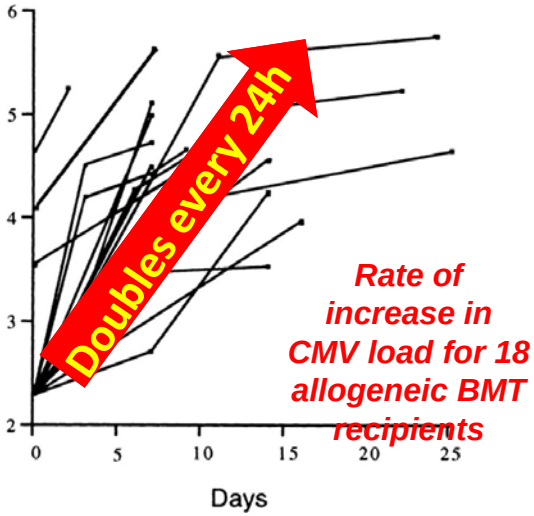
- Common themes across immunocompromised patients
- Invasive fungal infection (IFI)
- **DNA viruses: Cytomegalovirus (CMV)**
- Respiratory viruses

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)







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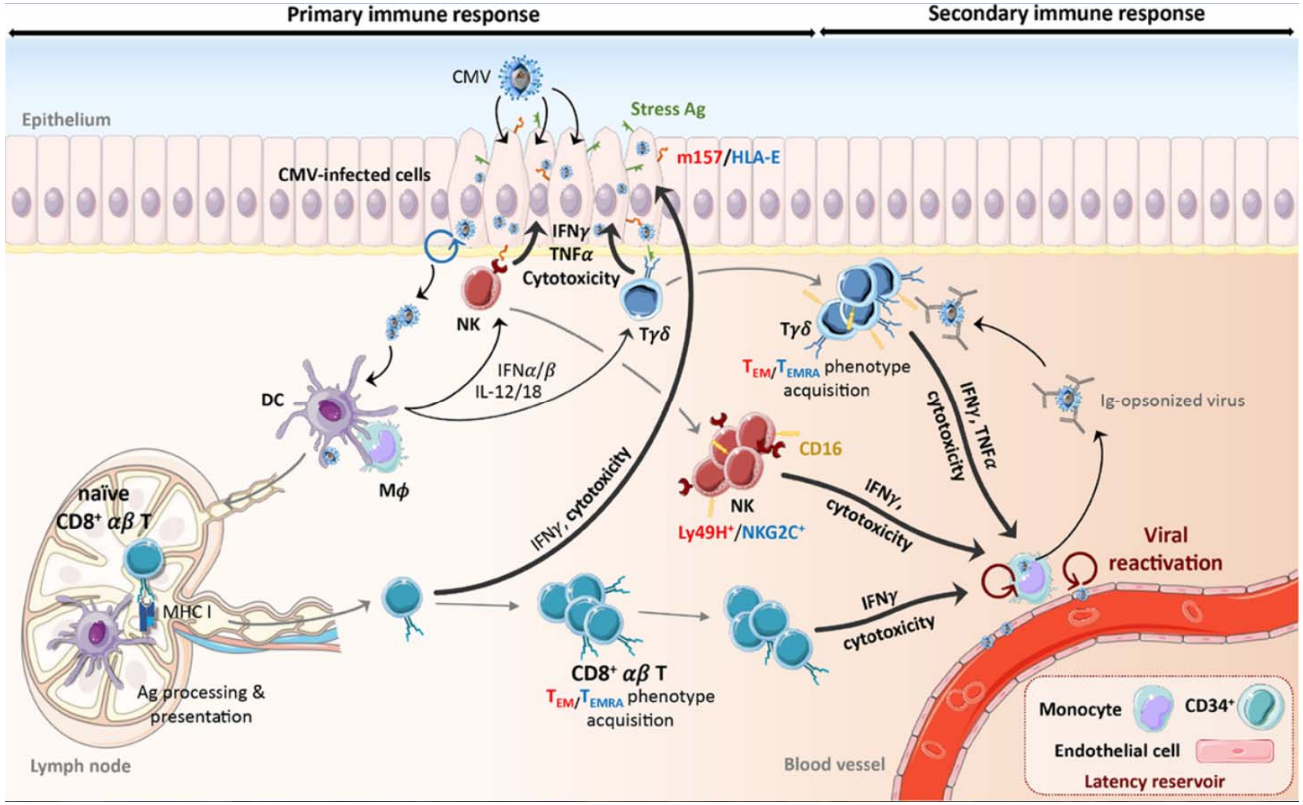
***Cancer Letters* 2014; 342 : 1**
***BMT* 2010; 16: 1309**
***J Infect Dis* 2002; 185: 273**

Immune response to CMV



Front Immunol 09 February 2017

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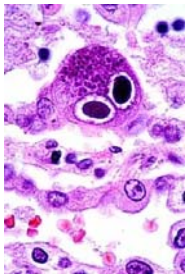
Risk factors

- 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)



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

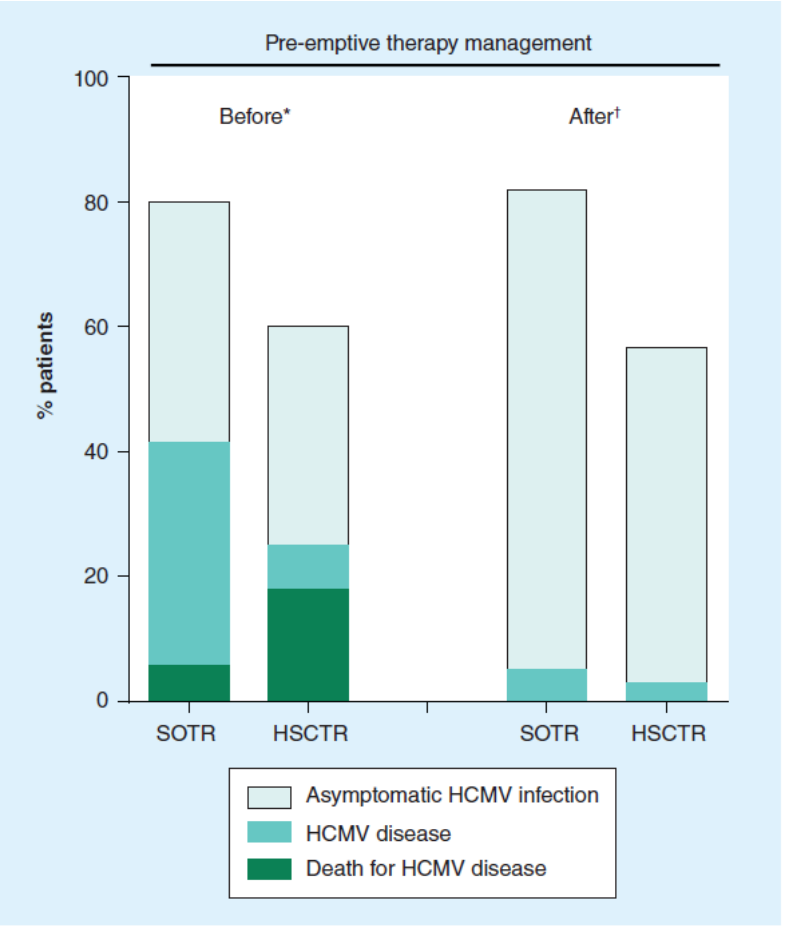


Figure 1. Rate, morbidity and mortality of HCMV infection in solid organ transplant recipients (SOTR) and hematopoietic stem cell transplant recipients (HSCTR) before and after introduction of pre-emptive therapy.
*Historical data [4,6,130,131,132,133,134].
†Data from patients (272 SOTR and 325 adult 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].

***Immunotherapy* 2016; 8: 1135**

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Systemic antiviral therapies: A limited armamentarium

Property	Acyclovir (ACV)	Ganciclovir (GCV)	Foscarnet (FOS)	Cidofovir (CDV)	Brincidofovir (CMX-001)	Other Agents
Activity:						
- ADV	-	-	-	1st line	+	-
- BK	-	-	-	1st line	+	-
- CMV	-	1st line	2nd line	+	+	LRV, MBV
- EBV	-	+	+	+/-	+	Ritux, MBV
- HHV6	-	+	+	+	+	-
- HSV / VZV	1st line	+	2nd line	-	-	-
Administration	IV/PO	IV/PO	IV	IV	IV/PO	IV/PO
Mechanism	DNA polymerase inhibition (nucleoside analogues except FOS)					Variable
CNS penetration	Yes	Yes	Yes	No	No	Variable
Adverse effects	Renal	BM>>Renal	Renal	Renal	Hepatic, GI	Variable

Efficacy ~ 40%
Toxicity ~ 60%
Resistance!

LRV = Letermovir
MBV = Maribavir
Ritux = Rituximab

J Pharmaceut Biopharm Analysis 2018; 147: 400
J Ped Infect Dis Soc 2013; 2: 286

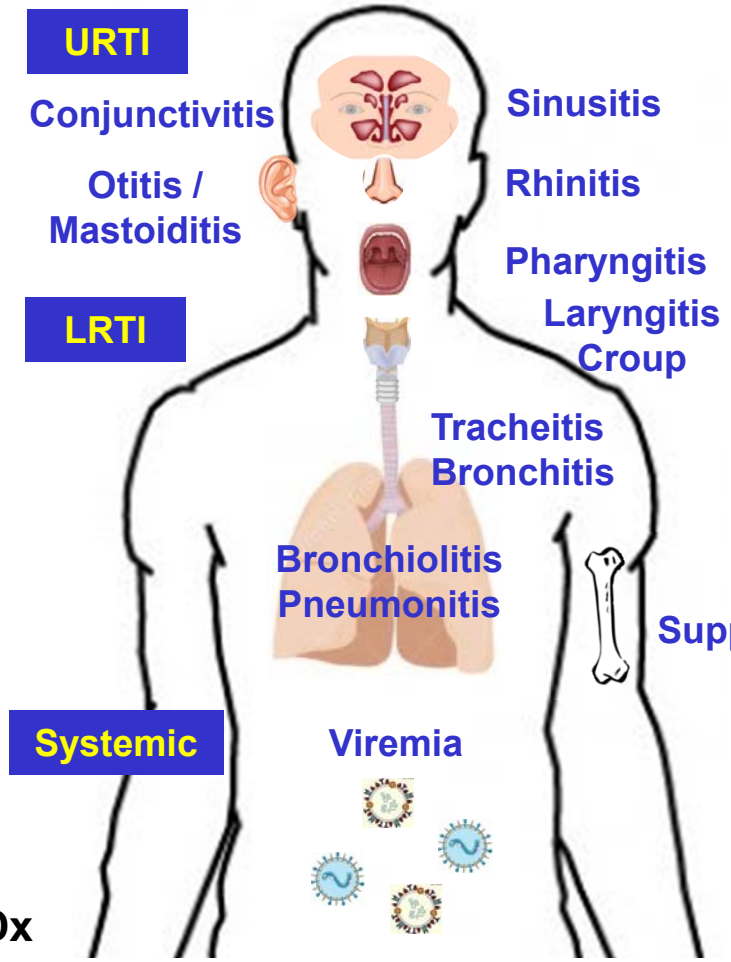
Infections in immunocompromised patients

- 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 = Parainflu

RhV = Rhino

Post-Transplant Outcomes

↑ TRM (Lung injury)

-- Alveolar damage

-- ARDS / BOOP

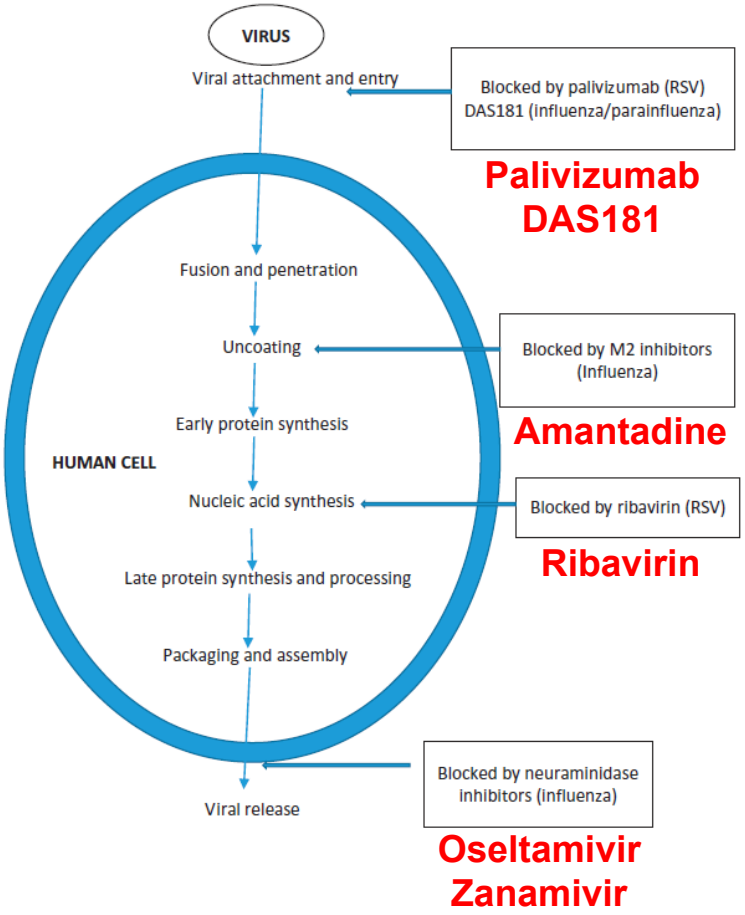
-- Respiratory failure

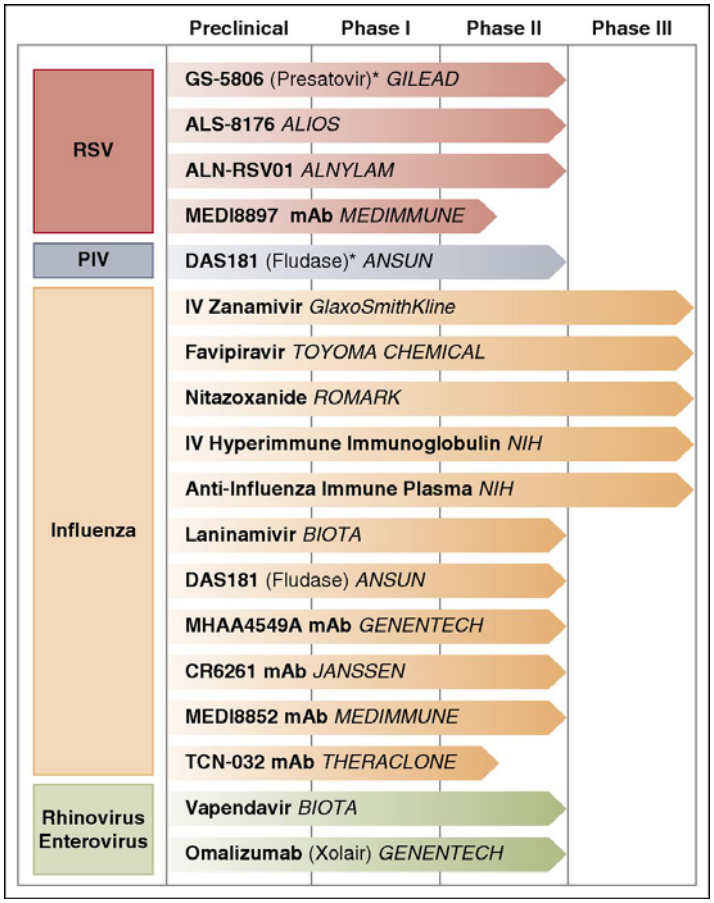
↑ TRM (Infection)

-- Bacterial superinfection

↓ Overall survival

Anti-respiratory viral Rx: Limited drugs, poor efficacy



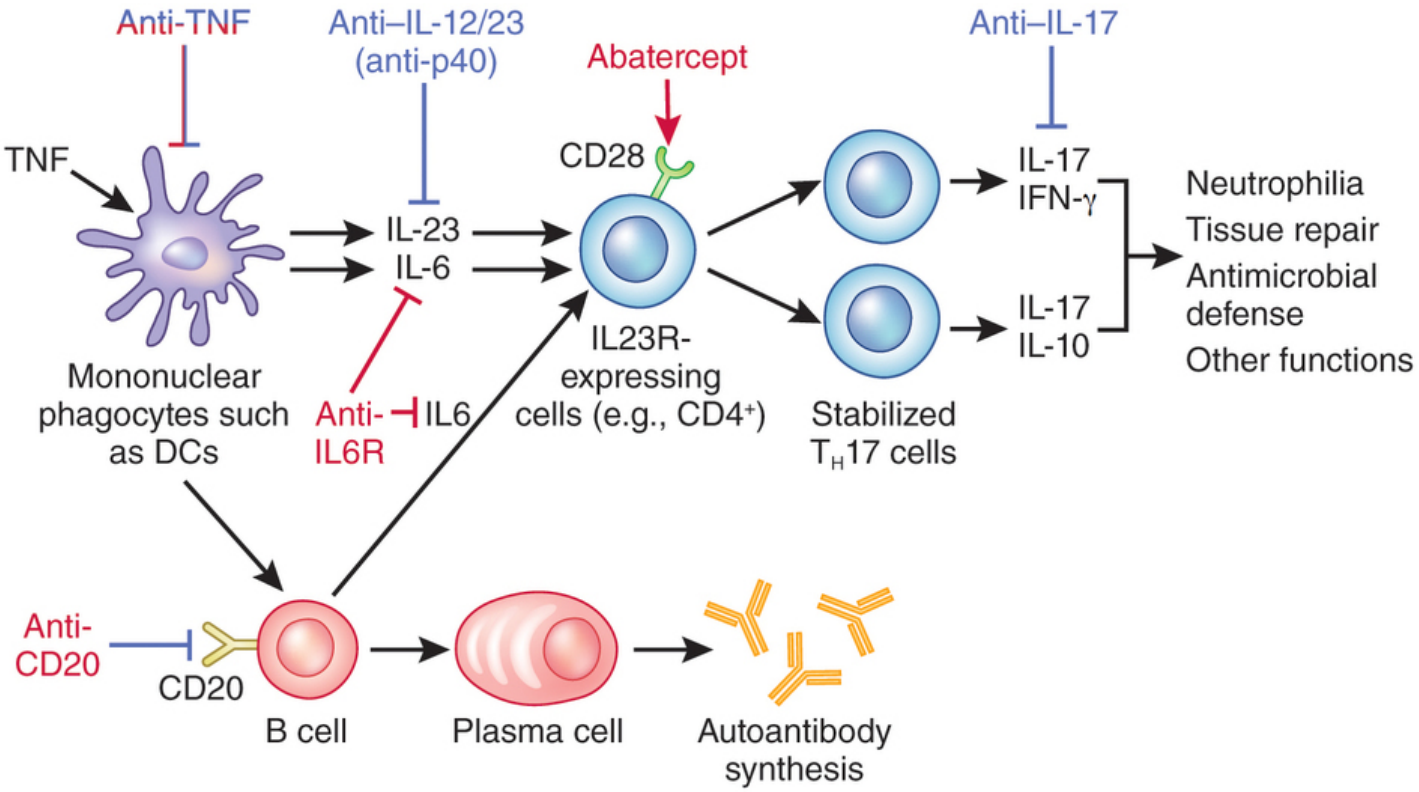


Expert Rev Anti Infect Therapy 2017; 15: 401
Blood 2016; 127: 2682

Therapy-associated infections

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

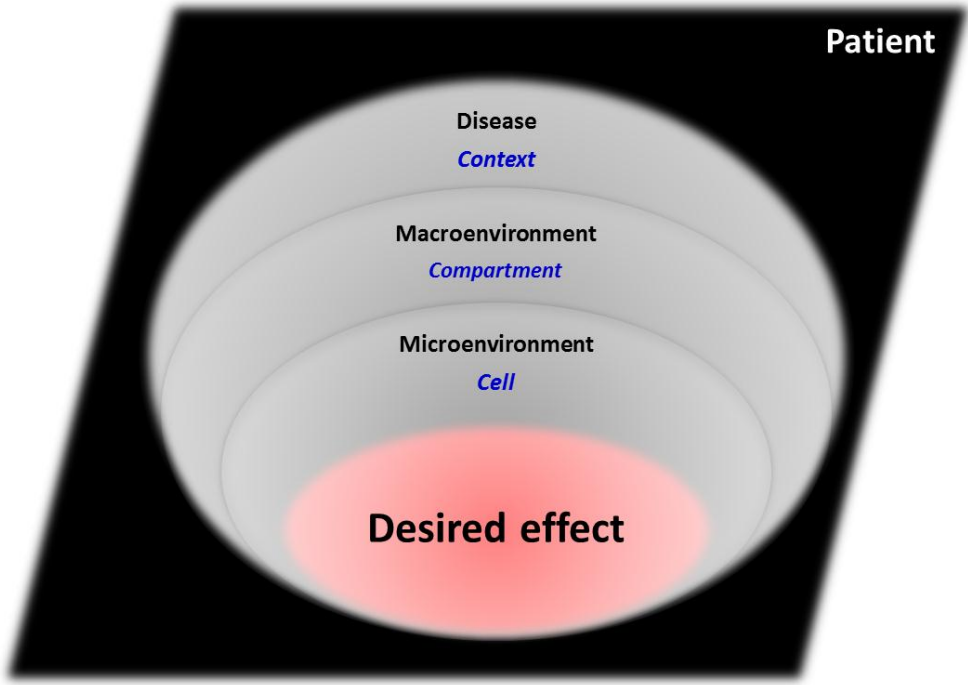
Biologic Rx: Mechanisms of action



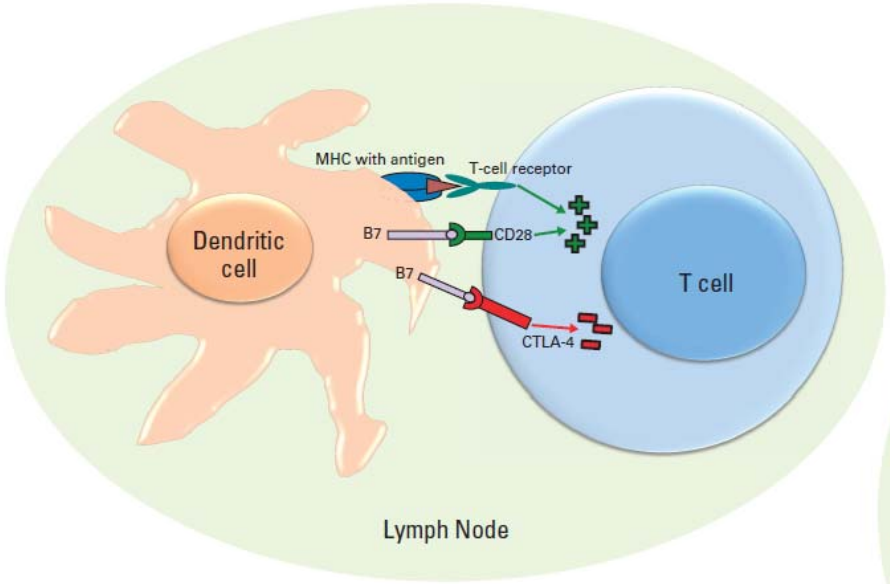
Nat Med 2015; 21: 730

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**



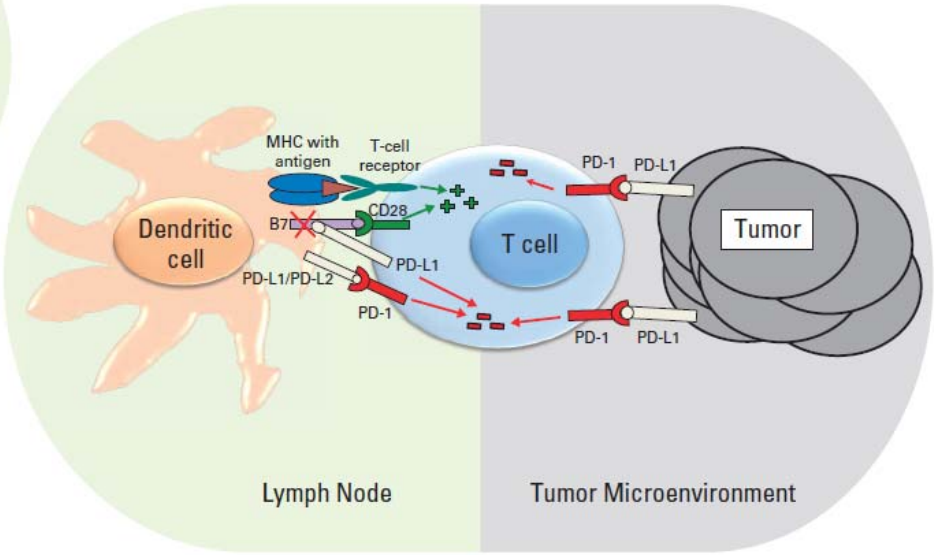
Consideration #2: Exchanging problems



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



J Clin Oncol **2015; 33: 1974**

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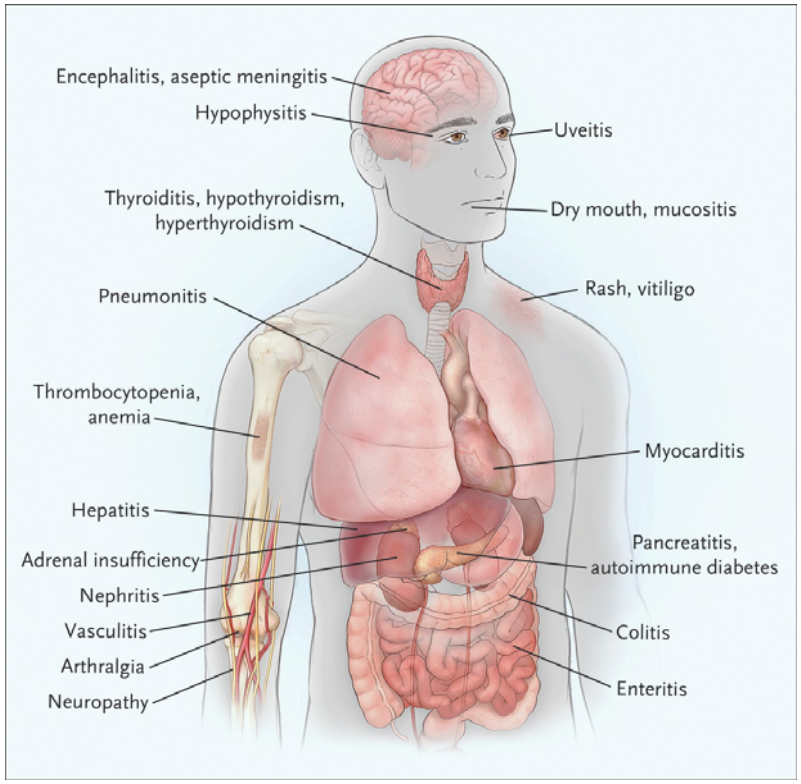
Check-point blockade: Immune-related AEs

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

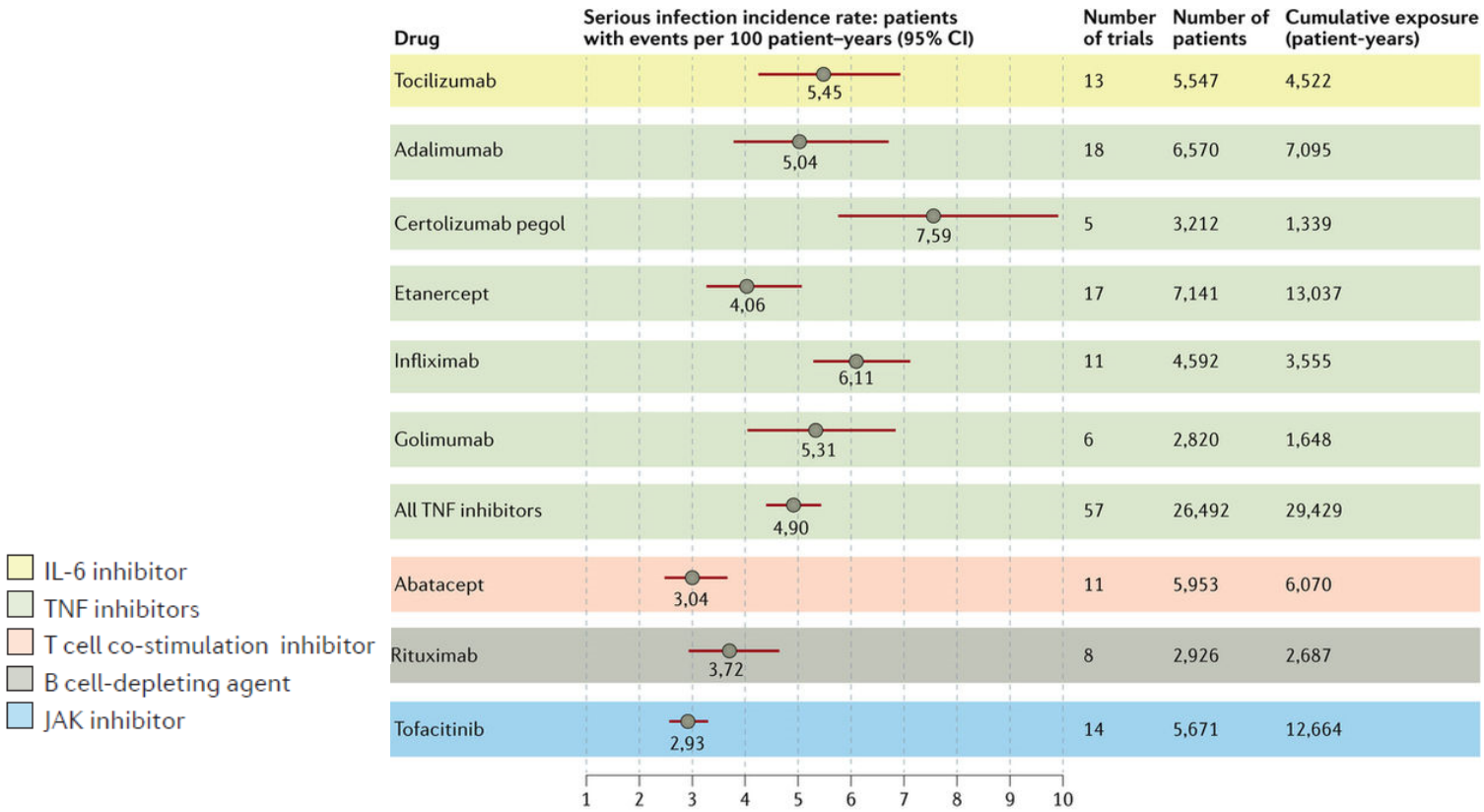
Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	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 microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.



NEJM 2018; 378: 158

Serious infection rates* for RA patients Rx biologics



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

***Nat Rev Rheumatol* 2017; 13: 399**

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Table 1
Biologics and associated infectious events

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

Biologic Rx Infectious sequelae

Not enough published experience!

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

***Infect Dis Clin N Am* 2018: 32; 225**

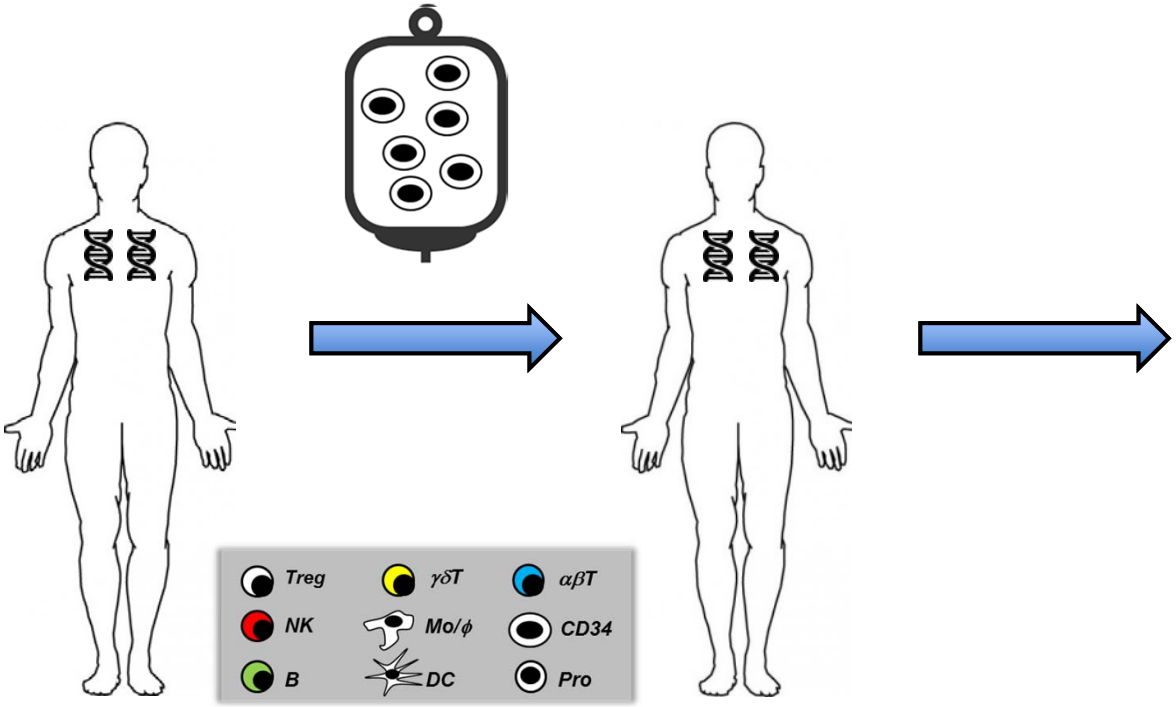
Therapy-associated infections

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

Stem Cell Mobilization

Graft Content Matters!

Post-transplant Outcomes



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

HLA matching

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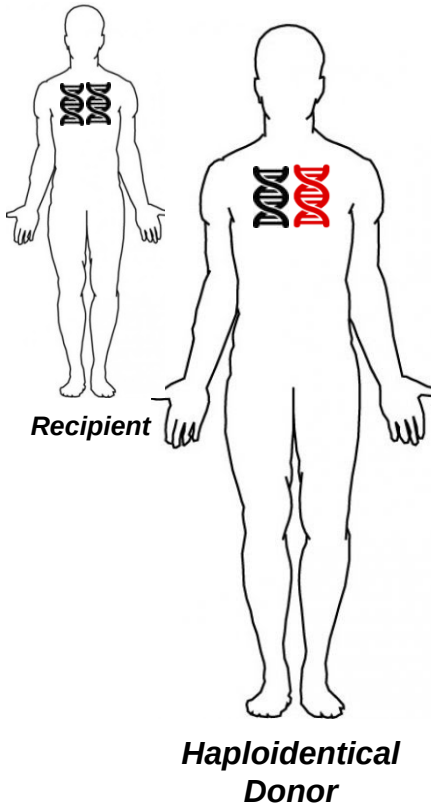
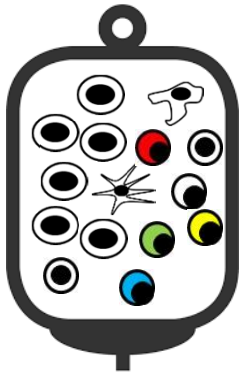
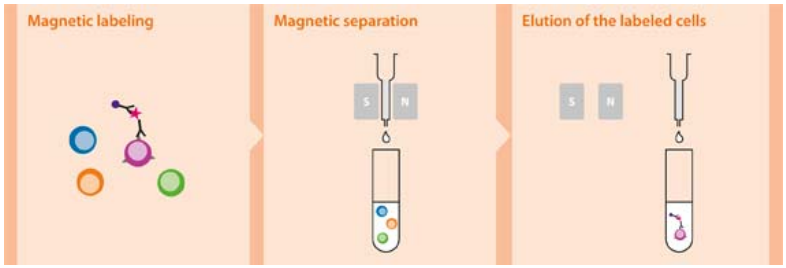
Mobilization

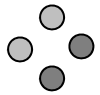




Selection/Depletion

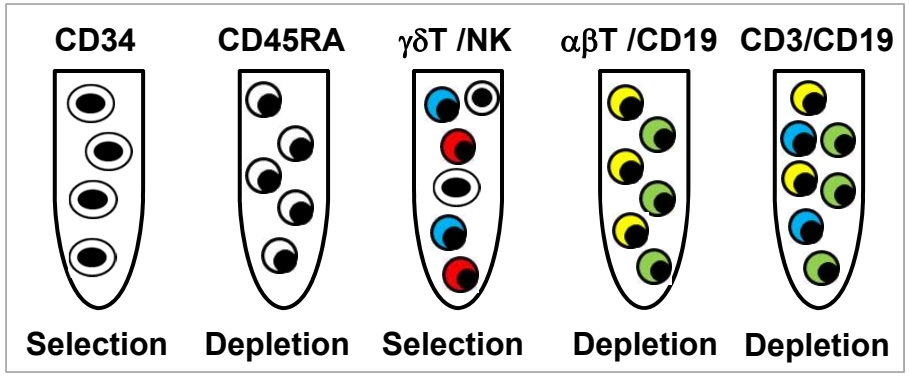
"Depletion" -Selection | *"Enrichment"* +Selection

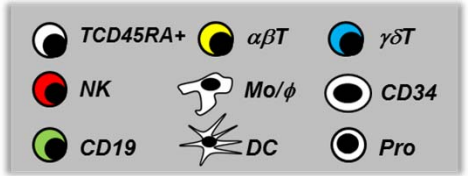




MACS® MicroBeads

CliniMACS Prodigy®





HLA matching

Implications of graft manipulation

Manipulation Graft Content

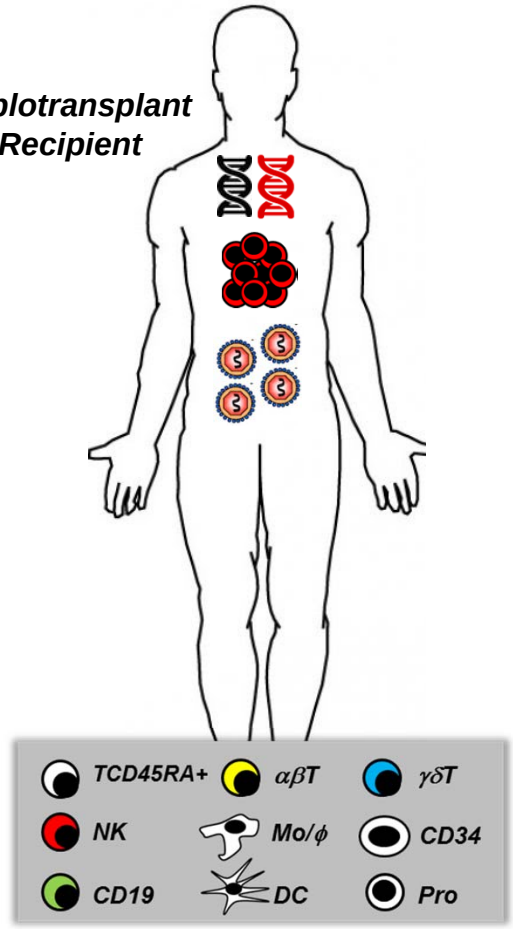
None

Naïve CD45RA$^+$ T cell depletion

$\alpha\beta$T- and B-cell depletion

CD3$^+$ and CD19$^+$ depletion

CD34$^+$ selection



Post-transplant Outcomes

Engraftment

GvHD

+ Reduce immunosuppression
+ Reduce side effects

GvL

+ Reduce disease relapse

Immune reconstitution

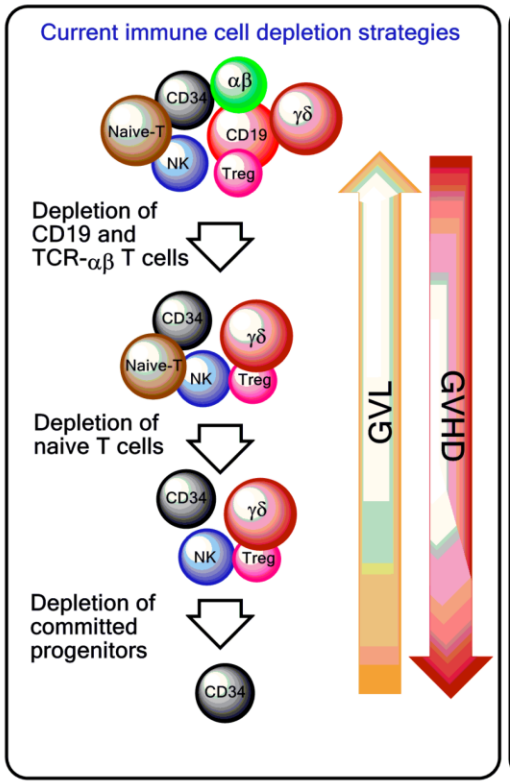
+ DC recovery
+ NK recovery
+ $\delta\gamma$T recovery

Infection

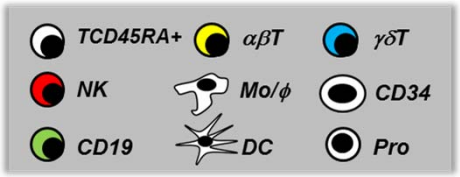
+ Antiviral host defense

Post-transplant lymphoproliferative disease (PTLD)

αβT and B-cell (CD19) depletion



αβT-cell and CD19-cell depletion



No post-transplant immunosuppression!

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Haploidentical PBSC αβT-cell and CD19 depletion

Key Points

- Children with AL given haplo-HSCT after αβ 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%

TRANSPLANTATION

Outcome of children with acute leukemia given HLA-haploidentical HSCT after αβ T-cell and B-cell depletion

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***Blood* 2017; 130: 677**

CI = cumulative incidence, PGF = primary graft failure
GRFS = cGvHD-free, relapse-free survival

Key Points

- Removal of $\alpha\beta^+$ T and $CD19^+$ B cells is an effective strategy for successful HLA-haploidentical hematopoietic stem cell transplantation.
- The high probability of disease-free survival renders this transplant option attractive for any child with a nonmalignant disorder.

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

TRANSPLANTATION

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

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***Blood* 2014; 124: 822**

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Risk Factors for and the Clinical Impact of Cytomegalovirus and Epstein-Barr Virus Infections in Pediatric Recipients of TCR-α/β– and CD19-Depleted Grafts

Alexandra Laberko [1], Anna Bogoyavlenskaya [2], Larisa Shelikhova [2], Zhanna Shekhovtsova [2], Dmitriy Balashov [2], Kirill Voronin [3], Elena Kurnikova [4], Elena Boyakova [5], Elena Raykina [6], Varvara Brilliantova [6], Valentina Pirumova [7], Galina Novichkova [8], Alexei Maschan [2], Michael Maschan [2,*]

- **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**

Biol Blood Marrow Transpl
2017; 23: 483

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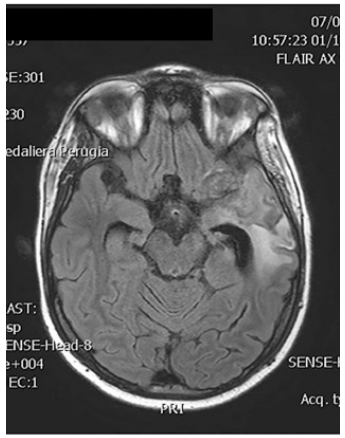
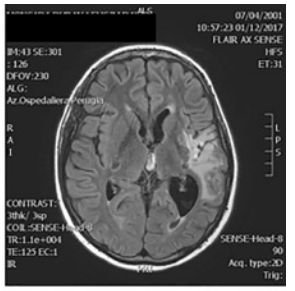
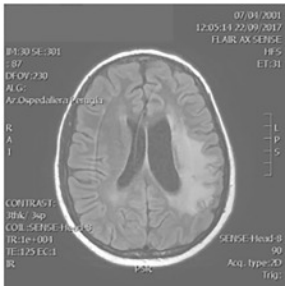
High Incidence of Early Human Herpesvirus-6 Infection in Children Undergoing Haploidentical Manipulated Stem Cell Transplantation for Hematologic Malignancies

Katia Perruccio[1,*], Luisa Sisinni[2], Antonio Perez-Martinez[3], Jaime Valentin[3], Ilaria Capolsini[1], Maria Speranza Massei[1], Maurizio Caniglia[1], Simone Cesaro[4]







- **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%)

Biol Blood Marrow Transpl
2018; 24: 2549

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 Boeckh,[1,2] and Cameron J. Turtle[1,4]

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KEY POINTS

- The incidence of infections after CD19 CAR–T-cell immunotherapy was similar to the incidence after other salvage chemoimmuno-therapies.
- Infections were more frequent in patients who had ALL, more prior antitumor treatment, a higher CAR–T-cell dose, or greater CRS severity.

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 ($2x10^7$ cells/kg)**
- **IFI (6 pts, 5%) and life-threatening (5 pts, 4%)**
- **MVA ↑ Infection risk: Severity of cytokine release syndrome (CRS)**
- ***Incidence of infection is comparable to salvage chemotherapy***

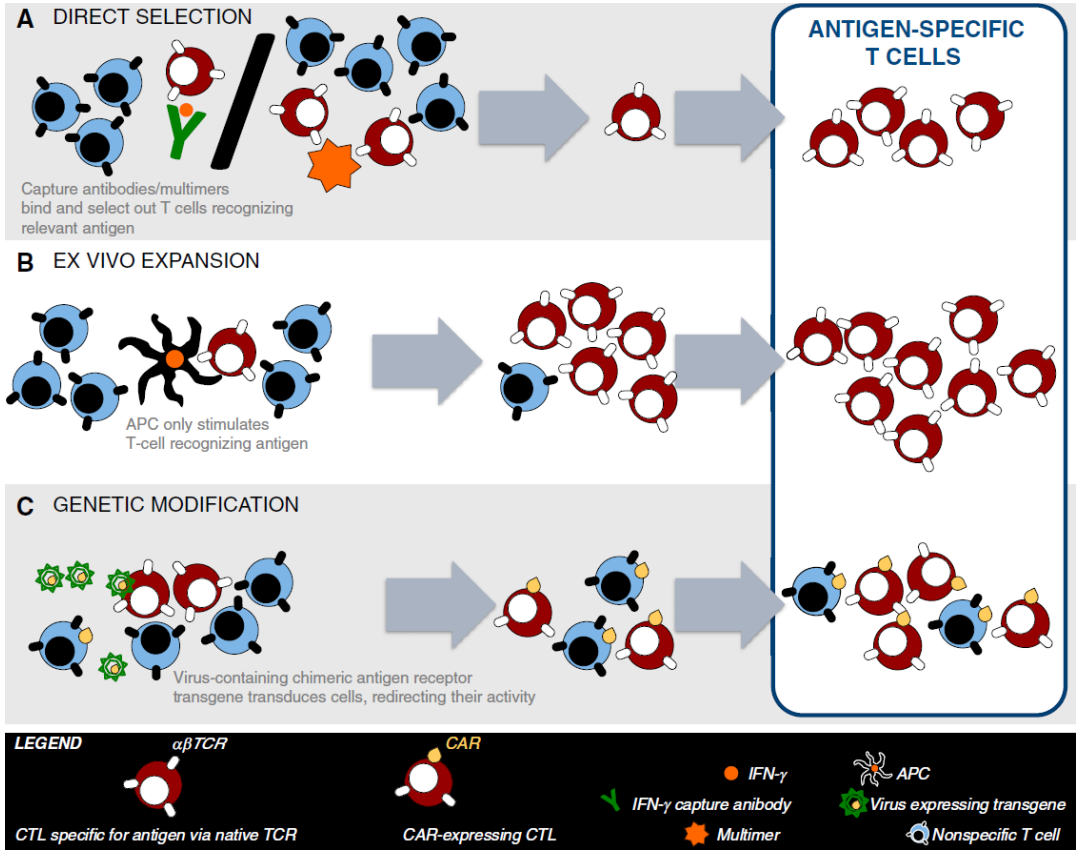
➢ Prophylaxis
➢ Monitoring
➢ Therapy

Blood 2018; 131: 121

Anti-microbial cellular therapies

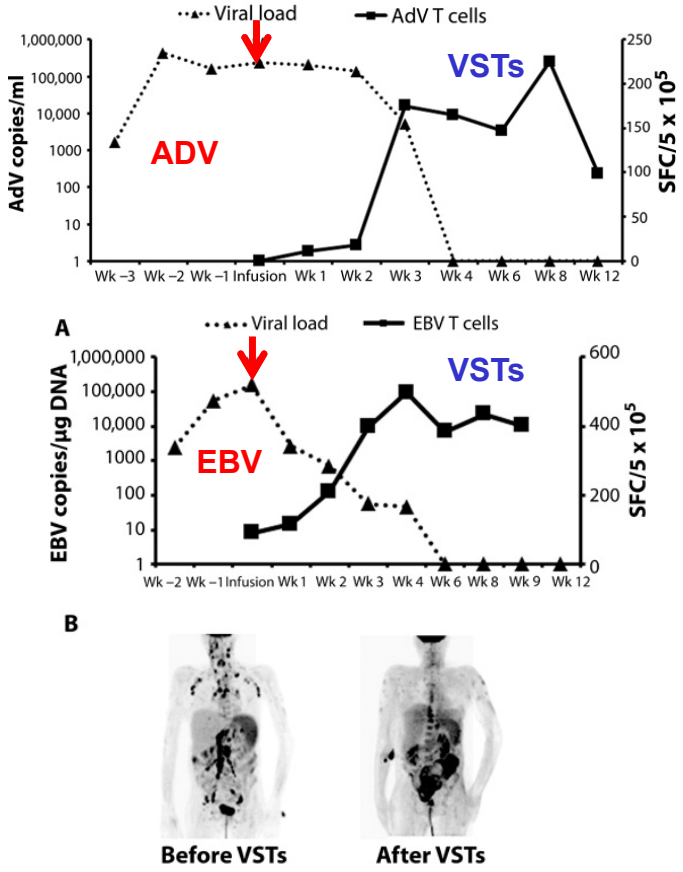
- **Virus-specific T cells (VSTs)**

Virus-specific T lymphocytes (VSTs)



Blood 2016; 127: 3331

SFCs = IFNγ-producing spot-forming cells



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

Ifigeneia Tzannou, Anastasia Papadopoulou, Swati Naik, Kathryn Leung, Caridad A. Martinez, Carlos A. Ramos, George Carrum, Ghadir Sasa, Premal Lulla, Ayumi Watanabe, Manik Kuvalekar, Adrian P. Gee, Meng-Fen Wu, Hao Liu, Bambi J. Grilley, Robert A. Krance, Stephen Gottschalk, Malcolm K. Brenner, Cliona M. Rooney, Helen E. Heslop, Ann M. Leen, and Bilal Omer

- **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

***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

Emily Blyth,[1-5] Leighton Clancy,[1-3] Renee Simms,[1] Chun K. K. Ma,[1] Jane Burgess,[1] Shivashni Deo,[1] Karen Byth,[5,6] Ming-Celine Dubosq,[2] Peter J. Shaw,[5,7] Kenneth P. Micklethwaite,[1-5] and David J. Gottlieb[1-6]

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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 2×10^7cells/m^2 after day 28 post-transplant. Twenty-six patients reactivated CMV posttransplant (only 5 post-CTL infusion) and 9 required therapy with ganciclovir or foscarnet (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)

***Blood* 2013; 121: 3745**

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Reviews

Will Post-Transplantation Cell Therapies for Pediatric Patients Become Standard of Care?

Arjan C. Lankester [1,*], Franco Locatelli [2], Peter Bader [3], Eva Rettinger [3], Maarten Egeler [4], Satyendra Katewa [4], Mich… hultz [7], Rupert Handgretinger [8], S… erine M. Bollard [11], on behalf of the Westhaf…

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[10] Department of Pediatrics, Blood and Mar… NCE), Lab Translational Immunology, University Medical Center Utrecht, Utrecht, …
[11] Departments of Pediatrics and Microbiol… and George Washington University, Division of Pediatric Hematology-Oncology, Washington, DC

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