

Infection in Immunocompromised Hosts

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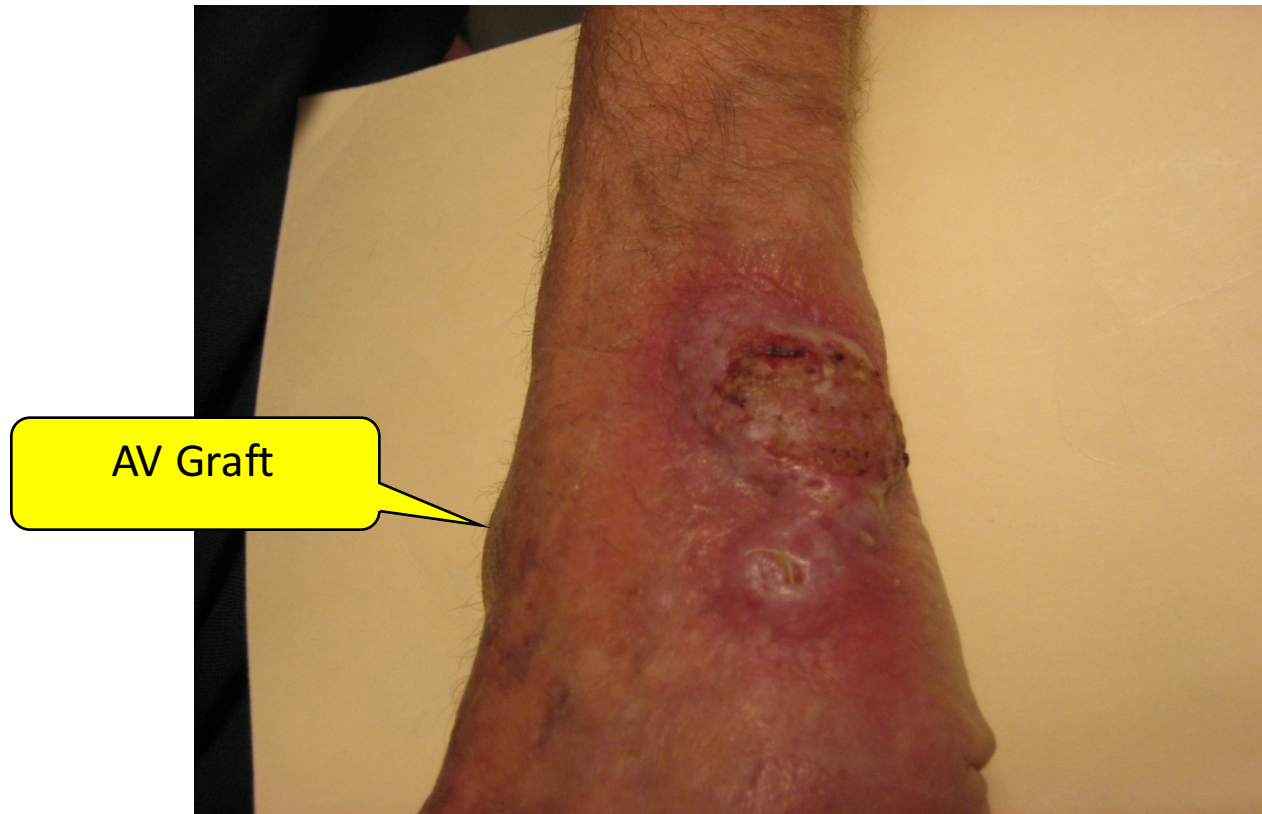


Key Concepts:

Infection in Immunocompromised Hosts

- More effective immunosuppressive regimens have reduced rates of acute graft rejection
 - More atypical presentations (humoral)
 - Persistence of “Chronic Allograft Dysfunction”
- Infections are common
 - Presentations are often atypical without fever or other signs
 - Now exceed rejection as a cause of hospitalization.
 - Prophylaxis is effective in delaying infection (not indefinitely)
 - Infection is increasingly recognized as a risk factor in provoking graft rejection.
- Microbiological assays (molecular) are routinely used in diagnosis and management.

63 yo man with 2nd deceased donor renal graft for diabetes, early humoral rejection, baseline Cr=2.2, immunosuppression with rapamycin and mycophenylate mofetil. Non-healing skin ulcer growing *S. aureus*. Poor response to multiple courses of antibiotics.



This patient has?

1. Ischemic ulcer – steal from AV graft → Possibly
2. Resistant *Staphylococcus aureus* infection No
3. *Fusarium* species No
4. *Nocardia asteroides*
Yes! – *on biopsy*
5. Rapamycin-induced poor wound healing → Likely



Consider ... New Renal Transplant recipients
with discharge serum creatinine 1.8 and
falling – similar presentations

Time	Cr	U/A	WBC	Fever?	DX
1 week	1.4	5-10 wbc	2200	no	
1 week	2.6	neg	6100	no	
3 months	2.6	5-10	6100	no	
6 months	2.6	neg	2000	Low grade	
9 months	2.6	5-10 wbc	2200	Low Grade	

Diagnosis of infection is more difficult in immunocompromised hosts:

- ⇒ Diminished signs of inflammation
- ⇒ Dual infections (or processes) are common
- ⇒ Infection is advanced at presentation
- ⇒ Antimicrobial resistance is common
- ⇒ Toxic effects of drugs (antimicrobial agents)
- ⇒ Anatomic and surgical alterations

General Principles: Diagnosis and Treatment of infection

- ✓ Demonstration of Anatomy (CT/MRI)
- ✓ **Tissue Histology** -- invasive procedures (**biopsy**), special stains
- ✓ Demonstration of nucleic acids or proteins
(Note: serologic tests are not generally useful for acute diagnosis)
- ✓ **Early and aggressive therapy (surgical debridement)** – cannot eradicate infection unless primary source is resolved (e.g. hematoma)

Great Variability of Rates of Infection

TABLE 3. Incidence of infectious diseases in solid-organ transplant recipients^a

Type of infection	Incidence of infection (%) ^b in patients receiving:				
	Liver	Kidney	Heart	Lung/ heart-lung	Pancreas/ kidney- pancreas
Bacterial	33–68	47	21–30	54	35
CMV	22–29	8–32	9–35	39–41	50
HSV	3–44	53	1–42	10–18	6
VZV	5–10	4–12	1–12	8–15	9
<i>Candida</i> spp.	1–26	2	1–5	10–16	32
Mycelial fungi	2–4	1–2	3–6	3–19	3
<i>P. carinii</i>	4–11	5–10	1–8	15	

From: Patel R and Paya C. Clin Micro Rev 1997, 10:1; p86-124.

Fever is unreliable as a sign of infection in solid organ recipients

- In transplant recipients, fever is defined as an oral temperature of 37.8°C or greater on at least two occasions during a 24-hour period
- Antimetabolites (mycophenolate mofetil, and azathioprine) are associated with significantly lower maximum temperatures and leukocyte counts
- Patients with significant infection (bowel perforation) may lack fever or localizing signs

Sources of Fever

- Fever is due to infection in up to 80% of episodes and to noninfectious causes in 22%.
 - 40% of infections were not accompanied by fever, particularly in fungal diseases.
 - Febrile viral infections were often due to viruses other than cytomegalovirus (HHV6, EBV, recurrent hepatitis)
- Rejection accounts for 4-6% of the episodes.
- Highest rates were in heart and lung recipients (30-60%)

R.G. Sawyer, T.D. Crabtree, T.G. Gleason, *et al.* Clin Transpl, 13 (3) (1999), pp. 260–265

F.Y. Chang, N. Singh, T. Gayowski, *et al.* Clin Infect Dis, 26 (1) (1998), pp. 59–65

J.G. Montoya, L.F. Giraldo, B. Efron, *et al.* Clin Infect Dis, 33 (5) (2001), pp. 629–640 [Epub 2001 Aug 6]

Common Infections

- **Bloodstream** infections in immediate post-op period – ~18 episodes per 100 patient years (Year 1)
- **Pneumonia** accounts for 30% to 80% of infections suffered by SOT recipients and for a great majority of episodes of fever.
 - Highest in the early postoperative period (especially with intubation)
 - Crude mortality of bacterial pneumonia in solid organ transplantation >40%
 - Increased over 4-fold vs. normals in first year after renal transplantation
- **Gastrointestinal** symptoms are common and often ignored
 - Peritonitis, intra-abdominal infections, and *Clostridium difficile* colitis common after liver transplantation in the ICU
 - CMV and *C difficile* are the most common causes of infectious diarrhea in solid organ recipients.

N. Singh, T. Gayowski, M.M. Wagener, *et al.* Transplantation, 67 (8) (1999), pp. 1138–1144

L.A. Mermel, D.G. Maki Semin Respir Infect, 5 (1) (1990), pp. 10–29; USRDS 2002, KC Abbott et al, Am J Nephrol. 2001; DJ Tveit et al, J. Nephrol 2002; MJ Hanaway et al.NEJM, 364: 1909, 2011.

Newer Pathogens in Transplantation

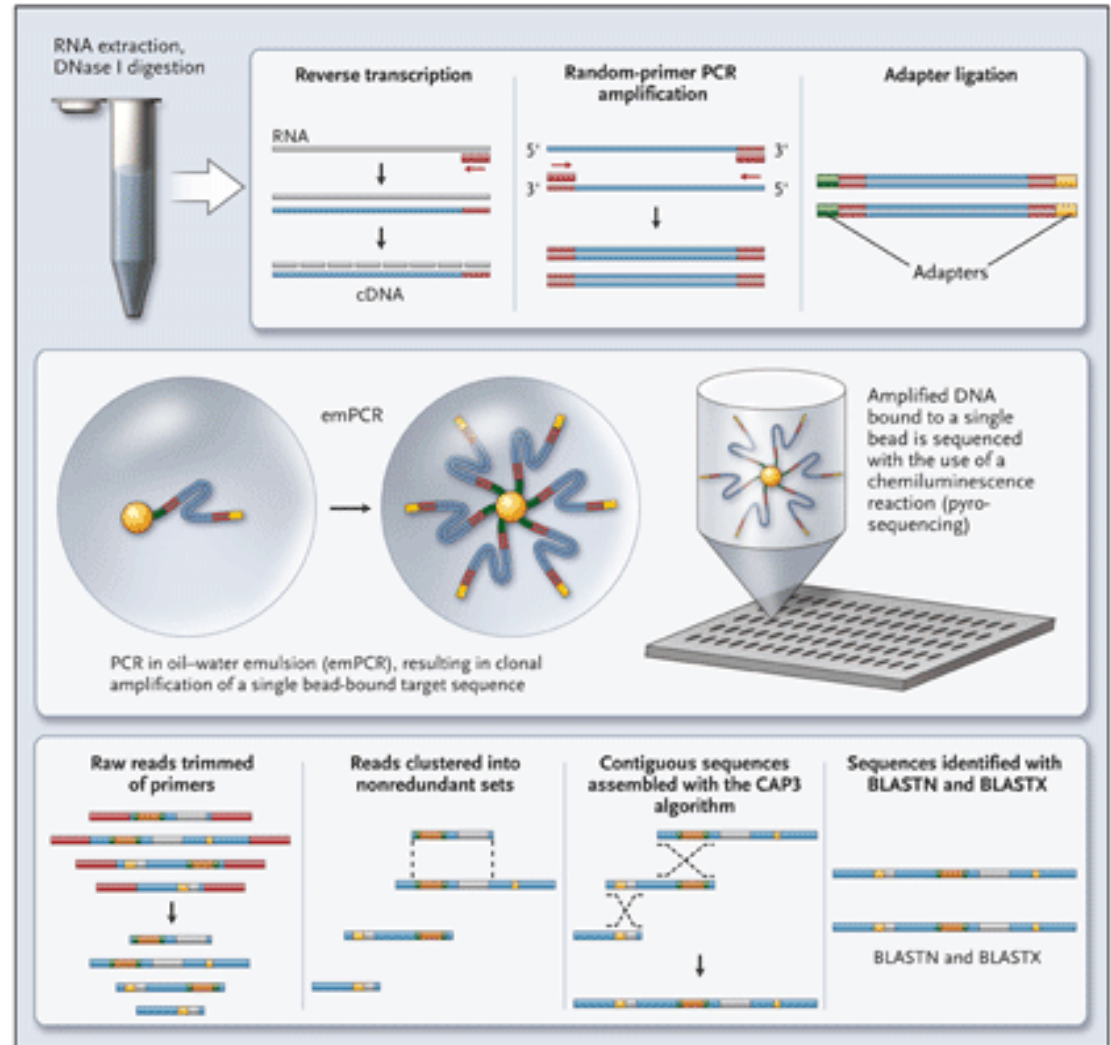
- Bacteria: Non-TB mycobacteria, Antimicrobial Resistance: VRE, MRSA, Carbapenem-Resistant GNR (CRE)
- Fungi: Azole-resistant *Candida spp.* *Candida auris*, *Mucor*, *Scedosporium*, Dematiaceous moulds.
- Viruses: Zika, multidrug-resistant CMV, adenovirus vectors, parainfluenza in HSCT, SARS, HHV6,-7,-8,
- Parasites: *Cryptosporidium*, *T. cruzi*, *Leishmania*, *Strongyloides*.

Why new(er) pathogens?

- Prolonged **patient survival**
- Broad **geographic exposures** (endemic infections, travel, employment)
- Shifts in **nosocomial flora** with prolonged hospitalizations, organ shortage
 - ✓ Routine prophylaxis (fluconazole, vancomycin, cephalosporins, antivirals) → **antimicrobial resistance**
 - ✓ Renal, hepatic, pulmonary dysfunction (sicker patients)
- **Intensified Immunosuppression**
- **Improved diagnostic assays**

High-Throughput Sequencing Method

G. Palacios et al, NEJM 3



Risk for infection is a semiquantitative relationship between:

Epidemiologic exposures
(including latent infections)
and

“The Net State of Immune Suppression”

After: Robert Rubin (1970's)

Careful Medical History: Epidemiologic Exposures May Be Recent or Distant

Recent

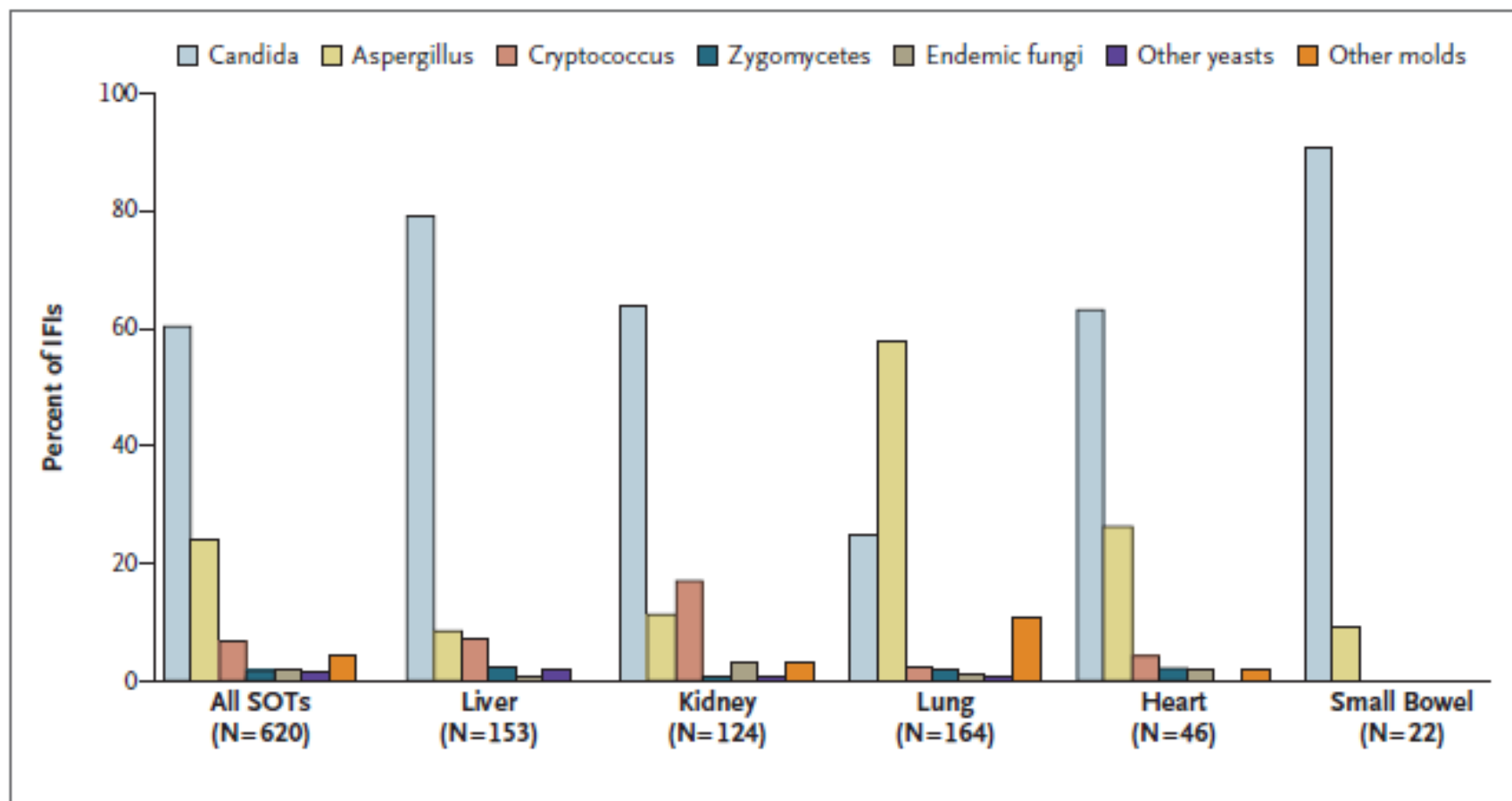
- **Nosocomial flora**
- Catheter-related
- Complex Surgery
- Community acquired
- Urinary tract infection
- Aspiration
- *Cryptococcus*
- *Legionella*
- **Donor-derived***

Distant

- Tuberculosis
- Colonization (remote)
- Non-tuberculous mycobacteria
- *Strongyloides*
- Herpesviruses
- Toxoplasmosis
- *Leishmania*, *T. cruzi*
- Histoplasmosis, *Coccidioides*
- HTLV, HIV, HCV, HBV

*e.g., Dengue, Chikungunya, LCMV, Rabies, VRE, **MDRO, Candida, TB**

HTLV, human T-cell lymphotropic virus; HIV, human immunodeficiency virus.



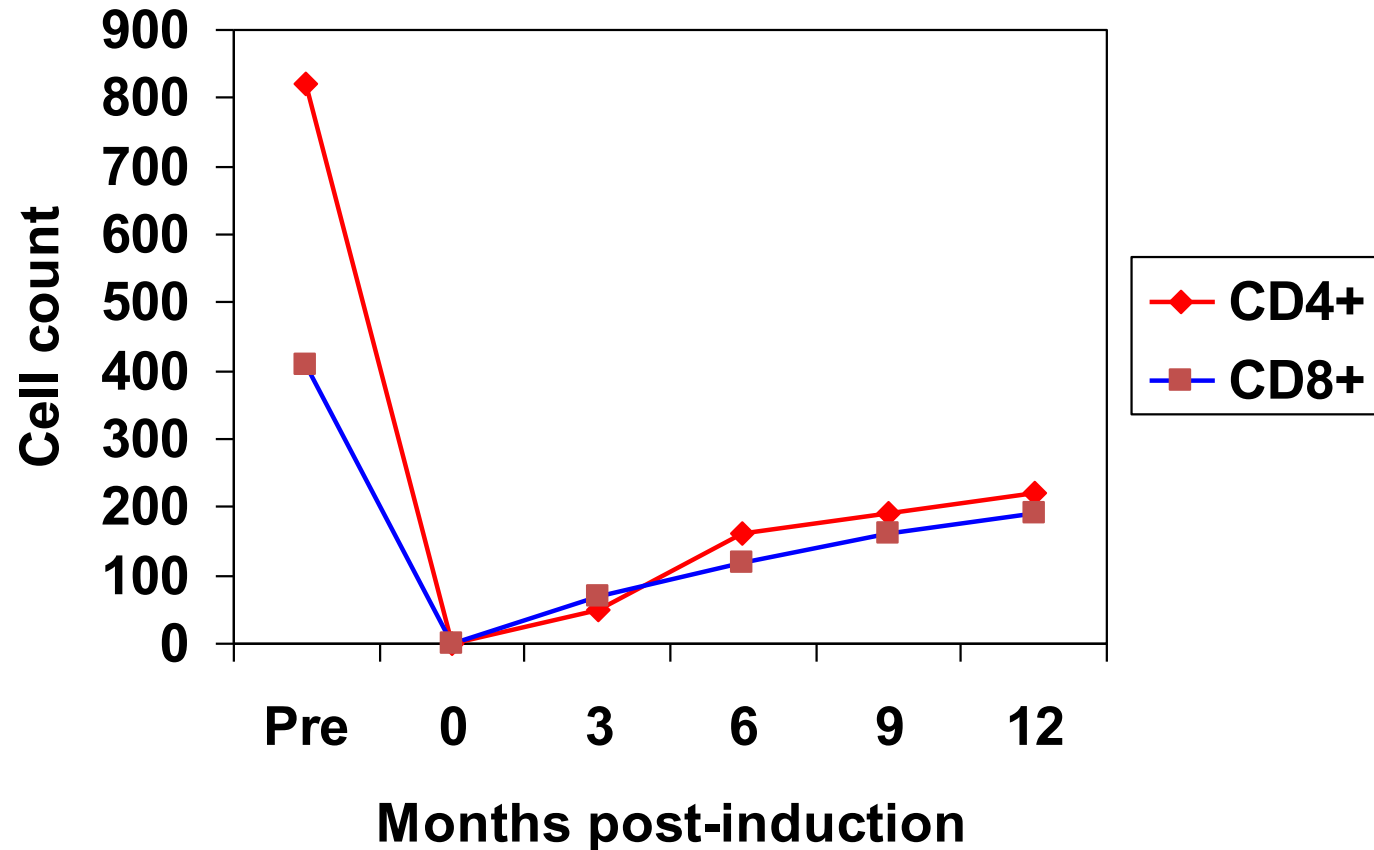
“Net State of Immune Suppression”

- **Immunosuppressive Therapy:** Type/Temporal Sequence/Intensity -- “AUC”
- Prior therapies (Chemotherapy, Antimicrobials)
 - ***Role of disrupted Microbiome?***
 - Altered colonization patterns, C. difficile
- Mucocutaneous Barrier Integrity (catheters)
- Neutropenia, Lymphopenia (depth, duration)
- Underlying Immune Deficiency & Metabolic conditions: Uremia, **Malnutrition**, Diabetes, Alcoholism/cirrhosis, Anatomy (leaks, COPD/bronchiectasis)
- **Viral Co-Infection** (CMV, Hepatitis B and C, RSV): Immune Modulation/Rejection/Cancer

Selected Types of Immunosuppression and Infection: “Biologic” Agents

- **Antilymphocyte globulins** – deplete lymphocytes (T and/or B cells, possibly NK and dendritic cells depending on drug)
 - Usually used in “induction” therapy or treatment of rejection
- **T-cell depletion** predisposes to viral infection, mimics alloimmune response & activates latent (herpes)viruses, $\text{TNF}\alpha \rightarrow$ fever $\rightarrow$ cytokines
 - Rabbit (Thymoglobulin), horse, humanized monoclonal
 - Reconstitution with effector/memory phenotypes under CNI’s
- **B-cell depletion** (anti-CD20, not plasma cells): $\downarrow$ antibodies (encapsulated bacteria, yeasts?)
- **Co-stimulatory blockade**: few effects but late EBV-PTLD? (Belatacept)

Single-Dose Alemtuzumab leads to Long-Term T-Cell Depletion

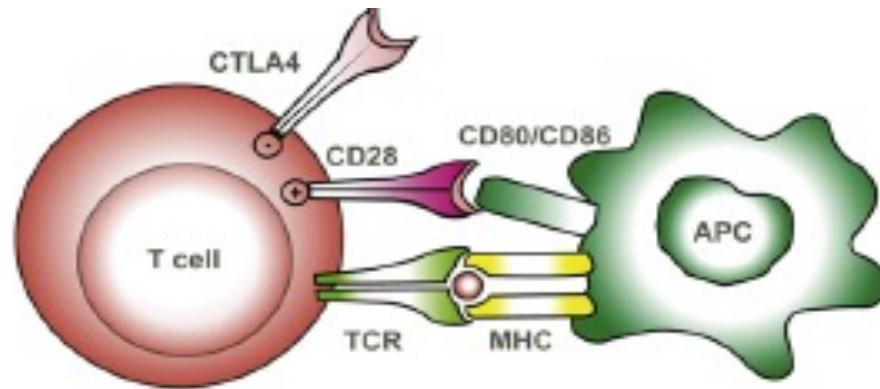


CTLA-4Ig Inhibitors: (Belatacept)

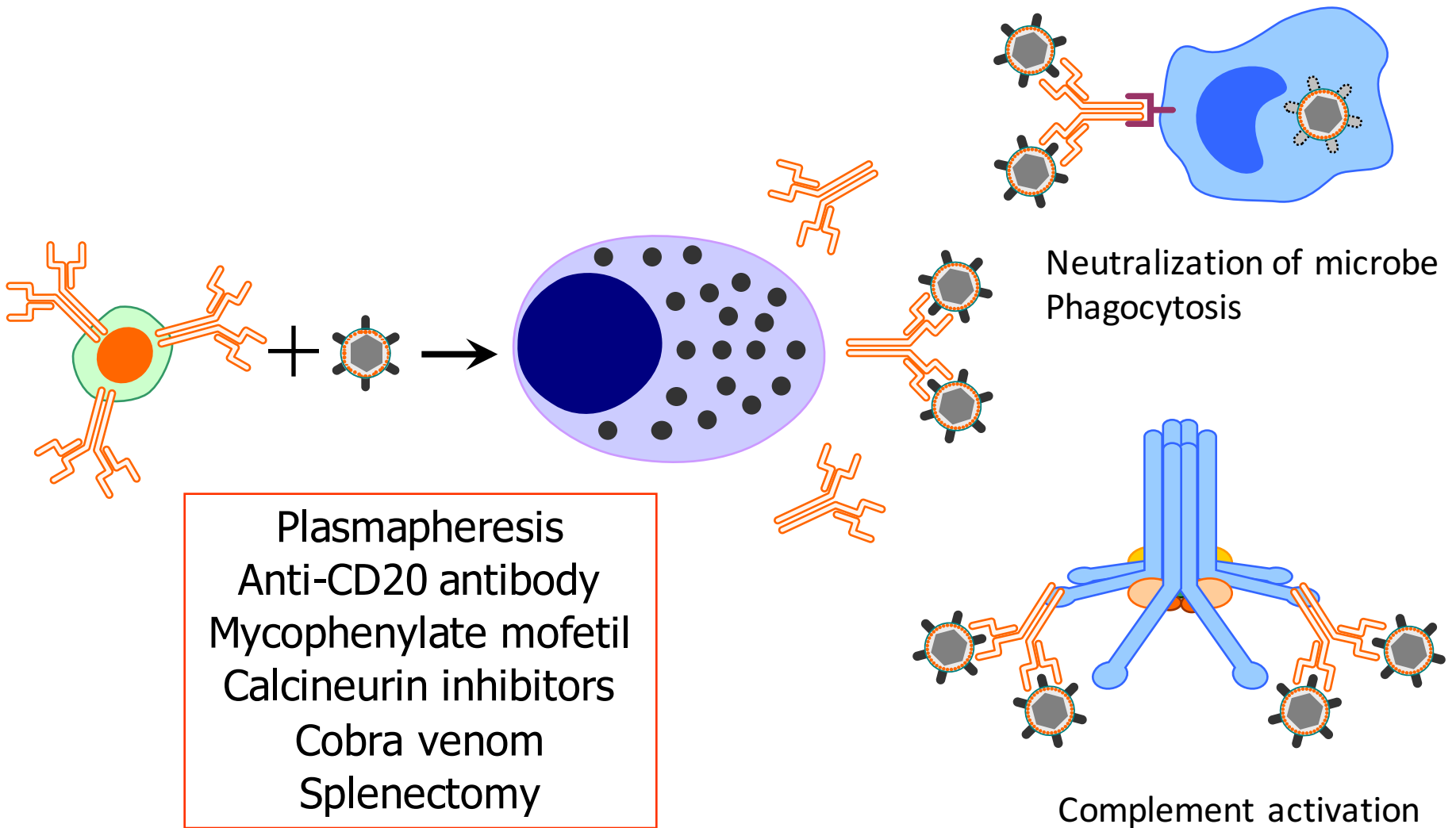
Costimulation blockade (signal 2: CD28/B7-CD80/CD86):
Costimulatory pathways are normally required for optimal and sustained activation of naïve T-cells. Costimulation involves a complex array of developmentally regulated surface receptors and intracellular pathways.

Figure courtesy of Flavio Vincente.

See: XC Li et al, Immunological Rev 229:271-293, 2009

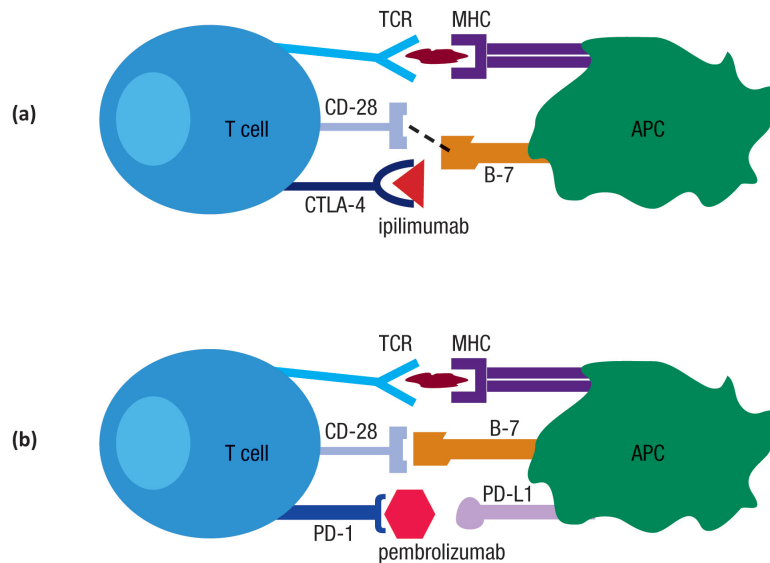


B lymphocyte function



Newer Agents

- **Signal transduction inhibitors** block the activities of molecules that participate in signal transduction, the process by which a cell responds to signals from its environment.
- **Gene expression modulators** modify the function of proteins that play a role in controlling gene expression.
- **Apoptosis inducers** cause cancer cells to undergo a process of controlled cell death = apoptosis.
- **Angiogenesis inhibitors** (small molecules) block the growth of new blood vessels to tumors (a process called tumor angiogenesis) e.g., vascular endothelial growth factor (VEGF).
- **Immunotherapies** including **monoclonal antibodies that deliver toxic molecules.**
- **Checkpoint inhibitors:** autoimmune disorders
- **Car-T cells:** Neurologic syndromes



Drug or Drug Class (Mechanism of possible effect)	Plasma Exposure to CNI/mTOR	Plasma Exposure to Drug (Mechanism)	Recommended Approach+
Azole antifungal agents (CYP2C9, CYP2C19, CYP3A4 Inhibition)	Increased	Increased	TDM essential, depends on drug
Warfarin		PT/INR increased (CYP2C9 Inhibition)	TDM, evaluate for risk for bleeding
Omeprazole (proton-pump inhibitors)	increased (gastric pH with CYP2C19/CYP3A4 Inhibition)	Increased (CYP2C19/CYP3A4 Inhibition)	TDM, avoid if possible
HMG-CoA Reductase Inhibitors (statins)		Increased (CYP3A4 Inhibition)	Monitor for side effects
Calcium Channel Blockers (Dihydropyridine)	Increased	Increased (CYP3A4 Inhibition)	Dose adjustment, avoid
Oral Contraceptives (ethinyl estradiol , norethindrone) (CYP3A4 Inhibition)	Increased	Increased (CYP2C19 Inhibition)	TDM
Corticosteroids	Increased (CYP3A4 Inhibition)	Increased?	Monitor for efficacy, steroid levels may increase
Rifampin, Rifabutin (CYP450 Induction)	Reduced	Increased (CYP3A4 Inhibition)	TDM, avoid if possible (contraindicated)
HAART May increase CNI levels but drop HIV meds	Increased (CYP450 Induction)	Reduced (CYP2C9 and CYP2C19 induction)	TDM, avoid if possible (contraindicated), monitor for antiviral effectiveness
Terfenadine, astemizole, cisapride, Quinidine, Pimozide	Increased (CYP3A4 and P-gP Inhibition)	Varies	Potential for QT prolongation, arrhythmias, contraindicated. Elevated quinidine levels.

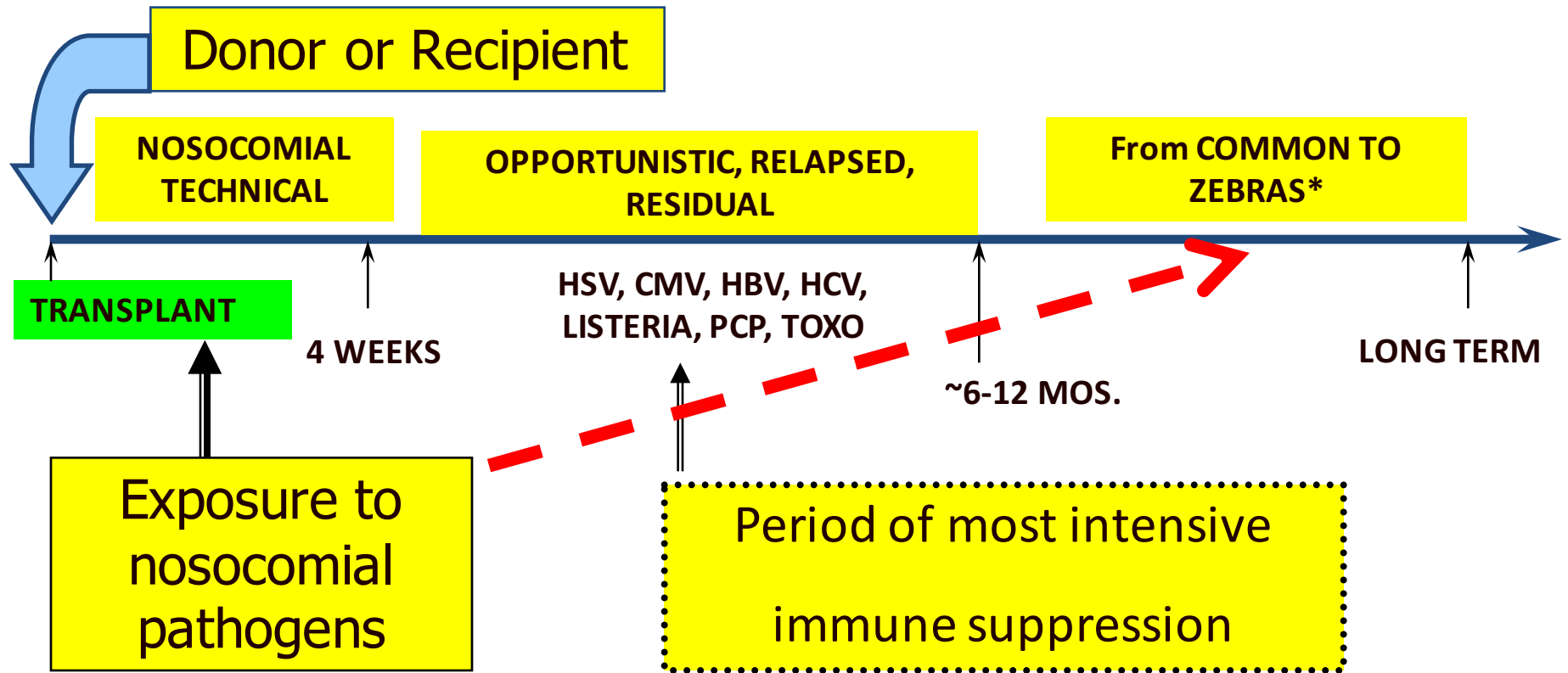
Measures of “Immune Deficits”

Most patients have mixed immune deficits

- Multiple drugs (changing)
- Variable metabolism
- Unknown native “immune function”
- Unknown meaning of drug levels in individual
- Differing exposures and background immunity
- Few relevant assays – lymphocyte markers

**Must individualize immune suppression,
but generally lack appropriate assays**

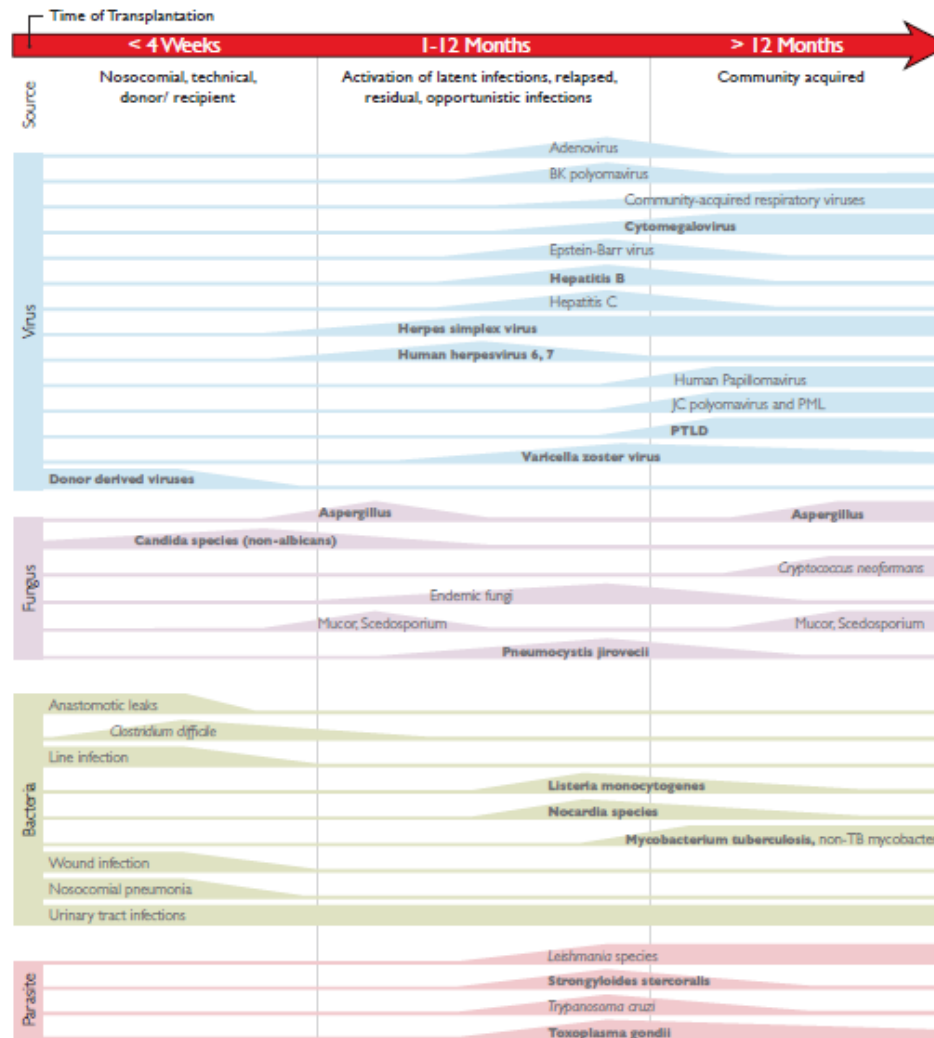
The Timeline of Post-Transplant Infections



COMMON VARIABLES in IMMUNE SUPPRESSION:

- ☹️ MANY DIFFERENT REGIMENS (steroid-free, CNI-free, Antibody Induction, costimulatory blockade)
- ☹️ TREATMENT OF REJECTION -- “Resets clock”
- ☹️ NEUTROPENIA (virus or drug-induced)
- ☹️ VIRAL INFECTIONS (CMV, HCV, EBV, RSV ...)

Timeline of Common Post-Transplant Infections



Key

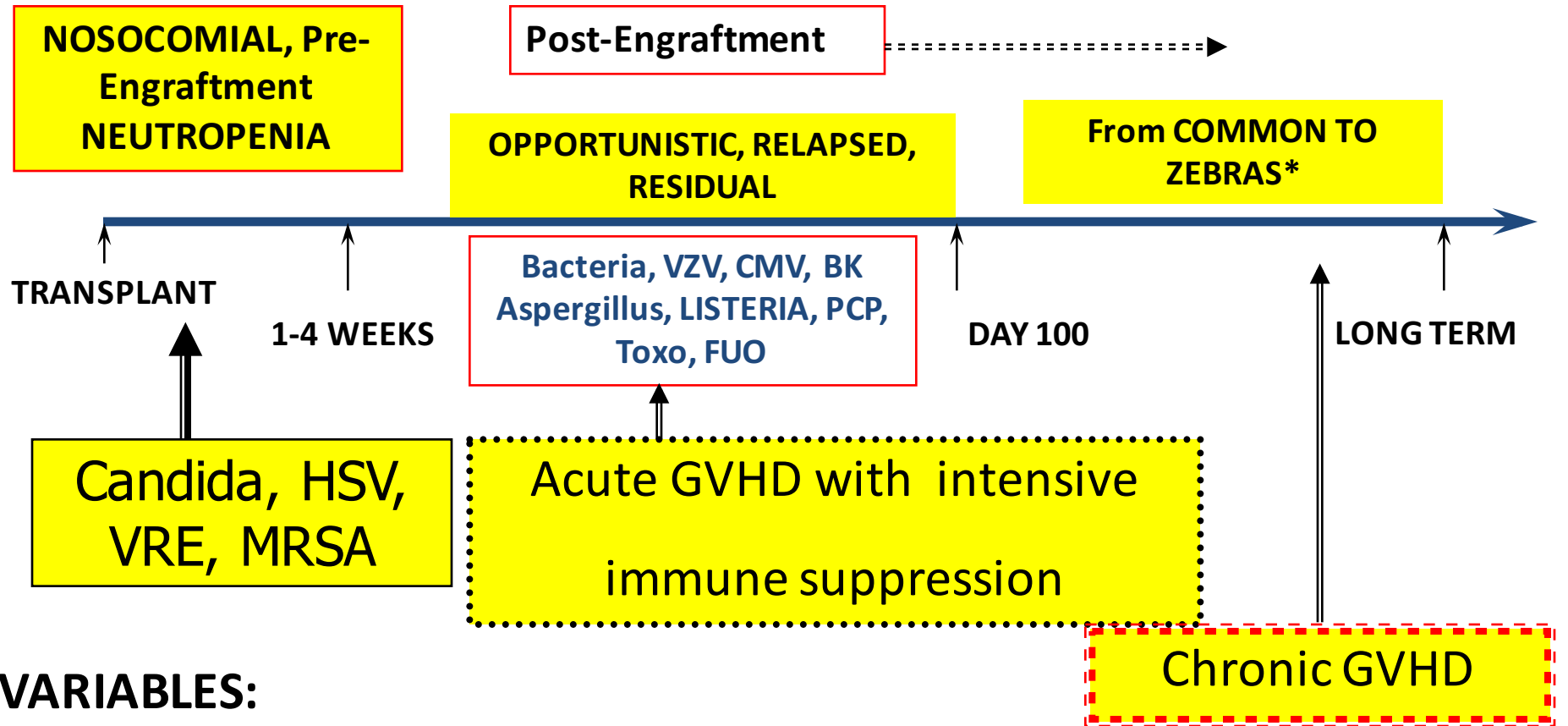
Thickness of line indicates relative risk.

Bold type indicates infections potentially preventable by prophylaxis. May be delayed until prophylaxis is discontinued.

Impact of routine prophylaxis: What infections don't they have?

- **Surgical prophylaxis** for common pathogens (e.g., UTI – renal; fungi - liver, bowel, pancreas or lung) or known colonizers of the individual patient (VRE, Aspergillus)
- **Pneumocystis carinii** (jirovecii) – Note: TMP-SMX has activity vs. common urinary-GI-Respiratory pathogens, most Nocardia, Listeria (6 months to life)
- **Cytomegalovirus** (HSV, VZV): 3-6 months (based on risk) – usually ganciclovir or valganciclovir (Note: not FDA approved for liver transplantation)

The Timeline of Post-BMT/HSCT Infections



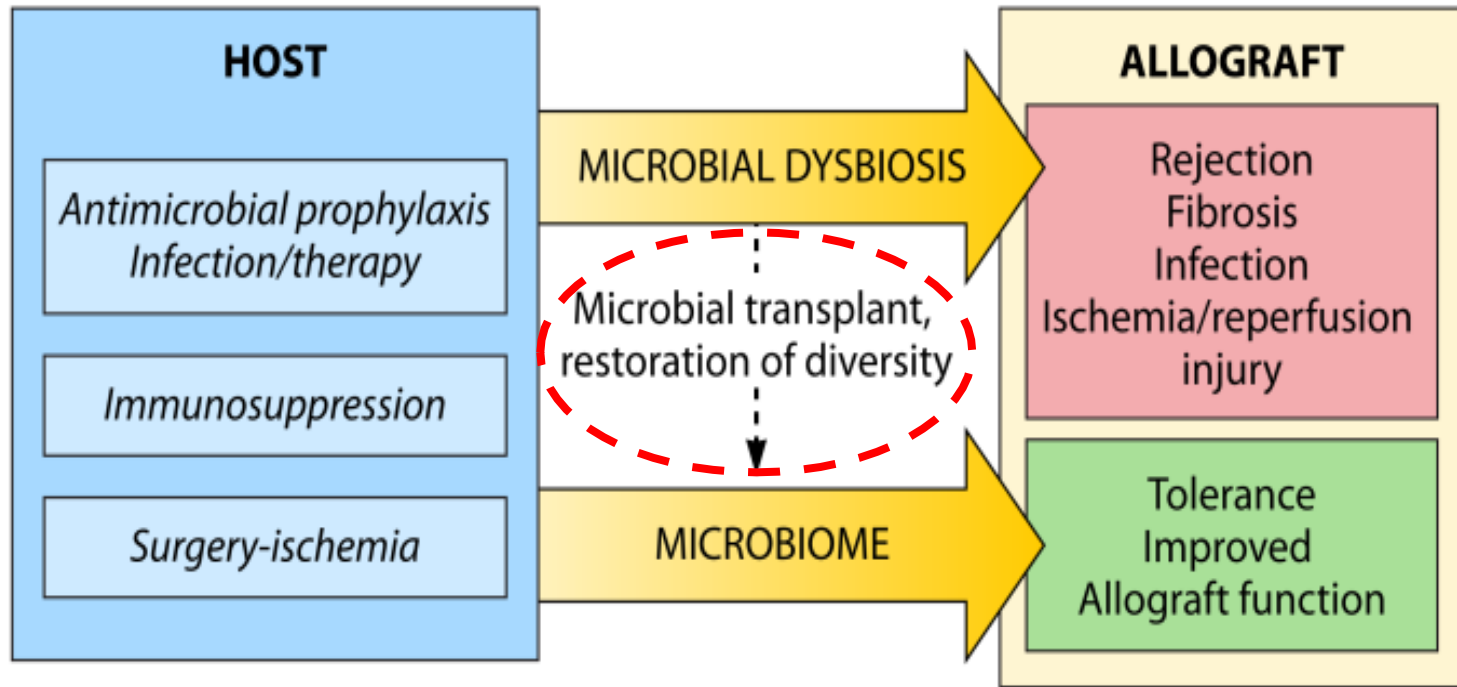
VARIABLES:

- ☹ **Greater variability in timing; Engraftment syndrome**
- ☹ **Central roles of neutropenia & GVHD**
- ☹ **ANYTIME: CMV, VZV, EBV, PCP, Adenovirus, HHV6, MYCOBACTERIA, LEGIONELLA, NOCARDIA**

Before we leave ... and lest you think
we now what are doing...

- Let's just play with some newer concepts.

Microbial Shifts in Transplantation



- Can GI microbiome be manipulated to produce sustainable immune changes that allow reduction or elimination of exogenous immunosuppression?
- Can microbiome studies be used as a biomarker for graft rejection and tolerance?

“Normal Microbiome” Prevents Chronic Rejection: **Good Pseudomonas in the Lungs?**

- Microbial communities in CF lung transplant patients fall into two mutually exclusive groups
 - Dominated by Pseudomonas (do not contain Aspergillus)
 - Dominated by Streptococcus and Veillonella (Gram +)
- Recolonization of the allograft by Pseudomonas in individuals with cystic fibrosis is **not associated with BOS.**
- In general, **reestablishment of pre-transplant lung microbiomes in the allograft seems to have a protective effect against BOS**
- **De novo acquisition of microbial populations often belonging to the same genera may increase the risk of BOS.**

Infection with TLR-ligation can block tolerance induction (Innate immune function)

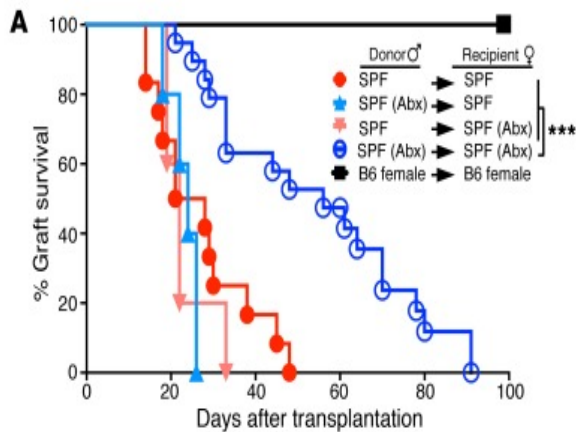
- Tissue inflammation (infection, surgery) and injury → increased trafficking of T-cells
- *Listeria monocytogenes* (intracellular bacterium) → IFN β blocks heart and skin tolerance (T Wang et al, AJT, 10:1524, 2010)
- *Staphylococcus aureus* (but not *Pseudomonas aeruginosa*) → IL-6 (EB Ahmed et al, AJT, 11:936, 2011)
- Newcastle disease virus → IFN α by dendritic cells (DC) and macrophages (Y Kumagi et al, Immunity, 27:240, 2007)

Mechanism: Non-specific stimulation (cytokines, chemokines) of T-cells or increased antigen presentation by APCs?

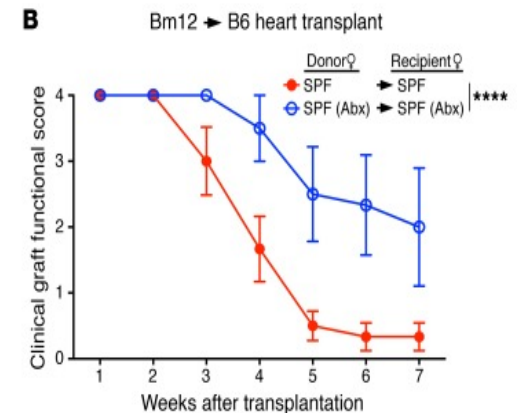
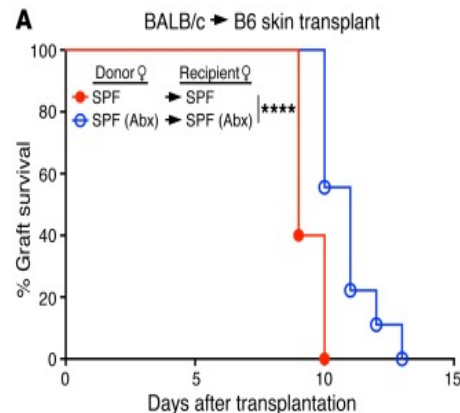
The composition of the microbiota modulates allograft rejection

(Lei YM et al. J Clin Invest. 2016 Jul 1;126(7):2736-44)

- The influence of host and donor microbiota on skin and cardiac transplant rejection
- Pretreatment of donors and recipients with broad-spectrum antibiotics (Abx) or use of germ-free (GF) donors and recipients resulted in prolonged survival of minor antigen-mismatched skin grafts. Increased graft survival correlated with reduced type I IFN signaling in antigen-presenting cells (APCs) and decreased priming of alloreactive T cells.**
- Colonization of GF mice with fecal material from untreated conventional mice (but not ABX treated mice) increased APC priming of alloreactive T cells and accelerated graft rejection → **Alloimmunity is modulated by the composition of microbiota rather than the quantity of bacteria.**
- **Targeting microbial constituents is a potential therapeutic strategy for enhancing graft acceptance.**

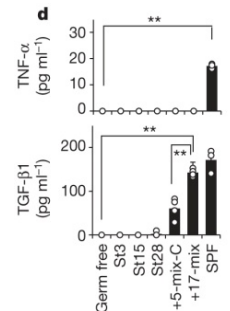
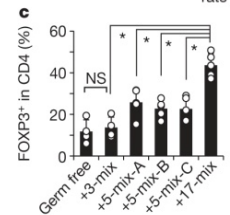
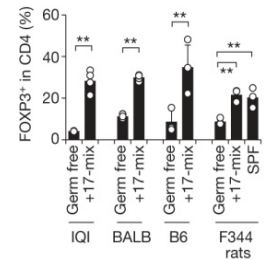
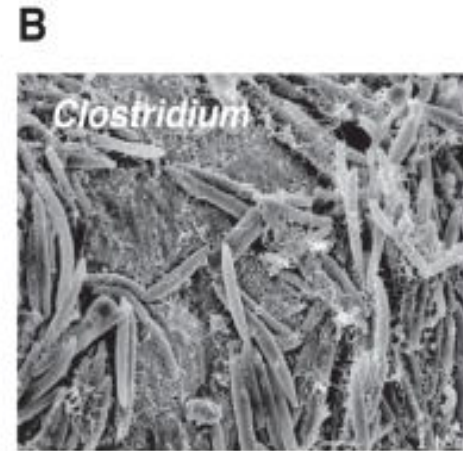
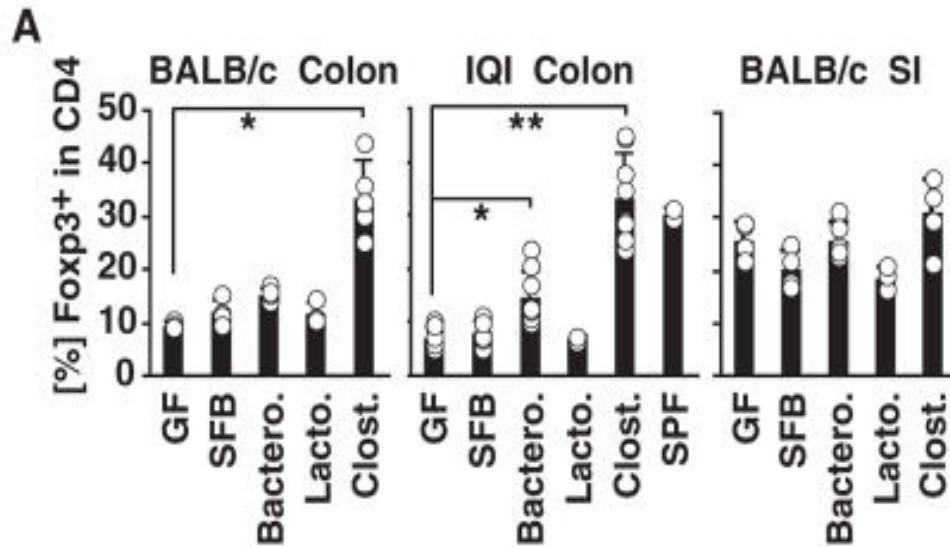


Skin: Minor Ag Mismatch



Abx pretreatment delays rejection of major antigen-mismatched skin (BALB/c → B6) and MHC class II-mismatched cardiac (Bm12 → B6) allografts

Clostridia and mixtures of Clostridia species available to this project from Vedanta induce T_{reg} accumulation in colonic lamina propria.



(A) GF BALB/c or IQI mice were colonized with segmented filamentous bacteria (SFB), 16 strains of *Bacteroides* (Bactero.), 3 strains of *Lactobacillus* (Lacto.), or 46 strains of *Clostridium* (Clost.) for 3 weeks. The percentage of Foxp3⁺ cells within the CD4⁺ cell population in the colon and SI of individual mice was analyzed by flow cytometry ($n \geq 5$ mice per group). (B) Electron micrograph showing the proximal colon of Clost.-colonized B6 mice. (Arpaia N et al. Nature. 2013; 504:451-455)

K Atarashi et al. Nature 1-5 (2013) doi:10.1038/nature12331

Infection, Immunity and Transplantation

Transplant Phase

Pre-Transplantation

- Organ dysfunction
- Colonization (ICU)
- Antimicrobials
- Infections
- Vaccination

Transplant Surgery

- Infection (technical)
- Tissue injury
- Organ dysfunction

Post-Transplantation

- Depletion and Immune reconstitution
- Immunosuppression
- Community exposures
- Opportunistic infection

Immune Effects

Immune memory

- Heterologous or cross-reactive epitopes
- Vaccination
- Latent or persistent infections
- Microbiome
 - Commensals
 - Colonization

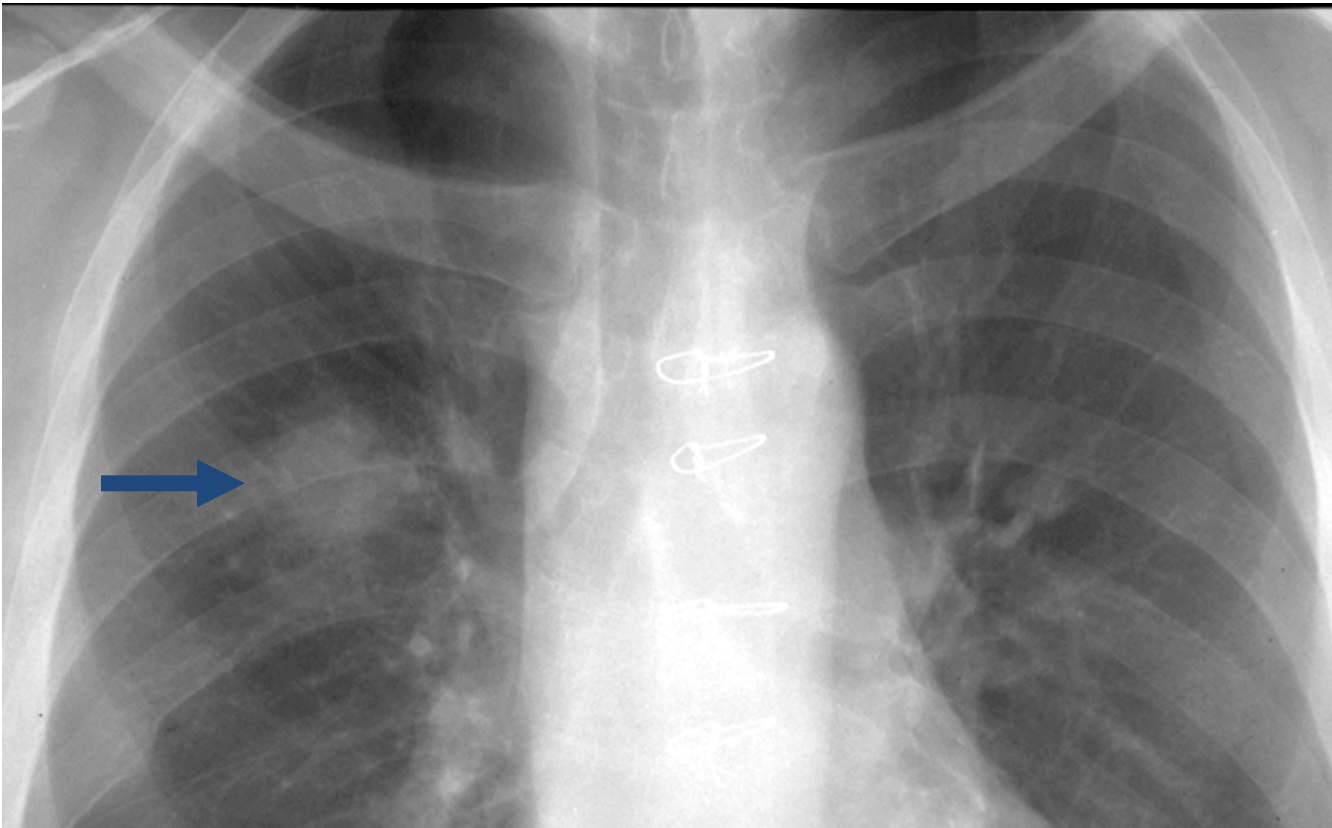
Immune Stimulation

- **Innate:** Ligands for PRR → cytokines, chemokines
- Microbial derived antigens
- Allograft Damage-associated molecular pattern molecules
- Enhanced antigen presentation
- **Adaptive:** Alloimmune stimulation → ↓ tolerance, ↑ rejection

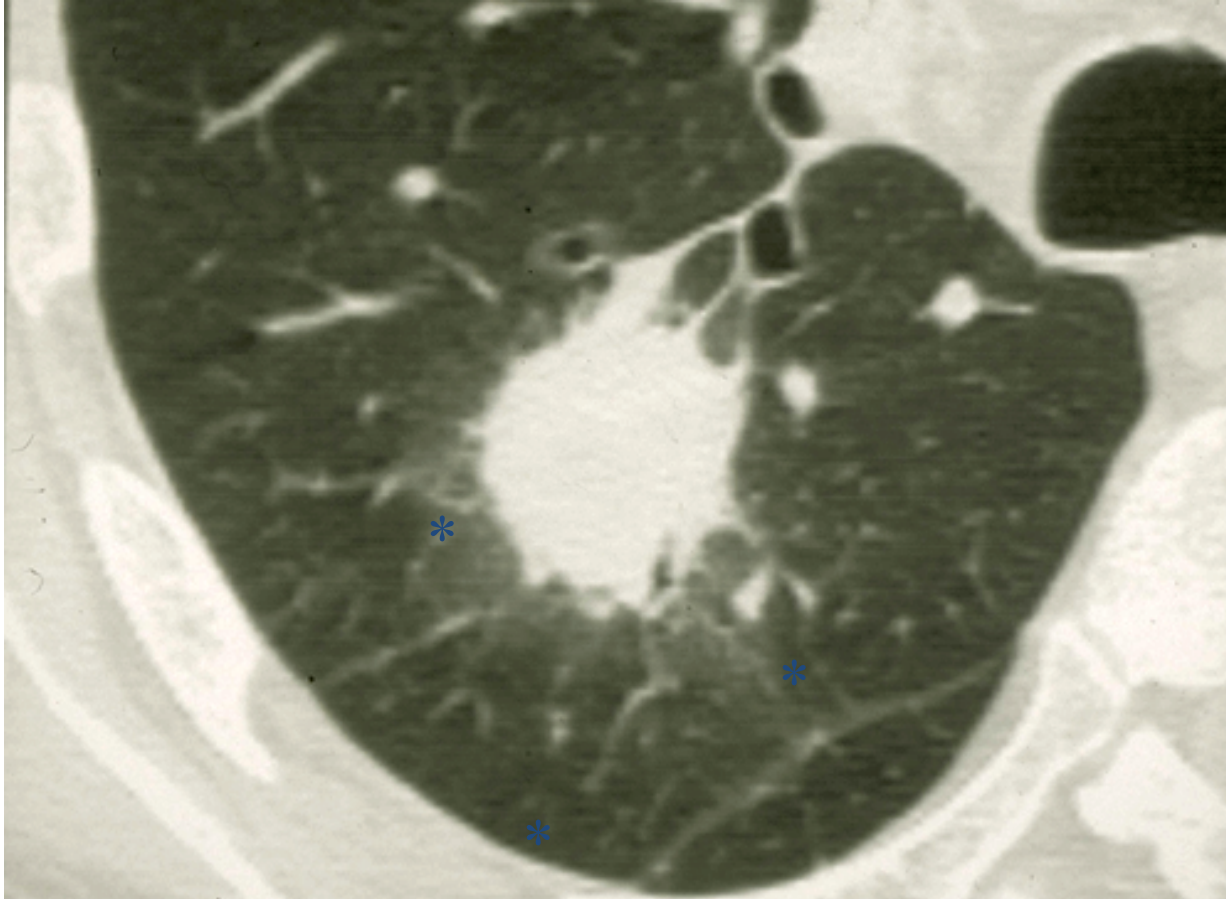
Heterologous or cross-reactive memory

- Acute/Chronic Rejection
- Failed costimulatory blockade
- Narrowed immune responses (infections)
- Stimulation by new or “persistent infections” (graft injury) → cytokines, chemokines
- Increased effector over Tregs

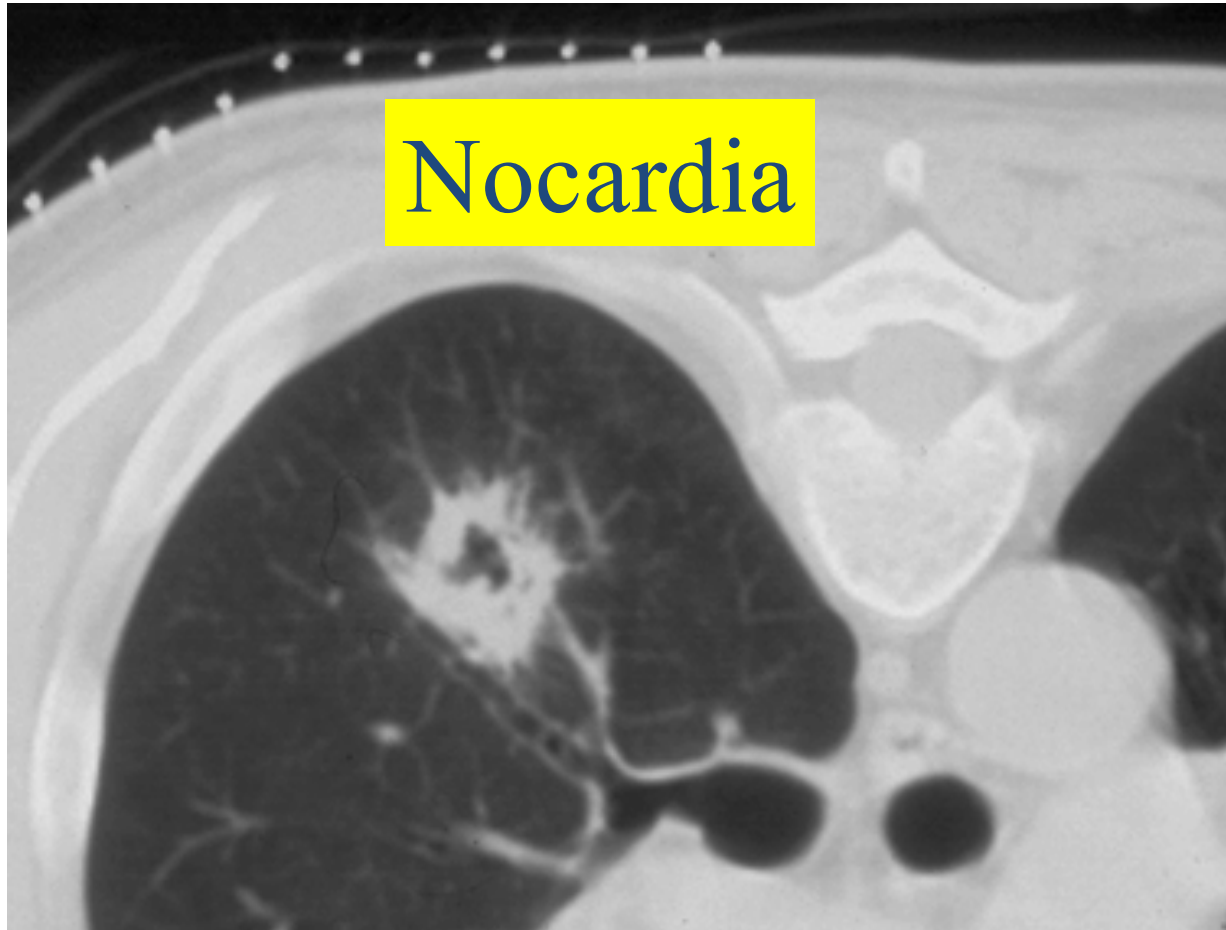
Specific Diagnosis Remains Key:
Fever, Cough Two Years Post Cardiac Transplant



Nodule with Faint Halo at Onset



Cavitated Nodule Five Days Later--No Response to Antifungal therapy



Summary - Infection in the Immunocompromised Patient

- More difficult to diagnose
- Advanced at the time of diagnosis
- Drug toxicity is common – specific diagnosis is key!!
- The intensity of immune suppression (including anatomic defects) is as important as antimicrobial therapy in caring for these patients

Thank you!!



If I can help:
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