



OPTUMHealth™
Education

The Challenge of Infection in Transplantation

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Disclosure

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Which of the following patients are immunocompromised?

1. Insulin dependent diabetic?
2. Organ transplant recipient?
3. Stem cell recipient?
4. Dialysis-dependent individual?
5. Person with COPD on low (15 mg/day) does steroids?
6. Patient with *Aspergillus pneumonia*?

Immunocompromised patients with infection generally do not have fevers?

1. True?
2. False?

Infections due to cytomegalovirus can be prevented?

1. True?
2. False?

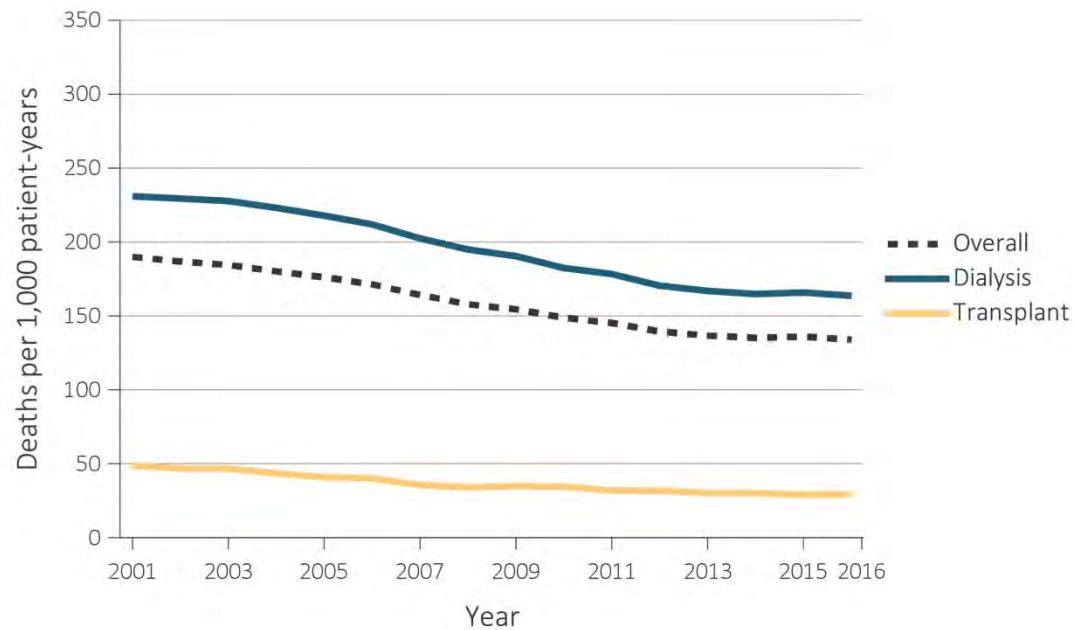
We have good assays to measure
immune competence?

1. True?
2. False?

You should always avoid
immunosuppression if possible?

- Too little is better ... ?

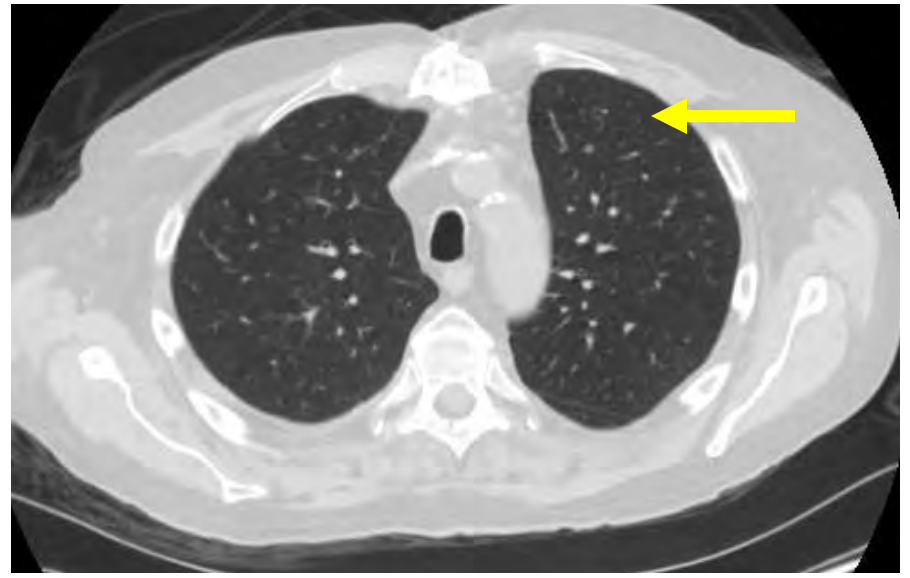
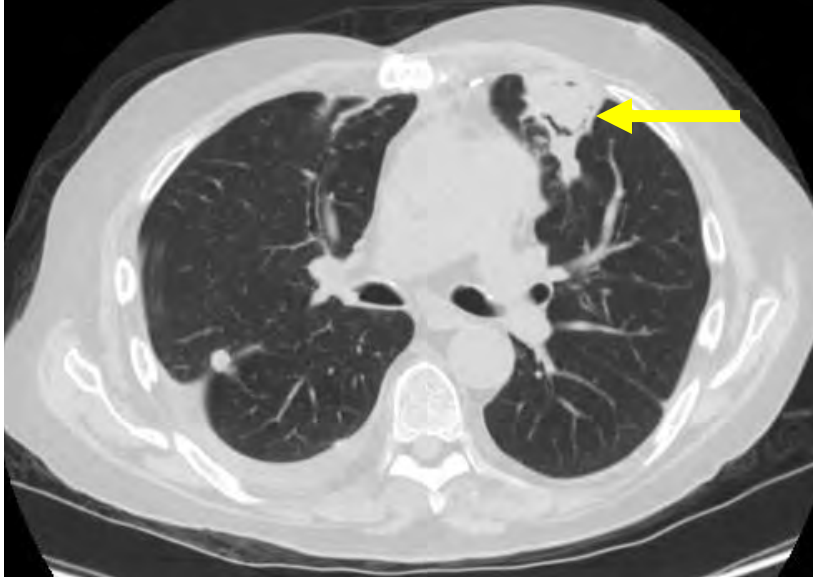
ESRD. Mortality by treatment modality



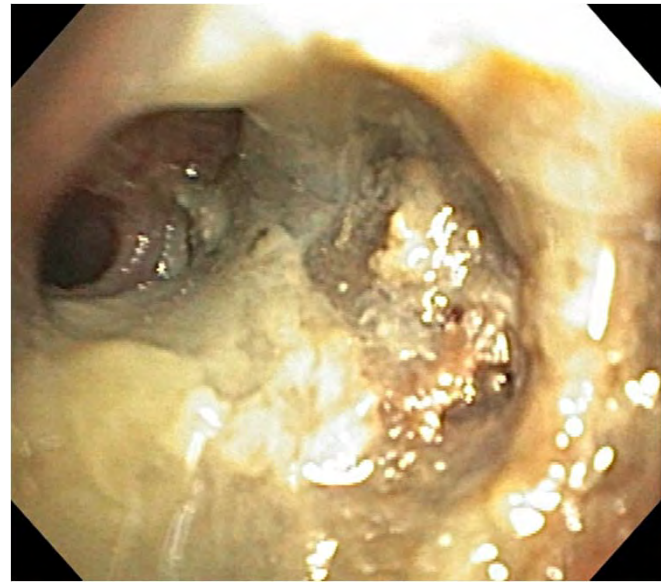
Immunosuppression

65 year old male with a history of ischemic cardiomyopathy underwent heart transplantation (CMV D+/R-). Received minimal immunosuppression (basiliximab, delayed tacrolimus) due to poor post-op renal function (now Cr=1.4). Post transplant course has been complicated by high grade allograft rejection requiring high dose steroids.

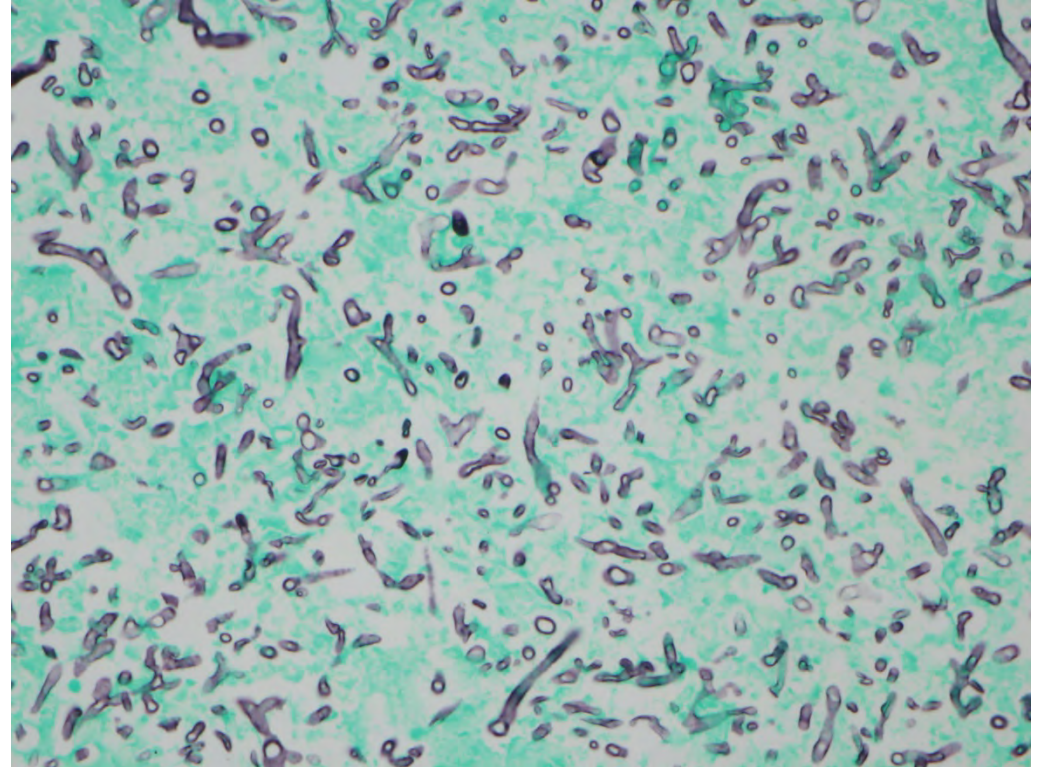
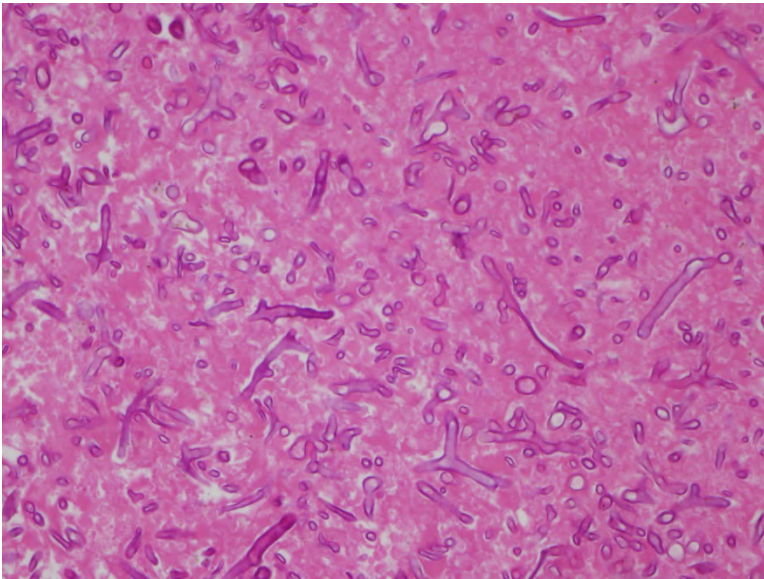
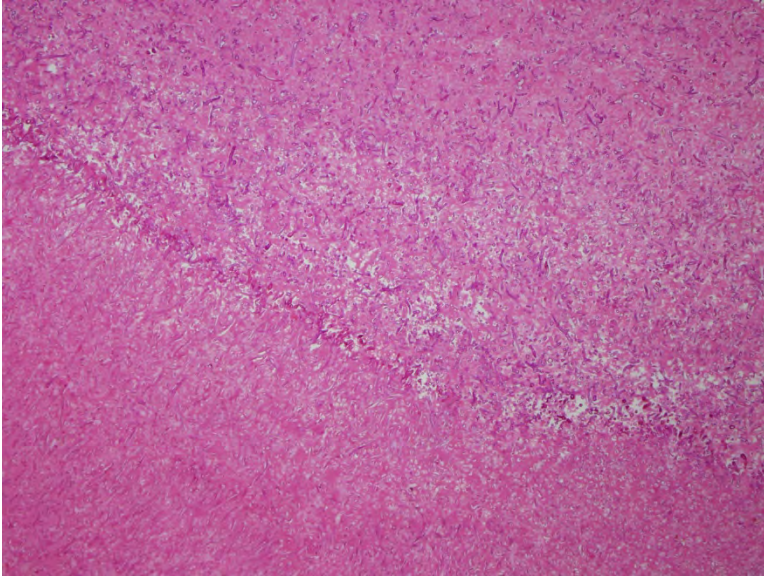
- Admitted for CMV colitis associated with a gram negative bacteremia (Enterobacter)
- Subsequent invasive pulmonary aspergillosis requiring liposomal amphotericin → voriconazole.
- New right sided pulmonary lesions and concern of breakthrough fungal infection. Bronchoscopy demonstrates a necrotic mass obstructing anterior segment RUL = mucormycosis + Nocardia. He is now on liposomal amphotericin and posaconazole and Imipenem and has undergone surgical right upper lobectomy.
- Diarrhea is positive for C.difficile



Bronchoscopy



Pathology



Key Concepts:

Infection in Immunocompromised Hosts

- More effective immunosuppressive regimens have reduced rates of acute graft rejection
 - More atypical presentations (e.g., humoral graft rejection)
 - Persistence of “Chronic Allograft Dysfunction”
 - New therapies (CAR-T, checkpoint inhibitors)
- Infections are common
 - Presentations are often atypical without fever or other signs
 - Infection exceeds rejection as a cause of hospitalization.
 - Prophylaxis is effective in delaying infection (not indefinitely)
- **Microbiological assays (molecular)** are now 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



What do I need to know?

- Multiple simultaneous processes
 - Broad Infectious Differential
 - Graft Rejection/GVHD
 - Immune status (IRIS, checkpoints)
- Imaging (collections, vascular issues, drainage)
- Prophylaxis: What don't they have?
- Drugs and interactions
 - **Calcineurin inhibitors: prerenal vasoconstriction – all have diminished renal function**
 - Azoles: ↑ CNI levels 2-3 fold or more
 - Toxicity of aminoglycosides and amphotericin
 - Can sacrifice kidneys to save a life
- **Urgency for specific diagnosis**
- **Prior microbiology (including VRE, MRSA, MDRO, molds)**
- Always consider **CMV status** (viral load) = **Fever and relative leukopenia**
- Graft function (**rejection**)

Organ	Consider
Kidney	BK virus
Liver	Cryptococcus, cholangitis, portal vein, hepatic artery
Heart	Chagas', CMV
Lung	CARV, BOS, Fungal, Nocardia
BMT/HSCT	Engraftment, tumor, GVHD
CAR-T	Cytokine release, encephalopathy syndrome
Checkpoint Inhibitors	immune-related adverse events

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
- ⇒ **Immune deficits are cumulative.**

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)

Fever is unreliable as a sign of infection 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. Up to 5% is due to graft rejection!
- 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

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: MDRO including VRE, MRSA, Carbapenem-Resistant GNR (CRE)
- Fungi: Azole-resistant *Candida spp.* *Candida auris*, *Mucor*, *Scedosporium*, Dematiaceous moulds.
- Viruses: Zika, multidrug-resistant CMV, TTV, adenovirus vectors, 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**

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

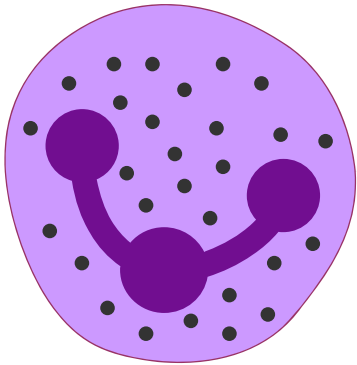
*e.g., Dengue, Chikungunya, LCMV, Rabies, VRE, **MDRO, Candida, TB**

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

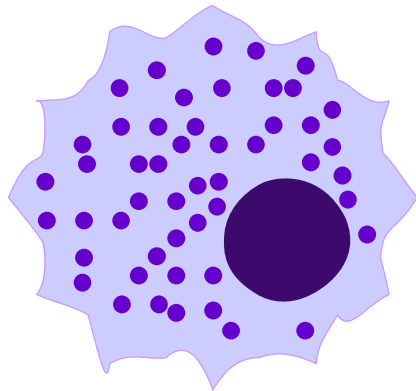
“Net State of Immune Suppression”

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

Old Immunology

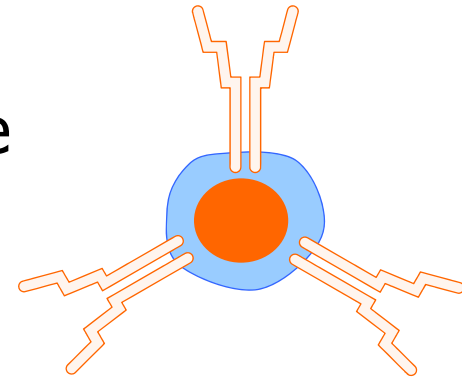


Neutrophil

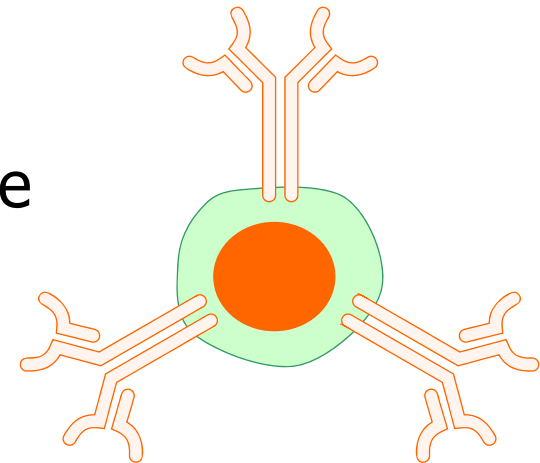


Macrophage

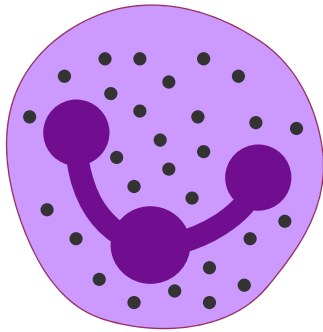
B-lymphocyte



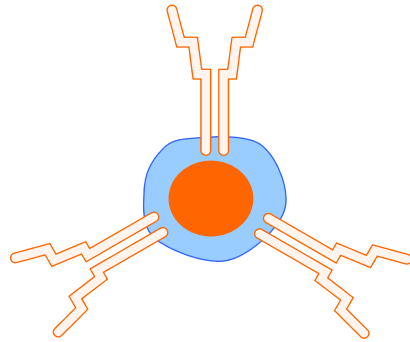
T-lymphocyte



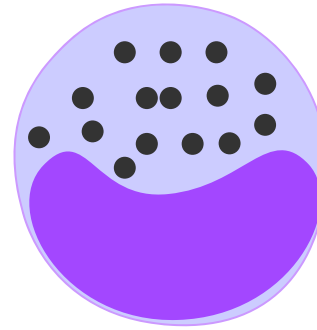
Neutrophil



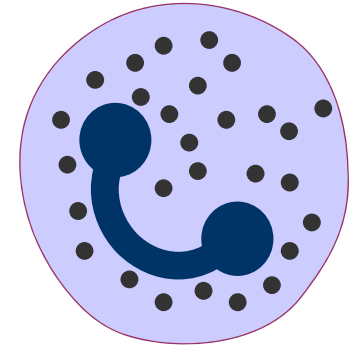
B-lymphocyte



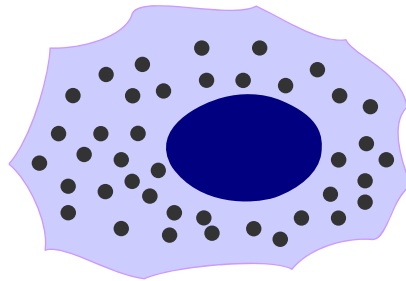
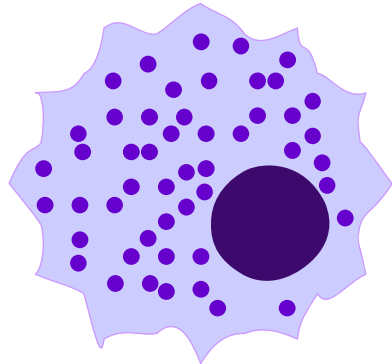
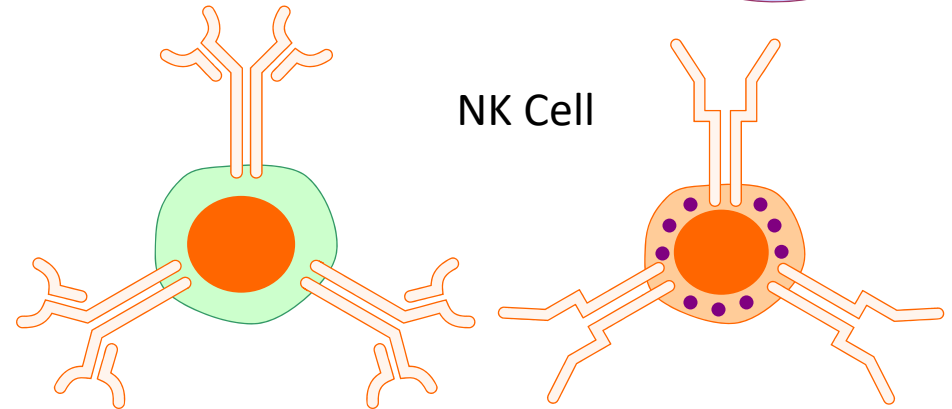
Monocyte



Basophil



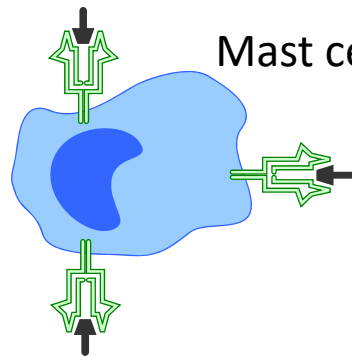
NK Cell



Macrophage

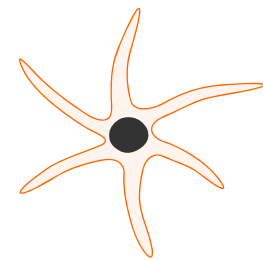
Mast cell

T-lymphocyte



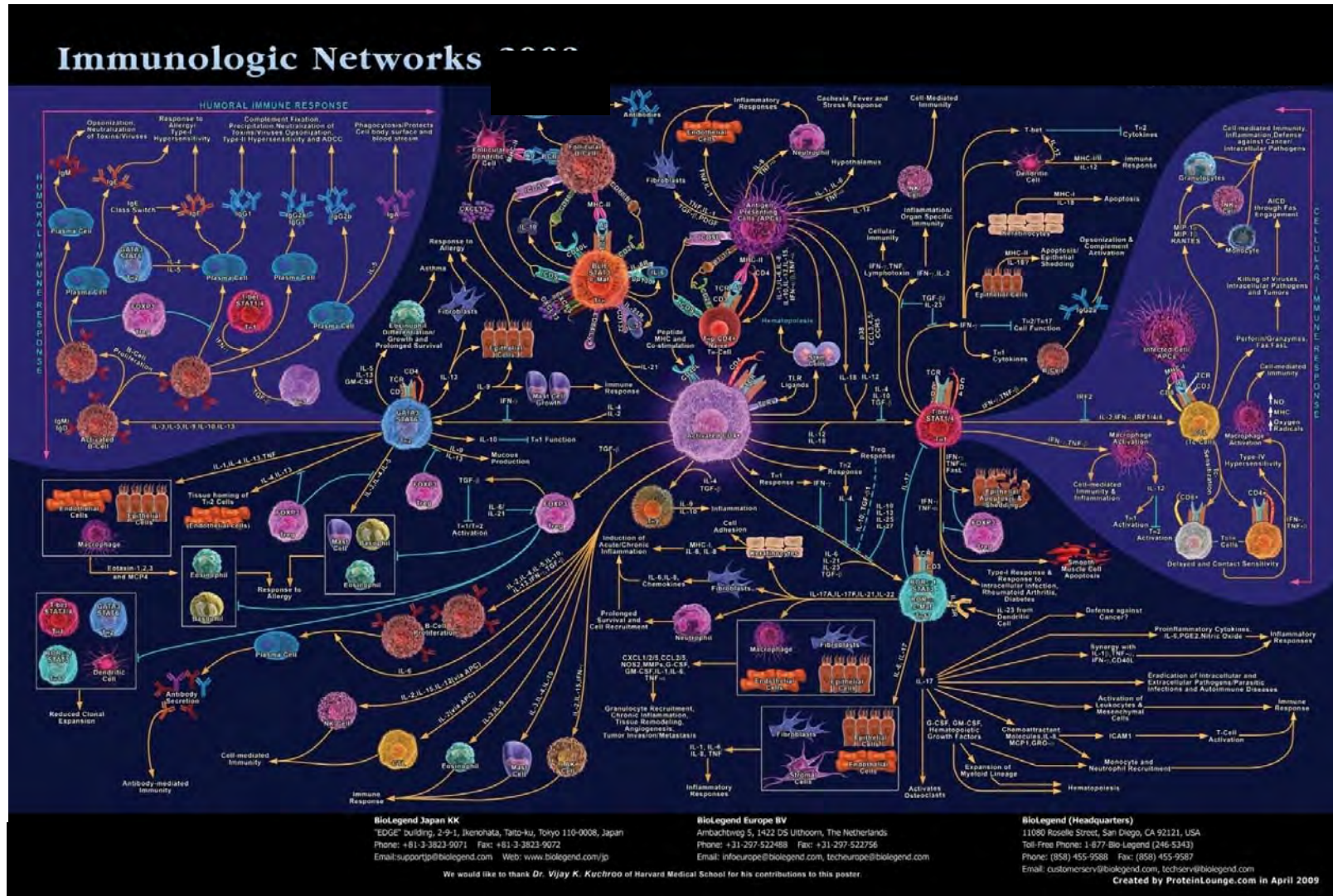
Antigen-presenting cell (macrophage)

Newer Immunology



Dendritic cell

...and interactions are increasingly complex!!



Immunosuppression and Infection: The Drugs (Quick Overview)

Standard Immunosuppression Protocols

High Risk

Thymoglobulin (1.5mg/kg/daily)

Tacrolimus 2mg BID (0.1mg/kg/d)

MMF 1gm BID



0 day 7

Alemtuzumab (30mg)

Tacrolimus 2mg BID (0.1mg/kg/d)

MMF 1gm BID



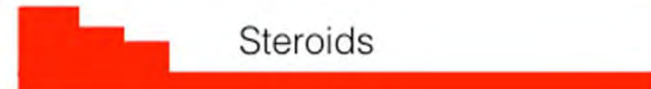
0 day 7

Low Risk

Basiliximab (20mg day 0,+4)

Tacrolimus 2mg BID (0.1mg/kg/d)

MMF 1gm BID



0 day 7

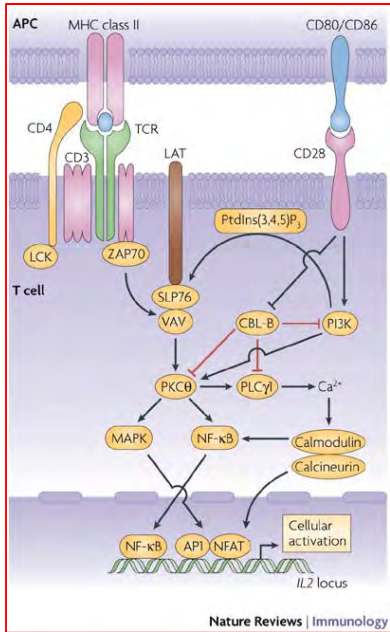
Only Steroids

Tacrolimus 2mg BID (0.1mg/kg/d)

MMF 1gm BID



0 day 7

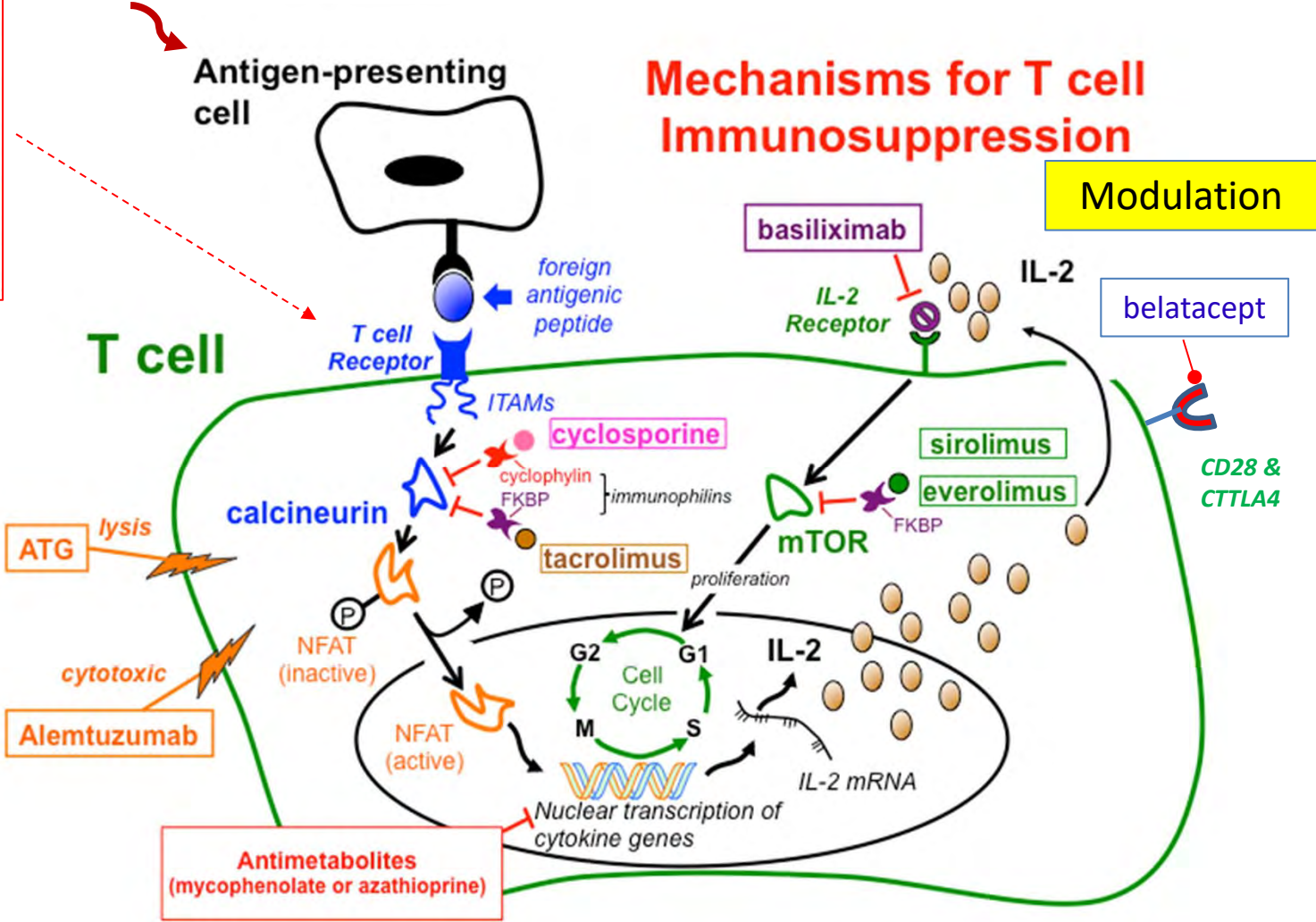


T-cell "Synapse" = TCR ("Signal 1")+ Costimulatory Receptor ("Signal 2")

Note: Effects of Steroids and CMV on APC

Mechanisms for T cell Immunosuppression

Modulation



Depletion

Antimetabolites (mycophenolate or azathioprine)

Immunosuppression and Infection: T-cells

- **Antilymphocyte globulin** – **deplete** lymphocytes (T and/or B cells, possibly NK and dendritic cells depending on drug)
 - **T-cell depletion** predisposes to **viral infection**, mimics alloimmune response & **activates latent (herpes)viruses (CMV, EBV)**, BK polyomavirus ...
 - Chimeric monoclonals → TNF α → **fever** → cytokines
 - Anti-CD52 **lymphocyte-depleting antibody** (Alemtuzumab) – excess infections **including bacterial** (depletion of innate immune cells) (see AY Peleg et al, Clin Infect Dis, 2007, 44:204-12.)
 - **Co-stimulatory blockade**: few infectious effects other than late CNS **EBV-PTLD and atypical CMV** (Belatacept). **Excess graft rejection?**
 - **Tolerance induction** via bone marrow/stem cell transplantation (requires leukocyte depletion)

Immunosuppression and Infection: **Calcineurin inhibitors**

Calcineurin inhibitors (CNI: Cyclosporine & Tacrolimus)

- Inhibit calcineurin-dependent activation of NFAT (nuclear factor of activated T cells) blocks gene transcription.
- Pre-renal **vasoconstriction** (ATN) with ↑ susceptibility to drug toxicity
- T-cell dysfunction → **viral infections, late fungal infections**

- Hyperkalemia
- Hypertension
- **Hyperglycemia**
- **Gingival Hyperplasia**
- Hepatotoxicity
- Hyperuricemia
- Hyperlipidemia
- Hypomagnesemia ?
- Hypertrichosis (hairy)
- **Hemolytic Uremic Syndrome**
- Nephrotoxicity
- **Neurotoxicity**
- **Neoplasia**

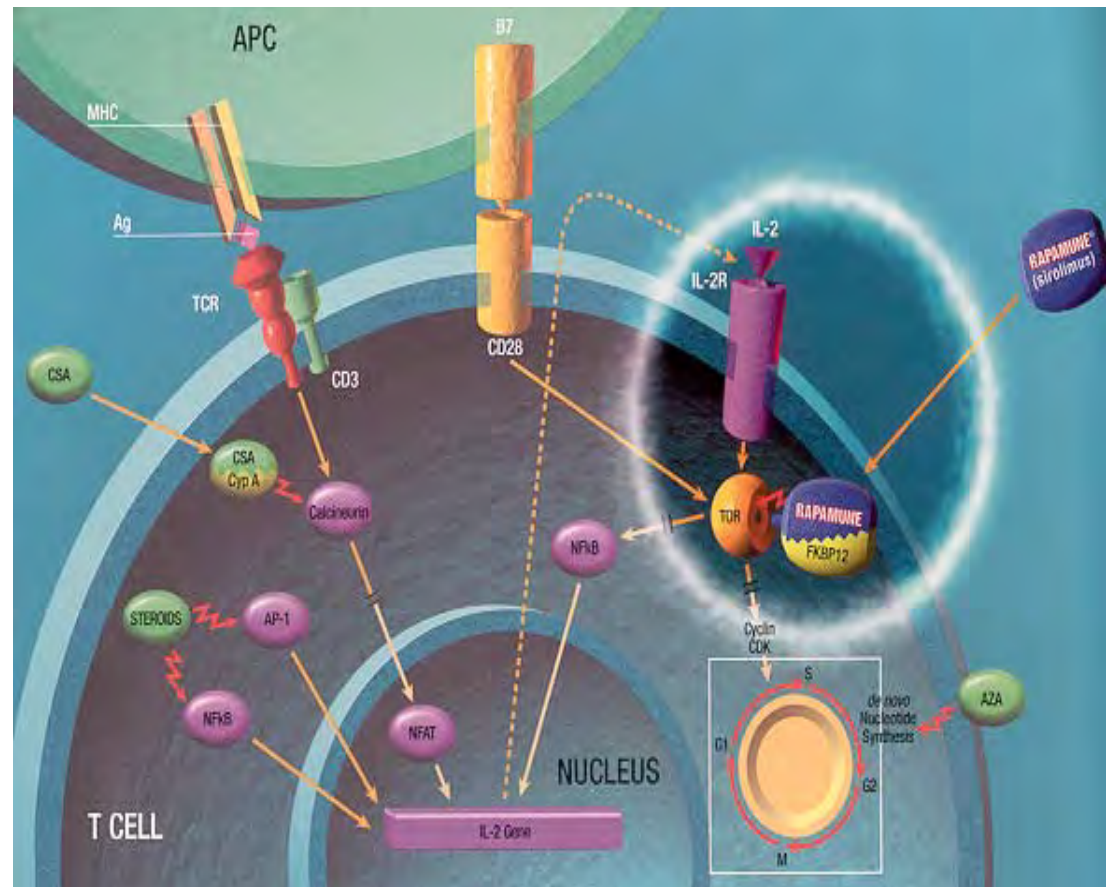
Maintenance immunosuppression

mTOR Inhibitor Mechanisms : Sirolimus and Everolimus

- Binds to FK Binding protein
- Binds to mTOR regulatory kinase
- Arrests G1 to S phase cell cycle

- Antiproliferative – cancers, atherogenesis
- Antiviral – ↓CMV, herpes viruses
- Anti-inflammatory

- Poor wound healing
- Portal vein thrombosis
- Edema
- Proteinuria
- Pneumonitis

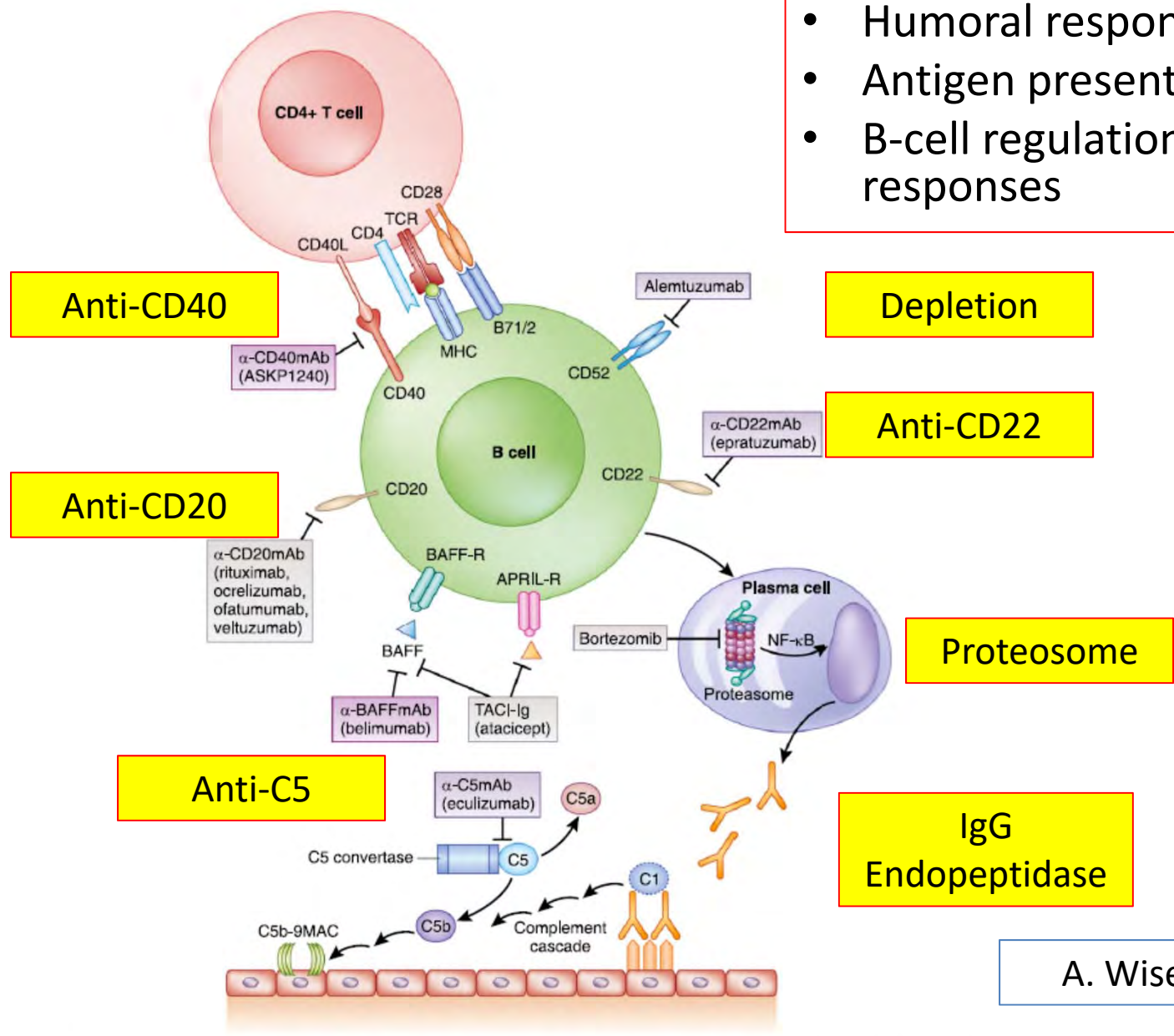


Possibly reduced CMV infection?: Brennan DC et al. Am J Transplant 2011, 11(11):2453-62; Kobashigawa J et al. Transpl Infect Dis, 2013 Apr; 15(2):150-62.

Linkage of Immunosuppression to Infections and Prophylaxis

- **Corticosteroids**
 - Bacterial infections
 - **Pneumocystis jiroveci**
 - **Fungal infections**
 - Accelerated Hepatitis B, possibly HCV
- **Azathioprine & Mycophenylate mofetil** – cell cycle inhibitors
 - Neutropenia, papillomavirus?
 - Bacterial infection, late CMV?
- **Calcineurin inhibitors:**
 - ↑viral replication, PML
 - Intracellular pathogens (TB, Listeria, Nocardia)
 - Fungal infection (*Cryptococcus*, *Aspergillus*, *Pneumocystis*)
 - Parasites (*T. gondii*, *Toxoplasma*, *Leishmania*, *Strongyloides*)
- **mTOR inhibition: Rapamycin/Sirolimus:**
 - Poor wound healing, idiosyncratic pulmonary edema & pulmonary infections
 - Less CMV?

- Humoral response
- Antigen presentation
- B-cell regulation of T-cell responses



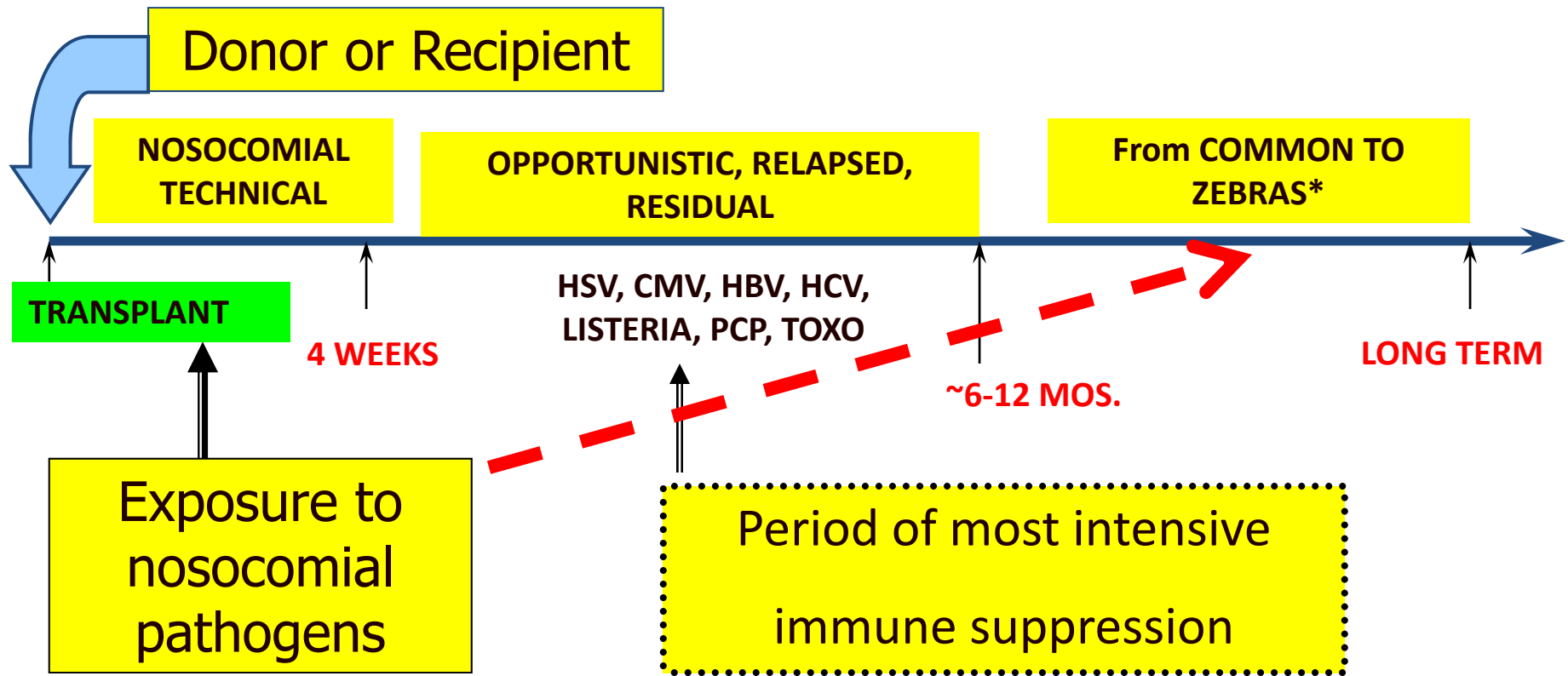
A. Wiseman ... improved

Figure 3. | Immunosuppressive agents targeting T cell/B cell interaction, plasma cell function, and complement-mediated injury. APRIL, proliferation-inducing ligand; BAFF, B cell-activating factor; MAC, membrane attack complex; TACI, transmembrane activator and CAML interactor; TCR, T cell receptor.

Immunosuppression: B-cells and Antibodies

- **Anti-CD20** on pre- and mature B-cells (Rituximab - chimeric)
 - Depletion 3 to 12 months
 - **Fever, bronchospasm**
 - **Nonchimeric -> severe infections**
 - **Hepatitis B activation**
 - **Encapsulated organisms**
- **Anti-CD22** (Epratuzumab)
 - B cell activation
- **Anti-CD52** (Alemtuzumab)
- Differentiation (**B-cell activating factor BAFF/BlyS**) (Belimumab)
 - **Severe pneumonias, low Ig**
- **Plasma cell: Bortezomib**
 - Proteasome inhibitor
 - Neurotoxicity
 - **Shingles**
- **Complement:** (Eculizumab – terminal factor C5)
 - Blocks neutrophil migration
 - Antibody-mediated rejection, desensitization
 - **Encapsulated organisms including Pneumococcus, H. influenza, and Neisseria meningitidis → requires vaccination for meningococcus A and B!**
- **IgG degrading enzyme of Streptococcus pyogenes** – prolonged IgG depletion including on CD19+ cells → anti-IdeS Ab+

The Timeline of Post-Transplant Infections



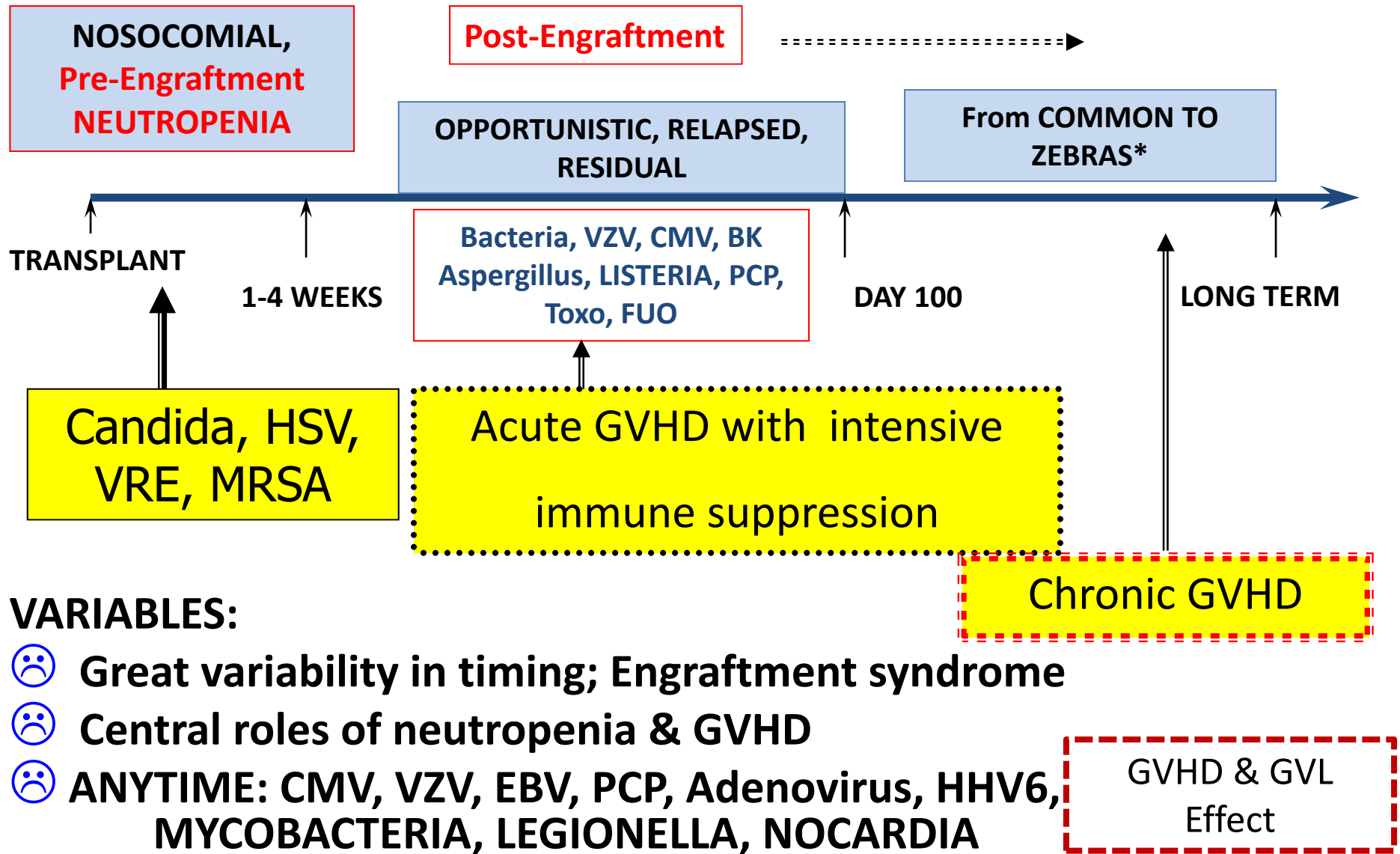
COMMON VARIABLES in IMMUNE SUPPRESSION:

- ☹️ 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 ...)

Impact of routine prophylaxis: What infections can we prevent?

- **Surgical prophylaxis** – should be as limited as possible:
 - Donor pathogens (data are often too late)
 - Common pathogens for complex surgery
 - Known colonizers of the individual patient (MRSA, VRE, Aspergillus, increasingly MDRO)
 - *C. difficile* (with prior history)
- **Pneumocystis jirovecii and Toxoplasma gondii**
 - TMP-SMX has activity vs. many common pathogens, most **Nocardia**, **Listeria** (6 months to life); true allergy much less common than reported
 - Dapsone (G6PD deficiency?); Atovaquone
- **Cytomegalovirus** (HSV, VZV): valganciclovir 3-6 months (based on risk, notably hearts and lungs) vs. pre-emptive therapy
 - **Epstein-Barr virus** – monitoring only
 - **Herpes simplex and Varicella zoster** – worth prevention!
- **Antifungal prophylaxis** – based on prior colonization, hospital epidemiology, and in lung recipients (Note: increasing resistance, side effects and drug interactions). Acutely: *Candida*/*Aspergillus* in livers, *Aspergillus* in lungs.
- **Hepatitis B and C** – individualized decisions re. timing and drugs

The Timeline of Post-BMT/HSCT Infections



Use of Timelines of Infection for Immunocompromised Hosts

- ⇒ Differential Diagnosis by time post-transplant with appropriate preventative strategies
- ⇒ Develop prophylactic strategies
- ⇒ Identify Excess Epidemiologic Hazards:
 - ⇒ Nosocomial: Aspergillus, MRSA, VRE, -- clustered in time and space, by hospital, physician, Clinical Unit
 - ⇒ Community: Influenza, RSV, Legionella
 - ⇒ Individual: Gardening, Travel, Pets
- ⇒ Excessive Immune Suppression Overall: Too many infections, too severe, or at the wrong time on time line

Timetable of Infection after Transplantation

First Month following Transplantation

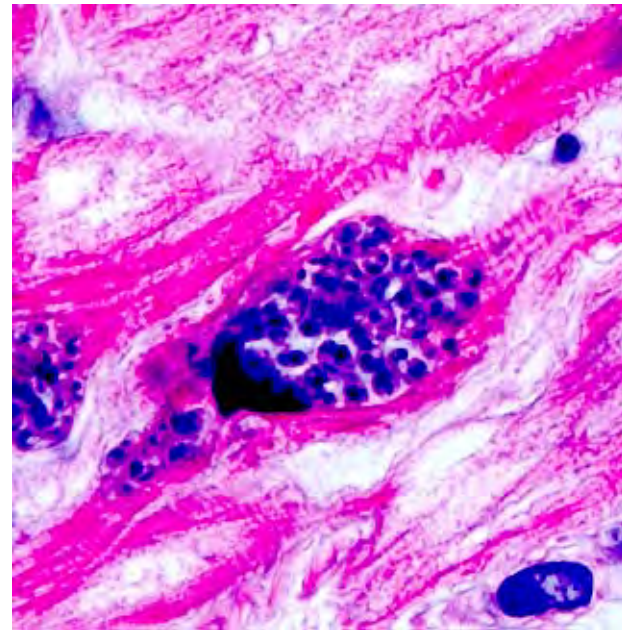
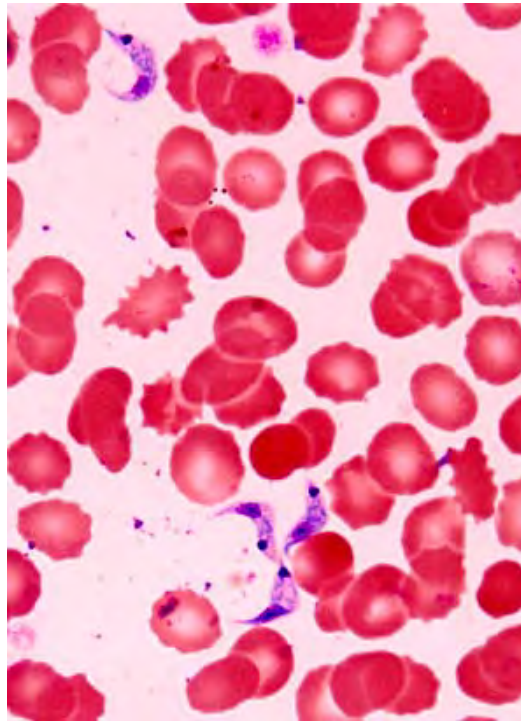
- Infection carried with donor cells or organ
- Present in recipient prior to transplant
- Technical complications (unforgiving surgery)
 - Obstructed stents, organ damage in procurement
 - Hemorrhage, hematoma, leaks, ischemia
- Post-operative complications
 - Aspiration, pulmonary embolus
 - Lines, Drains, Catheters

Types of Infection Transmitted with Allograft Transplantation

Unexpected disease transmission rate: ~0.2-1.0%

- Bacterial infection: bacteremia or infection of tissues (e.g., VRE, MRSA, TB)
- Fungus: fungemia (*Candida* – *C. auris*) or colonization (e.g., *aspergillus*, *cryptococcus*)
- Parasites: latent or acute infections (e.g., *Toxoplasma*, *Strongyloides*, *T. cruzi*, *Balmuthia*)
- Viruses: latent infection (CMV, EBV, HIV, HCV) or viremia (HTLV, LCMV, West Nile, Chikungunya, Rabies, influenza)

Donor-derived Chagas' Disease after Cardiac Transplantation



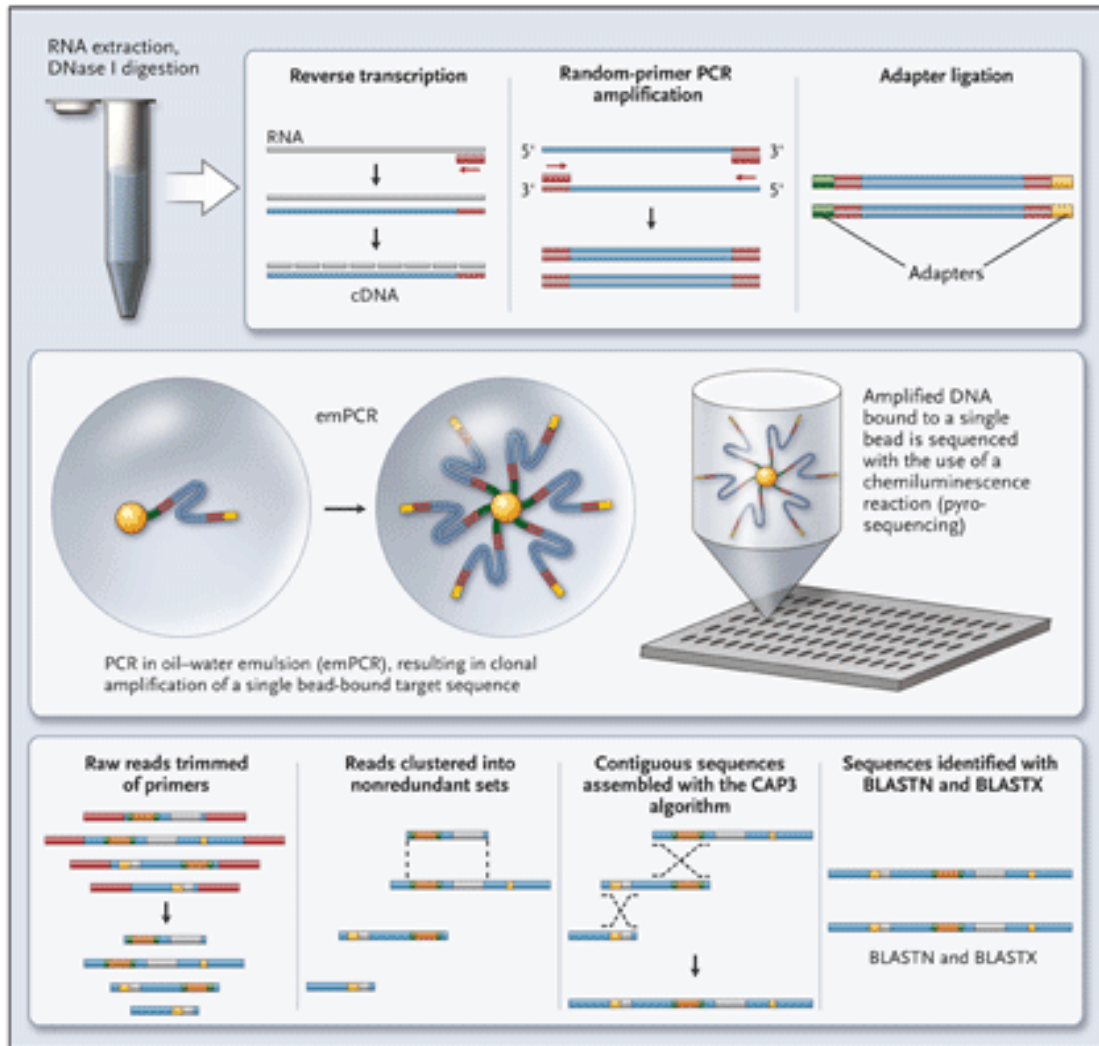
Courtesy of B. Kubak

Donor-derived Transmission Events Reported to
UNOS/OPTN/DTAC

Pathogen	Clinically Significant?
Histoplasma	Yes
Cryptococcus	Yes
Aspergillus, Candida species	Yes
VRE, MRSA, Pseudomonas	Yes
Toxoplasma	Yes
T. cruzi	Yes
LCMV	Yes
HCV	Yes, NAT and/or Sero(-) Donors
Listeria	not transmitted (donor culture)
Influenza A, B	No
Tuberculosis	Yes, No
West Nile Virus	False + assay
HIV	Yes; Also false + assay (x2)

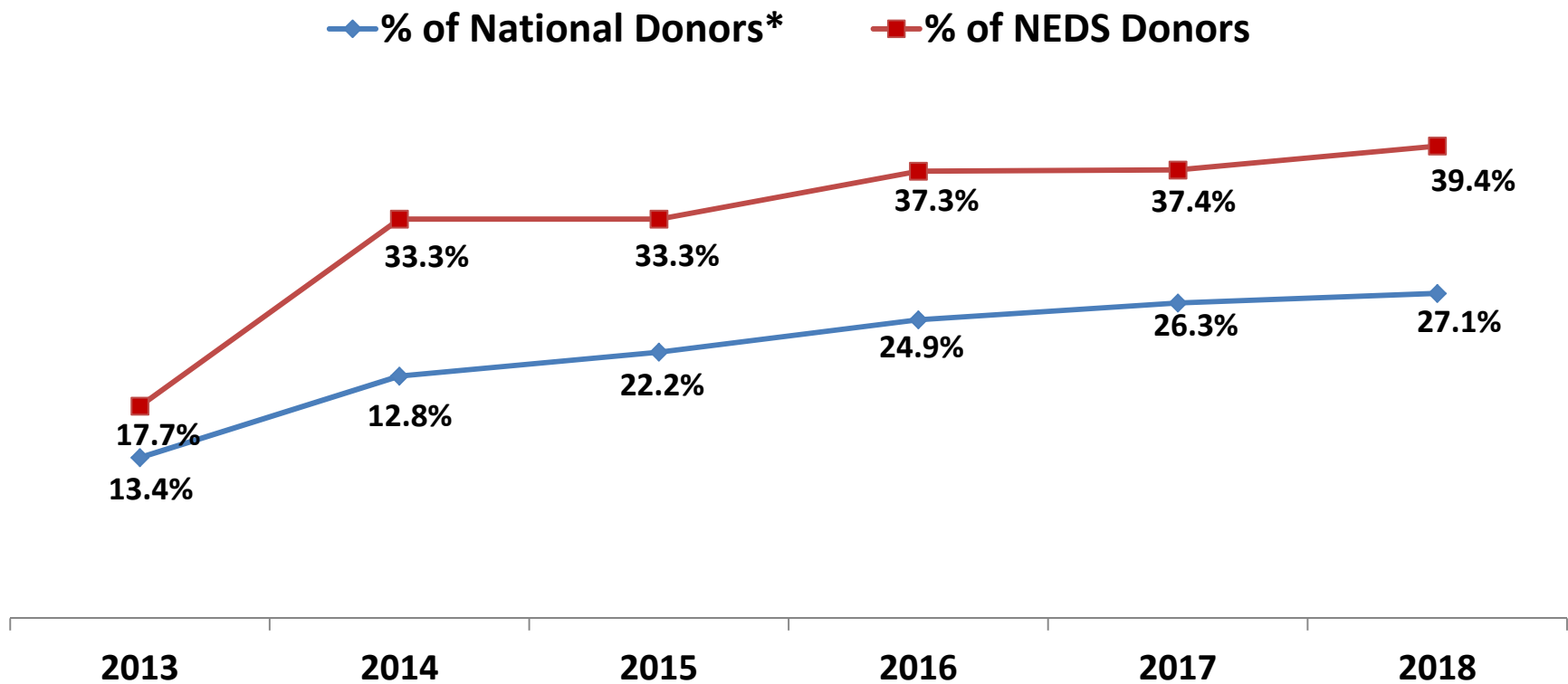
High-Throughput Sequencing Method

G. Palacios et al, NEJM 358: 991



NEDS Donors Meeting PHS Guidelines by Calendar Year

Does Not include all Potential Donors



*Based on OPTN data as of January 4, 2019

MGH has been a Leader in Developing Screening Paradigm for these Potential Donors

MGH Published Data:

- 165 deceased donor organs and 3 live donors met the definition of “increased risk” 2011-2015 representing ~40% of transplants
- No transmission events (HIV, Hepatitis B and C) have been detected on rescreening of recipients of organs from increased risk donors at MGH.
- Preemptive studies in cardiac and liver recipients
 - Donors with HCV viremia and HCV antibody +
 - All patients with sustained virologic response at 12 weeks (SVR12)
 - Median time to undetectable/unquantifiable viral load was 15 days (IQR 0 to 47)

- Irwin L, Kotton CN, Elias N, Palafox J, Basler D, Shao SH, Lester W, Zhang X, Kimball B, Trencher C, Fishman JA. Utilization of increased risk for transmission of infectious disease donor organs in solid organ transplantation: Retrospective analysis of disease transmission and safety. *Transplant Infect Dis.* 2017;19:e12791.
- Bethea E. et al. Preemptive Pan-genotypic Direct Acting Antiviral Therapy in Donor HCV-positive to Recipient HCV-negative Cardiac Transplantation: A Novel Strategy to Enhance Donor Organ Supply. *Lancet Gastroenterol Hepatol.* 2019 Jul 25. pii: S2468-1253(19)30240-7.
- Bethea E. et al, Liver transplantation from HCV-infected Donors to Uninfected Recipients Using Immediate Administration of Direct Acting Antiviral Therapy: Implications for Therapeutic Planning, submitted

PHS Tracking – Day 0, 1-3 months and 6-12 months post-transplant

Day	HBV Ab/Ag	HBV sAg	HBV sAb	HBV cAb	HBV viral loads	HCV viral loads	HIV viral loads	1-3 months: HBV Ab/Ag	1-3 months: HBV sAg	1-3 months: HBV sAb	1-3 months: HBV cAb	1-3 months: HBV viral load	1-3 months: HCV viral load	6-12 months: HBV					
3/30/2017	yes	3/30/17 neg	ND	ND	IGM CORE negative 3/30	3/30/17 neg	3/30/17 neg	3/30/17 neg				4/28/17 neg viral load	4/28/17 neg	ND	4/28/17 neg	4/28/17 neg	4/28/17 neg	4/28/17 neg	9/12
4/1/2017	yes	4/1/17 neg	4/1/17 neg	4/1/17 neg	ND	4/1/17 neg	ND	ND				ND	6/21/17 neg	6/21/17 neg	6/21/17 neg	6/21/17 neg			
7/5/2017	yes	ND	ND	ND	ND	ND	7/5/17 neg	7/5/17 neg				8/2/17 neg	8/2/17 neg	ND	8/2/17 neg	8/2/17 neg	8/2/17 neg	8/2/17 neg	2/28
7/7/2017	yes	ND	ND	ND	ND	ND	ND	ND				8/4/17 neg	8/4/17 neg	ND	8/4/17 pos	8/4/17 neg	8/4/17 neg	8/4/17 neg	2/28
7/17/2017	yes	7/17/17 neg	7/17/17 neg	7/17/17 neg	7/17/17 neg	7/17/17 neg	7/17/17 neg	7/17/17 neg				8/16/17 neg	8/16/17 neg	8/16/17 neg	8/16/17 neg	8/16/17 neg	8/16/17 neg	8/16/17 neg	1/23
7/21/2017	yes	ND	ND	ND	ND	ND	ND	ND				8/31/17 neg	8/31/17 neg	ND	8/31/17 neg	8/31/17 neg	8/31/17 neg	8/31/17 neg	1/3/18
8/15/2017	yes	8/15/17 neg	ND	8/15/17 neg	ND	8/15/17 neg	ND	ND				9/26/17 neg	9/26/17 neg	ND	9/26/17 neg	9/26/17 neg	9/26/17 neg	9/26/17 neg	4/18
8/26/2017	yes	8/26/17 neg	8/26/17 neg	ND	8/26/17 neg	8/26/17 neg	8/26/17 neg	8/26/17 neg	ND			10/25/17 neg	10/25/17 neg	10/25/17 neg	10/25/17 neg	10/25/17 neg	10/25/17 neg	10/25/17 neg	2/16
11/29/2017	yes	ND	ND	ND	ND	ND	ND	11/28/17 neg				1/7/18 HIV viral load neg	1/7/18 neg	6/19/18 neg	1/7/18 neg	12/8/17 neg	1/7/18 neg	12/13/17 neg	6/19
12/8/2017	yes	12/7/17 neg	ND	ND	ND	12/7/17 neg	12/8/17 pos	12/7/17 neg	12/8/17 pos			1/5/18 neg	1/5/18 neg	1/5/18 neg	1/5/18 neg	1/5/18 pos	1/5/18 neg	1/5/18 neg	6/13
12/17/2017	yes	12/17/17 neg	12/16/17 neg	12/16/17 pos	12/16/17 neg	12/16/17 neg	12/16/17 neg	12/16/17 neg	12/16/17 neg			1/18/18 neg	1/18/18 neg	ND	1/18/18 neg	1/18/18 neg	1/18/18 neg	1/18/18 neg	6/29
12/29/2017	yes	ND	ND	ND	ND	ND	12/29/17 neg	12/29/17 neg				1/26/18 neg	1/26/18 neg	ND	1/26/18 neg	1/26/18 neg	1/26/18 neg	1/26/18 neg	
1/21/2018	yes	ND	ND	ND	ND	ND	ND	ND	ND			2/20/18 neg	2/20/18 neg	ND	2/20/18 neg	2/20/18 neg	2/20/18 neg	2/20/18 neg	
2/7/2018	yes	ND	ND	ND	ND	ND	ND	ND	ND			3/6/18 HIV viral load neg	3/6/18 neg	3/6/18 neg	3/6/18 neg	ND	3/6/18 neg	3/6/18 neg	
3/9/2018	yes	ND	ND	ND	ND	3/9/18 neg	ND	3/9/18 neg				5/8/18 neg	5/8/18 neg	ND	5/8/18 neg	5/22/18 neg	5/8/18 neg	5/8/18 neg	
3/23/2018	yes	3/22/18 neg	ND	3/22/18 neg	ND	3/22/18 neg	ND	ND				5/18/18 neg	5/18/18 neg	5/18/18 neg	5/18/18 neg	5/18/18 neg	5/18/18 neg	5/18/18 neg	
3/25/2018	yes	ND	ND	ND	ND	3/24/18 neg	ND	3/24/18 neg				5/18/18 neg	5/18/18 neg	5/18/18 pos	5/18/18 neg	5/18/18 pos	5/18/18 neg	4/20/18 neg	
4/4/2018	yes	4/3/18 neg	4/3/18 neg	4/3/18 pos	4/3/18 neg	4/3/18 neg	ND	4/3/18 neg							4/25/18 pos			5/2/18 neg	
4/8/2018	yes	4/7/18 neg	4/7/18 neg	4/7/18 neg	4/7/18 neg	4/7/18 neg	4/7/18 neg	4/7/18 neg				5/9/18 neg	5/9/18 neg	5/9/18 neg	5/9/18 neg	5/9/18 pos		5/9/18 neg	
4/21/2018	yes	ND	4/12/18 neg	4/12/18 neg	4/12/18 neg	4/12/18 neg	ND	4/20/18 neg				5/21/18 neg	5/21/18 neg		5/21/18 neg	5/21/18 neg	5/21/18 neg	5/21/18 neg	
4/27/2018	yes	4/26/18 neg	4/27/18 neg	4/27/18 pos	4/27/18 neg	4/27/18 neg	4/26/18 neg	4/26/18 neg	ND			6/7/18 neg	6/7/18 neg	6/7/18 pos	6/7/18 neg	6/7/18 neg	6/7/18 neg	6/7/18 neg	
5/31/2018	yes	ND	ND	5/31/18 neg	ND	5/31/18 neg	5/31/18 neg	5/31/18 neg	5/31/18 neg			7/4/18 neg	7/4/18 neg		7/4/18 neg	7/4/18 neg		7/4/18 neg	
6/3/2018	yes	6/2/18 neg	6/2/18 neg	ND	6/2/18 neg	6/2/18 neg	6/2/18 neg	6/2/18 neg	ND						7/3/18 neg			7/3/18 neg	
6/4/2018	yes	ND	6/3/18 neg	ND	6/3/18 neg	6/3/18 neg	6/3/18 neg	6/3/18 neg	ND			7/2/18 neg	7/2/18 neg	7/2/18 pos	7/2/18 neg	7/2/18 neg	7/2/18 neg	7/2/18 neg	
6/7/2018	yes	6/7/18 neg	ND	ND	ND	ND	6/7/18 neg	6/7/18 neg	ND									7/5/18 pos	
6/13/2018	yes	6/12/18 neg	6/12/18 neg	ND	6/12/18 neg	6/12/18 neg	6/12/18 neg	6/12/18 neg	ND										
6/14/2018	yes	6/14/18 neg	6/14/18 neg	ND	6/14/18 neg	6/14/18 neg	6/14/18 neg	ND	ND										

Timetable of Infection: 2-12 Months Post-Transplant

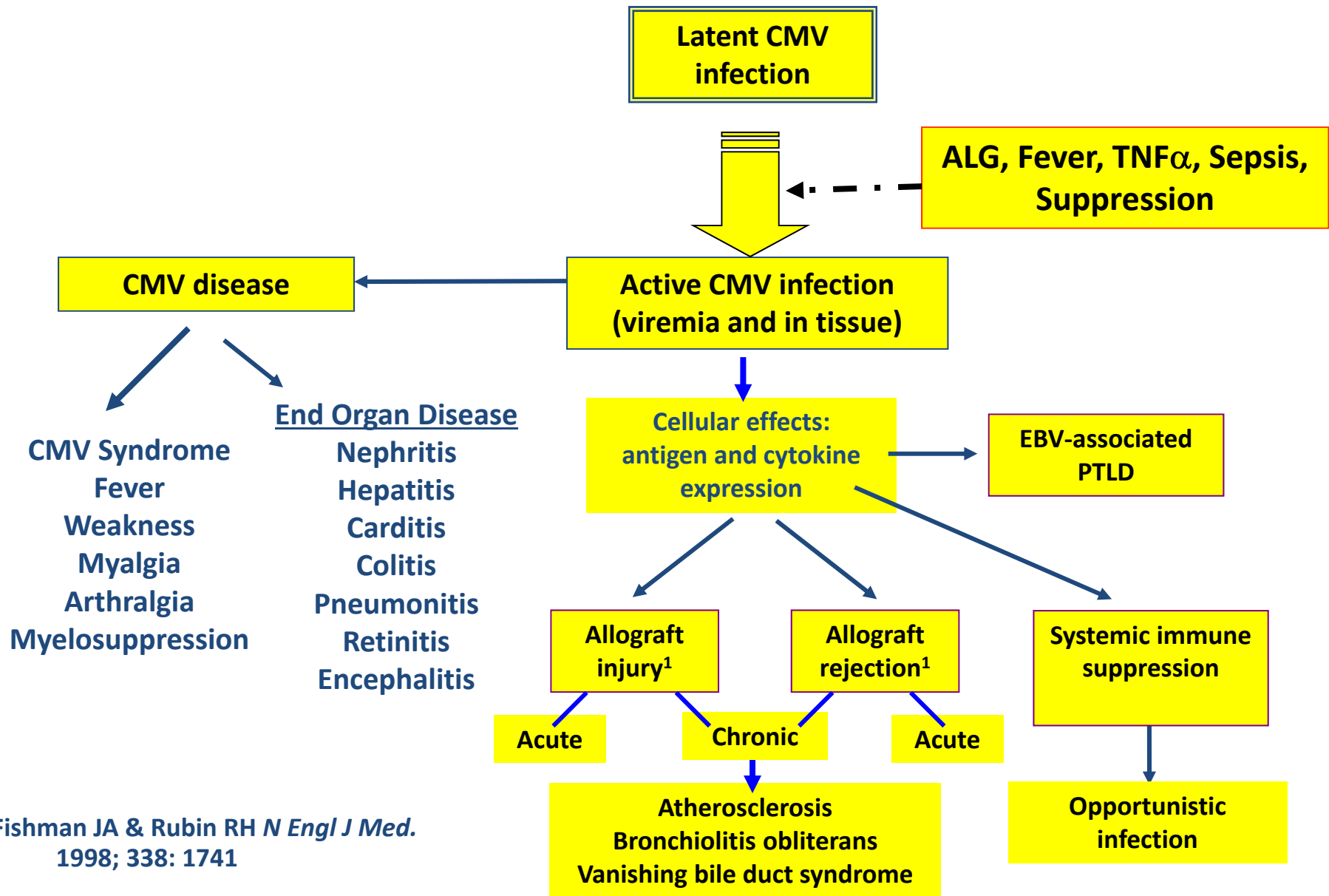
- Residual (technical) from first month
- Undiagnosed nosocomial infections
- Community acquired infections
- Classic “opportunistic infections”
 - *P. jirovecii*, *T. gondii*
- Endemic/Geographic pathogens
 - *T. cruzi*, *Strongyloides stercoralis*, *Leishmania*
 - Geographic fungi: *Histoplasma*, *Coccidioides*, *Paracoccidioides*
 - Tuberculosis
- Community acquired: Ubiquitous
 - *Cryptococcus neoformans*
 - *Nocardia asteroides*
 - *Aspergillus* sp.

Timetable of Infection: Months 2-12
following Transplantation

**Reactivation of latent viral infections *in the absence of prophylaxis* remains common:
e.g., CMV, EBV, HSV, VZV, hepatitis B & C, BK
polyomavirus, adenovirus and other
respiratory viral infections, papillomavirus, ...**

A Growing Family of Viral Pathogens in Transplantation

- **HERPES SIMPLEX**
- **VARICELLA ZOSTER**
- **EPSTEIN-BARR VIRUS**
- **CYTOMEGALOVIRUS**
- **HHV6 (& role with CMV)**
- **HHV7 (role?)**
- **HHV8/KSHV**
- **HIV, LCMV, WEST NILE, RABIES**
- **Hepatitis B (and C)**
- **Hepatitis E**
- **PAPILLOMAVIRUS**
- **POLYOMAVIRUS BK/JC**
- **ADENOVIRUS, RSV, INFLUENZA, PARAINFLUENZA, METAPNEUMOVIRUS**
- **PARVOVIRUS B19**
- **SARS/MERS CoV**
- **Live Vaccines (e.g., MMR, VZV)**



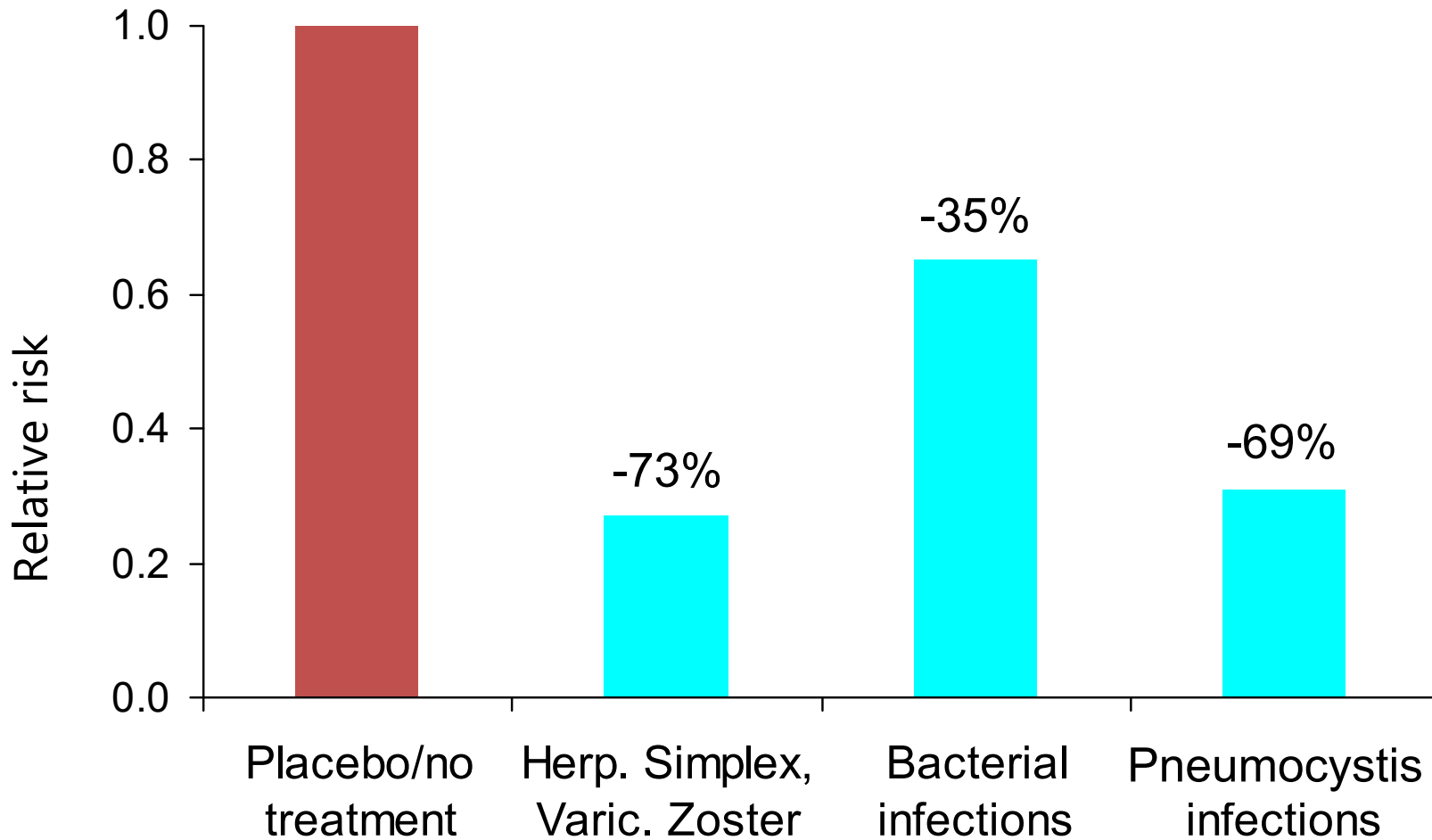
Fishman JA & Ruben RH *N Engl J Med.*
1998; 338: 1741

Effects of Viral Infection in Transplantation

- **“DIRECT EFFECTS” -- CAUSATION OF INFECTIOUS DISEASE SYNDROMES**
 - Fever and neutropenia, hepatitis
 - Colitis, Retinitis, Nephritis, Pancreatitis
- **“INDIRECT” or IMMUNOMODULATORY EFFECTS**
 - Systemic Immune Suppression → OI’s
 - Graft Rejection, GVHD
 - Abrogation Of Tolerance
- **Oncogenesis/Cellular Proliferation**
 - Hepatitis B and Hepatitis C: hepatocellular carcinoma
 - Epstein Barr Virus: B-cell lymphoma (PTLD)
 - Hepatitis C: splenic lymphoma (villous lymphocytes)
 - Papillomavirus: Warts, Actinic keratosis, Squamous cell & anogenital cancer
 - HHV8 (KSHV): Kaposi’s sarcoma, effusion lymphoma
 - Accelerated atherogenesis, BK-ureteric obstruction

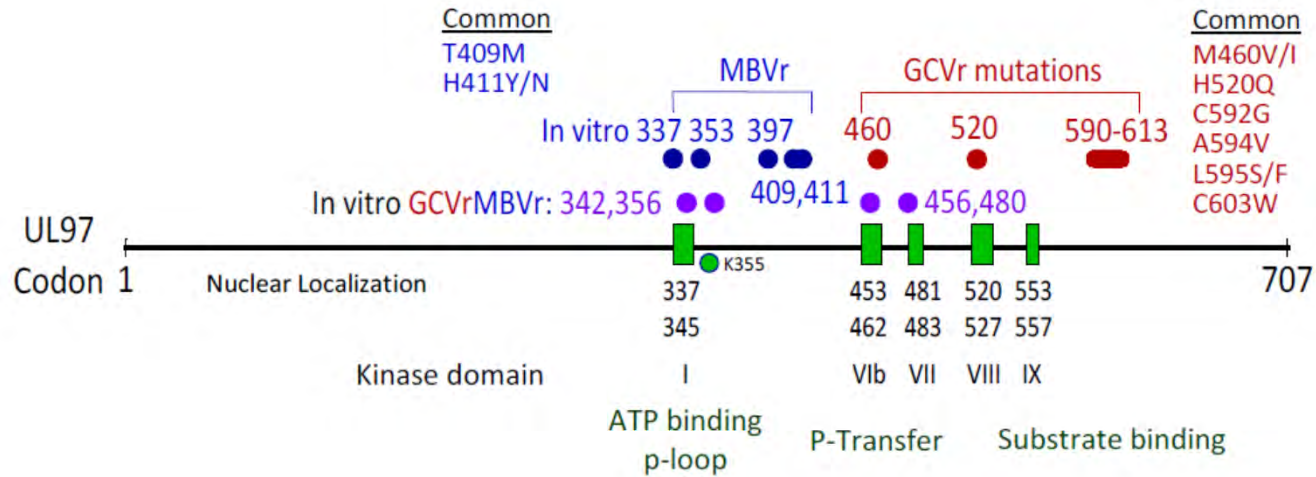
Do we know how to Prevent CMV
Infection?
Universal vs. Pre-emptive therapy

Effect of anti-CMV prophylaxis on concomitant infections



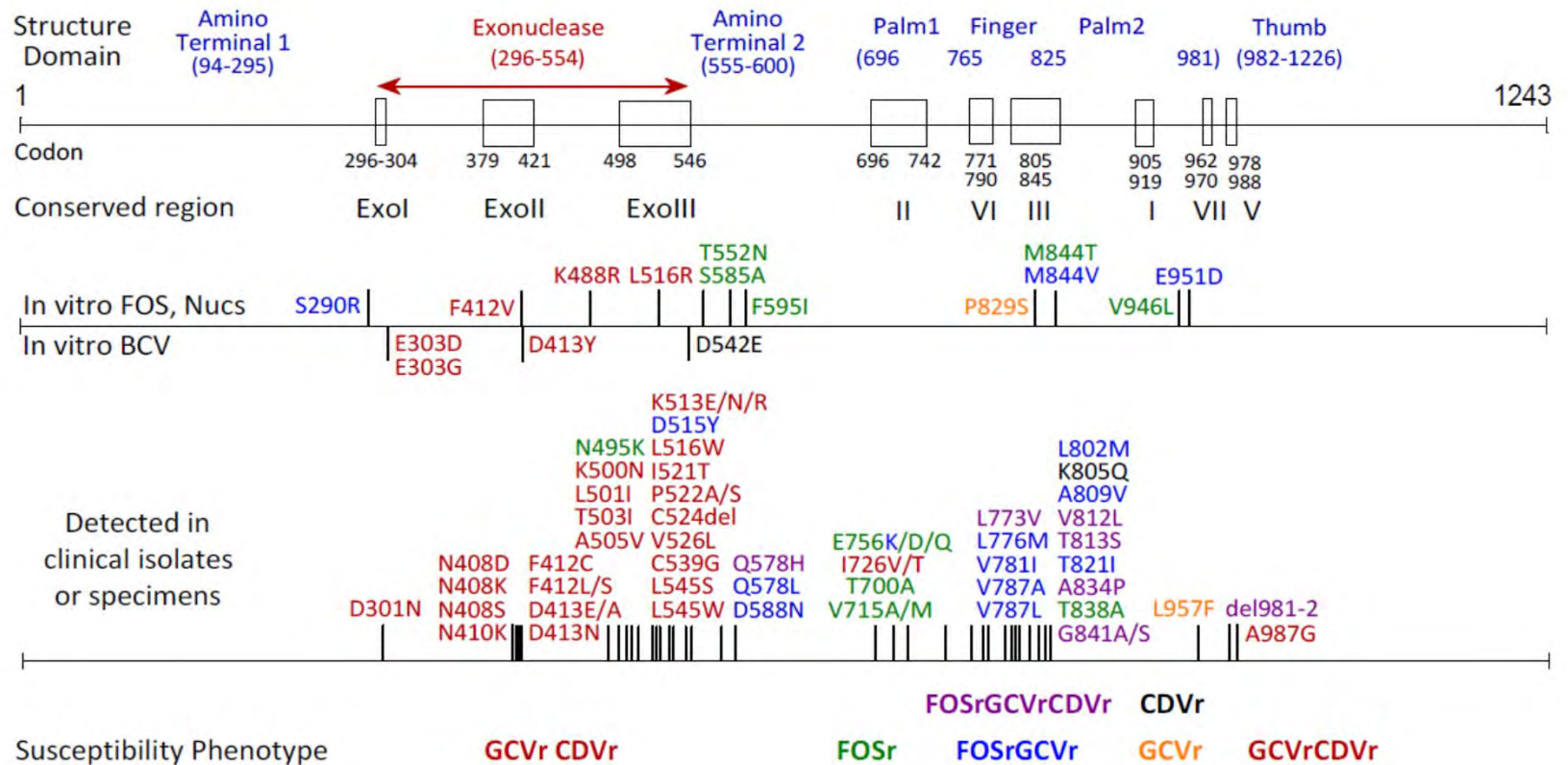
CMV Resistance UL97 Targets

UL97 Mutation Map - Updated 02-02-2017



Note: in vitro selected GCVrMBVr mutants are growth impaired to varying degrees; in vivo significance unclear

Antiviral resistance – Polymerase targets

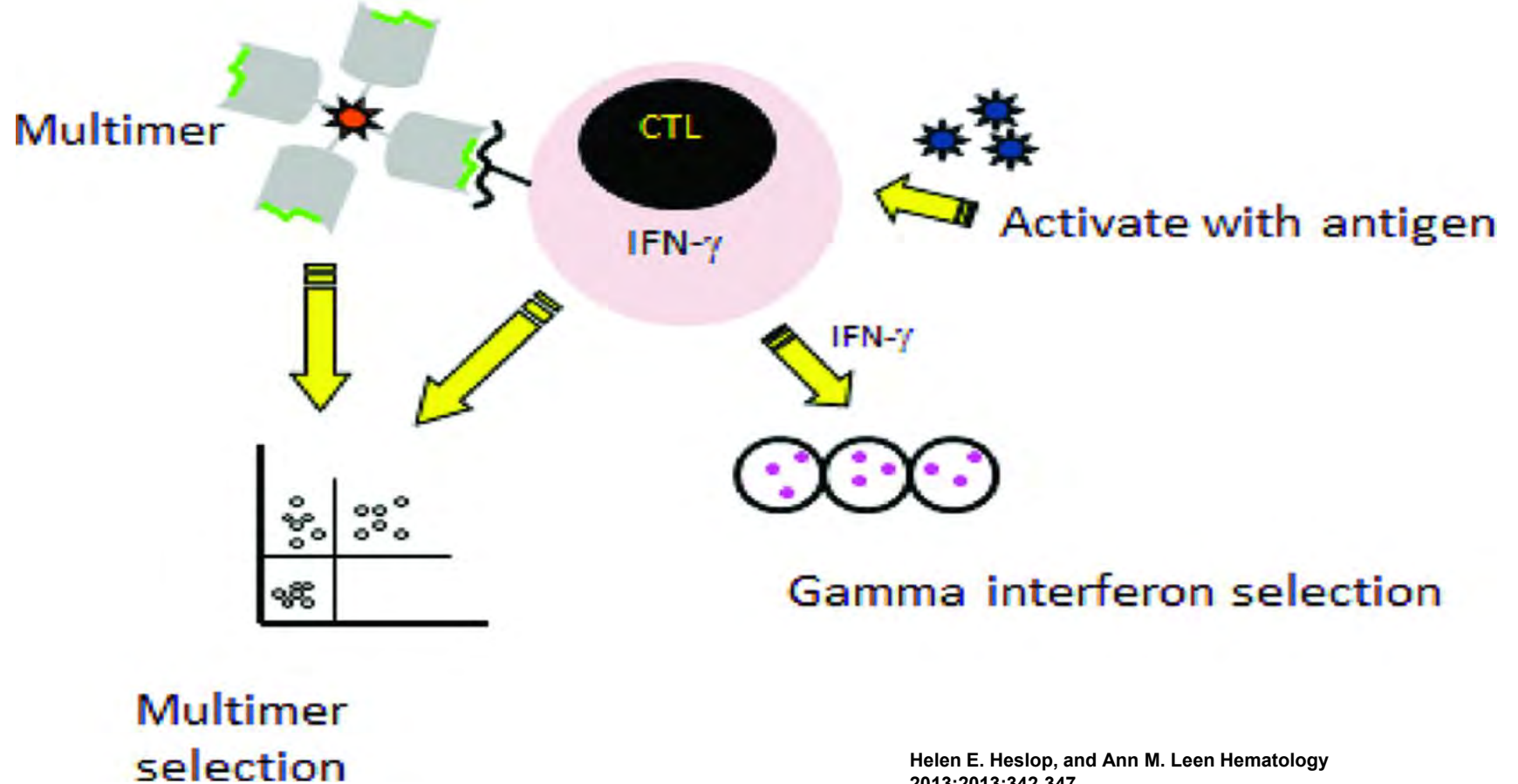


From Chou et al in CMV Guidelines, Transplantation 2018, in press.

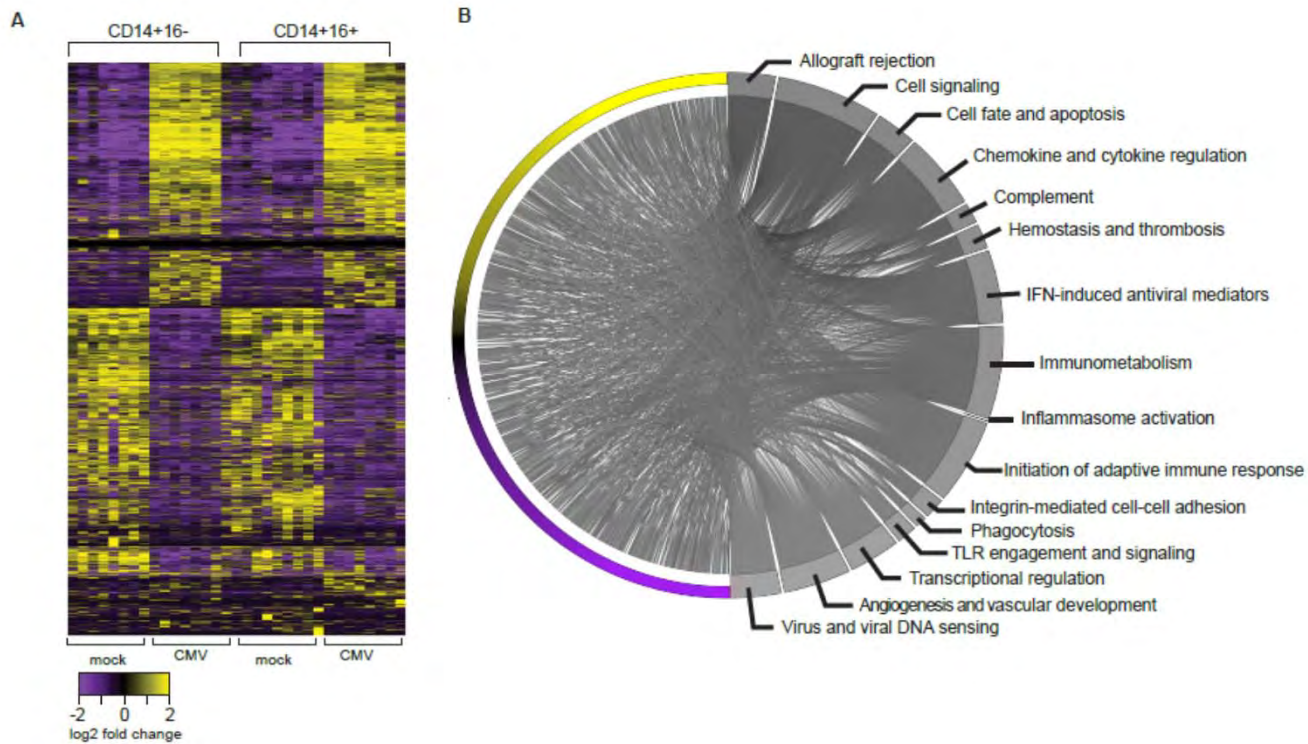
CMV Newer Options – the basics

- **Maribavir** (UL97 – viral maturation and egress) – failed prophylaxis study in SOT (wrong dose?)
 - **Does not cover HSV/VZV**
 - Mixed results in therapy
 - Failed in liver SOT and HSCT Prophylaxis (but low dose)
 - Effective in small trials at higher doses but relapse occurred ~37%
 - Unique resistance mutations in UL97 (not cross reactive with GCV)
- **Letermovir** (viral terminase) UL56, oral and intravenous (studied in HSCT)
 - Prophylaxis only trials
 - **Does not cover HSV/VZV**
 - Easy resistance in vitro / *Drug interactions* with CyA, tacrolimus, voriconazole, others
 - Activity for treatment is unknown.
- CMX001 (**Brincidofovir**) lipid cidofovir prodrug (oral only), covers herpesviruses
 - **GI toxicity**
 - Iv under development
 - Expected UL54 mutations (like cidofovir)

Autologous T-cell therapies



Pathways altered by CMV



Timetable of Infection after Transplantation

> 6-12 Months after Transplantation

- Most patients are doing well -- gradual decrease in immunosuppression
- Infections are common in community
 - Community acquired pneumonia
 - Influenza, RSV, Chlamydia, Mycoplasma
 - Urinary tract infections
 - HSV, Shingles

Timetable of Infection after Transplantation

> 6-12 Months after Transplantation

- Chronic viral infections
 - CMV (now uncommon)
 - Hepatitis C (very common but now treatable), HBV
 - EBV (PTLD)
 - Shingles (VZV), HSV
 - Papillomavirus
 - BK virus nephropathy
- Chronic anastamotic issues
- Recurrent C. difficile colitis

Timetable of Infection after Transplantation

> 6-12 Months after Transplantation

- Chronic “n’er do wells” with poor allograft function and higher levels of immune suppression to preserve function
- At highest risk for opportunistic infections
- May reflect allelic variation in immune response?

The “chronic n’er do well”



The “chronic n'er do well”



Cryptococcus neoformans



So, how do we approach immunocompromised patients with infectious syndromes?

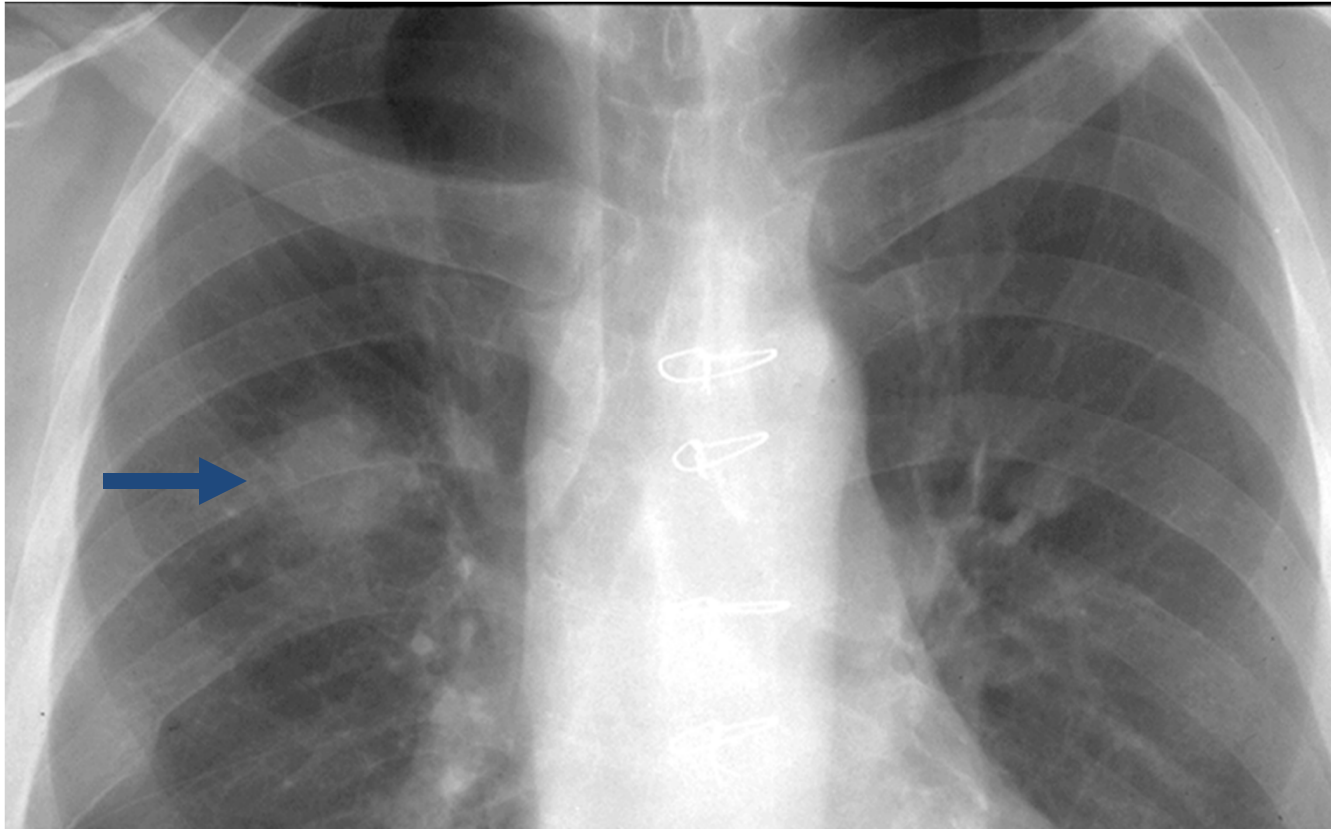
Simple!

- Just reduce immune suppression and treat any infection!
- How do we know how much to reduce immune suppression? A little? A lot?
- And what about graft rejection?!!

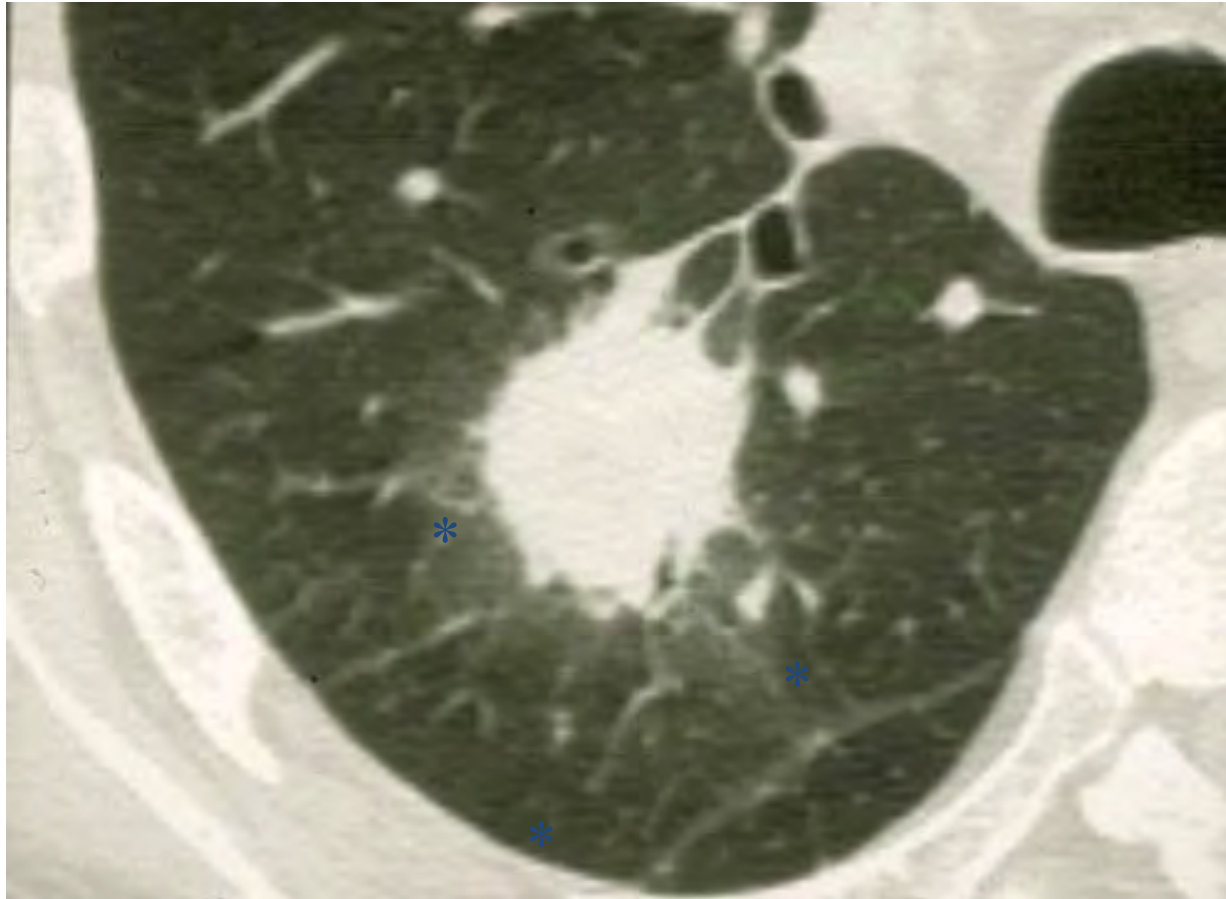
Assumption/Hypothesis: If we can quantify immune deficits, and understand the common infections, then we can design prophylactic strategies including:

- Vaccination
- Reduction in exogenous immunosuppression
- Antimicrobial prophylaxis
- Repair of immune deficits (*Host-directed therapies: specific and nonspecific*)

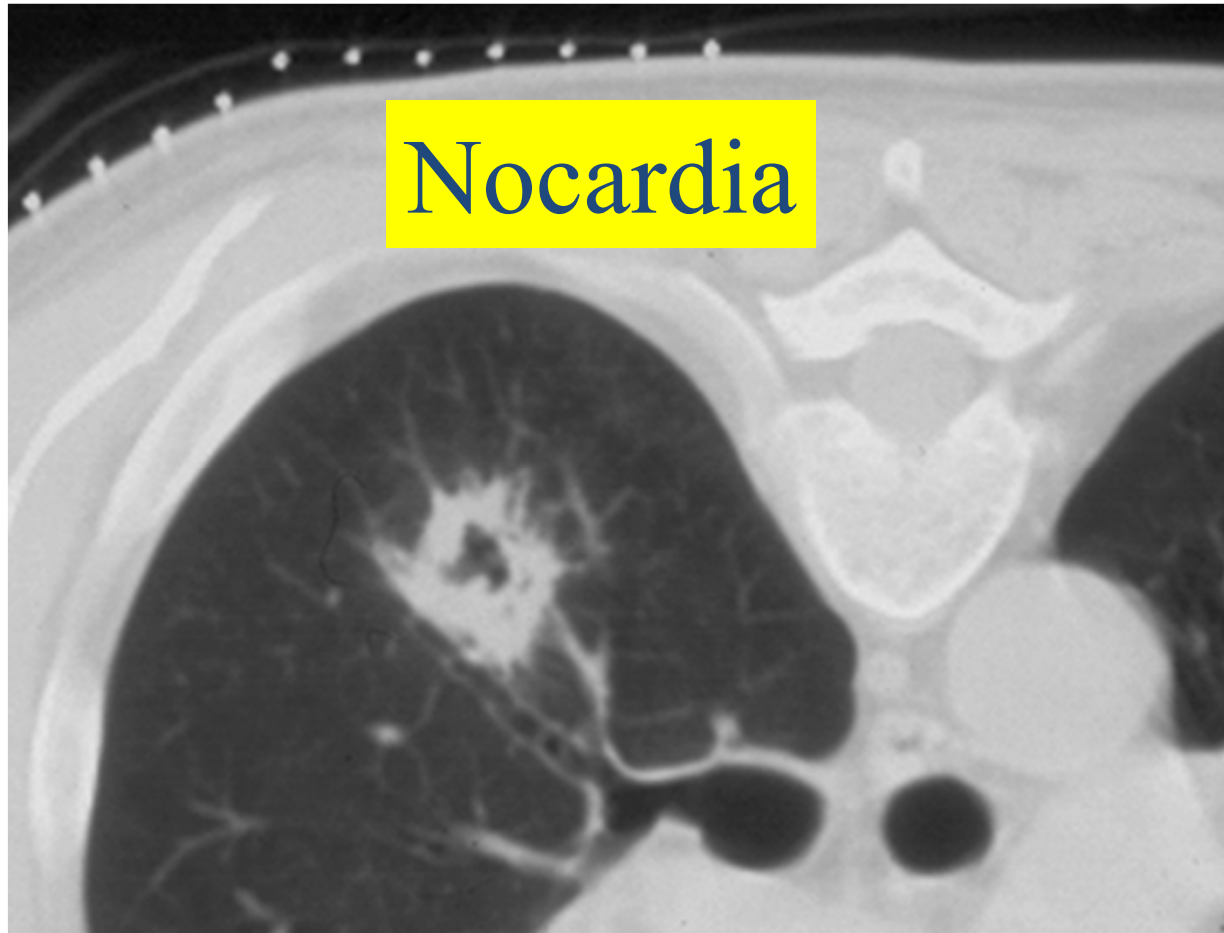
Specific Diagnosis Remains Key:
Fever, Cough Two Years Post Cardiac Transplant



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 and often advanced at the time of diagnosis
- Drug toxicity is common – so need specific diagnosis to minimize toxicities
- The intensity of immune suppression (including anatomic defects) is as important as antimicrobial therapy – but don't be afraid of immunosuppression
- Infection is linked to patient and graft (organ and stem cell) survival – prevention (and early recognition) is the key to excellent outcomes.
- New technologies are available for diagnosis and therapy (e.g., CAR-T cells) but lacking for assessment of immune function.

Thanks!



If I can help:
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