IMMUNOSUPPRESSION IN SOT & ITS INFECTIOUS COMPLICATIONS

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INFECTIOUS DISEASES

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OUTLINE

- Net state of immunosuppression
    - What is it? How is it measured? Why does it matter?
- Overview of the immune system
- Explain the effects of various immunosuppressive drugs on the immune system and how that impacts infection development
- List and briefly discuss commonly encountered infections post-transplant

BACKGROUND

- Solid organ transplantation has increased throughout the world since the first successful human kidney transplant in 1954
    - Living donor transplanted kidney performed between 23-year-old identical twins
- Medicine as a field has improved our ability to suppress immune systems and have longer organ survival
    - As a result, infection and cancer have become the primary barriers to survival after organ transplantation
- Prevention of infection is vital to secure excellent outcomes

KEY ITEMS TO REMEMBER

- Sources for infectious complications include:
  - Community-acquired, reactivation of latent infections, donor-derived, and nosocomial (hospital-acquired)
- The inflammatory response in an immunosuppressed individual can be muted
- Altered anatomy following transplantation may change physical findings associated with infection
- Immunosuppressive drug levels provide a crude measurement of how immunosuppressed an individual is (“net state of immunosuppression”)
  - Patients are often more or less immunosuppressed than anticipated
  - Some drug regimens have side effects that mimic infection

NET STATE OF IMMUNOSUPPRESSION

- A conceptual assessment of the factors contributing to the risk of infection in an immunosuppressed individual
  - Type, dose, duration and temporal sequence of immunosuppressive therapies
  - Underlying diseases or comorbidities
  - Presence of invasive devices (vascular access, urinary catheters, drains, VADs)
  - Other host factors that affect immune function (neutropenia, hypogammaglobulinemia, metabolic problems)
  - Simultaneous infection with immunomodulating viruses (ex: CMV, EBV, HCV, HIV, HBV, etc).

NET STATE OF IMMUNOSUPPRESSION

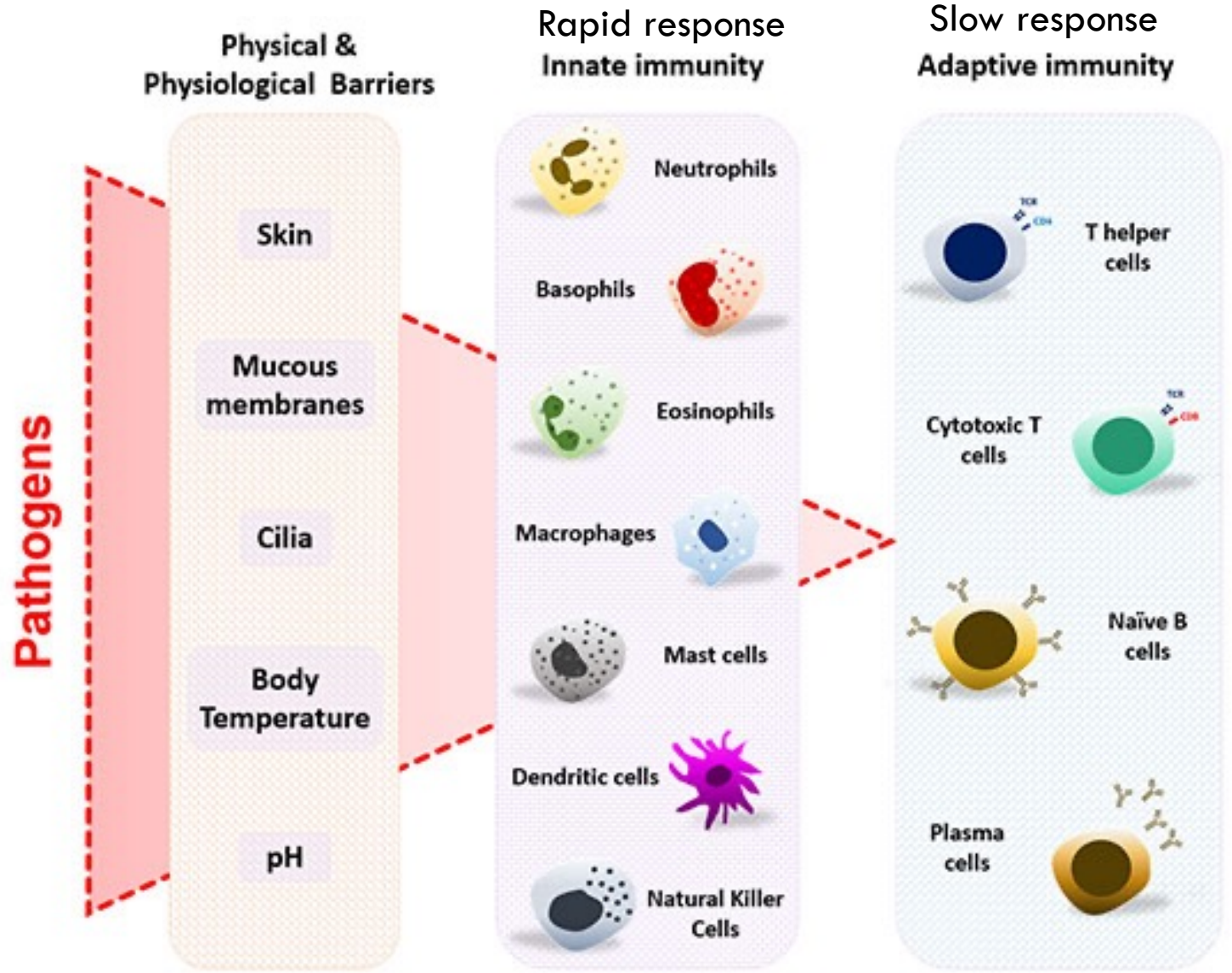
- The sum of congenital (born with), acquired, metabolic, operative, and transplant-related factors is the patient's "net state of immunosuppression"
- Multiple factors are generally present in one individual
- We can very roughly measure the net state of immunosuppression by looking at a patient's white blood cell count, immunosuppression drug levels, and noting the frequency and severity of common infections
    - A variety of blood tests are being developed to better measure this concept in order to understand one's risk for infectious complications

IMMUNE SYSTEM 101

IMMUNE SYSTEM OVERVIEW

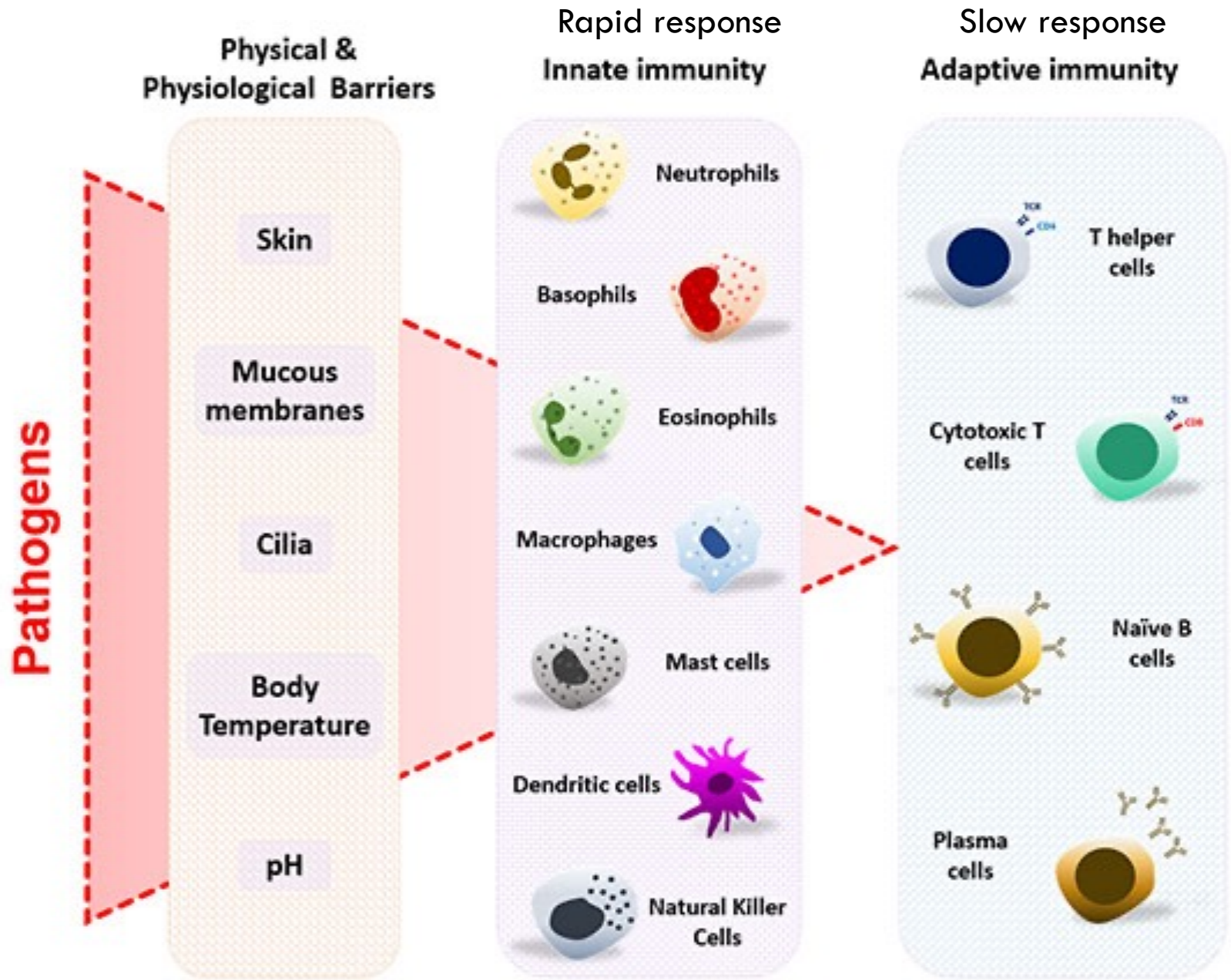
- Body's defense against infections
- Cells and organs work together to protect the body against invaders and abnormal cells
- When the immune system is weak, germs and other abnormal cells in the body can more easily cause infection and other diseases

IMMUNE SYSTEM OVERVIEW



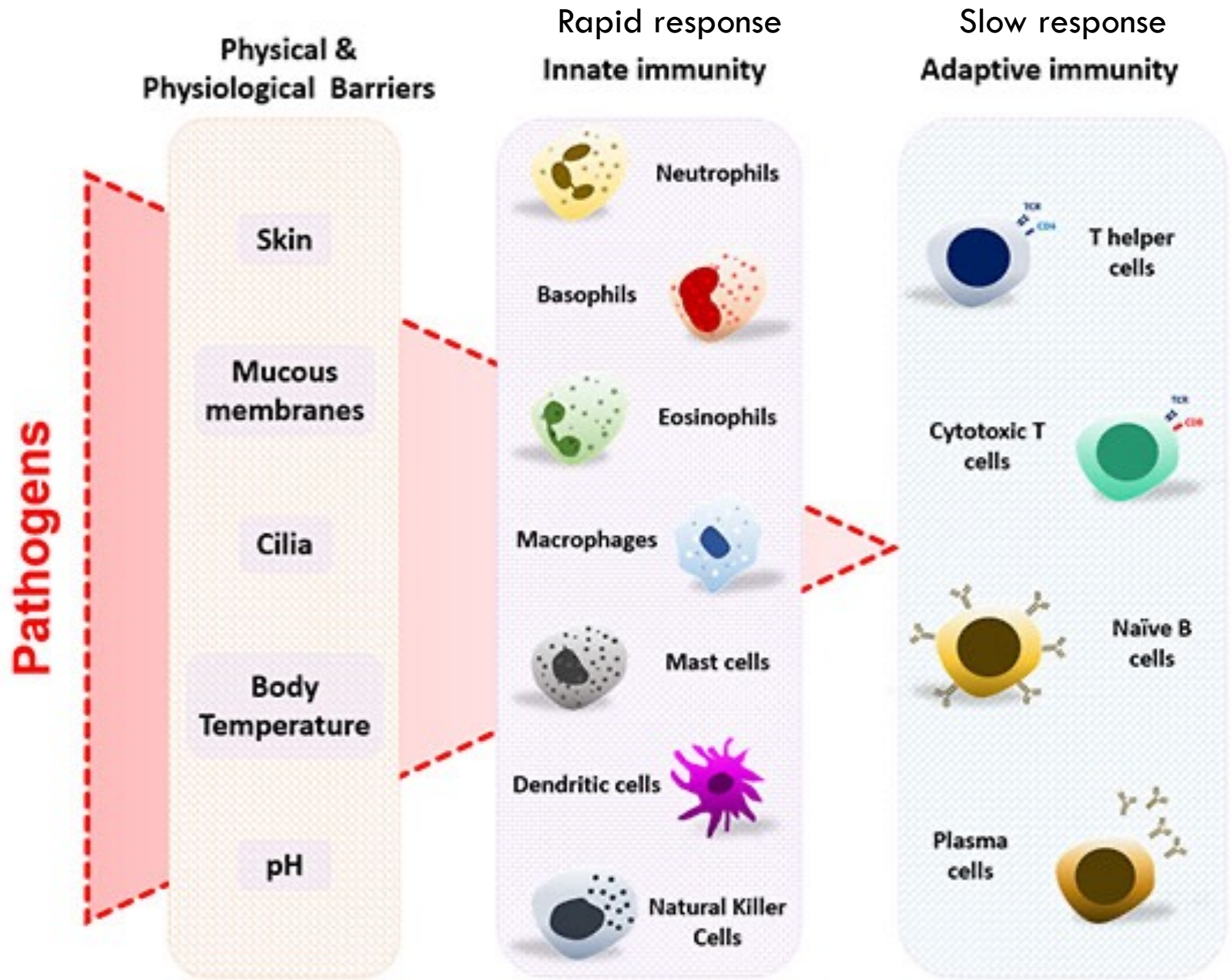
ORGANS OF THE IMMUNE SYSTEM

- Skin – first line of defense
- Bone marrow – where white blood cells first develop
- Lymph organs – where mature white blood cells live and await instruction to go out and fight invaders/abnormal cells
  - Spleen
  - Lymph nodes
  - Thymus
  - Appendix
  - Tonsils & adenoids
  - Patches of tissue in the small intestine (Peyer's patches)


Physical &
Physiological Barriers
Rapid response
Innate immunity
Slow response
Adaptive immunity
Pathogens
Skin
Mucous membranes
Cilia
Body Temperature
pH
Neutrophils
Basophils
Eosinophils
Macrophages
Mast cells
Dendritic cells
Natural Killer Cells
T helper cells
Cytotoxic T cells
Naïve B cells
Plasma cells

CELLS OF THE IMMUNE SYSTEM: INNATE ARM

- Dendritic cells (type of White Blood Cell (WBC))
  - Live in the skin and mucous membranes – protect the openings of the body
  - Capture & carry invaders to lymph nodes or spleen
- Macrophages (type of WBC)
  - "Big eaters" ; capture & carry invaders to lymph nodes or spleen
- Above are known as scavenger cells – they eat foreign invaders, break them apart and display pieces of the germs (antigens) on their surfaces
  - The body produces antibodies to these antigens which allow for memory of the antigen in the future
  - These cells also produce chemicals which tell other immune cells to go into action and do their job fighting invaders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CELLS OF THE IMMUNE SYSTEM: ADAPTIVE ARM – T-CELLS

- T-cells – Helpers, Killers and Suppressors
  - Once antigens are presented on macrophages, helper T-cells (also known as CD4 cells) see the antigen and coordinate and direct the activity of other types of immune cells telling them to fight the invader
  - Killer T-cells (CD8 cells) directly attack and destroy our body's cells that are infected by germs as well as abnormal cells that may become cancerous
  - Suppressor T-cells (CD8 cells) "call off the attack" by your immune system once the invader is conquered

CELLS OF THE IMMUNE SYSTEM: ADAPTIVE ARM – B-CELLS

- B-cells and Antibodies
- B-cells help to produce antibodies (called immunoglobulins)
- Antibodies attach to antigens like two perfectly fitting puzzle pieces
- When you are exposed to a germ for the first time, your body produces antibodies over weeks to months to fight it
    - This is similar to vaccine responses
- If you were exposed to a germ your body has seen before, your B-cells have memory and recall the repeat invader and initiate the immune system to attack much quicker

WHAT ARE THE COMMON IMMUNOSUPPRESSIVE DRUGS AND THEIR IMPACT ON THE IMMUNE SYSTEM?

Drug	Effect on Immune system	Infection Risk
Antilymphocyte globulins (Anti-thymocyte globulin – ATG)	Antibodies that deplete T-cells	Reactivation of latent viruses
Glucocorticoids (Prednisone, methylprednisolone, dexamethasone)	”Jack of all trades” → change WBC function and survival; deplete T-cells > B-cells	Bacteria, PJP, molds, viruses, poor wound healing
Azathioprine (Imuran)	Decreases the number of circulating B- and T-cells	Human papilloma virus?
Mycophenolate mofetil (Cellcept)	Decreases B- and T-cell production and antibody production	Bacteria, CMV
Calcineurin inhibitors (Tacrolimus & Cyclosporin)	Decreases T-cell growth	Viruses

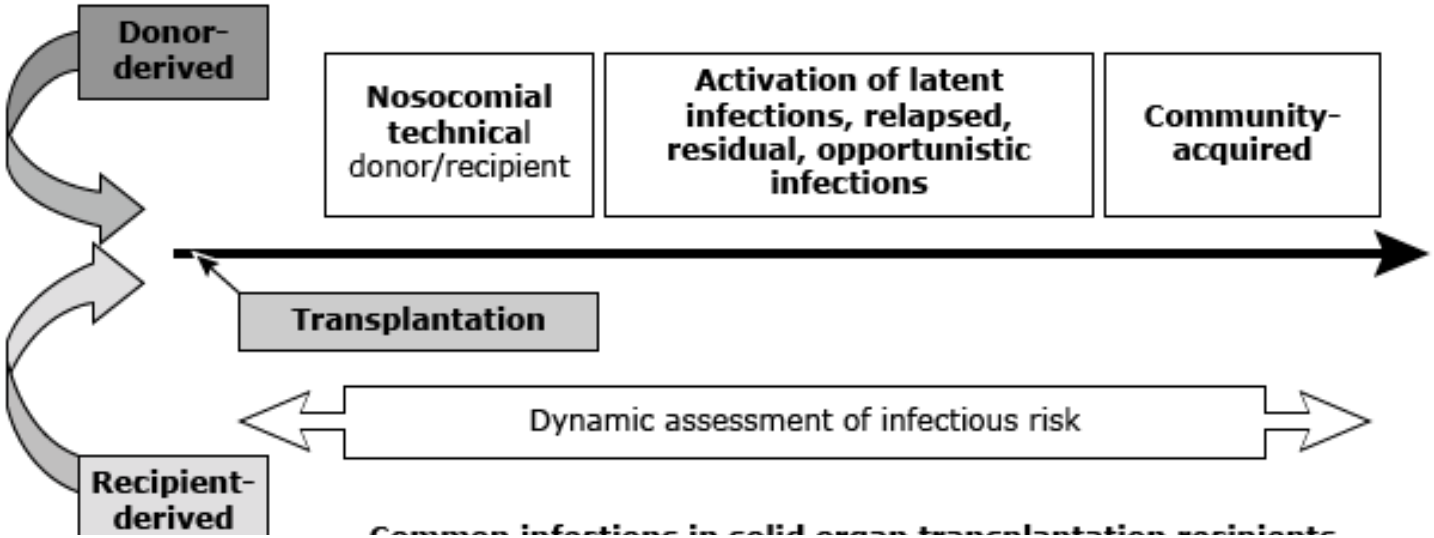
Drug	Effect on Immune system	Infection Risk
Rapamycin (mTor inhibitor ("mammalian target of rapamycin inhibitor")) (Sirolimus & Everolimus)	Blocks the response of B- and T-cell activation	Poor wound healing, respiratory infections
Belatacept (CTLA-4 inhibitor/costimulation blocker) (Nulojix)	Blocks activation of T-cells	EBV, CMV, viral infections, PJP
Rituximab (anti-CD20 antibody/B-cell depleting antibody) (Rituxan)	Monoclonal antibody that targets CD20 – a protein expressed on B-cells. Thereby depleting B-cells.	Bacterial, viral, hepatitis B
Eculizumab (Terminal complement system inhibitor) (Soliris)	Inhibits complement – a system that recognizes features of germs on surfaces and marks them for destruction	Encapsulated bacteria
Plasmapheresis	Can remove complement and immunoglobulins	Encapsulated bacteria

INFECTIOUS COMPLICATIONS

Sources for infectious complications include:

- Nosocomial (hospital-acquired)
- Donor- or recipient-derived
- Reactivation of latent infections
- Community-acquired

The timeline of infections following solid organ transplantation[1-3]

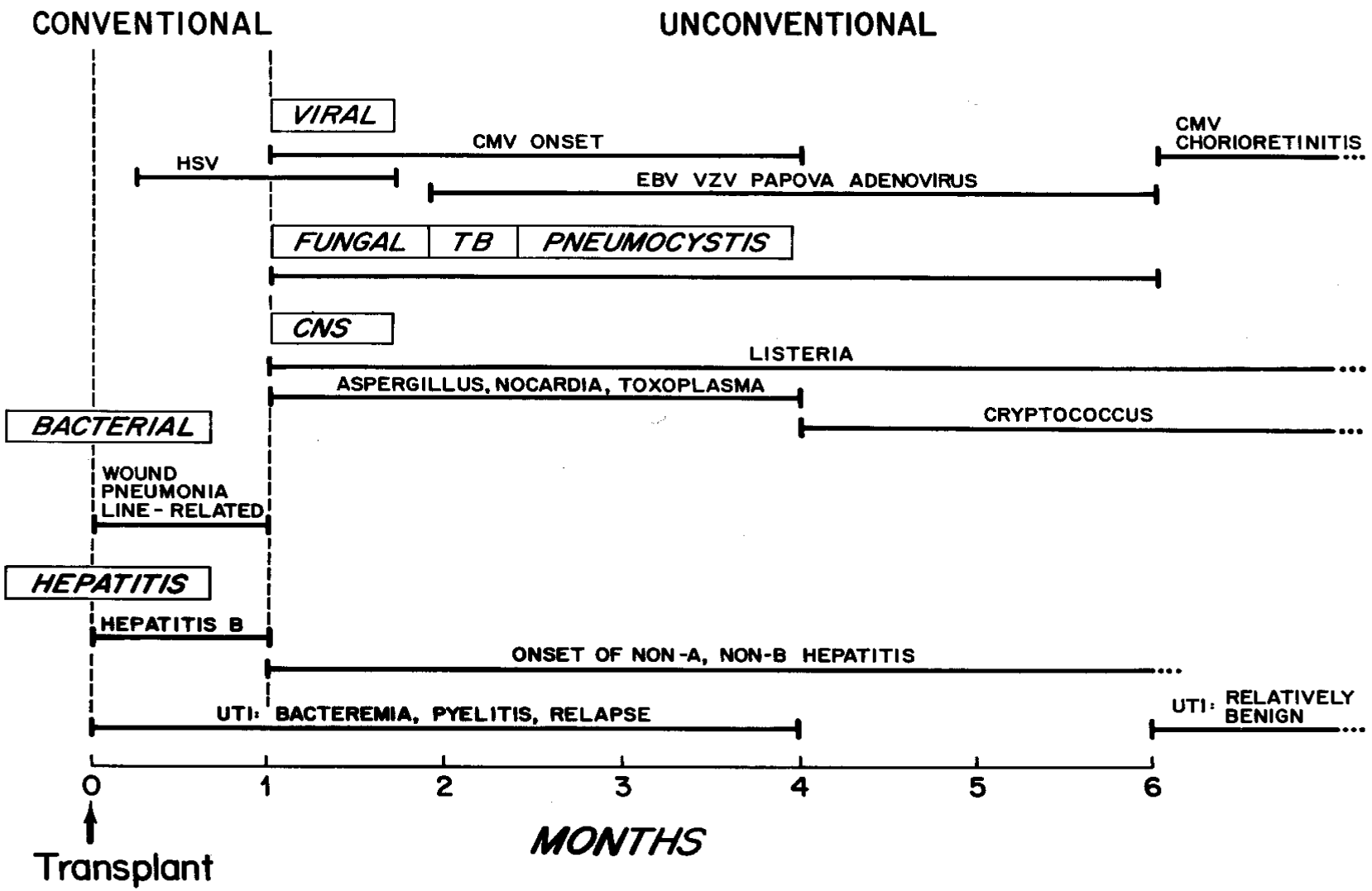


Common patterns of opportunistic infection are observed following solid organ transplantation based on epidemiologic exposures and the "net state of immunosuppression." The timeline is altered based on the immunosuppressive regimen and prophylactic medications. The dynamic assessment of infectious risk represents assays that will measure an individual's risk for infection due to specific pathogens or in general.

CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus; MRSA: methicillin-resistant *Staphylococcus aureus*; PML: progressive multifocal leukoencephalopathy; PTLD: posttransplant lymphoproliferative disorder; SARS: severe acute respiratory syndrome; VRE: vancomycin-resistant enterococcus; VZV: varicella-zoster virus.

Modified from:

1. *Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357:2601.*
2. *Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE. Infection in the renal transplant recipient. Am J Med 1981; 70:405.*
3. *Fishman JA, Rubin RH. Infection in organ-transplant recipients [see comments]. N Engl J Med 1998; 338:1741.*



Fishman and Rubin, NEJM 1998; 338:1741-51

INFECTION BY TIME POST-TRANSPLANT

- Post-transplant course can be divided into 3 time periods:
  - Early period: 0-1 month
  - Intermediate period: 1-6 months
  - Late period: more than 6 months
- Because the full impact of immunosuppression accumulates over time, the greatest risk for infection is actually in the 2nd (intermediate) period
- Any intensified immunosuppression (i.e. treatment of organ rejection) “resets the clock” to the initial period

FIRST MONTH

- 2 major causes of infection in all SOT recipients:
  - Pre-existing in the donor or recipient
  - Infectious complications of the transplant surgery and hospitalization
- Effects of immunosuppression are not yet obvious
  - Exception would be those who are receiving immunosuppression before the SOT (e.g. lupus or rheumatoid arthritis) or living with immunodeficiencies (e.g. HIV)

FIRST MONTH: DONOR-DERIVED

- Donor-derived infections
  - Unanticipated infections that arise from donor organ and are activated in the recipient
  - Some are latent infections
  - Some may simply be a result of bad timing (unappreciated active infection at the time of donation)
  - Efficiency of transmitting the infection from donor to recipient is enhanced due to immunosuppression
  - Living and deceased organ donors are screened to avoid transmission of certain infections, nonetheless transmission of infection may still occur
  - Recipients of organs from donors who are known to be infected or considered at high risk for transmission of HIV, Hepatitis C, Hepatitis B, or COVID-19 require informed consent prior to transplantation

FIRST MONTH: RECURRENT INFECTIONS

- Recurrent infections
  - Infection that may have been present in the recipient prior to transplantation
    - Hepatitis B
    - Hepatitis C
    - Herpes simplex virus (HSV) 1 and/or 2 (cold sores/genital herpes)
  - These infections can re-emerge early after transplantation

FIRST MONTH: COMPLICATIONS OF SURGERY AND NOSOCOMIAL

- Infectious complications related to surgery and the hospitalization
  - Pneumonia
  - Surgical wound infection
  - Bloodstream infections due to presence of catheters
  - UTI
- Organisms responsible for most of these infections are often the bacteria and fungi that live on/in the recipient and the donor

1-6 MONTHS

- The effect felt by immunosuppression is maximal
- Patients are at greatest risk for developing infections
- We give patients various antibiotics, antifungals, and antivirals during this period to try to prevent infections from occurring
    - This may delay infection but does not eliminate risk altogether, especially the risk of infection after the medicines have stopped

1-6 MONTHS: BUGS WE SEE

- **PJP** – *Pneumocystis jirovecii* pneumonia (previously called PCP – *P. carinii)* – type of fungal infection
- Viruses – **Cytomegalovirus**, **Epstein-Barr Virus**, Varicella zoster virus, Herpes simplex virus 1 and 2, Human herpesviruses -6, -7, -8; Hepatitis B and C; BK polyomavirus; community acquired viruses (influenza, parainfluenza, RSV, adenovirus, human metapneumovirus, COVID-19)
- Latent infections – strongyloides, toxoplasmosis, Chagas disease
- Other fungal infections – *Histoplasma, Coccidiomycosis, Paracoccidiomycosis*, *Cryptococcus, Blastomyces, Aspergillus*
- Mycobacterial infections (Tuberculosis)
- Parasitic infections – *Cryptosporidium, Microsporidium*
- UTIs

>6-12 MONTHS

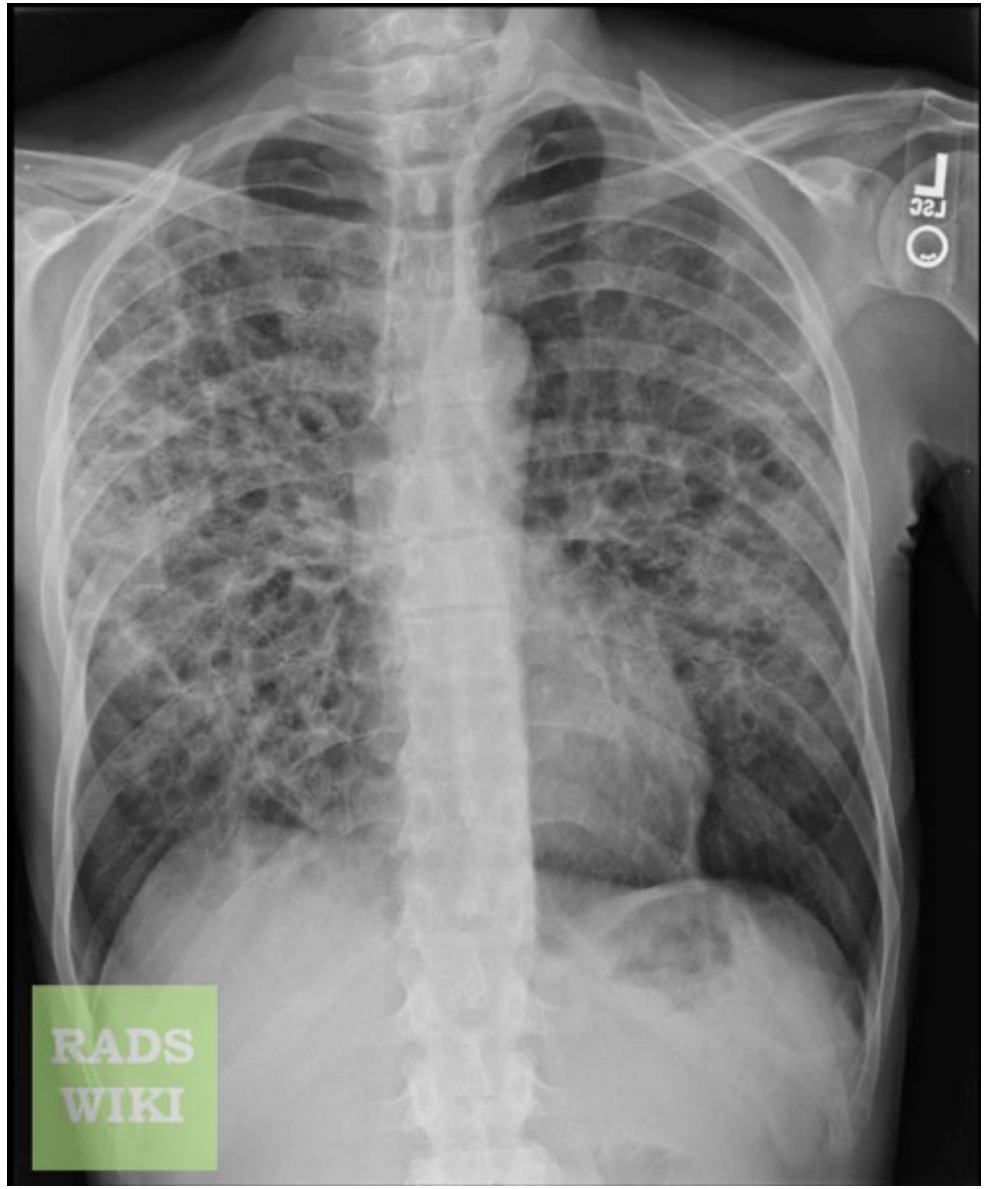
- Patients are usually on stable immunosuppression and possibly even reduced amounts
- Community-acquired infections more commonly seen
    - Pneumonia
- “Late CMV”

PNEUMOCYSTIS JIROVECII

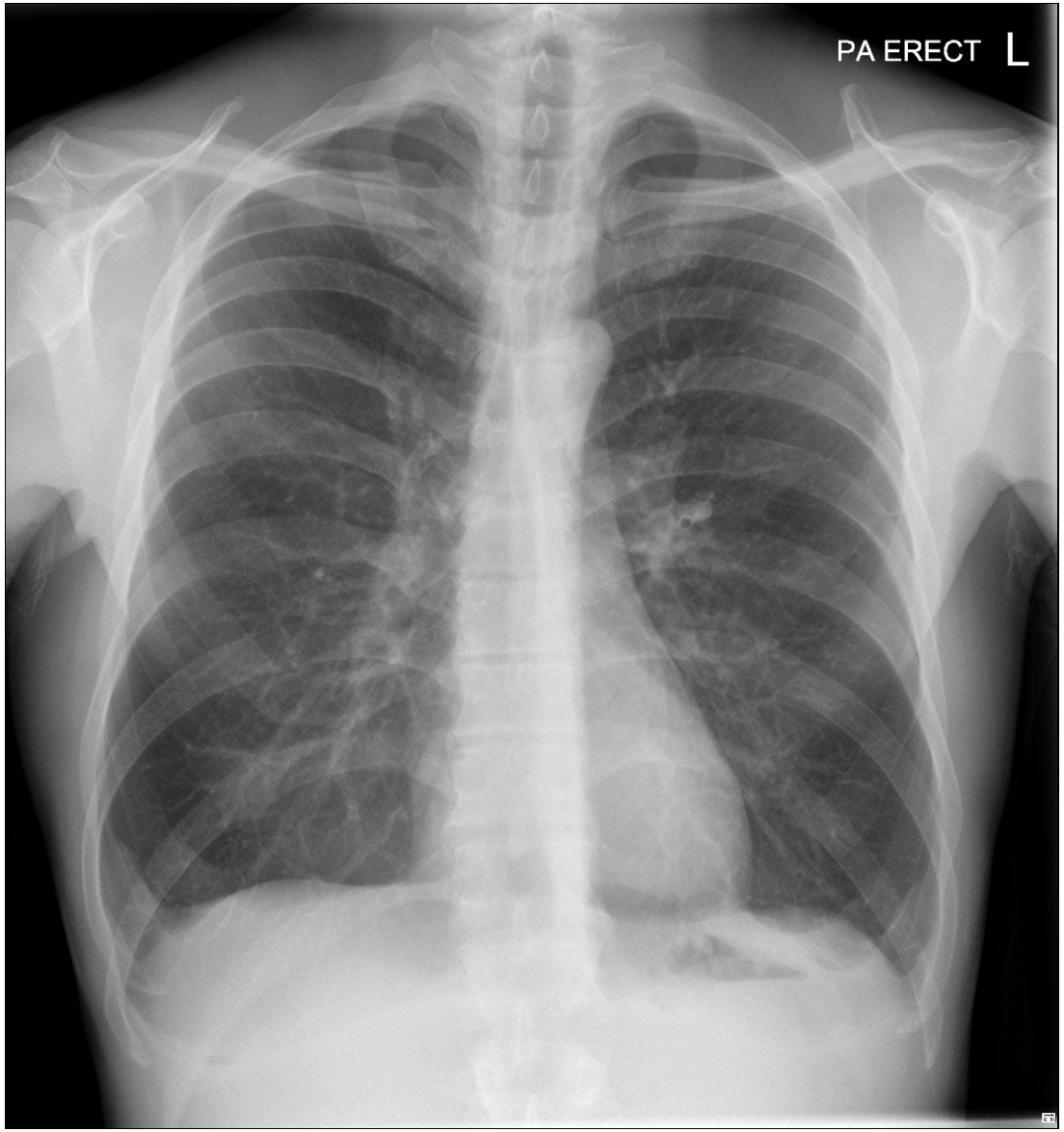
PJP – *PNEUMOCYSTIS JIROVECII* PNEUMONIA

- Potentially life-threatening fungal infection that usually involves the lungs
  - Less commonly infects organs outside of the lungs
- Airborne transmission
  - Non-immunocompromised people likely carry this in their lungs and spread in the environment where immunocompromised people can breathe it in
- Steroids, belatacept, and rituximab can increase the risk for developing PJP
- mTor inhibitors (sirolimus, everolimus) MAY increase one's risk, it's not clear based on literature
- Seen more often in heart and lung transplant recipients than kidney or liver transplant recipients

P J P

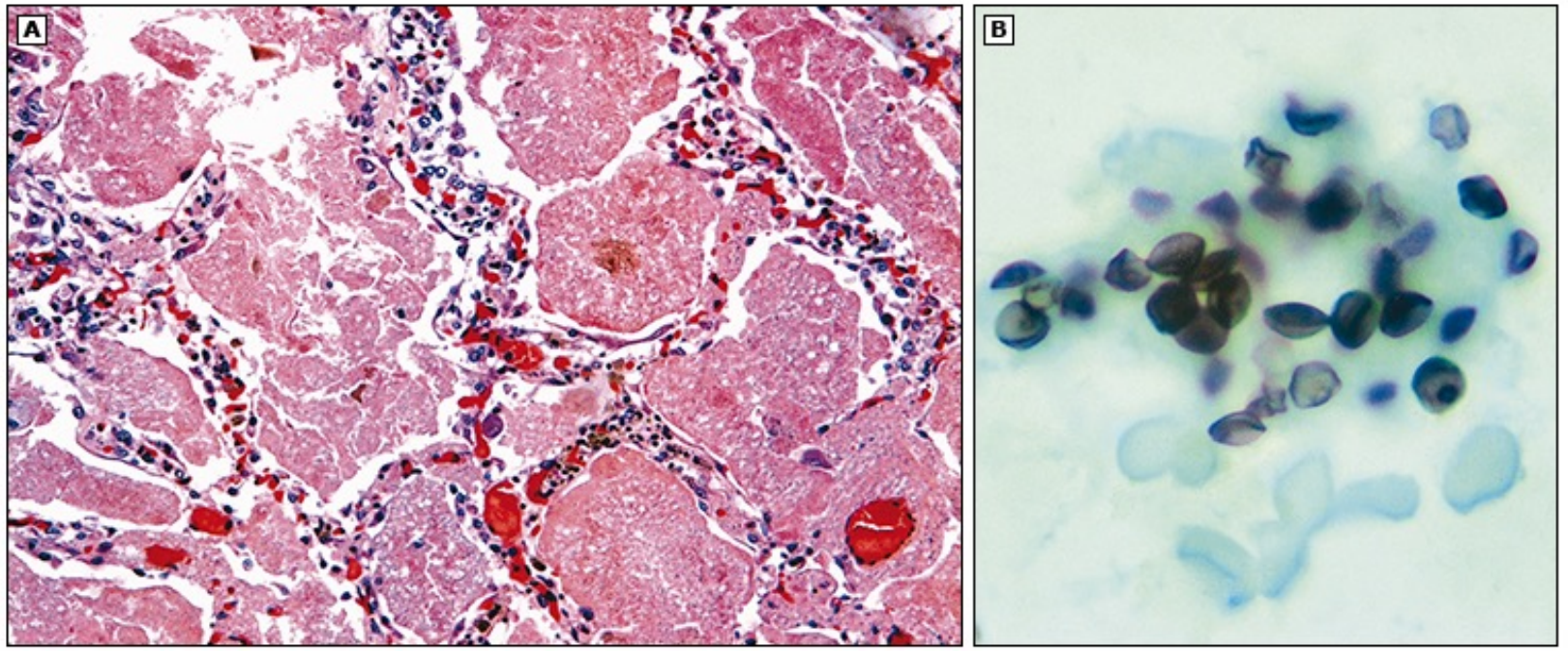


Case courtesy of The Radswiki, Radiopaedia.org, rID: 11789



Case courtesy of Andrew Dixon, Radiopaedia.org, rID: 49228

Histopathology and staining of lung tissue in a patient with *Pneumocystis* pneumonia



(A) Photomicrograph shows mild alveolar interstitial thickening by a lymphocyte infiltrate and extensive filling of airspaces by finely vacuolated eosinophilic material.

(B) Magnified view of the material in one of the airspaces shows silver positive (black) round or helmet-shaped structures typical of *Pneumocystis jirovecii*.

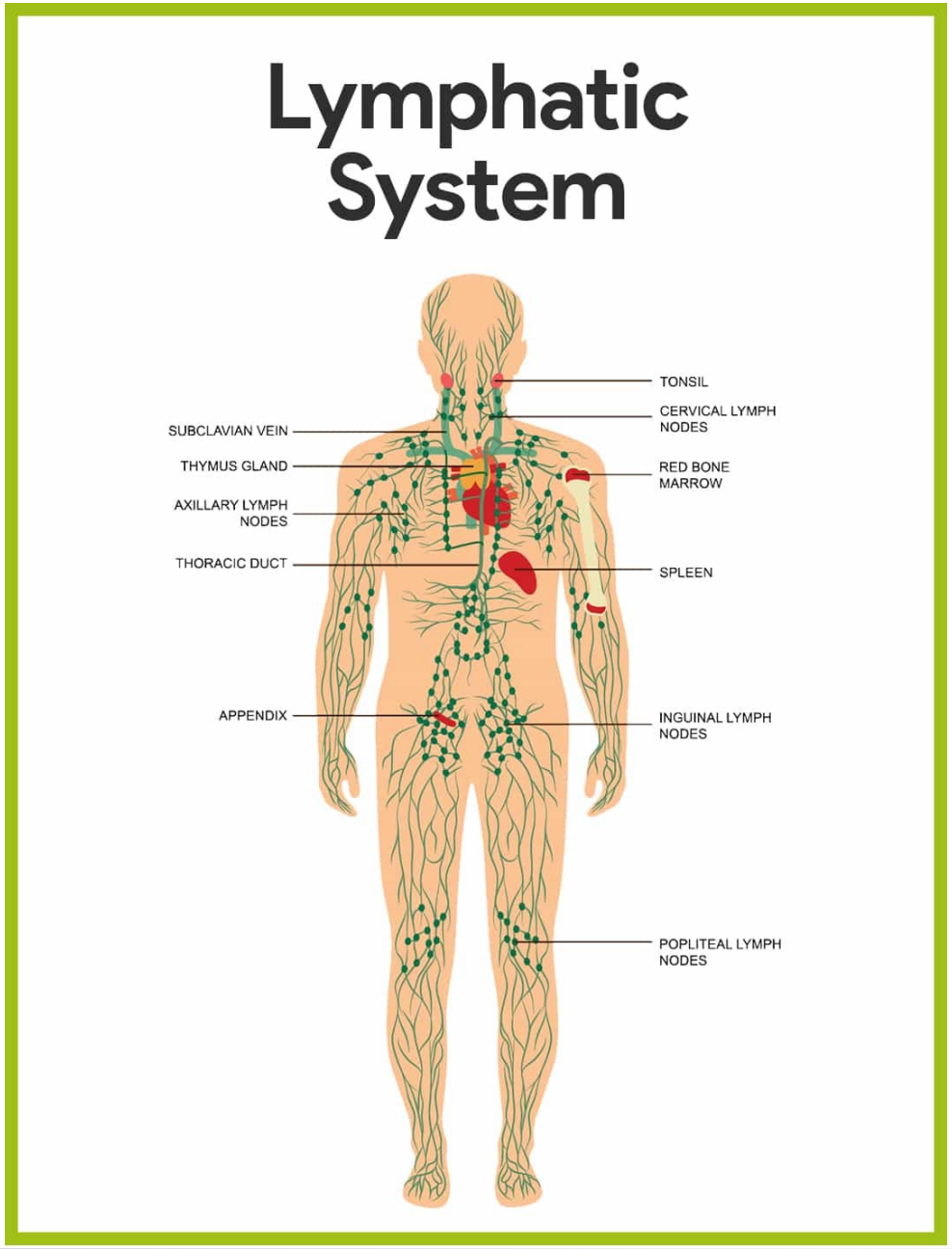
P J P

- We aim to prevent PJP pneumonia by giving medicines to prevent it for the first 6 months after transplant
    - Bactrim, Atovaquone, Dapsone, or Pentamidine
- Can present with insidious onset of shortness of breath and coughing. Fevers may/may not be present.
- Treatment is dependent upon severity of illness
    - Usually requires a 3-week course of therapy followed by lifelong prevention

EPSTEIN-BARR VIRUS & PTLD

P T L D

- PTLD = Posttransplant Lymphoproliferative Disorder
- A spectrum of lymphoproliferative disorders
  - Refers to abnormal overgrowth (cancerous growth) of cells of the lymphatic system
- Two types of lymphatic cells involved in PTLD: T-cells and B-cells
  - 85-90% of PTLD arise from B-cells
  - 10-15% of PTLD arise from T-cells
- Epstein Barr Virus (EBV) is the viral infection most commonly associated with PTLD



PTLD RISK

- Greatest risk in the 1st year post-transplant
  - More than 80% occur occur in the 1st year after transplant
  - Most common cancer in pediatric transplant recipients
  - 2nd most common cancer in adult recipients – accounts for ~20% of all cancers in transplant patients

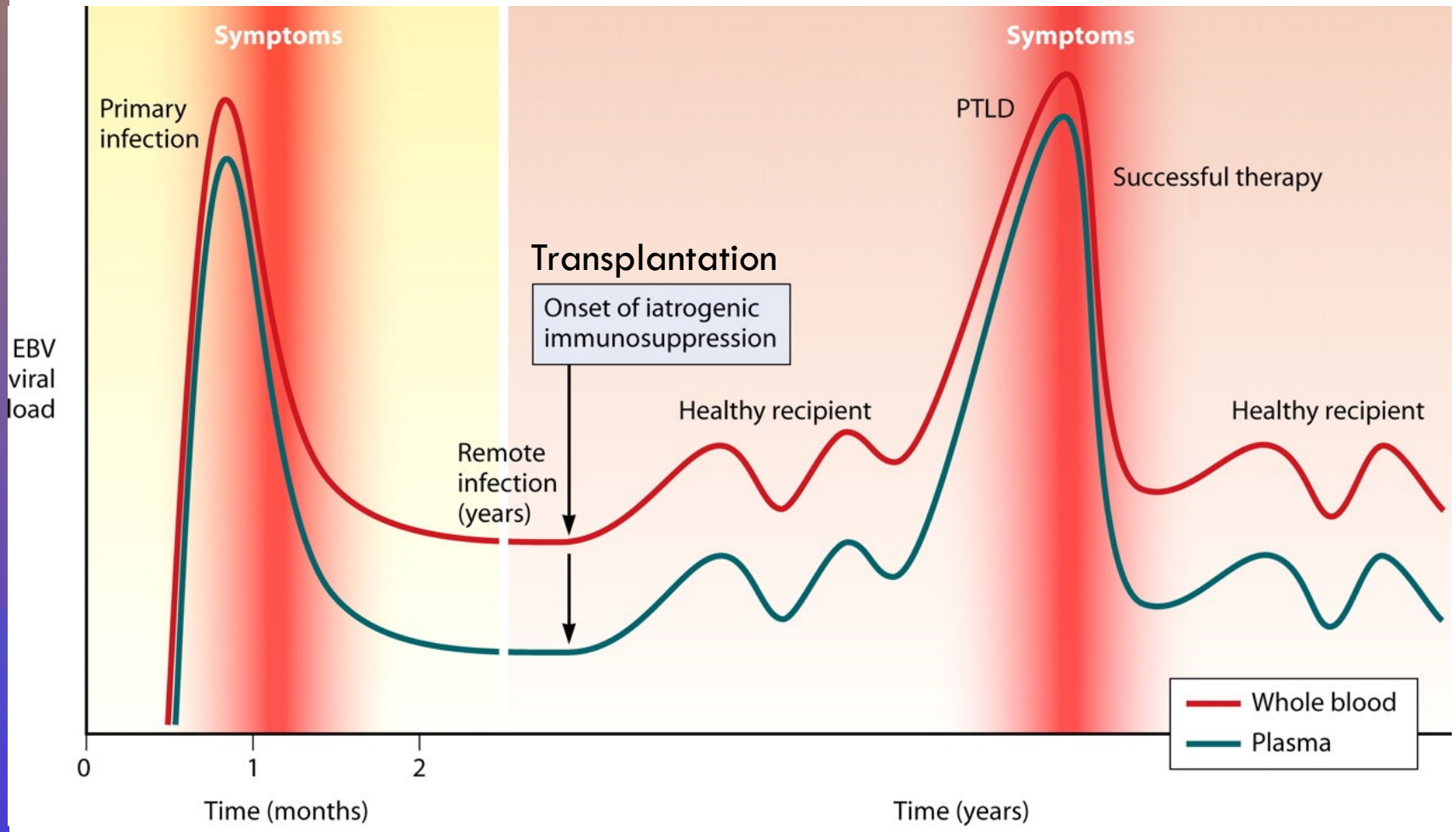
- Risk factors:
  - Genetics
  - Degree of immunosuppression
  - Recipient age (<10 and >60)
  - Type of transplanted organ
    - 20% for small bowel; 2-10% for heart and lung; 1-5% for liver and/or kidney
  - EBV infection

EBV & PTLD

- 60-70% of B-cell PTLDs are associated with EBV infection
- 10-40% of T-cell PTLDs are associated with EBV infection
- Increased risk of PTLD among EBV-positive donors that give organs to EBV-negative recipients (EBV D+/R-)
    - Incidence of PTLD risk for EBV-negative recipients was 24x higher than that for EBV-positive recipients

HOW CAN WE PREVENT/DETECT PTLD?

CAN BE DETECTED EARLY BY MONITORING OF EBV BLOOD LEVELS



Gulley ML, Tang W. Using Epstein-Barr viral load assays to diagnose, monitor, and prevent posttransplant lymphoproliferative disorder. *Clin Microbiol Rev.* 2010;23(2):350-366. doi:10.1128/CMR.00006-09

PTLD DIAGNOSIS

- Disease presentation is often non-specific
  - Fevers, weight loss, fatigue
  - Enlarged lymph nodes
  - Compression of surrounding organs due to mass development
  - Delays diagnosis

- Diagnosis made with imaging and biopsy

- Presents on imaging as a new mass or enlarged lymph nodes

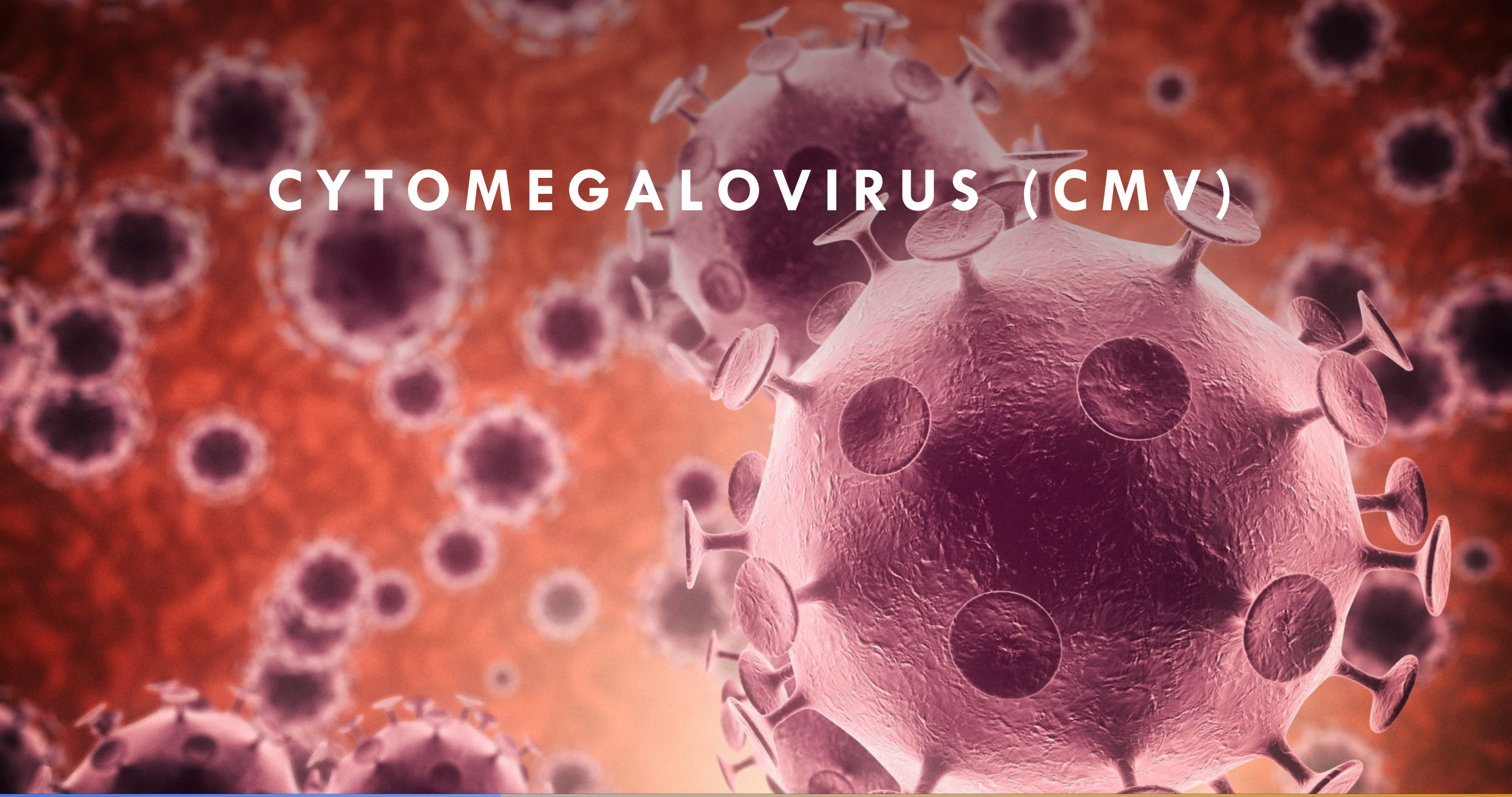
- PTLD may involve the transplanted organ in ~50% of the cases

- Can be detected early by monitoring EBV blood levels

PTLD TREATMENT

- Reduction of immunosuppression
- Chemotherapy
- Antivirals (if viral cause is proven)
- Radiation therapy
- Mortality is 30% - 60%
- It is important to seek medical care when things don't feel quite right.
    - Advocate for yourself.

CYTOMEGALOVIRUS (CMV)



CMV – CYTOMEGALOVIRUS

- Globally wide-spread virus that becomes latent after initial infection
  - Many people have been exposed to CMV at some point in their life before transplant/organ donation (some show signs of infection at initial exposure, others do not)
    - 40-60%
  - Latent virus can reactivate and become active infection/disease
- CMV infection/disease is associated with risk of organ failure and patient death
  - CMV infection – defined as the presence of CMV actively growing/replicating in the blood regardless of whether signs/symptoms are present
  - CMV disease – defined as presence of CMV actively replicating in the blood along with other clinical symptoms/signs
    - CMV syndrome – active CMV replication with symptoms but without organs being affected
    - Tissue-invasive CMV disease – active CMV replication with symptoms and with organ(s) being affected
      - Organs that can be affected: colon, small bowel, liver, pancreas, kidneys, lungs, eyes, and central nervous system

CMV: WHO'S AT RISK?

- Primary risk factor for CMV infection/disease is the CMV serostatus of the donor/recipient (D/R) pair
  - Serostatus = presence/absence of antibodies against CMV
    - If present, it means that person has been exposed to CMV previously
    - Serostatus can be + (antibodies present) or – (antibodies absent)
- The pairs can be:
  - D+/R- (highest risk)
  - D+/R+
  - D-/R+
  - D-/R-

CMV DISEASE PRESENTATION

- Gastrointestinal disease – diarrhea, nausea, vomiting, difficulties swallowing, abdominal pain
  - One of the most common presentations, especially in kidney transplant recipients
- Hepatitis (liver) – elevated liver enzymes/jaundice, abdominal pain
- Pancreatitis (pancreas) – abdominal pain
- Pneumonitis (lungs) – cough, shortness of breath
- Meningoencephalitis (central nervous system) – headache, stiff neck, confusion/altered behaviors, paralysis
- Retinitis (eyes) – changes in vision
- Nephritis (kidneys) – change in kidney function, decreased urine output, blood in the urine

CMV: PREVENTION IS KEY

- Prevention strategies include universal prophylaxis or preemptive therapy
  - Universal prophylaxis = administration of antiviral medication to high-risk patients beginning within 10 days of transplant and continuing for 3-6 months
    - Valganciclovir (Valcyte); Letermovir
  - Preemptive therapy = monitoring for CMV replication in the blood at regular intervals (weekly) and valganciclovir is started when viral replication is detected at a particular threshold (threshold varies by transplant center and by test being used).
  - Surveillance after prophylaxis = combination of the above two measures.
    - Less commonly used preventative method

CMV: PREVENTION STRATEGY USED

- The 2018 International Consensus Guidelines on the Management of CMV in Solid Organ Transplantation
  - Universal prophylaxis for D+/R+, D-/R+, and D+/R-
    - Valganciclovir is started in the immediate posttransplant period
    - For D+/R- patients, they receive valganciclovir for 6 months
    - For CMV R+ (D+/R+ and D-/R+) patients, they receive valganciclovir for 3 months
  - Preemptive therapy (for the low-risk group: D-/R-)
    - Monitor for CMV replication weekly for 3 months following transplantation
    - These patients receive medications to prevent HSV/VZV (Valacyclovir or Acyclovir)
- Prophylaxis is also often used when a patient is treated for rejection

VIRUSES: THE OTHER IMPACT

- Viruses, specifically CMV, serve as a means by which someone can develop other opportunistic infections by immunosuppressing the patient
  - Hepatitis B, Hepatitis C, EBV, respiratory syncytial virus (RSV), adenovirus, human herpesvirus-6, etc.
- Direct effects and Indirect effects from viral infection
  - Direct effects = virus-specific clinical syndromes
  - Indirect effects =
    - Immune suppression and predisposition to other infections ("fungal after viral" infections)
    - Organ rejection
    - Oncogenesis (cell proliferation/overgrowth leading to cancer)

CONCLUSIONS

- The “net state of immunosuppression” is a conceptual assessment of the factors contributing to the risk of infection in an immunosuppressed person
- The immune system is complex and can be variably impacted by the drugs we use to prevent rejection of transplanted organs
- The ways in which we suppress the immune system impacts what infections we can see post-transplant
- PJP, CMV, and EBV and commonly encountered infections post-transplant that carry high morbidity and mortality
    - Viruses can impact the immune system further by leading to more infections, organ rejection, and even cancer

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-JIM ROHN
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