First: Why immunosuppress?

- Suppress immune system to a moderate degree
- Prevent cellular rejection
- Prevent antibody-mediated rejection
- For whom is this most problematic? Why?
Adverse effects or complications of ALL immunosuppression

- Infection
- Cancer
- Lymphoma – PTLD

Why prophylaxis?

- Prevent infections common to patients with compromised immune systems
- Pneumocystis jirovecii pneumonia
- Cytomegalovirus
- Fungal infections

Induction

- High dose steroids
- Basiliximab
- Anti-thymocyte globulin
THE CALCINEURIN INHIBITORS (CNI'S)
These are the game changers

Mechanism of action

- Originally made from a fungus
- Calcineurin is one step in the process of upregulating mediators which lead to increased T cell concentration in response to antigens
- Calcineurin inhibitors block this response by binding proteins which then bind to calcineurin, inhibiting it and thus decreasing the T cell response

(Cazi, Sayegh, & Mallat, 2013)

Cyclosporine

- CSA
- IV or oral
- IV with a caveat
- Take at the same time every day, 12 hours apart
- Draw troughs 30 minutes before next dose
- Renal impairment, neurological adverse reactions, PRES, tremors, hirsutism, hyperkalemia
- Interactions: some of the statins, antifungals, diltiazem, other antiarrhythmics
**Tacrolimus**

- FK
- PO, SL, IV
- Not often given IV
- Same time every day, 12 hours apart
- Inhibits FK binding protein in early process of T cell proliferation
- Draw troughs 30 minutes before next dose
- Renal impairment, neurological adverse reactions, PRES, tremors, hair loss, hyperkalemia, hypomagnesemia
- Interactions: some of the statins, antifungals, diltiazem, other antiarrhythmics
- First line!

**Next in line: MMF**

**Mycophenolate**

- Inhibits an enzyme responsible for one of the steps of lymphocyte synthesis
- Also has an inhibitory effect on B cell antibody response
**Mycophenolate mofetil**

- PO, IV
- IV very expensive
- ED dosing
- Cytopenias
  - Neutropenia can be intolerable
  - Calculating absolute neutrophil count
- Upper GI side effects, lower GI side effects
- First line

(Clinical Pharmacology, 2017)

**Mycophenolate sodium**

- Enteric coated
- Dosing is different: 180 mg of mycophenolate sodium is equal to 250 mg of mycophenolate mofetil
- Can help with upper GI side effects, and anecdotally some lower GI side effects as well
- Still causes the cytopenias

(Clinical Pharmacology, 2017)

**Azathioprine**

- Inhibits purine metabolism. Decreases the initial hypersensitivity and cellular response in the post-transplant period
- Not as effective for "established" rejection or "secondary responses"

(Clinical Pharmacology, 2017)
+ STEROIDS

+ Prednisone, Methylprednisolone

- Glucocorticoid, some mineralocorticoid activity
- Multitude of immunosuppressive effects
- Hyperglycemia
- Moon facies
- Myopathy
- Osteoporosis

+ MTORs
### Sirolimus

- **Macrolide**
- Structurally similar to tacrolimus, but not the same (not a calcineurin inhibitor!)
- Whereas tacro inhibits FKBP, sirolimus inhibits mammalian target of rapamycin (mTOR)
- Also reduces B cell response
- Given PO, daily dosing
- Check trough level
- HTN, hypertriglyceridemia, muscle pains, GI side effects

(From Clinical Pharmacology, 2017)

### Everolimus

- Similar MOA to sirolimus but different portion of the cycle.
- PO, daily dosing
- Check trough level
- Hypercholesterolemia, hypertriglyceridemia, anemia, stomatitis, elevated LFT’s

(From Clinical Pharmacology, 2017)
Belatacept

- Suppresses T-cell stimulation
- Binds to sites of antigen-presenting cells which suppresses these T-cell costimulators
- Less direct effect on antibody levels
- Adverse effects: HTN, HL, GI side effects
- IV infusion, more frequently at time of transplant then monthly after that

(Clinical Pharmacology, 2017)

Infection prophylaxis

- Pneumocystis prophylaxis

- It works!
- Sulfamethoxazole/Trimethoprim
  - 1 DS tab-TW (M/W/F)
- Dapsone
- Methemoglobinemia
- Atovaquone
  - Patients hate it
- Pentamidine
  - Monthly inhalation
  - Compliance (could be better or worse)
**CMV prophylaxis**

- Valgancyclovir
- Gancyclovir
- Most common side effect is pancytopenia, especially leukopenia/neutropenia (which is also a complication of CMV viremia)
- Providers seeing patients with CMV should use universal precautions

**General viral prophylaxis**

- Acyclovir, valacyclovir

**Antifungals**

- Voriconazole
- Itraconazole
- Posaconazole
- Amphotericin B inhaled
Treatment of acute rejection

- High dose oral steroids
- High dose IV steroids
- ATG
- Alemtuzumab
- Bortezomib
- Rituximab
- Plasmapheresis
- IVIG

A brief note on azithromycin

- Not used as prophylaxis for lung transplant patients.
- Anti-inflammatory properties can help slow the progression of chronic rejection

Case study 1

- A 35 y/o female presents to the ED with her husband. She appears dehydrated and ill. She is oriented to person and year but is intermittently confused about where she is and what the date is.
- Her husband states that she underwent a bilateral lung transplant 5 years ago for cystic fibrosis and she has been doing well lately with no recent acute illnesses. He reports they stopped yesterday on their way back from visiting family and got fast food, and later last night she began vomiting and having diarrhea. She was able to hold down her immunosuppression last night.
He states that this morning she has become progressively more “out of it,” and that she has been “saying things that don’t make any sense.

- What kind of workup do you initiate?
- Labs?
- What are your first steps?

Case study 2

- You are working in a primary care clinic when a new patient presents for a sick visit. She has just moved here from another city and states that she had a heart transplant a little over a year ago.
- She states that she didn’t know where else to go. She states she feels “terrible” with a cough and chills for 2 days and a fever of 100.8 this morning. She is achy and feels like she can barely get out of bed. She called her transplant center but it is several hours away so they asked her to be seen locally first.
- What are your first steps?

Question time

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References


Azzil, J., Sayegh, M., & Mallat, S. G. (2013). Calcineurin inhibitors: 40 years later, can’t live without... The Journal of Immunology, 191, 5785-5791. doi:10.4049/jimmunol.1390055


