Immunosuppressant Medications

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Presentation outline

• Evolution of immunosuppressive therapies
• Common indications for immunosuppression
• Discussion of immunosuppressive drug classes
• Prophylaxis, Immunization and Pregnancy considerations

Goals of immunosuppressive therapies

• Prevent allograft rejection after transplant
• Control baseline inflammatory disease
• Prevent and/or treat disease flares
• Minimize adverse effects
• Avoid infectious complications

Indications

• Solid organ and bone marrow transplantation
• Autoimmune disease
  - Rheumatoid arthritis
  - Multiple sclerosis
  - Psoriasis
  - SLE
  - Crohn’s disease
  - Ulcerative colitis
  - Behcet’s
  - FSGS
  - Myasthenia gravis
  - Ankylosing spondylitis
  - Sarcoidosis
• Asthma
• Pre-20th century attempts at transplantation
  – 300 B.C.: Pien Chi’ao, Chinese physician
  – 3rd century A.D.: Cosmas & Damian
  – “biochemical barrier to transplantation” Ernst Unger (1909)
• 1910s – use of cytotoxic medications
• 1950s – sublethal total-body irradiation
• 1954 – successful kidney transplant between identical twins

1950 Nobel Prize in Physiology or Medicine
Edward Calvin Kendall | Philip Showalter Hench | Tadeusz Reichstein
Biochemist | Rheumatologist | Chemist

History of Immunosuppression

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1950s</td>
<td>1960s</td>
<td>1980s</td>
</tr>
</tbody>
</table>


Diagram showing the mechanism of action of various immunosuppressive drugs and their targets.
Immunosuppressant Medications

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Department of Anesthesiology
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Corticosteroids

- Nonspecific anti-inflammatory affects both B and T cell lines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Activity Duration of Action (hours)</th>
<th>Equiptotent Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1 1 8-12</td>
<td>20</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4 0.8 18-36</td>
<td>5</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5 0.5 18-36</td>
<td>4</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>30 0 36-54</td>
<td>0.75</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>10 125 18-36</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- Do not discontinue abruptly (≥ 7 days)

Adverse Effects

- Gout
- Osteoporosis
  - Consider calcium/vitamin D supplement
- Hyperlipidemia
- Hypertension
- Impaired wound healing

Disease-modifying Antirheumatic Drugs (DMARDs)

- Methotrexate
  - Inhibits cytokine production and purine biosynthesis = reduction in inflammation
  - 1st line in the treatment of RA
  - Available PO, IV, subQ
  - Onset of action: 3-4 weeks
  - Typically dosed once a week or split dosing (>15mg/week)
  - Renally eliminated


https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f1260de-b60c-4f9a-ba9f-6c937b3428f1
DMARDs

• Methotrexate
  – Adverse effects: nausea/vomiting/diarrhea, thrombocytopenia, leukopenia, ↑ LFTs, pulmonary fibrosis
  – Can induce folic acid deficiency
    • Give with 1mg/day to reduce adverse effects
  – Monitoring
    • CBC w/platelets, LFTs every 1-2 months
    • Levels rarely obtain, usually reserved for high dose (hematologic malignancies)

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8f1260de-b60c-4f0e-8af6-0e957b0a281b

DMARDs

• Sulfasalazine
  – Sulfapyridine ↓ erythrocyte sedimentation rate and C-reactive protein
  – Used in RA (combination), IBD, spondyloarthritis
  – Available PO
  – On set of action: 4- 9 weeks
  – Dose: 500 mg daily x 1 week then ↑ the dose by 500 mg daily on a weekly basis until a dose of 2 g daily (divided doses) is achieved


DMARDs

• Sulfasalazine
  – Adverse effects
    • Hepatotoxicity, rash
      – Usually occur within the first 12 weeks of treatment
    • Dose related: nausea/vomiting/diarrhea, headache, leukopenia
  – Monitoring
    • Glucose-6-phosphate dehydrogenase (G6PD) before initiating therapy
    • CBC, LFTs every 1-2 months and after increasing dose


DMARDs

• Hydroxychloroquine
  – ↓ cytokine production, lymphocyte proliferation, and autoantibody production
  – Used in lupus and RA
  – Available PO
  – Onset of action: 1-3 months
  – Dose
    • Lupus: 200mg – 400mg (daily or divided doses)
    • RA: 400mg – 600mg (daily or divided doses)

DMARDs

• Hydroxychloroquine
  – Adverse effects
    • Corneal deposits, retinopathy
    • Pruritic maculopapular lesions, hyperpigmentation,
    • Dose related: nausea/vomiting/diarrhea, headache
  – Monitoring
    • Eye examination at baseline and yearly
    • No routine lab monitoring required

DMARDs

• Leflunomide
  – Inhibits T-cell proliferation and production of B lymphocytes by inhibiting the production of multiple tyrosine kinase
  – Interferes with viral assembly
  – Used in RA, Crohn’s disease, psoriatic arthritis, transplant (active BK virus or CMV)

DMARDs

• Leflunomide
  – Available PO
  – Onset of action: 3-4 weeks
  – Dose
    • RA
      – 100mg daily x 3 days then 20mg daily or 10-20mg/daily without loading dose
    • Transplant
      – 100mg daily x 3 days then 20-60mg daily

DMARDs

• Leflunamide
  – Adverse effects
    • Nausea/vomiting/diarrhea, alopecia
    • Leukopenia, anemia, thrombocytopenia
  – Monitoring
    • CBC and LFTs monthly initially then every 8 weeks
    • Teriflunomide (leflunomide metabolite) can be monitored in transplants: target goal > 50,000ng/mL

Immunopharmacology. 2000;47:291-298
Dialysis & Transplantation. 2011;40:102-107
Immunopharmacology. 2000;47:291-298
Biologic DMARDs

- Growing field
  - Kinase inhibitors
  - TNF alpha inhibitors
  - IL-6 receptor inhibitors
  - T cell costimulatory modulators
- Used in RA, Crohn's disease, psoriatic arthritis
- Typically available subq or IV
- Risk of infection and malignancy

Antimetabolites

- Mycophenolate
  - Interferes with purine synthesis → ↓ T-cell and B-cell proliferation
  - Used in transplant immunosuppression, autoimmune hepatitis, lupus nephritis

Antimetabolites

- Mycophenolate
  - Available PO (tablets, capsules, liquid) and IV
  - Dosing
    - Cellcept (mycophenolate mofetil): 500mg-1500mg Q12H
    - Myfortic (mycophenolate sodium): 360mg-1080mg Q12H
    - Conversion: Myfortic 720mg = Cellcept 1000mg
  - Adverse effects
    - Nausea/vomiting/diarrhea
    - Leukopenia, thrombocytopenia
    - Headache
    - Hypertension
  - Monitoring
    - CBC monthly
    - No correlation between drug levels and prevention of rejection/efficacy and toxicity

### Antimetabolites

<table>
<thead>
<tr>
<th><strong>Mycophenolate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REMS program</strong></td>
</tr>
<tr>
<td>- Increased risk of miscarriage in the 1st trimester</td>
</tr>
<tr>
<td>- Increased risk of congenital malformations</td>
</tr>
<tr>
<td><a href="https://www.mycophenolaterems.com/">https://www.mycophenolaterems.com/</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Azathioprine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibits purine synthesis</strong></td>
</tr>
<tr>
<td>- Used in RA, transplant immunosuppression, lupus, IBS</td>
</tr>
<tr>
<td>- Available PO and IV (been on backorder)</td>
</tr>
<tr>
<td>- Dose</td>
</tr>
<tr>
<td>- 1-3 mg/kg/day or 50-150mg daily</td>
</tr>
<tr>
<td><a href="https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/016324s034s035lbl.pdf">https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/016324s034s035lbl.pdf</a></td>
</tr>
</tbody>
</table>

### Azathioprine

- **Adverse effects**
  - Leukopenia, thrombocytopenia (dose dependent)
  - Nausea/vomiting
    - Give with food
- **Monitoring**
  - CBC monthly
  - No correlation between drug levels and prevention of rejection/efficacy and toxicity

### Calcineurin Inhibitors

<table>
<thead>
<tr>
<th><strong>Cyclosporine (CSA)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhibits activation of T-cells</strong></td>
</tr>
<tr>
<td>- Used in transplant immunosuppression, ulcerative colitis, lupus, RA, psoriasis</td>
</tr>
<tr>
<td>- Available PO (capsule, oral solution) and IV</td>
</tr>
<tr>
<td>- Dosing</td>
</tr>
<tr>
<td>- Neoral (modified cyclosporine) is not bioequivalent to Sandimmune (cyclosporine)</td>
</tr>
<tr>
<td>- Absorption of Sandimmune can be erratic; increased bioavailability with Neoral</td>
</tr>
<tr>
<td>- 1-5 mg/kg/day (divided into BID dosing)</td>
</tr>
</tbody>
</table>

[https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf)
## Calcineurin Inhibitors

<table>
<thead>
<tr>
<th>CSA</th>
<th>Drug interactions (inhibitor and substrate of CYP3A4 and P-glycoprotein)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CYP3A4</td>
</tr>
<tr>
<td></td>
<td>‒ Inhibitors: atorvastatin, amlodipine, amiodarone, fluconazole, etc.</td>
</tr>
<tr>
<td></td>
<td>‒ Inducers: carbamazepine, phenytoin, rifampin, phenobarbital</td>
</tr>
<tr>
<td></td>
<td>Grapefruit and grapefruit juice († CSA levels)</td>
</tr>
</tbody>
</table>

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038bl.pdf

<table>
<thead>
<tr>
<th>CSA</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More nephrotoxicity but less neurotoxicity than tacrolimus (tremor, seizures)</td>
</tr>
<tr>
<td></td>
<td>Hypertension, hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>Hair growth</td>
</tr>
</tbody>
</table>

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038bl.pdf

<table>
<thead>
<tr>
<th>CSA</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chem-7 and BP every 2 weeks for the first 3 months then monthly</td>
</tr>
<tr>
<td></td>
<td>Troughs and C2 levels (2 hours post dose) have been used</td>
</tr>
<tr>
<td></td>
<td>Important to clarify goals</td>
</tr>
</tbody>
</table>

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038bl.pdf

## Calcineurin Inhibitors

<table>
<thead>
<tr>
<th>Tacrolimus (TAC)</th>
<th>Inhibits activation of T-cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Used in transplant immunosuppression, RA, Crohn’s disease, psoriasis</td>
</tr>
<tr>
<td></td>
<td>Shown to have better outcomes than cyclosporine in transplant immunosuppression</td>
</tr>
<tr>
<td></td>
<td>Available PO (capsule, extended release capsule) and IV</td>
</tr>
</tbody>
</table>

**Calcineurin Inhibitors**

- Tacrolimus (TAC)
  - Dosing
    - Oral: 0.05-0.15 mg/kg/day in two divided doses
    - IV: 0.01-0.02 mg/kg/24 hours (continuous infusion)
  - Drug interactions (inhibitor and substrate of CYP3A4 and P-glycoprotein)
    - CYP3A4
      - Inhibitors: atorvastatin, amlodipine, amiodarone, fluconazole, etc.
      - Inducers: carbamazepine, phenytoin, rifampin, phenobarbital
    - Grapefruit and grapefruit juice (↑ TAC levels)

**Calcineurin Inhibitors**

- TAC
  - Adverse effects
    - Neurotoxicity (tremors and seizures) → more common in TAC vs CSA
    - Nephroxicity (less than CSA)
    - Hyperkalemia, hypomagnesemia
    - Hyperglycemia, hypertension (more common in CSA)
    - Alopecia
      - Try Rogaine or biotin supplementation

**mTOR**

- Sirolimus and everolimus
  - Inhibit T-cell proliferation
  - Used in transplant immunosuppression
  - Everolimus has better bioavailability and a short t1/2 compared to sirolimus (30 vs. 60 hours)
  - Available PO (tablet, suspension)
  - Dosing
    - Sirolimus: 0.5-5mg daily
    - Everolimus: 0.25-1mg q12H

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*Drug. 2007;67:369-391.*

mTOR

• Sirolimus and everolimus
  – Drug interactions (substrate of CYP3A4 and P-glycoprotein)
    • CYP3A4
      – Inhibitors: atorvastatin, amlodipine, amiodarone, fluconazole, etc.
      – Inducers: carbamazepine, phenytoin, rifampin, phenobarbital
    • Grapefruit and grapefruit juice (↑ levels)

Drugs. 2007;67:369-391.

mTOR

• Sirolimus and everolimus
  – Adverse effects
    • Leukopenia and thrombocytopenia (dose dependent)
    • Hyperlipidemia
    • Proteinuria
    • Increased LFTs (dose dependent and reversible)
    • Abnormal wound healing (reported more with sirolimus)

Drugs. 2007;67:369-391.

mTOR

• Sirolimus and everolimus
  – Monitoring
    • CBC, lipid profile, quantitative monitoring of urinary protein excretion routinely
    • Troughs are routinely utilized
    • Clarify trough goals

Drugs. 2007;67:369-391.

Immunosuppressant Medications

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021083s062,021110s081lbl.pdf
### Infection ppx: *Pneumocystis jiroveci*

- **Risk factors:**
  - Corticosteroids > 15 mg/day
  - High-intensity immunosuppression
  - Age > 65 years
  - Coexisting lung disease
  - Treatment of rejection
  - CMV infection
  - Lymphopenia
  - Low albumin level
  - Hypogammaglobulinemia

- **Drugs:**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Spectrum of Activity</th>
<th>Prophylaxis Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMX-TMP</td>
<td>Inhibits fungal replication</td>
<td>PCP 400mg/80 mg daily or 800mg/160 mg TiW</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Inhibits fungal replication</td>
<td>PCP 100 mg daily</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Inhibits fungal cell energy production</td>
<td>PCP 1500 mg daily</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Inhibits fungal replication</td>
<td>PCP 300 mg monthly</td>
</tr>
</tbody>
</table>

**References:**
- Crit Care Nurs Q 2017;40:383

### Infection ppx: Other fungal infections

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Spectrum of Activity</th>
<th>Prophylaxis Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>Inhibits sterol synthesis</td>
<td>Most C. albicans Select non-albicans 100-400 mg daily</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Inhibits sterol synthesis</td>
<td>Most C. albicans Select non-albicans Aspergillus spp. 200 mg BID</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Inhibits sterol synthesis</td>
<td>Candida spp. Aspergillus spp. 200-400 mg BID</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Inhibits sterol synthesis</td>
<td>Candida spp. Aspergillus spp. Micromycoses spp. 300 mg daily</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Disrupts fungal cell wall</td>
<td>Most C. albicans 500,000 units QID</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Inhibit fungal cell wall synthesis</td>
<td>Candida spp. Aspergillus spp. 50 mg daily 100 mg daily 50-100 mg daily</td>
</tr>
</tbody>
</table>

**References:**
- Crit Care Nurs Q 2017;40:383

### Infection ppx: Viral infections

- Cytomegalovirus (CMV)
- Herpes simplex virus (HSV)
- Varicella zoster virus (VZV)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Spectrum of Activity</th>
<th>Prophylaxis Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Prevents viral replication by disrupting DNA</td>
<td>HSV VZV 400 mg BID</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>Same as acyclovir; better pharmacokinetics</td>
<td>HSV VZV 500 mg BID</td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>Inhibits viral replication (blocks DNA synthesis)</td>
<td>CMV HSV VZV 900 mg daily or 450 mg BID</td>
</tr>
</tbody>
</table>

**References:**
- Crit Care Nurs Q 2017;40:383

### Immunization considerations

- Recommend vaccination at time of diagnosis or prior to transplant
- Variable vaccination response with immunosuppression
  - Affected by depth and duration of immunosuppression

**References:**
- J Infect 2017;74:433
**Inactive vaccines**

- No increased risk of vaccine reaction
- No worsening or reactivation of underlying disease or development of allograft rejection
- Include recombinant, subunit, toxoid, polysaccharide, conjugated polysaccharide, inactivated or heat-killed vaccines

<table>
<thead>
<tr>
<th>Influenza</th>
<th>Td/Tdap</th>
<th>HPV</th>
<th>PCV13</th>
<th>PPSV23</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepA</td>
<td>HepB</td>
<td>MenB</td>
<td>Hib</td>
<td></td>
</tr>
</tbody>
</table>

- Follow routine vaccine schedule (per CDC)
- Household contacts should also be vaccinated

**Live attenuated vaccines, the jury is still out**

- Relatively few studies of live vaccines in setting of immunosuppressive therapy
- Most studies suggest live vaccines are safe, but…
- Per CDC, live vaccines (MMR, VAR, HZV) contraindicated
- Serious vaccine-related adverse outcomes do occur, including death
- While live vaccines are generally discouraged in setting of immunosuppressive therapy, risks and benefits must be weighed on an individual basis.

**Pregnancy and immunosuppression**

- Category C: adverse fetal effects in animals; insufficient human data
  - Corticosteroids
  - Ciclosporine A
  - Tacrolimus
  - Sirolimus
  - Everolimus
  - Hydroxychloroquine

- Category D: evidence of human fetal risk; benefit of drugs may outweigh risk
  - Azathioprine
  - Mycophenolate

- Category X: contraindicated
  - Methotrexate
  - Leflunomide

**Clinical Pearls**

- Balance effectiveness with risk of infection and malignancy
  - Sun protection, regular screening
- Typically advocate against the use of herbals and homeopathic medications
  - Drug interactions
  - Inability to verify Good Manufacturing Practices

http://blogs.oregonstate.edu/linuspaulinginstitute/2015/02/24/whats-supplement-bottle/
**Immunosuppressants**

- You may see your patients on a combination of therapies
- Regularly communicate with the primary prescriber of the immunosuppressants
  - Ongoing labs
  - Status of patient

Primary care physician

Patient

Prescribing team (e.g. Transplant)