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>
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<tbody>
<tr>
<td>1950s</td>
<td>1960s</td>
<td>1970s</td>
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</tbody>
</table>
Immunosuppressant Medications

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Corticosteroids

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

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

- Do not discontinue abruptly (≥ 7 days)


Corticosteroids Adverse Effects

- Nausea/vomiting
  - Give with food
- Increased appetite
- Hyperglycemia
- Confusion, nervousness, depression, mood changes
- Insomnia
- Edema
- 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

### 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)

**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

**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

### 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

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### DMARDs

### Leflunomide
- **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

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*American Journal of Transplantation. 2011;11:1079-1084*
*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

*Pharmacotherapy. 1997;17:1178-1197.*

### 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

*Pharmacotherapy. 1997;17:1178-1197.*

- Adverse effects
  - Nausea/vomiting/diarrhea
    - May be less with mycophenolate sodium (Myfortic)
  - Leukopenia, thrombocytopenia
  - Headache
  - Hypertension
- Monitoring
  - CBC monthly
  - No correlation between drug levels and prevention of rejection/efficacy and toxicity

*Pharmacotherapy. 1997;17:1178-1197.*
### Antimetabolites

- **Mycophenolate**
  - REMS program
  - Risk of taking mycophenolate and pregnancy
    - Increased risk of miscarriage in the 1st trimester
    - Increased risk of congenital malformations
  - [https://www.mycophenolaterems.com/](https://www.mycophenolaterems.com/)

- **Azathioprine**
  - Inhibits purine synthesis
  - Used in RA, transplant immunosuppression, lupus, IBS
  - Available PO and IV (been on backorder)
  - Dose
    - 1-3 mg/kg/day or 50-150mg daily
  - [https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf)

### Calcineurin Inhibitors

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

- **CSA**
  - 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 (↑ CSA levels)

- **Adverse effects**
  - More nephrotoxicity but less neurotoxicity than tacrolimus (tremor, seizures)
  - Hypertension, hyperlipidemia
  - Hair growth

- **Monitoring**
  - Chem-7 and BP every 2 weeks for the first 3 months then monthly
  - Troughs and C2 levels (2 hours post dose) have been used
  - Important to clarify goals

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Calcineurin Inhibitors

- **Tacrolimus (TAC)**
  - Inhibits activation of T-cells
  - Used in transplant immunosuppression, RA, Crohn’s disease, psoriasis
  - Shown to have better outcomes than cyclosporine in transplant immunosuppression
  - Available PO (capsule, extended release capsule) and IV

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

Calcineurin Inhibitors

- TAC
  - Monitoring
    - Chem-7 every 2 weeks for the first 3 months then monthly
    - Troughs are routinely utilized
    - Clarify trough goals

Calcineurin Inhibitors

- 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: 0.5-1mg Q12H

mTOR

- Drugs. 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)

**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)

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**Immunosuppressant Medications**

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### 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>

### Infection ppx: Other fungal infections

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<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. Mucormycoses 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>

### Infection ppx: Viral infections

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

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<th>Mechanism of Action</th>
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<th>Prophylaxis Dose</th>
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</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>

### Immunization considerations

- Recommend vaccination at time of diagnosis or prior to transplant
- Variable vaccination response with immunosuppression
  - Affected by depth and duration of immunosuppression
# 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
  - Influenza
  - Td/Tdap
  - HPV
  - PCV13
  - PPSV23
  - HepA
  - HepB
  - MenB
  - Hib
- Follow routine vaccine schedule (per CDC)
- Household contacts should also be vaccinated

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## Pregnancy and immunosuppression

- Category C: adverse fetal effects in animals; insufficient human data
  - Corticosteroids
  - Cyclosporine 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

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## 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.

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### 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