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
  - Crohn's disease
  - Myasthenia gravis
  - Multiple sclerosis
  - Ulcerative colitis
  - Ankylosing spondylitis
  - Psoriasis
  - Behcet's
  - Sarcoidosis
  - SLE
  - FSGS
- 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

<table>
<thead>
<tr>
<th>Edward Calvin Kendall</th>
<th>Philip Showalter Hench</th>
<th>Tadeusz Reichstein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemist</td>
<td>Rheumatologist</td>
<td>Chemist</td>
</tr>
</tbody>
</table>
History of Immunosuppression

1949: Cortisol  
1961: Methotrexate  
1987: Tacrolimus

1940s  
1950s  
1960s  
1970s  
1980s  
1990s

1959: Cyclophosphamide  
1959: 6-mercaptopurine  
1976: Cyclosporin A  
1977: Rapamycin  
1978: Leflunomide  
1991: Mycophenolate  
1994: Rituximab  
1994: TNF inhibitors

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Diagram showing T cell and B cell activation pathways with various immunosuppressive drugs indicated.
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</th>
<th>Duration of Action (hours)</th>
<th>Equipotent Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glucocorticoid</td>
<td>Mineralocorticoid</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)

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


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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)

*Immunopharmacology. 2000;47:291-298*
### DMARDs

<table>
<thead>
<tr>
<th>Leflunomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available PO</td>
</tr>
<tr>
<td>Onset of action: 3-4 weeks</td>
</tr>
<tr>
<td>Dose</td>
</tr>
<tr>
<td>RA</td>
</tr>
<tr>
<td>100mg daily x 3 days then 20mg daily or 10-20mg/daily without loading dose</td>
</tr>
<tr>
<td>Transplant</td>
</tr>
<tr>
<td>100mg daily x 3 days then 20-60mg daily</td>
</tr>
</tbody>
</table>

*American Journal of Transplantation. 2011;11:1079-1084*
*Immunopharmacology. 2000;47:291-298*

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### DMARDs

<table>
<thead>
<tr>
<th>Leflunamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effects</td>
</tr>
<tr>
<td>Nausea/vomiting/diarrhea, alopecia</td>
</tr>
<tr>
<td>Leukopenia, anemia, thrombocytopenia</td>
</tr>
<tr>
<td>Monitoring</td>
</tr>
<tr>
<td>CBC and LFTs monthly initially then every 8 weeks</td>
</tr>
<tr>
<td>Teriflunomide (leflunomide metabolite) can be monitored in transplants: target goal &gt; 50,000ng/mL</td>
</tr>
</tbody>
</table>

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

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**Antimetabolites**

- **Mycophenolate**
  - 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
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/

Antimetabolites

• 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
Antimetabolites

• 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

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
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)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf

Calcineurin Inhibitors

• CSA
  – Adverse effects
    • More nephrotoxicity but less neurotoxicity than tacrolimus (tremor, seizures)
    • Hypertension, hyperlipidemia
    • Hair growth

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050715s035,050716s038lbl.pdf
Calcineurin Inhibitors

- **CSA**
  - 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

[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

- **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


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: 0.5-1mg Q12H

\textit{Drugs.} 2007;67:369-391. \\
\textit{Transplantation.} 2012;94:659-668.
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.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021083s062,021110s081lbl.pdf

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</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Inhibits fungal replication</td>
<td>PCP</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Inhibits fungal cell energy production</td>
<td>PCP</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Inhibits fungal replication</td>
<td>PCP</td>
</tr>
</tbody>
</table>

Crit Care Nurs Q 2017;40:383

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**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</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Inhibits sterol synthesis</td>
<td>Most C. albicans Select non-albicans Aspergillus spp.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Inhibits sterol synthesis</td>
<td>Candida spp. Aspergillus spp.</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Inhibits sterol synthesis</td>
<td>Candida spp. Aspergillus spp. Mucormycoses spp.</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Disrupts fungal cell wall</td>
<td>Most C. albicans</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Inhibit fungal cell wall synthesis</td>
<td>Candida spp. Aspergillus spp.</td>
</tr>
</tbody>
</table>

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>Drug</th>
<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</td>
<td>400 mg BID</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>Same as acyclovir; better pharmacokinetics</td>
<td>HSV, VZV</td>
<td>500 mg BID</td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>Inhibits viral replication (blocks DNA synthesis)</td>
<td>CMV, HSV, VZV</td>
<td>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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Influenza</th>
<th>Td/Tdap</th>
<th>HPV</th>
<th>PCV13</th>
<th>PPSV23</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HepB</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MenB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hib</td>
<td></td>
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</tbody>
</table>
- Follow routine vaccine schedule (per CDC)
- Household contacts should also be vaccinated

*Best Pract Res Clin Rheum 2015;29:306*

### 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.

*Vaccine 2017;35:1216*
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

**Clinical Pearls**

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

[Link to blog post](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