The Transplant Patient and the Internist
American College of Physicians – Wisconsin
Annual Scientific Meeting

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Objectives

- Be aware of the major side effects of the common classes of immunosuppression
- Understand the impact that transplantation, and immunosuppression in particular, has on common cardiovascular, endocrine, infectious, and oncologic diseases
Transplantation – The statistics

- To date in Wisconsin, there have been 16,958 organ transplants
  - 685 transplants in 2013

- By organ type
  - 9523 kidney transplants
  - 3123 liver transplants
  - 1697 heart transplants
  - 797 lung transplants
  - 303 pancreas transplants

Source: http://optn.transplant.hrsa.gov/latestData/rptData.asp

Immunosuppression and transplantation

- Almost all transplant recipients will require immunosuppressive medications

- Degree of immunosuppression depends on a number of factors
  - Organ transplanted
  - Time from transplant
  - Rejection history
  - Underlying disease leading to transplant
  - Other co-morbid conditions
The problem with immunosuppression

- Infectious
- Malignant
- Side-effects of immunosuppressive medications
  - The Metabolic syndrome
    - Obesity
    - Diabetes mellitus
    - Hypertension
    - Hyperlipidemia
- Bone health
- Kidney effects

Infection timeline

- First 3 months
  - Post-operative infections – UTI, hospital acquired pneumonia, surgical wound
- 3-12 months (period of maximum immunosuppression)
  - Community acquired infections
  - Opportunistic infections
    - Cytomegalovirus
      - Risk depends on donor/recipient exposure status
    - Pneumocystis jirovecii (PJP)
    - Fungal infections
      - Cryptococcus
      - Aspergillus
Infection timeline

- Greater than 12 months
  - Generally similar to community
  - Transplant specific infections
    - e.g. cholangitis – Liver
  - Opportunistic infections in periods of immunosuppression augmentation
  - Rejection

Immunization-general rules

- Immunization is less effective after transplantation
- Live vaccines are NOT safe after transplantation
  - Should not get:
    - Measles, mumps, rubella
    - Varicella
    - Zoster
    - Live influenza
    - Rotavirus
  - Immunize prior to transplantation

Immunization recommendations for transplant recipients

Pre-transplant only
- Varicella if not immune
- Zoster if indicated
- MMR

Pre or Post-transplant
- Hepatitis A
- Hepatitis B
- Tdap
- Influenza
- Pneumococcal polysaccharide (PPSV-23)
- Pneumococcal conjugate (PCV-13)


Other recommendations
- Household contacts should update vaccinations
  - Annual influenza
  - Live vaccination OK
    - Avoid contact if rash develops
  - Don’t change diapers for one month of infant that received rotavirus vaccination
- Avoid unpasteurized products
- Water precautions
  - Tap water OK
  - Boil well water
  - Don’t drink from rivers or streams.
- Avoid high-risk pets
  - Birds, reptiles, rodents
Infectious disease-take home points

- Degree of immunosuppression important
  - Early post-transplant or augmented immunosuppression – could be opportunistic
  - Stable more than 1 year post-transplant - Community infections

- Immunizations important
  - No live vaccines
  - Family members need it too

- Take precautions to avoid food/water borne illness

Malignancy

- Immunosuppression increases the risk of malignancy
  - mTor inhibitors (sirolimus) an exception

- Oncogenic viruses
  - EBV – Post-transplant lymphoproliferative disorder (PTLD)
  - HPV – Cervical and anogenital cancers
  - HHV-8 – Kaposi’s sarcoma
  - Merkel-Cell polyomavirus – Merkel cell carcinoma

- Smoking/Alcohol history
  - Heart, lung, and liver transplant recipients
Highest risk malignancies

- Skin
  - Squamous cell and basal cell predominantly
- Head and neck
  - Especially with smoking/alcohol history
- Lung
  - Smoking history
- Cervical/Anogenital cancer
  - HPV infected

General cancer prevention recommendations

- Stop smoking!!!!
  - Liver transplant recipients, I’m looking at you
- Skin cancer prevention
  - SPF 30 sunscreen
  - Annual physician exam
  - Monthly self exam
- Cancer screening recommendations
  - Generally fall in line with USPSTF recommendations
Neoplasia take home points

- All transplant patients are at higher risk for neoplasia
- Risk factor modification is important
  - Skin cancer prevention
  - Smoking and alcohol abstinence
- Screening important
  - Cancer generally more aggressive in transplant patients

The immunosuppressives

- Calcineurin Inhibitors (CNIs)
  - Tacrolimus
  - Cyclosporine
- Antimetabolites
  - Mycophenolate Mofetil
  - Mycophenolic Acid
  - Azathioprine
- Corticosteroids
- mTor inhibitors
  - Sirolimus
  - Everolimus
Picking your poison

**Calcineurin inhibitors**

- Tacrolimus, Cyclosporine
- Backbone of immunosuppression for most patients
  - Bind to calcineurin
  - Prevent cytokine release and decrease lymphocyte proliferation
- Common side effects
  - Kidney injury
  - Hypertension (cyclosporine > tacrolimus)
  - Diabetes mellitus (tacrolimus > cyclosporine)
  - Neurologic symptoms
    - Tremors
    - Headaches
    - Hyperkalemia

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Corticosteroids</th>
<th>CNIs</th>
<th>mTOR Inhibitors</th>
<th>Mycophenolate Mofetil</th>
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<tr>
<td>Kidney injury</td>
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<td>+ (proteinauria)</td>
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<td>Bone disease</td>
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Lucey MR. et al. *Liver Transplantation* 2013
Antimetabolites

- Mycophenolate Mofetil/Mycophenolic acid
  - Inhibit lymphocyte replication
  - Usually inadequate as monotherapy to prevent rejection
  - Common side effects
    - Bone marrow suppression
    - Gastrointestinal upset – nausea, vomiting, diarrhea
- Azathioprine/6-mercaptopurine
  - Similar mechanism of action
  - Principle side effect is bone marrow suppression

Corticosteroids

- Used in high doses for induction of immunosuppression or in the treatment of rejection
- Goal is minimize or sometimes eliminate entirely
- Side effects are well known
  - Diabetes
  - Osteoporosis
  - Hypertension
  - Weight gain
  - Acne
  - Cataracts
mTor inhibitors

- Inhibit the mammalian target of rapamycin
  - Sirolimus
  - Everolimus
- Most often used in patients that
  - Have chronic renal insufficiency
  - Patients with cancer
    - May have an anti-proliferative effect
- Theory that may help promote graft tolerance
- Side effects:
  - Hyperlipidemia
  - Proteinuria
  - Pulmonary fibrosis
  - Poor wound healing (should be stopped for elective surgery)

Side effects-take home points

- Calcineurin inhibitors
  - Kidney injury
  - Hypertension
- Antimetabolites
  - Bone marrow suppression
  - GI symptoms [Mycophenolate]
- Corticosteroids
  - Well known
- mTor inhibitors
  - Hyperlipidemia
  - Proteinuria
  - Poor wound healing
Management of specific complications of immunosuppression

- Hypertension
- Hyperlipidemia
- Diabetes mellitus
- Chronic kidney disease
- Osteopenia/Osteoporosis
- Pregnancy (not really a complication.....usually)

Hypertension

- Most transplant patients will develop hypertension
  - Obesity common after transplant
  - Medication side effects (calcineurin inhibitors)
- Lifestyle modifications
  - Limit sodium
  - Weight loss/exercise
Hypertension

- Pharmacologic agents
  - Calcium channel blockers (amlodipine/nifedipine)
    - Counteract vasoconstrictive effects of calcineurin inhibitors
  - ACE inhibitor/ARB if diabetes or proteinuria
    - May be limited by hyperkalemia due to concurrent calcineurin inhibitor use

Dyslipidemia

- Common post-transplant
  - Effects of calcineurin inhibitors, corticosteroids, mTor inhibitors
- Some potential for drug interactions
  - Especially cyclosporine!
- Generally consider transplant patients at high cardiovascular risk
  - Goal LDL < 100 mg/dL
- Statins are generally safe
  - Caution with cyclosporine
  - No problem in liver transplants
- Avoid fibrates in conjunction with statins in transplant patients
  - Rhabdomyolysis and worsening azotemia noted
Diabetes mellitus

- May precede transplant or be new-onset
- Multiple causes for DM post transplant
  - Worsening obesity
  - Medications
    - Corticosteroids
    - Calcineurin inhibitors
    - Sirolimus
- May improve from early after transplant
  - Lower doses of immunosuppression

Diabetes Treatment

- Lifestyle and dietary management
- No medications absolutely contraindicated
  - May be limited by renal function
    - Metformin
    - Sulfonylurea
    - Sitagliptin
    - Thiazolidinediones generally not recommended
- Insulin therapy is common
Chronic Kidney Disease

- Most transplant patients will develop chronic kidney disease at some point
  - Calcineurin inhibitors can be both acute and chronic component
- Transplant centers will minimize calcineurin inhibitors
- General treatments
  - Control blood pressure
  - ACE or ARBs
  - Blood glucose control

Bone disease

- Impaired bone mineral density is common both pre and post solid organ transplantation
- Rapid bone loss is expected in the first 6-12 months post-transplant
  - Glucocorticoids, cyclosporine
- General recommendations
  - Bone mineral density pre and post transplant
  - Calcium plus vitamin D supplementation
  - Bisphosphonates are safe in transplant patients
    - Treat per osteoporosis guidelines
Pregnancy

- Pregnancy can be successful in transplant recipients
  - Ideally a planned pregnancy
  - Birth control strongly encouraged
- Higher risk of prematurity and low birth weight
- Calcineurin inhibitors are generally safe
  - Azathioprine and Prednisone as well
- mTOR inhibitors and mycophenolate are likely teratogenic

Drug-drug interactions

- The immunosuppressives, particularly the calcineurin inhibitors have a number of drug interactions
  - Extensive list
  - Macrolides, Fluoroquinolones, and anti-fungals top the list
- Any new prescription requires a review of potential interactions
Overall take home points

- In general, transplant patients suffer from the same diseases you see every day, made worse by the effects of immunosuppression
- Opportunistic infections
  - Most common in the first 12 months or during episodes of rejection
  - Otherwise most infections are typical community
- Cancer is more common and more aggressive in transplant recipients
  - Screening is key

Questions??