Management of the Solid Organ Transplant Patient in the PICU

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Pediatric Solid Organ Transplantation

- Kidney
- Liver
- Heart
- Lung
- Small bowel
UNOS Data

- 245 kidney transplant programs
- 122 liver transplant programs
- 141 heart transplant programs
- 76 lung transplant programs
UNOS Data
National Transplant Waiting List By Age -12/31/01

- Age 0-5 years: 917
  - kidney 9% liver 62% heart 14% intestine 10%
- Age 6-10 years: 460
  - kidney 30% liver 45% heart 8% intestine 5%
- Age 11-17 years: 1121
  - kidney 43% liver 32% heart 6% intestine 2%
- Total Pediatrics: 2498
Pediatric Waiting List 1999
(N=2,158)

* Other includes pancreas, kidney-pancreas, heart-lung, and intestine.
Source: Snapshot of the OPTN waiting list on 12/31/99.
Pediatric Transplants in 1999
(N=1,622)

<table>
<thead>
<tr>
<th>Organs</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>16%</td>
</tr>
<tr>
<td>Liver</td>
<td>32%</td>
</tr>
<tr>
<td>Cadaveric Kidney</td>
<td>22%</td>
</tr>
<tr>
<td>Living Donor Kidney</td>
<td>23%</td>
</tr>
<tr>
<td>Other*</td>
<td>7%</td>
</tr>
</tbody>
</table>

* Other includes pancreas, kidney-pancreas, lung, heart-lung, and intestine.

Source: Scientific Registry data as of 9/5/00.
1-Year Pediatric Survival Rates
1997-1998 Transplant Cohort

Note: There were no cadaveric kidney patients less than 1 year old.
Source: Scientific Registry data as of 9/5/00.
1-Year Pediatric Graft Survival Rates
1997-1998 Transplant Cohort

Note: There were no cadaveric kidney recipients less than 1 year old.
Source: Scientific Registry data as of 9/5/00.
Pediatric Transplant Candidates
Median Waiting Times 1999*
Kidney, Liver, Heart

* Kidney and liver MWT time for recipients aged 11-17 shown for 1998, the most recent data available.
Source: OPTN waiting list and removal files as of 9/5/00.
Graft Rejection

- Recognition of donor tissue as foreign
- Recruitment of activated lymphocytes
- Initiation of immune response
- Graft destruction
B-Lymphocytes

- Humoral immunity
- Produce antibodies/immunoglobulins
- Cause hyperacute allograft rejection
T-Lymphocytes

- Cellular immunity
- 80-90% of total lymphocyte count
- Cause acute rejection
T-Lymphocyte Activation
T Lymphocyte Activation

Diagram:
- APC
- Naive T cell
- Costimuli
- IL-2
- Th0
- IL-4
- IL-12
- Th1
- IL-2
- IFN-γ
- Th2
- IL-4
- IL-10

Cell-mediated immunity
Humoral immunity
Phases of T-cell Activation

- Sensitization
- Multiplication
- Migration
- Cytokine synthesis
- Cytokine release
Types of Rejection

- Hyperacute rejection
- Acute rejection
- Chronic rejection
Managing Immunosuppression

- Graft survival
- Quality of Life
- Infection/Malignancy
- Drug-Related Toxicity
Stages of Immunosuppression

- Induction
- Maintenance
- Antirejection
Current Immunosuppressives

- Corticosteroids
- Calcineurin Inhibitors
- Anti-metabolites
- Monoclonal/polyclonal antibodies
- mTor Inhibitors
Immunosuppressive Targets
Immunosuppressive Targets

Resting T cell

Antigen-Presenting Cell (APC)

TCR
costimulatory signal

CTLA4-Ig Anti-CD40L

Resting T cell

OKT-3

Calcineurin NFAT

NF-kB

Steroids

early Activation

Calcineurin NFAT

CsA FK506

Late Activation

mTOR

Anti-IL-2 R

IL-2 R

Activated T cell

IL-2

DNA synthesis

Clonal expansion

T cell

mTOR

Rapamycin

MMF AZA

T cell

T cell
State of the Art Immunosuppression

Calcineurin Inhibitor
+ MMF or Sirolimus
+ Prednisone
++ IL-2 Receptor Antagonists
Corticosteroids

Toxicities

- Hyperglycemia
- Hypertension
- Metabolic
- Cataracts
- Osteoporosis
- Impaired growth
Calcineurin Inhibitors

Toxicities

• Cyclosporine
  • Nephrotoxicity, hypertension, neurotoxicity
  • Hepatotoxicity, hyperlipedemia, hyperglycemia
  • Hirsutism, gingival hyperplasia

• Tacrolimus
  • Less hypertension than CYA
  • No hirsutism or gingival hyperplasia
  • Alopecia
  • ?increased incidence of PTLD?
Mycophenolate mofetil

Toxicities

- Gastritis
- Nausea
- Diarrhea
- Myelosuppression
Azathioprine Toxicities

- Bone marrow suppression
  - Leukopenia, anemia, thrombocytopenia
- Gastrointestinal upset
- Alopecia, anorexia, arthralgia
- Hepatotoxicity
- Fever
**OKT3**

*Toxicities*

- Fever, chills, hypotension
- Bronchospasm, anaphylaxis
- Non-cardiogenic pulmonary edema
- Nausea, vomiting, diarrhea
- Aseptic meningitis, encephalopathy
Antithymocyte Globulins

Toxicities

- Fever, chills
- Infusion related reactions
- Myelosuppression
- Increased incidence PTLD
Sirolimus

**Advantages**
- MOA different from and synergistic with calcineurin inhibitors
- May allow for reduced dosages of other agents

**Disadvantages**
- lipid disorders
Sirolimus

Toxicities

- Thrombocytopenia
- Hypercholesterolemia
- Hypertriglyceridemia
**IL-2 Receptor Antagonists**
*Basiliximab and Daclizumab*

- Bind to 55kD alpha chain of IL-2 receptor
- Compete with IL-2 to inhibit IL-2 driven proliferative responses
- Target activated
- Toxicities less than antilymphocyte antibodies
Drug Level Monitoring

- Cyclosporine Levels
  - Range: 150 - 350 ng/mL
- Tacrolimus Levels
  - Range: 10 - 20 ng/mL
- Sirolimus Levels
  - Range: 5 - 15 ng/mL
Monitoring Parameters

- Corticosteroids
  - BP, glucose, electrolytes, stool for blood
- Cyclosporine
  - CYA levels, renal + liver fcn, BP, HR, electrolytes, glucose
- Tacrolimus
  - FK levels, weight, renal + liver fcn, electrolytes, BP, glucose
Monitoring Parameters

- Azathioprine
  - CBC, LFTs, platelets, bilirubin
- Mycophenolate mofetil
  - BP, weight, CBC, electrolytes, renal fcn
- Antithymocyte globulin
- Sirolimus
  - Test dose, pre-meds, CBC, platelets
  - BP, CBC, electrolytes, triglycerides, weight
Drug Interactions

Cyclosporine

- Increased Levels
  - Azole antifungals, macrolides, verapamil, diltiazem, metoclopramide, tacrolimus, methylprednisolone

- Decreased Levels
  - Rifampin, phenytoin, phenobarbital, TMP, carbamazepine, octreotide, primidone, AZA

- Additive Nephrotoxicity
  - Aminoglycosides, amphotericin, vancomycin, acyclovir, tacrolimus
Drug Interactions

- Azathioprine
  - allopurinol
- Corticosteroids
  - barbiturates, phenytoin, rifampin
  - oral contraceptives, ketoconazole, macrolides
- Mycophenolate mofetil
  - acyclovir, ganciclovir
  - antacids, cholestyramine
Drug Interactions

- Tacrolimus
  - azole antifungals, calcium channel blockers, cimetidine, macrolides, methylprednisolone, metoclopramide
  - aminoglycosides, amphotericin, cisplatin, CyA
  - carbamazepine, phenobarbital, phenytoin, rifampin
- Sirolimus
Renal Transplant
Post-op Complications

- Oliguria (maintain UO 1-2 cc/kg/hr)
  - Delayed onset ATN
  - Obstructed transplanted ureter
  - Early acute allograft rejection
  - Acute CYA nephrotoxicity
Renal Transplant

Post-op Complications

- Hypotension
- Hypertension
- Fever
- Acidosis
- Hypophosphatemia
- Hemorrhage
Renal Transplant

Post-operative Day 1-2

- Fluid replacement therapy
- Urine output replacement
- Blood pressure support
- CVP monitoring
- Cardiopulmonary status
- Pain management
Liver Transplant
Post-op Complications

- Hepatic artery thrombosis
- Biliary complications - strictures
- Hypertension
- Oliguria
- Electrolyte imbalance
Liver Transplant
Post-operative Day 1-2

- Bile production
- PT and lactate levels
- Ventilatory support
- Prophylactic antibiotics x 24 - 48 hrs
- Fluid replacement
- Aminotransferases and bilirubin levels unreliable in 1st 48 hrs
Infectious Complications

- Early Infections (0-30 days)
  - Bacterial, candida, HSV
- Intermediate Period (31-180 days)
  - Opportunistic (PCP), EBV, CMV
- Late Infections (>180 days)
  - Bacterial cholangitis, PTLD (EBV)
Immunizations

- Complete all age-appropriate vaccinations prior to transplant
- Live virus vaccines 1 month prior
- Hepatitis A and B
- Annual influenza vaccine (pt+caregivers)
- Passive immunization for VZV exposure
Pneumocystis carinii

- Low dose SMX/TMP for prophylaxis
- High dose SMX/TMP for treatment
- Alternative agents
  - Pentamidine
  - Dapsone
Tuberculosis

- Positive TB history +/- positive PPD
- Isoniazid
- Monitor hepatotoxicity
Cytomegalovirus

- Usually occurs 4-6 wks post-transplant
- Low risk vs. high risk recipients
- Cytogam
- Acyclovir
- Ganciclovir
Epstein-Barr Virus

- Ranges from mild mononucleosis to lymphoproliferative disease (PTLD)
- Children at greater risk
- Increased incidence of PTLD
  - OKT3 > FK506 > CYA
- Treatment
  - Decrease immunosuppression
  - Acyclovir/ganciclovir??interferon??
Herpes Simplex Virus

- Early reactivation
- Late reactivation
- Acyclovir
Varicella Zoster Virus

- Disseminated disease if not immune
- Acyclovir
Other Viruses

• Adenovirus
• Respiratory Syncytial Virus
• Influenza
• Parainfluenza
Fungal Infections

- Candida
  - Nystatin or clotrimazole prophylaxis
  - Fluconazole or amphotericin treatment
- Aspergillosis
  - Infrequent but may be fatal
Clinical Challenges for the Transplant Pharmacist

- Drug-specific toxicities
- Drug Interactions
- Therapeutic drug monitoring
- Optimizing immunosuppression
- Patient compliance