Immunosuppression: Induction and Maintenance

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Professor of Nephrology, Urology and Nephrology Center and Director of Medical E-Learning Unit, Mansoura University, and Executive Director of ESNT- Virtual Academy: http://lms.mans.edu.eg/esnt/

Cairo, September 14th, 2018
IPNA-AfPNA Master for Junior Classes
Second Cycle

CHRONIC KIDNEY DISEASE -
RENAL REPLACEMENT THERAPY

In Collaboration, with
Egyptian Society of Pediatric
Nephrology & Transplantation

ESPNT President:
Prof. Ramzi Elbaroudy

Course Coordinators:
Prof. Hesham Safouh
Prof. Fatina Fadel
Prof. Happy Sawires

Date
13th-14th September, 2018

Venue
Ramses Hilton Cairo, Egypt
Corners

1. Introduction
2. Induction therapy
3. Maintenance
4. Immunosuppression for pediatric patients
5. Special issues
6. UNC Experience
Evolution of Immunosuppressive Drugs

Balancing Immunosuppression

- Rejection
- Infection/Malignancy
Immunosuppression Protocol

Induction

Maintenance
Immunosuppression: Site of Action
1. Introduction

2. **Induction therapy**

3. Maintenance

4. Immunosuppression for pediatric patients

5. Special issues

6. UNC Experience
Induction Therapy: Why?

- To decrease rejection rate.
- To decrease graft loss.
- To lower DGF.
- To avoid or withdraw steroids.
- To avoid or delay CNIs.
- To transplant high risk patients.
- To induce tolerance……
### Table 1. Nomenclature to widely used biologic agents

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Related structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><code>-mab</code></td>
<td>monoclonal antibody</td>
</tr>
<tr>
<td><code>-ximab</code></td>
<td>chimeric monoclonal antibody</td>
</tr>
<tr>
<td><code>-zumab</code></td>
<td>humanized monoclonal antibody</td>
</tr>
<tr>
<td><code>-cept</code></td>
<td>fusion of a receptor to the Fc part of human immunoglobulin G1</td>
</tr>
</tbody>
</table>

Abbreviations at the end of names carry specific information with regard to the structure of the agent.
Induction agent use in adult kidney transplant recipients
Induction Therapy in AA: Cytolytic Versus IL2RA

Antibody Induction

Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients (Review)

Hill P, Cross NB, Barnett ANR, Palmer SC, Webster AC


Guideline 3.2 – KTR: Induction immunosuppression

We recommend induction therapy should take into account the following:

- Immunosuppressive drugs should be started before or at the time of renal transplantation (1B)
- Induction therapy with biological agents should be administered to all KTRs. In patients at low immunological risk this will generally involve an interleukin-2 receptor antagonist (IL2-RA). Recipients at higher immunological risk may be considered for T-cell (lymphocyte) depleting antibodies (TDAs)(1B)
- Induction therapy with TDAs may also be useful for lower immunological risk patients with the intention of either steroid or calcineurin inhibitor (CNI) avoidance (1C)
Desensitization: A Novel Strategy (n 25)

The IgG-degrading enzyme derived from Streptococcus pyogenes (IdeS)

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Immunosuppression: Maintenance

Steroid use in pediatric kidney transplant recipients.

- At transplant
- 1 year posttransplant

Year

Percent
mTORi: Current Use

mTOR inhibitor use in pediatric kidney transplant recipients
Steroids

Immunosuppression in Pediatric Kidney Transplantation

Burkhard Tönshoff, Anette Melk and Britta Höcker

Steroid Withdrawal: What is the effect on long-term?

Transplantation October 2017;101: 2590–2598

Rapid Discontinuation of Prednisone in Kidney Transplant Recipients: 15-Year Outcomes From the University of Minnesota

Oscar Kenneth Serrano, MD,¹ Raja Kandaswamy, MD,¹ Kristen Gillingham, PhD,¹ Srinath Chinnakotla, MD,¹ Ty B. Dunn, MD,¹ Erik Finger, MD, PhD,¹ William Payne, MD,¹ Hassan Ibrahim, MD,² Aleksandra Kukla, MD,² Richard Spong, MD,² Naim Issa, MD,² Timothy L. Pruett, MD,¹ and Arthur Matas, MD¹
Tacrolimus

Pediatric Nephrology, Accepted: 10 January 2018

Clinical aspects of tacrolimus use in paediatric renal transplant recipients

Agnieszka Prytula & Teun van Gelder

Diagram showing the mechanism of action of tacrolimus on T lymphocytes.
Tacrolimus Variability
Functional activity of glycoprotein-P in the transport of tacrolimus in the intestine epithelium.
CYP3A5

* Transplantation 2008;85: 163–165. Review

- **Black (n=40)**
  - 15%
  - 25%
  - 60%

- **Caucasian (n=272)**
  - 60%
  - 3%
  - 13%

- **South Asian (n=79)**
  - 13%
  - 49%
  - 38%

- **CYP3A5 expressers**
  - *1/*1
  - *1/*3

- **CYP3A5 non-expressers**
  - *3/*3
CNI and NFAT-RE Monitoring


Nuclear Factor of Activated T Cell-regulated Cytokine Gene Expression for Adjustment of Tacrolimus in Kidney Transplant Recipients: A Randomized Controlled Pilot Trial

Allison B. Webber, MD,¹ Vasishta Tatapudi, MD,¹ Thin T. Maw, MD,¹ Carmen Peralta, MD,² Joey C.Y. Leung, MS,³ and Flavio Vincenti, MD¹,³
MPA
TRANSFORM Study


2037 *de novo* kidney transplant recipients
Belatacept in Solid Organ Transplant: Review of Current Literature Across Transplant Types

Caroline P. Perez, PharmD, BCPS,¹ Neha Patel, PharmD,¹ Caitlin R. Mardis, PharmD,² Holly B. Meadows, PharmD,¹ David J. Taber, PharmD,³,⁴ and Nicole A. Pilch, PharmD⁵
Guideline 3.4 – KTR: Maintenance immunosuppression

We suggest that low-medium dose tacrolimus (trough target 4-8 ng/mL) is recommended as the CNI of choice in patients also taking steroids who are low and medium immunological risk and are not at high risk of developing post transplant diabetes mellitus (PTDM) (2C)
4. **Immunosuppression for pediatric patients**
Immunosuppression: In Pregnancy and Lactation

Reproductive health in women following abdominal organ transplant

Monika Sarkar1 | Kate Bramham2 | Michael J. Moritz3,4,5 | Lisa Coscia3

Am J Transplant. May 2018;18:1068–1076
Immunosuppressants in pediatrics

Induction and Standard Immunosuppression

David M. Newland and Thomas L. Nemeth

D. M. Newland · T. L. Nemeth (✉)
Seattle Children’s Hospital, Seattle, WA, USA
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S. P. Dunn, S. Horslen (eds.), Solid Organ Transplantation in Infants and Children, Organ and Tissue Transplantation, https://doi.org/10.1007/978-3-319-07384-5_45
# Immunosuppressants in pediatrics

## Table 1

Induction and initial maintenance immunosuppression medication therapies used in pediatric solid organ transplant recipients (Colvin et al. 2017; Hart et al. 2017; Kim et al. 2017; Smith et al. 2017; Valapour et al. 2017)

<table>
<thead>
<tr>
<th></th>
<th>Heart (%)</th>
<th>Intestine (%)</th>
<th>Kidney (%)</th>
<th>Liver (%)</th>
<th>Lung (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell depleting</td>
<td>64.2</td>
<td>58.1</td>
<td>61.6</td>
<td>12.5</td>
<td>41.5</td>
</tr>
<tr>
<td>IL-2 RA</td>
<td>14.4</td>
<td>14.0</td>
<td>33.3</td>
<td>23.1</td>
<td>43.9</td>
</tr>
<tr>
<td>No induction</td>
<td>22.8</td>
<td>34.6</td>
<td>9.1</td>
<td>65.3</td>
<td>19.5</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>88.7</td>
<td>90.4</td>
<td>96.3</td>
<td>94.0</td>
<td>97.6</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>93.1</td>
<td>20.6</td>
<td>93.2</td>
<td>34.7</td>
<td>97.6</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>60.0</td>
<td>66.9</td>
<td>59.9</td>
<td>78.5</td>
<td>100</td>
</tr>
<tr>
<td>mTORi</td>
<td>1.2</td>
<td>8.1</td>
<td>N/A</td>
<td>2.2</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Note: N/A data not available, IL-2 RA interleukin-2 receptor antagonists, mTORi mammalian target of rapamycin inhibitors*

## Table 2

Corticosteroid and mTORi use at 1-year posttransplant in pediatric solid organ transplant recipients (Colvin et al. 2017; Hart et al. 2017; Kim et al. 2017; Smith et al. 2017; Valapour et al. 2017)

<table>
<thead>
<tr>
<th></th>
<th>Heart (%)</th>
<th>Intestine (%)</th>
<th>Kidney (%)</th>
<th>Liver (%)</th>
<th>Lung (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>58.7</td>
<td>77.8</td>
<td>64.1</td>
<td>58.4</td>
<td>100</td>
</tr>
<tr>
<td>mTORi</td>
<td>13.8</td>
<td>N/A</td>
<td>7.7</td>
<td>9.0</td>
<td>N/A</td>
</tr>
</tbody>
</table>
# Immunosuppressants in pediatrics

## Table 3 Modern-day maintenance immunosuppression in pediatric solid organ transplant recipients: agents, dosing/therapeutic drug monitoring, potential adverse events, and administration considerations

<table>
<thead>
<tr>
<th>Immunosuppressant medication</th>
<th>Dosing/therapeutic drug monitoring</th>
<th>Potential adverse effects</th>
<th>Administration considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus (Prograf®)</td>
<td>0.15–0.20 mg/kg/day orally divided every 12 h&lt;br&gt;Trough better correlate of AUC&lt;br&gt;Trough goal 10–12 ng/mL first 3 months</td>
<td>Nephrotoxicity, neurotoxicity, hypertension, hyperlipidemia, hyperkalemia, hypomagnesemia, hyperglycemia/PTDM, alopecia, lymphoma and other malignancies, infections</td>
<td>Can be administered sublingually (PO:SL = 2:1)&lt;br&gt;IR and extended-release formulations&lt;br&gt;C/I with NSAIDs; avoid grapefruit&lt;br&gt;Fasting/empty stomach ↑ trough ~30%&lt;br&gt;PK unchanged in renal impairment; mean clearance may be lowered in setting of severe hepatic dysfunction</td>
</tr>
<tr>
<td>Cyclosporine [modified]</td>
<td>5-10 mg/kg/day orally divided every 12 h&lt;br&gt;C2 level better correlate of AUC&lt;br&gt;Trough concentration poor correlate of AUC but utilized for feasibility&lt;br&gt;C2 goal level ~1,700 ng/mL</td>
<td>Nephrotoxicity, neurotoxicity, hypertension, hyperkalemia, hypomagnesemia, hirsutism, gingival hyperplasia, hyperlipidemia, lymphoma and other malignancies, infections</td>
<td>C/I with NSAIDs. IV:PO = 1:3&lt;br&gt;Avoid grapefruit&lt;br&gt;Microemulsion (e.g., Gengraf® and Neoral®) and oil-based (Sandimmune®) formulations are NOT bioequivalent</td>
</tr>
<tr>
<td>Mycophenolate mofetil [MMF]</td>
<td>MMF: 1,200 mg/m²/day divided Q12H when used with tacrolimus or 1,800 mg/m²/day divided Q12H when used with cyclosporine for the first 2–4 weeks posttransplant&lt;br&gt;MPA AUC₀–₁₂h target 30–60 mg × h/L&lt;br&gt;MPA trough target 1.0–3.5 mg/L</td>
<td>Anemia, leukopenia, diarrhea, abdominal pain, nausea, infections, lymphoma and other malignancies, embryo-fetal toxicity</td>
<td>BBW: C/I during pregnancy; FDA-mandated MMF REMS program&lt;br&gt;MMF 250 mg = MPS 180 mg DR tab&lt;br&gt;IV:PO = 1:1&lt;br&gt;Use with caution in severe chronic renal impairment; MPA and MPAG not usually removed by dialysis</td>
</tr>
<tr>
<td>Corticosteroids (prednisone, prednisolone, methylprednisolone)</td>
<td>Dosing varies</td>
<td>Hyperglycemia, hypertension, emotional instability, insomnia, increased appetite, weight gain, peptic ulcer, osteoporosis, decreased growth velocity, leukocytosis</td>
<td>5 mg prednisone = 5 mg prednisolone = 4 mg methylprednisolone&lt;br&gt;May increase risk of peptic ulcer disease and gastritis; consider addition of H2RA or PPI for GI protection</td>
</tr>
</tbody>
</table>
## Immunosuppressants in pediatrics

**Induction and Standard Immunosuppression**

David M. Newland and Thomas L. Nemeth

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e-mail: David.Newland@seattlechildrens.org; Thomas.  
Nemeth@seattlechildrens.org

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S. P. Dunn, S. Hoelsén (eds.), *Solid Organ Transplantation in Infants and Children*, Organ and Tissue  
Transplantation. https://doi.org/10.1007/978-3-319-07284-5_45

| Sirolimus (Rapamune®) | Loading dose of 5–7 mg/m² BSA followed by daily dose of 2–4 mg/m² BSA adjusted to target trough 5–10 ng/mL in CNI-free regimen  
*Infants and young children may require total daily dose divided twice daily due to shorter $T_{1/2}$ | Hyperlipidemia, mouth ulcers, delayed wound healing, proteinuria, myelosuppression, peripheral edema, acne, rash | Consider additive goal if used with tacrolimus (e.g., tacrolimus goal trough 5 ng/mL plus sirolimus goal trough 5 ng/mL = 10 ng/mL) Should be taken 4 h after cyclosporine

| Everolimus (Zortress®) | 1.6–2.0 mg/m² BSA every 12 h with tacrolimus and/or MMF 0.8 mg/m² BSA every 12 h if concomitantly with cyclosporine  
Target trough 3 to 8 ng/mL | Hyperlipidemia, mouth ulcers, delayed wound healing, proteinuria, myelosuppression, peripheral edema, acne, rash | Consider additive goal if used with tacrolimus (e.g., tacrolimus goal trough 5 ng/mL plus everolimus goal trough 5 ng/mL = 10 ng/mL) Should be taken 4 h after cyclosporine Consider 1:1 sirolimus:everolimus conversion

# Immunosuppressants in pediatrics

<table>
<thead>
<tr>
<th>Interacting drug or class</th>
<th>Immunosuppressant impacted</th>
<th>Mechanism of interaction*</th>
<th>Severity of interaction</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA</td>
<td>SRL, EVR</td>
<td>CYP3A4 and P-gp inhibition</td>
<td>++</td>
<td>Take 4 h after CSA to minimize increases in SRL or EVR concentrations; monitor SRL/EVR trough levels closely when changing CSA doses or if CSA is added or removed from immunosuppression regimen</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 inhibition</td>
<td>+++</td>
<td>TAC and SRL may need to be dosed once or twice a week; CSA may need to be reduced to once daily</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 inhibition by azoles impacting CSA, TAC, SRL, EVR levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofibratezole</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ketoconazole</td>
<td></td>
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<tr>
<td>Fluconazole</td>
<td></td>
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<tr>
<td>Itraconazole</td>
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<tr>
<td>Voriconazole</td>
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<tr>
<td>Posaconazole</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Isavuconazole</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Isavuconazole inhibits UDP - glycosyltransferase decreasing conversion of MPA to MPAG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCBs</td>
<td></td>
<td>CYP3A4 inhibition</td>
<td>++</td>
<td>Dosage adjustment recommended; consider reducing CSA, TAC, SRL, or EVR dose 25–50% Monitor immunosuppressant levels closely</td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
<td>CYP3A inhibition</td>
<td></td>
<td>Dosage adjustment recommended; consider immunosuppressant dose 50% Monitor immunosuppressant levels closely</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CSA cyclosporine, TAC tacrolimus, SRL sirolimus, EVR everolimus, P-gp multidrug efflux transporter P-glycoprotein, CCBs calcium channel blockers, CYP3A4 cytochrome P450 3A4 enzyme, MP4 mycophenolic acid, MPAG inactive phenolic glucuronide of MPA

Severity of drug-drug interaction: +++ severe interaction; ++ moderate interaction; + minor interaction

Use of drugs in bold are not recommended per prescribing information

*CSA is a substrate and inhibitor of CYP3A4 and P-gp. SIR and EVR are substrates for both CYP3A4 and P-gp. Drugs italicized are known inhibitors of P-glycoprotein that can decrease the efflux of CSA, SIR, or EVR from intestinal cells and increase blood concentrations of these immunosuppressant drugs.
## Immunosuppressants in pediatrics

<table>
<thead>
<tr>
<th>Interacting drug/class</th>
<th>Immunosuppressant impacted</th>
<th>Mechanism of interaction</th>
<th>Severity of interaction</th>
<th>Consequence of interaction</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimycobacterials</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>Rifampin may ↓ EVR and SRL AUC 60% and 80%, respectively; rifabutin and rifapentine ↓ AUC to a lesser extent</td>
<td>Avoid rifampin if possible. Dosage adjustment and close monitoring of immunosuppressant drug levels recommended</td>
</tr>
<tr>
<td>Rifampin</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>↓ Immunosuppressant levels</td>
<td>Dosage adjustment and close monitoring of immunosuppressant drug levels recommended</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>↓ Immunosuppressant levels</td>
<td>Dosage adjustment and close monitoring of immunosuppressant drug levels recommended</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>↓ Immunosuppressant levels</td>
<td>Dosage adjustment and close monitoring of immunosuppressant drug levels recommended</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>↓ Immunosuppressant levels</td>
<td>Dosage adjustment and close monitoring of immunosuppressant drug levels recommended</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>↓ Immunosuppressant levels</td>
<td>Dosage adjustment and close monitoring of immunosuppressant drug levels recommended</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>↓ Immunosuppressant levels</td>
<td>Dosage adjustment and close monitoring of immunosuppressant drug levels recommended</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>↓ Immunosuppressant levels</td>
<td>Dosage adjustment and close monitoring of immunosuppressant drug levels recommended</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>↓ Immunosuppressant levels</td>
<td>Dosage adjustment and close monitoring of immunosuppressant drug levels recommended</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+++</td>
<td>↓ Immunosuppressant levels</td>
<td>Monitor immunosuppressant levels</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>CSA, TAC, SRL, EVR</td>
<td>CYP3A4 induction</td>
<td>+</td>
<td>↓ Immunosuppressant levels</td>
<td>Monitor immunosuppressant levels</td>
</tr>
<tr>
<td>CSA</td>
<td>MPA derivatives (MMF or MPS)</td>
<td>Interruption of enterohepatic recirculation of MPA</td>
<td>++</td>
<td>May decrease mean MPA AUC$_{0-12h}$, 30–50%</td>
<td>Consider dose adjustment if switching from CSA to TAC or vice versa due to potential for differences in MPA exposure</td>
</tr>
<tr>
<td>PPIs</td>
<td>MMF</td>
<td>Decreased MPA solubility at increased gastric pH</td>
<td>+</td>
<td>30% reduction in MPA AUC</td>
<td>Use with caution when coadministered</td>
</tr>
</tbody>
</table>
# Immunosuppressants in pediatrics

## Induction and Standard Immunosuppression

David M. Newland and Thomas L. Nemeth

<table>
<thead>
<tr>
<th>Cholestyramine</th>
<th>MPA derivatives (MMF or MPS)</th>
<th>Interruption of enterohepatic recirculation</th>
<th>+</th>
<th>40% reduction in MPA AUC</th>
<th>Coadministration should be avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer</td>
<td>MMF</td>
<td>May bind MPA metabolites in the GI tract, preventing their reabsorption and enterohepatic recirculation</td>
<td>+</td>
<td>25% reduction in mean MPA AUC</td>
<td>Give phosphate binder 2 h after MMF to minimize impact of absorption of MPA</td>
</tr>
<tr>
<td>Rifampin</td>
<td>MMF</td>
<td>Simultaneous induction of renal, hepatic, and GI UGT and organic anion transporters with inhibition of enterohepatic recirculation</td>
<td>++</td>
<td>67% decrease in MPA AUC&lt;sub&gt;0-12h&lt;/sub&gt;</td>
<td>Concomitant use should be avoided unless benefit outweighs risk</td>
</tr>
</tbody>
</table>

*CSA cyclosporine, TAC tacrolimus, SRL sirolimus, EVR everolimus, P-gp multidrug efflux transporter P-glycoprotein, CYP3A4 Cytochrome P450 3A4 enzyme, AUC area under the curve, MPA mycophenolic acid, MMF mycophenolate mofetil, MPS mycophenolate sodium, PPI proton pump inhibitors, GI gastrointestinal, UGT uridine 5′-diphosphogluconosyltransferase*

Severity of drug-drug interaction: ++++, severe interaction; +++, moderate interaction; +, minor interaction

Use of drugs in bold are not recommended per prescribing information

*CSA is a substrate and inhibitor of CYP3A4 and P-gp. SIR and EVR are substrates only for both CYP3A4 and P-gp. Drugs italicized are known inducers of P-glycoprotein that can increase the efflux of CSA, SIR, or EVR from intestinal cells and decrease blood concentrations of these immunosuppressant drugs
Effect of CYP3A5*1 expression on tacrolimus required dose for transplant pediatrics: A systematic review and meta-analysis

Fatemeh Hendijani¹,² | Negar Azarpira³ | Maryam Kaviani⁴
Converting immunosuppression from an oral suspension to a granule formulation of tacrolimus in pediatric renal transplant recipients

Georgia Malakasioti¹ | Christine Booth² | Stephen D. Marks¹,³
## Table 67.1  Semi-quantitative comparison of safety profiles of current primary immunosuppressive compounds

<table>
<thead>
<tr>
<th></th>
<th>Glucocorticoids</th>
<th>Sirolimus</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Mycophenolate mofetil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity(^a)</td>
<td>−</td>
<td>+</td>
<td>+++</td>
<td>++(+)</td>
<td>−</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+(+)</td>
<td>−</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>+</td>
<td>−</td>
<td>+++</td>
<td>++</td>
<td>−</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>+</td>
<td>−</td>
<td>+++</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>Post-transplant diabetes mellitus</td>
<td>++</td>
<td>−</td>
<td>++</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>−</td>
<td>++</td>
<td>−</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Gastrointestinal adverse effects(^b)</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Esthetical changes</td>
<td>++</td>
<td>−</td>
<td>++</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Wound healing problems(^c)</td>
<td>+</td>
<td>++</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Fetal toxicity</td>
<td>−</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>++</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Inhibition of longitudinal growth</td>
<td>+++</td>
<td>?</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>
Generic
Immunosuppressants

The institution of ‘innovator only’ policies

Generic immunosuppressants

Mara Medeiros\textsuperscript{1,2} · Julia Lumini\textsuperscript{3} · Noah Stern\textsuperscript{4} · Gilberto Castañeda-Hernández\textsuperscript{5} · Guido Filler\textsuperscript{4,6,7,8}
NICE Guidance: Immunosuppression for Children

NICE National Institute for Health and Care Excellence

Immunosuppressive therapy for kidney transplant in children and young people

Technology appraisal guidance
Published: 11 October 2017
nice.org.uk/guidance/ta482
1. Introduction
2. Induction therapy
3. Maintenance
4. Immunosuppression for pediatric patients
5. Special issues
6. UNC Experience
## Immunosuppression: Individualization

### Clinical Practice Guideline
**Post-Operative Care in the Kidney Transplant Recipient**
- **Final Version:** February 2017
- **Review Date:** February 2022

### Table: Risk Types and Possible Strategies

<table>
<thead>
<tr>
<th>Risk Type</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>Possible Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>Low BMI</td>
<td>Positive family history</td>
<td>Impaired GT</td>
<td>Avoid/minimise steroids and tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Age &lt;40</td>
<td>history ADPKD</td>
<td>BMI &gt;35 HCV positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal pre-Tx GTT</td>
<td></td>
<td>Age &gt;60 Previous CVD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Age &lt;40</td>
<td>Pre-malignant lesion</td>
<td>Previous cancer</td>
<td>Consider low immunosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hereditary syndrome e.g. VHL</td>
<td>load or sirolimus</td>
</tr>
<tr>
<td>Ischaemia-reperfusion injury</td>
<td>Living donor</td>
<td>CIT &gt;12 hours</td>
<td>DCD</td>
<td>Reduce CNI exposure</td>
</tr>
<tr>
<td></td>
<td>Deceased donor</td>
<td>Donor aged 50-60</td>
<td>CIT &gt; 24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;40</td>
<td>Extended criteria donor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Drug Adherence
Medications: Nonadherence

Drug Adherence: TAKE-IT

A Randomized Trial of a Multicomponent Intervention to Promote Medication Adherence: The Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial (TAKE-IT)

1. Introduction
2. Induction therapy
3. Maintenance
4. Immunosuppression for pediatric patients
5. Special issues
6. UNC Experience
Mansoura Renal Transplant Program

March 1976 to Today [September 11th, 2018]: n2981
Induction Therapy: Mansoura UNC Experience

Experimental and Clinical Transplantation (2011) 5: 295-301

Alemtuzumab Preconditioning Allows Steroid-calcineurin Inhibitor-free Regimen in Live-donor Kidney Transplant

Ayman F. Refaie,1 Khaled M. Mahmoud,1 Amani M. Ismail,2 Hussein A. Sheashaa,1 Ahmed I. Kamal,1 Mohamed A. Ghoneim3
Maintenance Therapy: Mansoura UNC Experience
Optimizing Immunosuppressive Regimens Among Living-Donor Renal Transplant Recipients

Mohamed Adel Bakr,¹ Ayman Maher Nagib,¹ Osama Ashry Gheith,¹ Ahmed Farouk Hamdy,¹ Ayman Fathi Refaie,¹ Ahmed Farouk Donia,¹ Ahmed Hassan Neamatalla,¹ Khaled Farouk Eldahshan,¹ Ahmed Abdelfattah Denewar,¹ Mohamed Hamed Abbas,¹ Amany Ismail Mostafa,² Mohamed Ahmed Ghoneim³

Immunosuppression: In A Nutshell

Curr Opin Organ Transplant 2018, 23:51–62

Biologics

Other immunosuppressants

Cell-based strategies (e.g. stem cells, Tregs...)?
Gene editing?

Timeline

1960
1970
1980
1990
2000
2010
2020

Polyclonal anti-lymphocyte sera (1967)
Muromonab-CD3 (OKT3) (1986)
Rituximab (1997)
Daclizumab (1997)
Basiliximab (1998)
Alemtuzumab (Campath-1H) (2001)
Abatacept (2005)
Belatacept (2011)

Irradiation (1908)
Azathioprine (1959)
Steroids (1961)
Thoracic-duct drainage (1963)
Cyclosporine (1983)
Tacrolimus (1994)
Mycophenolic acid (1995)
Sirolimus (1999)
Bortezomib (2008)
Everolimus (2009)
What is Urgently Needed?

The Nile Awards for advanced Technological Sciences
ESNT Virtual Academy

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- Management of UTI in children Dr. Mohamed Zedan
- Hemodialysis Adequacy in Children Prof. Ahmed Refaie
- Hemodialysis in Children Prof. Ashraf Bakr
- Hemodialysis in Children Ashraf Abdel Baset Bakr
- Reversibility of Hepatic fibrosis in Children with ALH Prof Ahmed Abdalla
- Hypertension in children Prof Ahmed elrefaie
- Hemodialysis for children. Prof Ashraf Bakr
التعليم - حياة
Living through learning
Immunosuppression Tutorial Prof Hussein Sheashaa, Monday 20 Nov 2017


immunosuppression CNI mTORi, What is new? prof Hussein Sheashaa

immunosuppression: Calcineurin Inhibitors and mTORi What is New? prof Hussein Sheashaa, February 26th, 2018.
Belimumab is a monoclonal antibody of.....nature

A. Chimeric

B. Humanized

C. Human

D. Fusion protein
Which one of the following biological drugs is used for maintenance immunosuppression?

A. Basiliximab
B. Belimumab
C. Rituximab
D. Belatacept
Q3

Which is correct?

A. Glucocorticoid effect of 20 mg prednisolone is equivalent to 3 mg of dexamethasone
B. Belatacept is more used in pediatric age
C. Sirolimus is taken 4h after tacrolimus
D. Cyclosporine increases MPA-AUC
He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all.

William Osler