CLINICAL PEARLS FOR PEDIATRIC SOLID ORGAN TRANSPLANT IMMUNOSUPPRESSION THERAPY

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CONFLICT OF INTEREST DISCLOSURE

I have no financial relationships to disclose

OBJECTIVES

- Pharmacist Objectives:
  - Describe appropriate induction and maintenance immunosuppression therapies for pediatric solid organ transplant patients
  - Specify methods for therapeutic drug monitoring of immunosuppressants and managing adverse effects
  - Identify appropriate supportive care measures for preventing infections

- Technician Objectives:
  - Define the role of pharmacists and pharmacy technicians in caring for pediatric solid organ transplant patients
  - Identify commonly used induction and maintenance immunosuppression therapies for pediatric solid organ transplant patients
  - Describe proper preparation and administration technique of immunosuppressants to promote patient safety

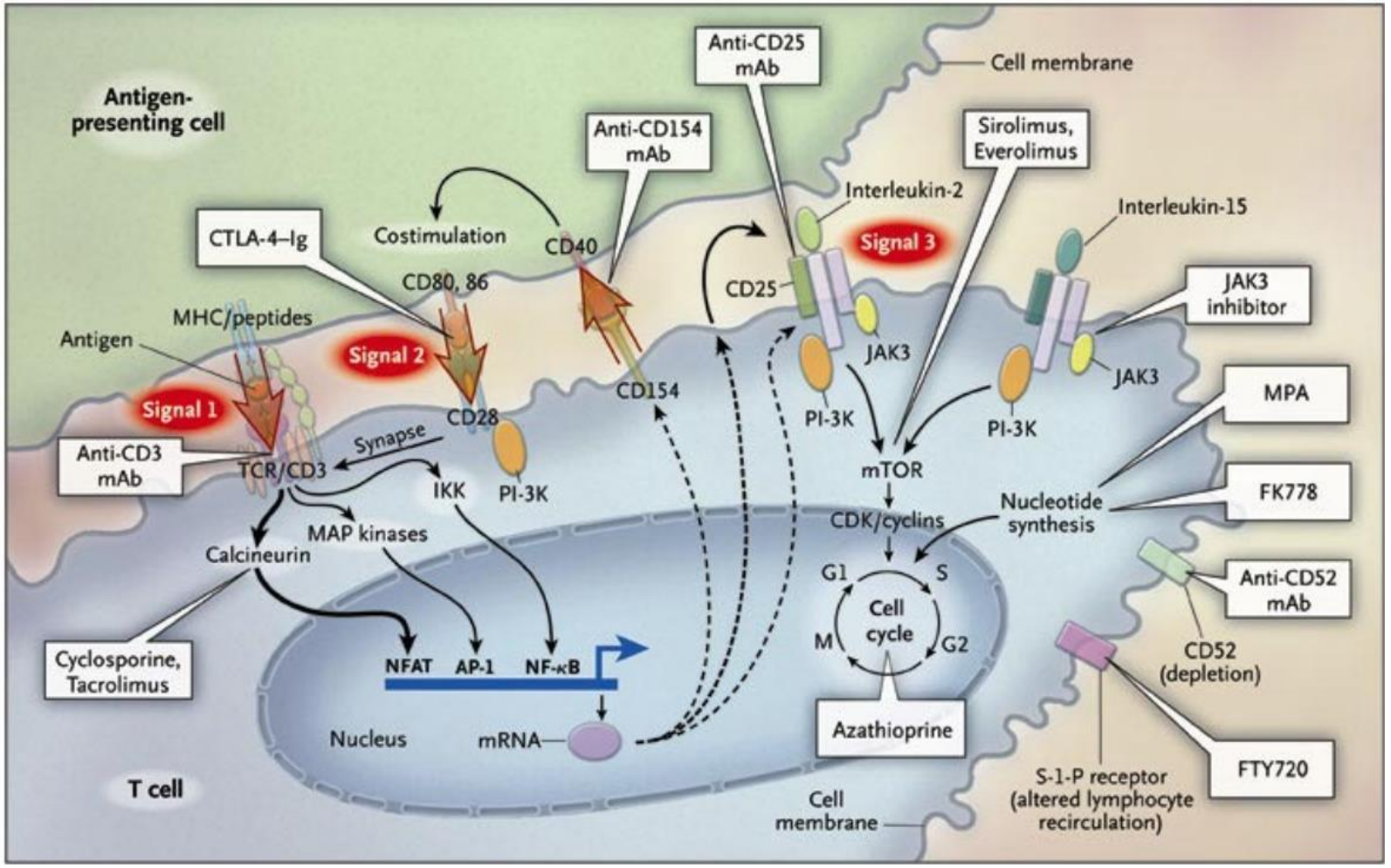
ABBREVIATIONS

- ANC: absolute neutrophil count
- AUC: area under the curve
- CNI: Calcineurin inhibitors
- CMV: cytomegalovirus
- ER: Extended release
- GI: gastrointestinal
- MMF: mycophenolate mofetil
- IR: Immediate release
- NIOSH: National institute for occupational safety and health
- PJP: Pneumocystis jirovecii pneumonia
- PK: pharmacokinetic
- PML: Progressive multifocal leukoencephalopathy
- UTI: urinary tract infection
- WBC: white blood cell count

GOALS OF IMMUNOSUPPRESSIVE THERAPY

- Prevent acute and chronic organ rejection
- Prolong allograft survival
- **Minimization of toxicities**

PATHOPHYSIOLOGY

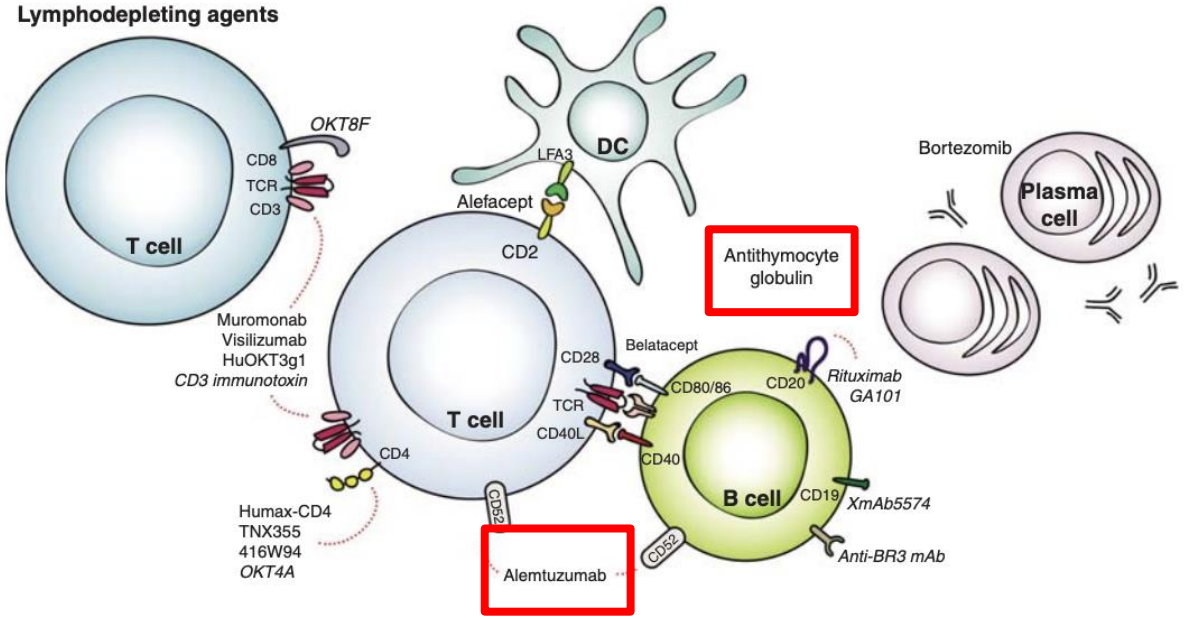


N Engl J Med. 2004;351(26):2715-2729. doi:10.1056/NEJMra033540

INDUCTION THERAPY

INDUCTION THERAPY OPTIONS

Lymphocyte Depleting Agents	
Equine anti-thymocyte (ATGAM®)	Polyclonal Antibody
Rabbit anti-thymocyte globulin (Thymoglobulin®)	
Alemtuzumab (Campath®)	Monoclonal Antibody
Non-Depleting Agents	
Basiliximab (Simulect®)	

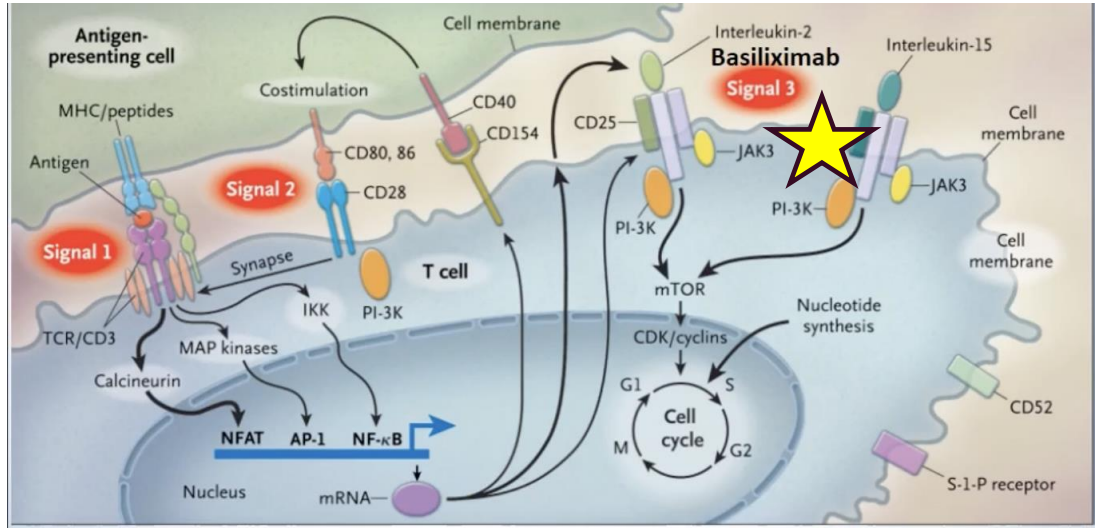


Med. 2013;3(7):a015511. Published 2013 Jul 1. doi:10.1101/cshperspect.a015511
Am J Transplant. 2007;7(2):285-292. doi:10.1111/j.1600-6143.2006.01612.x

J Heart Lung Transplant. 2023;42(5):e1-e141. doi:10.1016/j.healun.2022.10.015
Am J Transplant. 2009;9 Suppl 3:S1-S155. doi:10.1111/j.1600-6143.2009.02834.x

BASILIXIMAB (SIMULECT®)

- Place in therapy:
  - Low immunologic risk
  - Intolerance or hypersensitivity to anti-thymocyte globulin



- Basiliximab (Simulect): Total 2 doses
- Weight < 35 kg: 10 mg | Weight ≥ 35 kg: 20 mg
  - Day 0: 10 – 20 mg IV given in OR
  - Day 1: n/a
  - Day 2: n/a
  - Day 3: n/a
  - Day 4: 10 – 20 mg IV

Am J Transplant. 2009;9 Suppl 3:S1-S155. doi:10.1111/j.1600-6143.2009.02834.x

BASILIXIMAB ((SIMULECT®) ADMINISTRATION

- Administer via peripheral or central line
- Infusion duration: 30 minutes
- Monitoring:
  - Nausea, vomiting, local pain at injection site
  - Signs and symptoms of anaphylaxis (rare)

Basiliximab. Pediatric and Neonatal Lexi-Drugs. Hudson, OH: Lexicomp, 2023 http://online.lexi.com/

ANTI-THYMOCYTE GLOBULIN

- Place in therapy
  - High immunologic risk patients
  - Delayed CNI initiation
  - Steroid withdrawal

- Thymoglobulin (rATG): Total 4 doses
- Total cumulative dose: 6 mg/kg IV
  - Day 0: 1.5 mg/kg IV [max 150 mg] given in OR
  - Day 1; 1.5 mg/kg IV [max 150 mg]
  - Day 2: 1.5 mg/kg IV [max 150 mg]
  - Day 3: 1.5 mg/kg IV [max 150 mg]
- Dose often rounded to nearest vial size

Am J Transplant. 2009;9 Suppl 3:S1-S155. doi:10.1111/j.1600-6143.2009.02834.x

ANTI-THYMOCYTE GLOBULIN ADMINISTRATION

- Pre-medications: diphenhydramine, acetaminophen, methylprednisolone
- Administer via 0.22 micron in-line filter via central line
- Infusion duration: 6 hours
- Monitoring parameters
  - Hypersensitivity reaction: anaphylaxis [stop infusion]
  - Infusion reaction: fever, chills, nausea, muscle/joint pain
  - Cardiovascular: hypotension, hypertension, tachycardia

Antithymocyte Globulin (Rabbit). Pediatric and Neonatal Lexi-Drugs. Hudson, OH: Lexicomp, 2023 http://online.lexi.com/

ANTI-THYMOCYTE GLOBULIN MONITORING

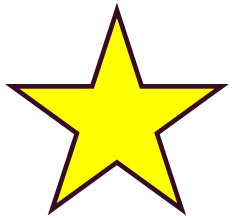
- Dose adjustments recommended in setting of leukopenia, thrombocytopenia and/or neutropenia
- Treatment duration may be prolonged to provide total cumulative dose of 6 mg/kg

	Reduce dose by 50%	Hold dose
WBC count (cells/mm^3)	2,000 – 3,000	< 2,000
Platelets (cells/mm^3)	50,000 – 75,000	< 50,000
ANC (cells/mm^3)	800 - 1,200	< 800

Thymoglobulin [package insert]. Lyon, France, Genzyme Corporation; 2017

STEROID IMMUNOSUPPRESSION

- Used with induction agents:
  - Day 0: methylprednisolone IV 10 mg/kg [max 500 mg] given in OR
  - Day 1: methylprednisolone IV 2.5 mg/kg [max 250 mg]
  - Day 2: methylprednisolone IV 1.25 mg/kg [max 125 mg]
  - Day 3: methylprednisolone IV 0.6 mg/kg [max 60 mg]
- Steroid continuation: continue as maintenance immunosuppressive therapy
- Steroid withdrawal: discontinue when tacrolimus trough levels within goal



Am J Transplant. 2007;7(10):2227-2235. doi:10.1111/j.1600-6143.2007.01936.x

QUESTION 1

1. Which of the following induction agents require pre-medication?
   a) Basiliximab
   b) Anti-thymocyte Globulin
   c) Alemtuzumab
   d) A and B
   e) B and C

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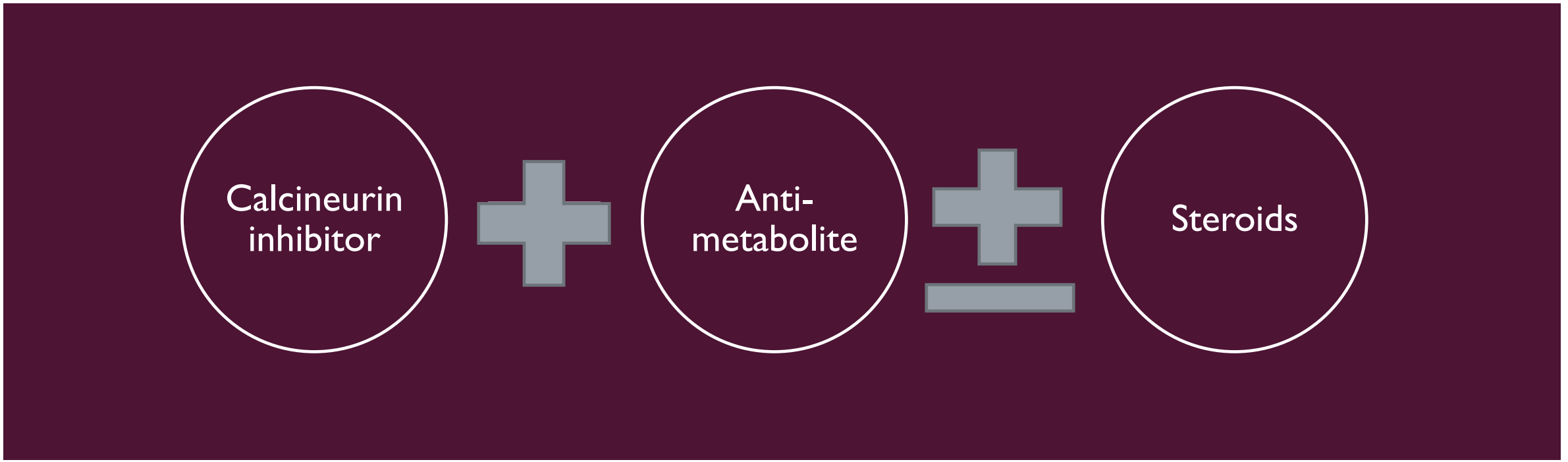
MAINTENANCE IMMUNOSUPPRESSION



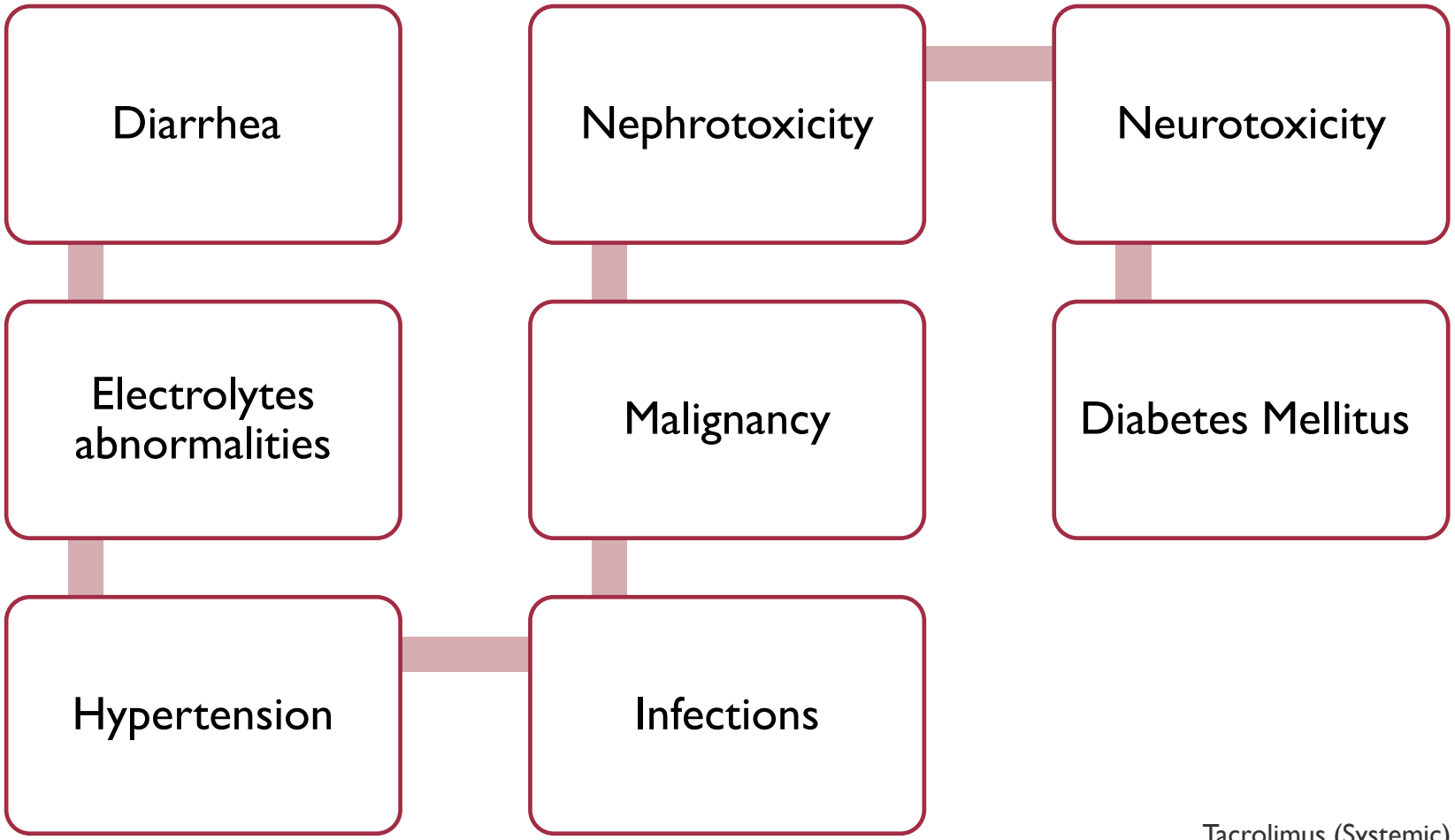
TACROLIMUS

- Dose: 0.05 mg/kg to 0.2 mg/kg q12h
- Dosage forms:
  - IR capsules (Prograf®): 0.5 mg, 1 mg, 5 mg
  - ER capsule (Astagraf®): 0.5 mg, 1 mg, 5 mg
  - ER tablet (Envarsus®): 0.75 mg, 1 mg, 4 mg
  - Extemporaneous preparation: 0.5 mg/mL, 1 mg/mL
  - Packet: 0.2 mg, 1 mg

Time since transplant	0-2 months	3-5 months	6-11 months	≥12 months
Goal trough	10-12 ng/mL	8-10 ng/mL	6-8 ng/mL	4-7 ng/mL

Tacrolimus (Systemic). In: Lexi-Drugs. Lexi-Comp, Inc.

TACROLIMUS ADVERSE EFFECTS



Tacrolimus (Systemic). In: Lexi-Drugs. Lexi-Comp, Inc.

FOOD & DRUG INTERACTIONS

- Substrate of CYP 3A4

CYP 3A4 Inhibitors	• Calcium channel blockers • Azole antifungals • Macrolide antibiotics • Food: grapefruit, pomegranate
CYP 3A4 Inducers	• Antiepileptics (phenytoin, phenobarbital, carbamazepine) • Antibiotics (nafcillin) • Anti-TB agents: Rifampin, rifabutin, isoniazid

Tacrolimus (Systemic). In: Lexi-Drugs. Lexi-Comp, Inc.

TACROLIMUS THERAPEUTIC DRUG MONITORING

- Trough levels obtained 12 hours after previous dose
  - Goal trough levels depend on time since transplant
  - Typical range: 4-12 ng/mL
- AUC monitoring
  - Population based PK model: Bayesian estimator
  - Limitations: variable AUC/C_0 ratios
  - Minimum AUC_{0-12} suggested for kidney transplant: 150 ng×h/mL[1]

AUC to trough correlations [2]				
Trough (ng/mL)	3-7	5-10	8-12	10-15
Equivalent AUC ng×h/mL	70-150	100-200	140-240	170-285

1. *Ther Drug Monit*. 2019;41(3):261-307. doi:10.1097/FTD.0000000000000640
2. Ther *Drug Monit*. 2021;43(4):472-480. doi:10.1097/FTD.0000000000000828

SUB-THERAPEUTIC TROUGHS

Increase	Dose and dosing interval to q8h
Initiate	Fluconazole as a ”boosting agent”
Switch	Extended-release formulation

MYCOPHENOLATE

- Mycophenolate Mofetil (CellCept®)
  - Dosage forms: 250mg capsules, 500mg tablets, 200 mg/mL suspension
  - Recommended dose: 600 mg/m^2 BID [max single dose: 1,000 mg]
  - May be given with or without meals

- Delayed Release Mycophenolate Sodium (Myfortic®):
  - No liquid formulation – 180mg tablets, 360mg tablets
  - Recommended dose: 400 mg/m^2 BID [max 720 mg BID]
  - Administer on empty stomach (1 hour before or 2 hours after meals)

Mycophenolate Mofetil [Package Insert], San Francisco, CA, 2022

MANAGING INTOLERANCE AND ADVERSE EFFECTS

1

Temporarily decrease dose in setting of infection or neutropenia

- Consider addition of corticosteroid

2

Switch to alternative agents [i.e azathioprine]

MYCOPHENOLATE MOFETIL REMS

- All female patients are provided counseling and education on teratogenic effects
- Recommended to use 2 forms of contraception during treatment and for 6 weeks after discontinuation
- Embryofetal Toxicity:
  - First trimester pregnancy loss
  - Congenital malformations
  - Anomalies of distal limb, heart, esophagus, kidney, nervous system

Mycophenolate Mofetil [Package Insert], San Francisco, CA, 2022

QUESTION 2

2) Which of the following can be consider to achieve therapeutic concentrations of tacrolimus?

a. Initiate nafcillin to increase tacrolimus concentration
b. Increase dose and frequency to every 8 hours
c. Encourage patients to eat grapefruit to increase tacrolimus concentration
d. Switch to oral suspension formulation

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HAZARDOUS PRECAUTIONS

- Non-neoplastic drugs that meet NIOSH criteria for hazardous drugs

Medication	Warning
Tacrolimus	Increased risk of lymphomas and other malignancies
Mycophenolate mofetil & Mycofenolic acid	Boxed warning for embryofetal toxicity, malignancies, serious infections • Tablets should not be crushed and capsules should not be opened • Avoid contact with skin or mucous membranes of the powder contained in capsules and oral suspension • If such contact occurs, wash thoroughly with soap and water

Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 27 Apr. 2023, www.cdc.gov/niosh/docs/2016-161/default.html.

IMMUNIZATIONS

- Pre-transplant
  - Live vaccines: administer at least 4 weeks prior to transplant
  - Inactivated vaccines: administer at least 2 weeks prior to transplant
- Post-transplant
  - Live vaccines generally contraindicated
  - Inactivated vaccines may be administered 3-6 months after transplant

Live vaccines

- Measles mumps rubella
- Varicella
- Rotavirus
- Smallpox
- Yellow fever
- *Salmonella typhi*
- Cholera vaccine

Clin Transplant. 2019;33(9):e13563. doi:10.1111/ctr.13563
Pediatrics. 2020;146(6):e20200696. doi:10.1542/peds.2020-0696

ANTIBIOTIC PROPHYLAXIS

Indication	Medication	Duration
PJP prophylaxis UTI prophylaxis [for renal transplant]	Sulfamethoxazole/trimethoprim (Bactrim)	6 months
Fungal	Nystatin Fluconazole	1-3 month
CMV prophylaxis	Valganciclovir	3 to 6 months

CMV Risk		
High risk	D+/R-	6 months
Intermediate risk	D+/R+ D-/R+	3 months
Low risk	D-/R-	Prophylaxis not required

D: Donor
R: Recipient

Am J Transplant. 2012;12(9):2414-2428. doi:10.1111/j.1600-6143.2012.04100.x

Am J Transplant. 2009;9 Suppl 3:S1-S155. doi:10.1111/j.1600-6143.2009.02834.x

ROLE OF PEDIATRIC SOT PHARMACIST

- Pre-transplant evaluation
- Induction and maintenance regimen
- Therapeutic drug monitoring
- Patient counseling and education
- Assist with transitioning to adulthood

REFERENCES

- Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9 Suppl 3:S1-S155. doi:10.1111/j.1600-6143.2009.02834.x
- Page E, Kwun J, Oh B, Knechtle S. Lymphodepletional strategies in transplantation. *Cold Spring Harb Perspect Med*. 2013;3(7):a015511. Published 2013 Jul 1. doi:10.1101/cshperspect.a015511
- Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2023;42(5):e1-e141. doi:10.1016/j.healun.2022.10.015
- Halloran PF. Immunosuppressive drugs for kidney transplantation [published correction appears in N Engl J Med. 2005 Mar 10;352(10):1056]. N Engl J Med. 2004;351(26):2715-2729. doi:10.1056/NEJMra033540
- Faro A, Mallory GB, Visner GA, et al. American Society of Transplantation executive summary on pediatric lung transplantation. Am J Transplant. 2007;7(2):285-292. doi:10.1111/j.1600-6143.2006.01612.x
- "Antineoplastic & Other Hazardous Drugs in Healthcare, 2016." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 27 Apr. 2023, www.cdc.gov/niosh/docs/2016-161/default.html.
- Sarwal M, Pascual J. Immunosuppression minimization in pediatric transplantation. *Am J Transplant*. 2007;7(10):2227-2235. doi:10.1111/j.1600-6143.2007.01936.x
- Brunet M, van Gelder T, Åsberg A, et al. Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy: Second Consensus Report. *Ther Drug Monit*. 2019;41(3):261-307. doi:10.1097/FTD.0000000000000640
- Danziger-Isakov L, Kumar D; AST ID Community of Practice. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice [published correction appears in Clin Transplant. 2020 Mar;34(3):e13806]. Clin Transplant. 2019;33(9):e13563. doi:10.1111/ctr.13563
- Katz DT, Torres NS, Chatani B, et al. Care of Pediatric Solid Organ Transplant Recipients: An Overview for Primary Care Providers. Pediatrics. 2020;146(6):e20200696. doi:10.1542/peds.2020-0696
- Tacrolimus (Systemic). In: Lexi-Drugs. Lexi-Comp, Inc.
- BasiliximabPediatric and Neonatal Lexi-Drugs. Hudson, OH: Lexicomp, 2023 http://online.lexi.com/
- Antithymocyte Globulin (Rabbit). Pediatric and Neonatal Lexi-Drugs. Hudson, OH: Lexicomp, 2023 http://online.lexi.com/
- Thymoglobulin [package insert]. Lyon, France, Genzyme Corporation; 2017
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QUESTIONS?