

Special Considerations in Pediatric and Geriatric Transplant Populations



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Special Considerations in Pediatric Transplant Populations

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Disclosure

- *The author of this presentation has no actual or potential conflicts of interest.*

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Learning Objectives

- Discuss practical differences of medication use in children with emphasis on pharmacokinetics, formulations, and monitoring of commonly used immunosuppressants.
- Describe the etiologic differences for organ disease and discuss associated complications after solid organ transplant in children.
- Design a pharmacotherapeutic treatment plan for pediatric patients undergoing intended ABO incompatible organ transplantation.
- Formulate an immunization plan for a pediatric organ transplant candidates.

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Challenges in Pediatric Pharmacotherapy

- Lack of safety and efficacy data
- Lack of commercially available formulations
- Lack of pediatric dosing guidelines

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Developmental Pharmacokinetics

- Physiological Differences Affecting Pharmacokinetics
 - Absorption
 - Distribution
 - Metabolism
 - Excretion

Kearns GL, et al. N Engl J Med. 2003;349(12):1157-67.
Lu H, et al. J Pediatr Pharmacol Ther. 2014;19:262-76.

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Absorption

- Rate and extent of gastrointestinal (GI) absorption are influenced by age-related changes
 - pH
 - Gastric emptying time
 - GI motility
 - Intestinal integrity

Kearns GL, et al. N Engl J Med. 2003;349(12):1157-67.
 Lu H, et al. J Pediatr Pharmacol Ther. 2014;19:262-76.

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Distribution




Magnitude of V_d provides insight into drug distribution

- Large V_d → absorption in fat or protein binding
- Small V_d → distribution in plasma only

Increased total body and extracellular water in pediatric patients

- When adjusted for weight, larger doses of hydrophilic and smaller doses of lipophilic drugs are required in neonates
- Disease states
 - Increased V_d : Cystic fibrosis, liver or heart failure
 - Decreased V_d : dehydration

Age	TBW (%)	Extracellular Water (%)	Adipose Tissue (%)
Preterm	87	50	1-5
Term	77	45	12-16
3 months	73	33	
1 year	59	28	
Adult	55	20	20

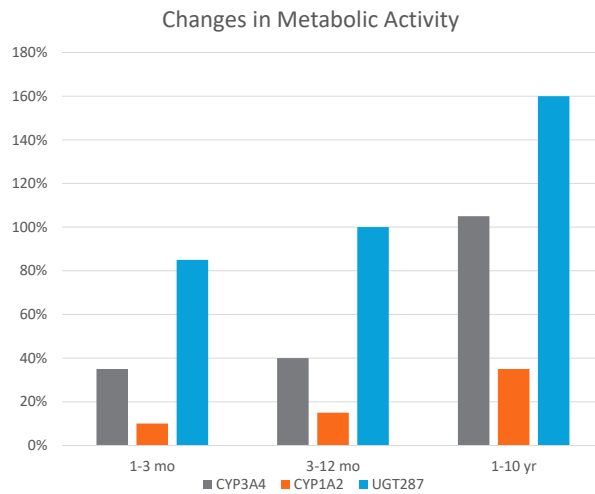
 DECREASE
  DECREASE
  INCREASE

Kearns GL, et al. N Engl J Med. 2003;349(12):1157-67.
 Lu H, et al. J Pediatr Pharmacol Ther. 2014;19:262-76.

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Metabolism in Children

- Liver: major site of drug biotransformation
- Children have reduced hepatic metabolism
 - ↓ hepatic blood flow
 - ↓ hepatocyte uptake
 - ↓ hepatic enzyme capacity and function
 - ↓ biliary excretion



Kearns GL, et al. N Engl J Med. 2003;349(12):1157-67.

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Elimination in Children

- Kidney maturation
 - Tubular activity still developing during and beyond the neonatal period
- Glomerular filtration rate (GFR)
 - 50-70% of adult values at birth
 - Reaches adult values by 3-5 months of age
 - Commonly estimated utilizing a modified Schwartz equation
 - $GFR, \text{ mL/min/1.73m}^2 = (0.413 \times \text{height (cm)}) / SCr \text{ (mg/dL)}$

Kearns GL, et al. N Engl J Med. 2003;349(12):1157-67.

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Drug Administration in Children

- Inability to swallow pills eliminates the ability to use many acceptable drug formulations
 - 1/3 of adolescent age children have difficulties due to taste, size, or feelings of discomfort
 - Fear, anxiety, intolerance of flavor, understanding of medical need
- Training can include behavioral therapies, scripted swallowing techniques, and head positioning

Patel A, et al. *Pediatrics*. 135(5):883-889

Polaha J, et al. *South Med J*. 2008;101(11):1106-1112

Hansen DL, et al. *Pharm World Sci*. 2008;30(1):65-69

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Routes of Enteral Administration

- Enteral access and use is increasing
 - Nasogastric
 - Nasoduodenal
 - Nasojejunal
 - Percutaneous gastro-, gastrojejuno- or jejunostomy
- Implications
 - Alterations in absorption
 - Site of drug delivery
 - Complications of enteral tubes
 - Drug-food and drug-drug interactions
 - Drug Errors

Adams D. *Br J Intensive Care* 1994;4: 10-17.

Silva RM, et al. *J Clin Pharm Ther* 2020;45:408-18.

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Enteral Nutrition Complications

- Complications of Enteral Nutrition
 - Nausea, vomiting, constipation, and/or diarrhea
 - High gastric residuals
 - Tube occlusion
 - Regular flushing reduces the risk of occlusion
 - Generally before and after drug administration
 - Clamping tube and hold feeds for set duration after CNI

Thomson FC, et al. *Hosp Pharmacist*. 2000;7(6):155–64.

Silva RM, et al. *J Clin Pharm Ther* 2020;45:408-18.

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Pediatric Antirejection Formulations

	Available Formulations	Strengths	Common Dosing	Considerations for Enteral Administration
Calcineurin Inhibitors				
Tacrolimus	Suspension (extemporaneously prepared)	0.5mg/mL & 1mg/mL	0.05-0.15 mg/kg twice daily oral or enteral titrated to goal trough	Can be administered directly into stomach or post pyloric* *Increased absorption observed
	Granule Packets	0.2mg & 1mg	Thrice daily dosing may be required in select individuals	Presence of gastric residuals may slow or decrease absorption. Recommended to monitor troughs -Potentially separate feeds from drug administration to maximize absorption when not obtaining target levels
Cyclosporine (Modified)	Solution	100mg/mL	2-5 mg/kg twice daily oral or enteral titrated to goal trough	
Antiproliferatives				
Mycophenolate Mofetil	Suspension	200mg/mL	300-600 mg/m ² twice daily oral or enteral	Can be administered directly into stomach or post pyloric. Limited information for MMF or derivatives -Avoid intrajejunal administration of MMF -Increased absorption observed for Azathioprine.
Azathioprine	Suspension (extemporaneously prepared)	50mg/mL	1-2 mg/kg daily oral or enteral	Presence of gastric residuals may slow or decrease absorption -Potentially separate feeds from drug administration for MMF

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Formulations Frequently Utilized in Children

	Available Formulations	Strengths	Common Dosing	Considerations for Enteral Administration
mTOR inhibitors				
Sirolimus	Solution	1mg/mL	0.5-1 mg/m ² 1-2 times daily oral or enteral Diluted in water or orange juice	Limited information available for either sirolimus or everolimus given via enteral tubes or post-pyloric administration. Acceptable with sirolimus solution with monitoring.
Everolimus	Tablets	0.25mg, 0.5mg, 0.75mg, & 1mg	0.8 mg/m ² twice daily oral or enteral	Give consistently with regards to feeds

Silva RME, et al. *J Clin Pharm Ther.* 2020;45:405-415

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Other Formulation Considerations

- Rates of nonadherence in pediatric transplantation
 - Estimates have ranged from 3% to 71%
 - Composite estimates from all studies
- Among pediatric heart transplant recipients (n=2,070):
 - Nearly one-tenth (9%) developed medication non-adherence post-transplant. Median first occurrence at 2 years after transplant
 - Increased rate of mortality observed in non-adherent patients (33% at 2 years; compared to 3% described in the literature)

Olivia M, et al. *J Heart Lung Transplant*, 2013;32:881–888.
 Shellmer DA. *Curr Opin Organ Transplant*, 2011;16(5):509-514

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Adherence Strategies

- Counseling routinely delivered to pediatric transplant recipients and caregivers both verbally and as written instructions
- Reducing complexity of regimen by eliminating unnecessary medications, reducing frequency, simplifying preparation, timing with daily routines
 - Once & twice-daily regimens
 - Dose rounding to avoid to minimize preparation errors
 - Oral Syringes
 - 1mL & 3mL: nearest 0.1mL
 - 5mL: nearest 0.2mL
 - Patient centered language when prescribing
 - Take two pills by mouth twice daily > Take 2 pills by mouth in the morning and 2 pills at bedtime

Smith SG, et al. *J Behav Med* 2014.

Davis TC, et al. *Ann Intern Med* 2006;145:887-894.

Wolf MS, et al. *Patient Education and Counseling* 2007;67:293-300.

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Question 1: In comparison to adult dosing, how would you expect to dose a hydrophilic, renally cleared drug in a 3-week old term neonate?

- A. Lower dose (mg/kg), more frequent
- B. Lower dose (mg/kg), less frequent
- C. Higher dose (mg/kg), more frequent
- D. Higher dose (mg/kg), less frequent

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Pharmacokinetic Differences

- Immunosuppressants are narrow therapeutic index drugs, but are relatively understudied in children
 - Substantial changes in metabolic capacity, integumentary development, distribution, and renal and hepatic function changes in children
 - Changes post-transplant
 - Improvement in organ function
 - Inflammation
 - Concomitant medications
 - Altered food intake
 - Dosing often initiated based on weight or body surface area

Vondrak K, et al. *Pediatr Transplant*. 2018;22(8):e13289

Knops N, et al. *Br J Clin Pharmacol*. 2017;83:863-874

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Calcineurin Inhibitors in Children

- Augmented clearance of calcineurin inhibitors
 - Age-based increases
 - Tacrolimus dosing up to a 2.7-fold higher relative dose per kg to achieve similar drug concentrations between young children and adolescents
 - After puberty, clearance of tacrolimus decreases
 - Genotype testing may help improve initial dosing in at risk ethnicities (CYP3A5*1)
 - Present in 43-73% of African Americans
 - 2-3 fold higher dose requirements of tacrolimus
- Abbreviated Area Under the Curve (AUC) Testing?
 - Not shown to improve rejection or adverse effects
 - Consider when adverse effects disproportionate to trough

Montini G, et al. *Pediatr Nephrol.* 2006;21:719–724.

Naesens M, et al. *Transplantation.* 2008;85:1139–1145.

Knops N, et al. *Br J Clin Pharmacol.* 2017;83:863-874.

Gijzen V, et al. *J Heart Lung Transplant.* 2011;30:1352-9.

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Antiproliferatives in Children

- Antiproliferatives
 - Mycophenolate Mofetil often initiated utilizing BSA-based dosing
 - 600 mg/m²/dose or 15-25 mg/kg every 12 hours
 - Noted to be equivalent to 1000mg BID in adults
 - Based on organ transplanted, protocol, interindividual differences, dosing may vary
 - E.G. steroid avoidance protocols utilizing depleting induction therapy
 - Overall higher clearance has been identified in infants compared to adolescents and adults
 - MPA therapeutic drug monitoring, either trough or AUC determinations, is used selectively

Weber LT, et al. *J AM Soc Nephrol.* 1998;9:1511-1520

Filler G, et al. *Ther Drug Monit.* 2014;36:353-357

Filler G, et al. *Transplant Proc.* 2004;36:1627-1331

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mTOR Inhibitors in Children

- Mammalian Target of Rapamycin Inhibitors
 - Sirolimus
 - Varied dosing reported
 - \pm Loading dose of 2-3mg/m²
 - Maintenance dose of 0.5-1 mg/m²/DAY in 1-2 divided doses
 - Hydroxylated metabolites result in dramatic half life differences
 - ~7 hours in preschool age children vs. 72 hours in adults
 - Diversity of metabolites
 - <10% of metabolites are 39-desmethyl sirolimus
 - » Possesses immunosuppressant action
 - » Cross reacts with assay used for therapeutic drug monitoring

Filler G, et al. *Pediatr Transplant*. 2009;13:44-53.

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Question 2: Assuming adherence, which of the following transplant recipients could you most likely expect to use higher than average tacrolimus dose/frequency to achieve goal trough levels?

- A. 14 year-old Caucasian female with primary glomerulonephritis s/p kidney transplant
- B. 11 month-old African-American male with dilated cardiomyopathy s/p heart transplant
- C. 13 month-old Hispanic female with biliary atresia s/p liver transplant
- D. 15 year-old Caucasian male with CF, s/p bilateral lung transplant on voriconazole for invasive aspergillus prophylaxis

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Pediatric Kidney Transplants

- 819 kidney transplants in recipients <18 years performed in 2021
- 93.6% 3-year graft survival from 2016-2017 deceased donor recipients
 - Most common indications
 - Congenital anomalies of the kidney and urinary tract (37.6%)
 - Posterior urethral valves or vesicoureteral reflux
 - Glomerulonephritis (5.6%)
 - Focal segmental glomerulosclerosis (8.4%)
- Extremely rare to transplant <1 year age
 - 45.1% are 1-10 years of age

United Network for Organ Sharing (UNOS). *Transplant Trends*. Accessed February 2022.

Lentine KL, et al. *Am J Transplant* 2022;22(suppl 2):21-136.

Hyun Cho M, et al. *Korean J Pediatr*. 2018;61(7):205-209.

Hussein AA, et al. *J Pediatr Urol*. 2018;14(2):166.e1-166.e7.

Ariza-Heredia EJ. *Ann Transplant*. 2013;18:195-204.

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Complications of Pediatric Kidney Allografts

- In patients <30 kg, allografts often placed intraperitoneally
 - Gastroenterological complications
 - Ascites
 - Gastroparesis and ileus
 - Parenteral nutrition and medications
 - Vesicoureteral reflux
 - Renal scarring and graft failure
 - Bladder training vs. surgical management
 - Urinary tract infection prophylaxis
 - Low grade VUR without recurrent UTI + risk factor
 - » Obstructive uropathy, pyelonephritis history, posterior urethral valves, age < 5 years
 - Low/high grade VUR with recurrent UTI

Taher A, et al. *Transplantation*. 2019;103(6):1234-1239.

Feygina VM, et al. *Pediatr Nephrol*. 2018;33(4):607-609.

Wu HS, et al. *Pediatr Transplant*. 2019;22(8):e13299

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Immunosuppressant Strategies in Pediatrics

- Adverse effect concerns due to chronic use of corticosteroids
 - Prior to transplant, 29% children with late stage chronic kidney disease have high bone turnover and 86% of mineralization abnormalities
 - Bone deformities, fractures, reduced growth, chronic pain
 - Utilization of steroid minimization protocols
 - Similar acute rejection, graft/patient survival, graft function
 - Growth benefits in prepubertal children
 - Potentially improves treatment for hypertension, diabetes, and dyslipidemia

Hahn D, et al. *Cochrane Database Syst Rev*. 2015;(11):CD008327.

Grenda R, et al. *Am J Transplant*. 2010;10(4):828-836.

Zhang H, et al. *PLoS One*. 2016;11(3):e0146523

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Corticosteroid Withdrawal/Avoidance in Pediatric Kidney Transplant

- Corticosteroid minimization with early withdrawal has been successful in pediatric renal transplant recipients
 - Low immunological risk
 - Anti-CD25 antibody or polyclonal antibodies therapy
- Future directions
 - Unknown efficacy in high immunological risk
 - Potential risk for recurrent glomerulonephritis
 - Focal segmental glomerulosclerosis recurrence 15-64%
 - High risk of graft loss
 - Relatively ineffective preemptive options

Kukla A, et al. *Transplantation*. 2011;91:1386–1391.

Koh LJ, et al. *Pediatr Transplant*. 2019;23(5):e13469.

Wang CS, et al. *Am J Kidney Dis*. 2018;71(3):392-398.

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Pediatric Liver Transplants

- 501 liver transplants in recipients <18 years performed in 2021
 - Most common indications
 - Biliary atresia and other cholestatic conditions (45.5%)
 - Metabolic conditions (16.3%)
 - α_1 -Antitrypsin deficiency, urea cycle disorders
 - Acute liver failure (10.1%)
 - Hepatoblastoma (7.3%)
 - Most patients are <6 years (64.8%)

United Network for Organ Sharing (UNOS). *Transplant Trends*. Accessed February 2022.

Oishi K, et al. *Pediatr Transplant*. 2016;20:756-769.

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Complications of Pediatric Liver Allografts

- Hepatic artery thrombosis (8.3%)
 - Risks include young donor/recipient, partial grafts, grafts procured after circulatory death, & complex vascular reconstructions
 - Post-transplant heparin followed by an antiplatelet agent (e.g. aspirin)
 - Prostaglandins in partial grafts
- Biliary complications (15-40%)
 - Biliary strictures, bile leaks, bilomas, & stones and cast formation
 - Ursodeoxycholic acid utilized to help improve bile flow

Voulgarelis S, et al. *Pediatr Transplant*. 2018;22:e13193.

Heaton N. *Liver Transplantation*. 2013;19:S14-S1.

Feier FH, et al. *World J Hepatol*. 2015;7:2162-70.

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Liver Transplant Immunosuppression

- Immunosuppressant utilization
 - Induction with agents other than corticosteroids rare
 - Varied approaches to maintenance therapy initially
 - CNI (tacrolimus) and corticosteroids (42.2%)
 - Protocols including +antiproliferative (35.3%)
 - Goal to be on CNI monotherapy at ~1 year post-transplant
- Potential for operational tolerance (experimental)
 - Candidates for controlled immunosuppressant withdrawal
 - Elective:
 - ≥4 years post transplant
 - Normal liver function
 - No recent acute rejection in last 2 years

Horst A, et al. *Cellular & Molecular Immunology*. 2016;13:277-92.

Koshiba T, et al. *Transplant Immunology*. 2007;17:94-97.

Feng S, et al. *Hepatology*. 2020;73(5):1985-2004

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Pediatric Heart Transplants

- 454 heart transplants in recipients <18 years performed in 2021
 - Most common indications
 - Dilated Cardiomyopathy (37-53%)
 - Congenital Heart Disease (23-42%)
 - Septal, obstructive, and cyanotic defects
 - Careful and complicated surgical techniques may prolong overall ischemic time

United Network for Organ Sharing (UNOS). *Transplant Trends*. Accessed February 2021.

Singh TP, et al. *J Heart Lung Transplant* 2020;39(10):1028-37.

Rossano JW, et al. *J Heart Lung Transplant*. 2017;36:1060-9.

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Pediatric Heart Transplant Immunosuppression

- Immunosuppression
 - Induction
 - Varied induction practices across institutions
 - Large observational studies have favored R-ATG vs. Anti-CD25
 - Maintenance
 - CNI + Antiproliferative +/- corticosteroid that is tapered off

Butts RJ, et al. *Transplantation*. 2017;101(6):1228-33

Carlo WF, et al. *Pediatr Transplant*. 2019;23:e13366

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Complications of Pediatric Heart Allografts

- Increased pulmonary vascular resistance
 - Right ventricular dysfunction
 - Treatment with pulmonary vasodilators: most frequently are phosphodiesterase-5 inhibitors
- Tachyarrhythmias
 - Only 12% of patients with tachyarrhythmias have rejection
 - Supraventricular tachycardia and ventricular arrhythmias
 - β -receptor antagonists are often first line (propranolol, metoprolol, or atenolol)

Lapage MJ, et al. *J Heart Lung Transplant*. 2010;29(3):273-277.

Brugada J, et al. *Europace*. 2013;15(9):1337-1382.

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Pediatric Lung Transplants

- 32 lung transplants in recipients <18 years performed in 2021 with a median graft survival of 5.7 years (double lung)
 - Most common indications
 - Cystic fibrosis: 51-66.3% in children 6-17 years
 - Pulmonary hypertension: 10.7% overall; up to 50.4% in children 1-5 years
 - Surfactant deficiency: 20.6% in infants < 1 year

United Network for Organ Sharing (UNOS). *Transplant Trends*. Accessed February 2020.

Hayes DJ, et al. *J Heart Lung Transplant* 2020;39(10):1038-49.

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CF Implications in Pediatric Lung Allografts

- Cystic fibrosis
 - Infectious complications account for 34% of deaths in year 1
 - Targeted and sometimes combination antimicrobial prophylaxis for the first 7-10 days following transplant
 - *Pseudomonas* spp., *Staphylococcus Aureus*, etc.
 - Medication pharmacokinetics
 - Mycophenolic Acid AUC significantly reduced compared to non-CF patients
 - Pancreatic insufficiency, fat malabsorption, and GERD reduces overall exposure to azole antifungal (posaconazole, itraconazole)
 - Voriconazole is most frequently used

Stuckey L, et al. *Ther Drug Monit.* 2014;36(2):148-151.

Zhang H, et al. *Antimicrob Agents Chemother.* 2016;60(6):3558-3562.

Husain S, et al. *Clin Transplant.* 2019;33(9):e13544.

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Question 3: Which of the following patients may *not* benefit from steroid minimization protocol with IL-2RA induction and tacrolimus and mycophenolate maintenance regimen?

- A. 9 year-old female with VACTERL with a history of cloacal anomaly with appendicovesicostomy with low class I & class II PRAs
- B. 10 year-old male with posterior urethral valves and hydronephrosis with low class I & class II PRAs
- C. 17 year-old female with primary glomerulonephritis with elevated class I & class II PRAs
- D. 6-year old female with congenital nephrotic syndrome with low class I & class II PRAs

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- B. 10 year-old male with posterior urethral valves and hydronephrosis with low class I & class II PRAs
- C. 17 year-old female with primary glomerulonephritis with elevated class I & class II PRAs
- D. 6-year old female with congenital nephrotic syndrome with low class I & class II PRAs

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Intentional Blood Group Incompatible Transplants

- Access to transplantation for children is limited by the shortage of donor organs
 - Waitlist mortality for pediatric heart, liver, and lung transplant candidates is high
 - ABO-incompatible transplant may broaden the deceased & living donor pool and result in timelier transplant

Leung DH, et al. *Liver Transpl.* 2016;22(11):1584-1592.
 Kwong A, et al. *Am J Transplant.* 2020;20(Suppl s1):193-299.
 Hsu EK, et al. *Gastroenterology.* 2017;153(4):988-995.
 Raut V, et al. *Surg Today.* 2011;41(3):317-322.
 Rana A, et al. *J Am Coll Surg.* 2016;222(4):681-689.

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Pediatric ABO-Incompatible Transplant Mechanisms

- Isohemagglutinin titers are preformed IgM antibodies reacting to blood group antigens on vascular endothelium
 - Lead to antibody mediated rejection via complement activation, inflammation, and necrosis
- Immature immune system of neonate and infants
 - Reduced or absent response towards polysaccharides including blood group antigens up to 24 months of age
 - Confirmation of reduced non-self blood group antibodies early in life
 - Following ABO-I, long term follow up has shown that antibodies toward donor blood group remained absent or low, suggesting accommodation

Dipchand AI, et al. *Am J Transplant.* 2011;10:389–397.
 Rana A, et al. *J Am Coll Surg.* 2016;222(4):681-689.

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Pediatric Waitlist Allocation for ABO-Incompatible

- Isohemagglutinin titers
 - Liver
 - No isohemagglutinin titer maximum
 - Heart (status 1A or 1B) and Lung (priority 1)
 - <1 year: No isohemagglutinin titer maximum
 - ≥1 year & listed before age 2 years: Maximum IH ≤ 1:16

Donor Blood Type	Recipient Blood Type	Isohemagglutinin Reporting
A	B or O	Anti-A
B	A or O	Anti-B
AB	A	Anti-B
AB	B	Anti-A
AB	O	Anti-A and Anti-B

United Network for Organ Sharing Policies 6, 9, &10—Allocation of Hearts and Heart-Lungs, Livers and Liver-Intestines, Lungs. Available at: https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf

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Immunosuppressive Strategies for ABO-I Transplant

- Heart (IH \leq 1:16 to donor blood type)
 - Intraoperative plasma exchange
 - Induction with rATG or IL-2RA + corticosteroids
 - Maintenance: calcineurin inhibitor + antiproliferative +/- corticosteroid
- Liver
 - IH \leq 1:16 to donor blood type: CNi + corticosteroids
 - IH \geq 1:32 to donor blood type:
 - Plasmapheresis 6X initiated intraoperatively
 - Rituximab 375mg/m²
 - IVIG 1g/kg
 - Maintenance: CNi + antiproliferative + corticosteroid

West LJ, et al. *N Engl J Med.* 2001;344-793-800

Heffron T, et al. *Liver Transpl.* 2006;12(6):972-978

Mysore KR, et al. *Pediatr Transplant.* 2018;22(7):e13263

Irving CA, et al. *J Heart Lung Transplant.* 2015;34(8):1095-102

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Post-transplant ABO Antigen Monitoring

- Post-transplant measurement of isohemagglutinin titers
 - POD0-2: twice daily
 - POD3-13: daily
 - POD14-3 months: weekly
 - 3-6 months: every 2 weeks
 - Annually or sooner if rejection suspected
- If titers increased or AMR develops
 - Augmentation of immunosuppression with mechanical antibody removal and/or anti B-cell therapy

Irving CA, et al. *J Heart Lung Transplant.* 2015;34(8):1095-1102.

West LJ, et al. *Curr Drug Targets Cardiovasc Haematol Disord.* 2005;5(3):223-232.

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Question 4: What dilution of isohemagglutinin titer(s) may require a more aggressive immunosuppression and antibody removal strategy in an infant with biliary atresia status 1A liver transplant candidate with O-type blood from an A-donor?

- A. Anti-A 1:16; Anti-B 1:16
- B. Anti-A 1:64; Anti-B 1:8
- C. Anti-A 1:8; Anti-B: 1:16
- D. Anti-A 1:4; Anti-B: 1:64

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- A. Anti-A 1:16; Anti-B 1:16
- B. Anti-A 1:64; Anti-B 1:8
- C. Anti-A 1:8; Anti-B: 1:16
- D. Anti-A 1:4; Anti-B: 1:64

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Infection Prophylaxis in Pediatrics SOT

- Surgical Site Infections
- Donor-derived infections
 - Bacterial
 - Viral
 - Fungus

Suggest Surgical Prophylaxis			
Organ	Primary	Secondary	Comments
Heart	Cefazolin	Vancomycin or Clindamycin ± Gentamicin, Aztreonam, or fluoroquinolone	Optimal duration unknown for open chest
Lung & Heart/Lung	Cefazolin		Consider coverage for organisms isolated from recipient airways
Liver	Piperacillin-Tazobactam	Vancomycin or Clindamycin + Gentamicin, Aztreonam, or fluoroquinolone	
Kidney	Cefazolin		Avoidance of nephrotoxic agents

Razonable RR, et al. *Clin Transplant*. 2019;33(9):e13512

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Infection Prophylaxis in Pediatrics SOT

- Limited information available regarding fungus and endemic molds
 - Risks for fungal infection
 - Liver (~20%)
 - Risks: Surgical complications, prolonged intubation, and significant transfusion
 - Lung (10-20%)
 - Tacrolimus-based regimen, CMV mismatch, age, rejection
 - Heart (~7%)
 - Mechanical support, procedural interventions, and underlying congenital heart disease

Gladdy RA, et al. *Liver Transpl Surg*. 1999;5(1):16–24.
 Zaoutis TE, et al. *Pediatr Transplant*. 2011;15(5):465–469.
 Mead L, et al. *Pediatr Transplant*. 2014;18(4):393–397.

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Infection Prophylaxis in Pediatric SOT

- Primary prevention strategies similar to adults
 - Candida
 - Fluconazole 3-6 mg/kg daily
 - Aspergillus
 - Voriconazole
 - Loading Dose: Oral/IV: 6-9 mg/kg X 2, depending on age
 - Maintenance: 6-8 mg/kg depending on age, weight
 - Pneumocystis Jiroveci
 - Sulfamethoxazole/Trimethoprim preferred
 - 5-10 mg/kg/DAY TMP on 2-3 days per week

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Viral Pathogens in Pediatric SOT

- Respiratory viral infections
 - Influenza
 - Respiratory syncytial virus (RSV)
 - Parainfluenza
 - Adenovirus
- Associated with morbidity and mortality in pediatric solid organ transplant recipients

Manuel O, et al. *Clin Transplant*. 2019;33(9):e13511.

Lo MS, et al. *Pediatr Transpl*. 2013;17(2):133-143.

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Viral Pathogens in Pediatric SOT

- Influenza
 - Inactivated influenza vaccine to all recipients and household contacts
 - Treatment and postexposure prophylaxis with neuraminidase inhibitor
- Respiratory Syncytial Virus (RSV)
 - Prophylaxis with palivizumab may be considered for children
 - 5 monthly 15mg/kg IM doses started at beginning of RSV season when indicated
 - Immunocompromised children <24months
 - Treatment with aerosolized or oral ribavirin
 - Lung transplant recipients with upper or lower respiratory tract infection
 - Non-lung recipients with lower respiratory tract disease
 - Supportive treatment corticosteroid or with IVIG or RSV enriched-IVIG can be considered

Lo MS, et al. *Pediatr Transpl.* 2013;17(2):133-143.

Robinson JL, et al. *Pediatr Transplant.* 2015;19(6):659-662.

American Academy of Pediatrics Committee of Infectious Diseases. *Pediatrics.* 2014;134(2):e620-638.

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Cytomegalovirus (CMV)

- Incidence of CMV infection and disease varies by:
 - Type of organ transplant
 - Serostatus of the donor and recipient
 - Characterize higher risk for CMV IgG positive recipient infants (<12months)
 - Treat D+/R+ as D+/R-
 - Maintain D-/R+ as D-/R+
 - Prevention strategy
 - Universal
 - Preemptive
 - Surveillance after prophylaxis


Selected CMV Risk Subtypes Based on Organ		
Organ Transplanted	D ⁺ /R ⁻ (High Risk)	D ⁻ /R ⁻ (Low Risk)
Kidney	19.2%	2.5%
Liver	31.3%	3.2%
Heart	25%	3.6%
Lung	45%	14.9%

Harvala H et al. *J Med Virol.* 2013;85:893-8.

Mendez-Eirin E et al. *Transplant Proc.* 2012;44:2660-2.


Hammond SP et al. *Transpl Infect Dis.* 2013;15:163-70

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Organ	Serostatus	Risk Level	Treatment Strategy
All (except small bowel)	D-/R-	Low	Monitor for clinical symptoms Consider prophylaxis against HSV infections
Kidney	D+/R-	High	3-6 months of GCV/VGCV
	D+/R+ D-/R+	Intermediate	3-6 months of VGCV <u>OR</u> Preemptive therapy
Liver	D+/R-	High	2-4 wk GCV/VGCV with surveillance after prophylaxis <u>OR</u>
	D+/R+ D-/R+	Intermediate	3-4 months GCV/VGCV <u>OR</u> Preemptive therapy
Heart	D+/R-	High	4 wk GCV/VGCV with surveillance after prophylaxis <u>OR</u> 3 months GCV/VGCV
	D+/R+ D-/R+	Intermediate	2-4 wk GCV/VGCV with surveillance after prophylaxis <u>OR</u> 3 months GCV/VGCV
Lung	D+/R-	High	6-12 months of GCV/VGCV
	D+/R+	High	6-12 months of GCV/VGCV
Small Bowel	D-/R-	Low	Preemptive therapy <u>OR</u> 2 wk with GCV with surveillance after prophylaxis
	D+/R-	High	3-12 months GCV/VGCV
	D+/R+		3-12 months GCV/VGCV <u>OR</u> 2 wk with GCV with surveillance after prophylaxis

Kotton CN et al. *Transplantation*. 2018;102:900-931.

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<h2>Valganciclovir Dosing</h2>	
<ul style="list-style-type: none"> FDA approved for prophylaxis in pediatric heart and kidney <ul style="list-style-type: none"> 7 X BSA X creatinine clearance <ul style="list-style-type: none"> $\text{CrCl (mL/minute/1.73 m}^2\text{)} = [\text{K} \times \text{height (cm)}] / \text{serum creatinine (mg/dL)}$ <ul style="list-style-type: none"> K = 0.33-0.7 based on age, birthweight, sex Maximum calculated CrCl = 150 mL/min/1.73m² Risk of dosing error <ul style="list-style-type: none"> Some centers use lower calculated CrCl maximum to reduce exposure Alternative dosing strategy <ul style="list-style-type: none"> 15-18 mg/kg once daily 	
<p>Kotton CN et al. <i>Transplantation</i>. 2018;102:900-931. Pappo A, et al. <i>Transplantation</i>. 2019;103(8):1730-1735.</p>	

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Vaccine-Preventable Illnesses in Pediatric SOT

- Transplant candidates and recipients are at increased risk from vaccine-preventable diseases
- In a large cohort (n=6980) pediatric solid organ transplant recipients
 - 1092 patients (15.6%) had 1490 cases of vaccine preventable infections within 5 years
 - Risk factors: Age < 2 years; heart, lung, or multivisceral transplantation
 - Most common VPIs:
 - Influenza (40% of cases), rotavirus (19%), varicella (11%), pneumococcus (10%), and RSV (10%)

Feldman AG, et al. *JAMA Pediatr.* 2019;173:260-8.

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Immunization Recommendations and Guidelines

- CDC Advisory Committee on Immunization Practices (ACIP) recommendations for children, adolescents, and adults
 - Selected additional recommendations for
 - Immunocompromised status
 - Kidney failure, ESRD, or hemodialysis; heart disease; chronic lung disease; chronic liver disease
 - Asplenia and complement deficiencies

CDC. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger. Available at CDC.gov
 Danziger-Isakov L, et al. *Clin Transplant.* 2019:e13563.
 Rubin LG, et al. *Clin Infect Dis.* 2014;58:e44-100.

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Timing Vaccinations

- Pretransplantation
 - Prior to planned immunosuppression, if possible
 - Inactivated vaccines:
 - Ideally ≥ 2 weeks before transplant to allow for immune response
 - Live vaccines
 - Administer ≥ 4 weeks before transplant to candidates
 - » Some centers may elect temporarily inactivate the patient from the waitlist
 - Administer on same day or separated 28 days apart
 - Measles, Mumps, Rubella (MMR), Varicella, Rotavirus (select cases)
 - Consider deferring if high waitlist status

Danziger-Isakov L, et al. *Clin Transplant*. 2019:e13563.

Rubin LG, et al. *Clin Infect Dis*. 2014;58:e44-100.

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Timing Vaccinations

- Post transplantation
 - Resume with inactivated vaccines 3-6 months post-transplantation
 - During viral seasons
 - Influenza: As early as 4 weeks post-transplant
 - Overall benefit questioned in those with recent use of T-cell depleting agents, rituximab, or have persistently elevated EBV due to net immunosuppression
 - Live vaccines?
- Family, close contacts, and pets
 - Full immunizations
 - Most routine live vaccines recommended: MMR, varicella to protect against wild-type
 - Annual influenza
 - Consider avoiding live attenuated influenza vaccine (LAIV)

Danziger-Isakov L, et al. *Clin Transplant*. 2019:e13563.

Rubin LG, et al. *Clin Infect Dis*. 2014;58:e44-100.

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Summary of Vaccine Recommendations

Vaccine	CDC Usual 1 st Dose	Comments
Diphtheria, tetanus & acellular pertussis (DTaP)	6 weeks	Routine schedule ^a
Hepatitis A	12 months Minimum: 6 months	Routine or accelerated schedule Consider early administration
Hepatitis B	Birth	Routine or accelerated schedule Potentially revaccinate post-TXP
Haemophilus influenza type b	6 weeks	Routine schedule ^a Combinations with DTaP available
HPV	9 years	3 dose series if not completed before
Influenza	6 months	Live attenuated vaccine not recommended post-SOT
Inactivated Poliovirus	6 weeks	Routine schedule ^a
MCV4	11-12 years Minimum: 2 or 9 months	Routine schedule ^a Consider early in high risk conditions

a: accelerated schedule available

CDC. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger. Available at [CDC.gov](https://www.cdc.gov/vaccines/imz/downloads/pdf/2022-05-16-practicing-pharmacist-vaccine-recommendations.pdf)

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Summary of Vaccine Recommendations

Vaccine	CDC Usual 1 st Dose	Comments
MenB	16-18 years Minimum: 10 years	Administer early in high risk conditions
MMR	12 months Minimum: 6 months	Consider early and accelerated schedule
Pneumococcal conjugate (PCV13)	6 weeks	Routine schedule ^a At least one of PCV13 if previous doses were PCV7
Pneumococcal polysaccharide (PPSV23)	Adults: 19-64 years Minimum: 2 years	Early administration often indicated Revaccinate in 5 years
Rotavirus	6 weeks Maximum: 14w6d	Routine schedule ^a Not recommended post-SOT
Tdap	11-12 years	Routine schedule Consider as early as 7 years
Varicella	12 months Minimum: 6 months	Consider early and accelerated schedule

a: accelerated schedule available

CDC. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger. Available at [CDC.gov](https://www.cdc.gov/vaccines/imz/downloads/pdf/2022-05-16-practicing-pharmacist-vaccine-recommendations.pdf)

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Selected Accelerated Schedule: Pneumococcal

- Pneumococcal Conjugate
 - General Recommendation (4 doses): 2 months, 4 months, 6 months, 12-15 months
 - High risk conditions: chronic heart, liver, kidney, or lung disease
 - Minimum Age: 6 weeks
 - Minimum Intervals
 - » Dose 2: 4 or 8 weeks
 - 8 if dose 1 was after 12 months
 - » Dose 3: 4 or 8 weeks
 - » Dose 3-4: 8 weeks

CDC. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger. Available at CDC.gov

Fox TG, et al. *Pediatr Nephrol.* 2019;34:579-91.

Rubin LG, et al. *Clin Infect Dis.* 2014;58:e44-100

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Pneumococcal Polysaccharide Vaccination

- Pneumococcal Polysaccharide (PPSV23)
 - General recommendations: adults ≥ 65 years or 19-64 years with risk factor or other indication
 - Minimum Age: 2 years in transplant candidates or recipients
 - Give ≥ 8 weeks after PCV13
 - Age ≥ 6 years: must received at least 1 dose of PCV13
 - Age 2-5 years: complete 4 dose PCV13 with at least 8 weeks between doses
 - Post-transplant: Single revaccination 5 years after first PPSV23
 - Monitor vaccine titers

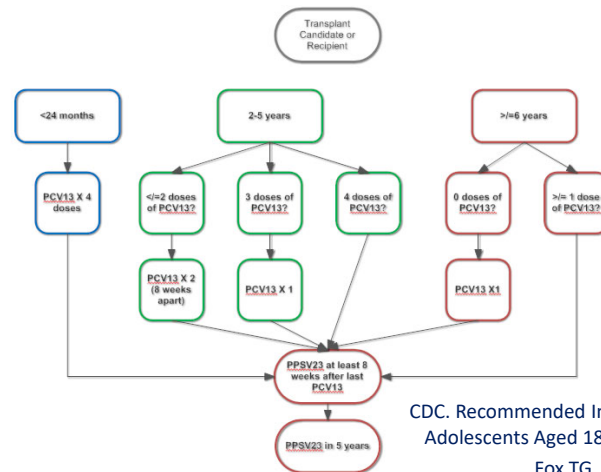
CDC. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger. Available at CDC.gov

Fox TG, et al. *Pediatr Nephrol.* 2019;34:579-91.

Rubin LG, et al. *Clin Infect Dis.* 2014;58:e44-100

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Pneumococcal Vaccination in Pediatric Candidates/Recipients



CDC. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger. Available at CDC.gov

Fox TG, et al. *Pediatr Nephrol.* 2019;34:579-91.

Rubin LG, et al. *Clin Infect Dis.* 2014;58:e44-100

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Meningococcal ACWY Vaccination

- Meningococcal: Serogroups ACWY (MCV4)
 - General recommendation (2 doses): Two dose series: 11-12 years, 16 years
 - High risk conditions: asplenia, HIV, persistent complement component deficiency, or receiving eculizumab
 - Minimum Age: 2 months: MenACWY-CRM (Menveo); 9 months: MenACWY-D (MenQuadfi)
 - Selected Accelerated Schedule
 - » Children age 2 or older: 2 doses at least 8 weeks apart
 - » <24 months

- Menveo: 2 or 4 dose series

- Dose 1 after age 8 weeks: 4 doses at 0, 2, 4, & 10 months
- Dose 1 at age 7-23 months: dose 2 at 8-12 weeks later and after 1st birthday

CDC. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger. Available at CDC.gov

McNamara LA, et al. *MMWR* 2017;66:734-7.

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Meningococcal B Vaccination

- Meningococcal: Serogroup B (MenB)
 - General recommendation: 2 dose series (16-18 years)
 - High risk conditions: asplenia, HIV, persistent complement component deficiency, or receiving eculizumab
 - Minimum age: 10 years
 - Available products not interchangeable
 - » Bexsero: 2 doses 1 month apart
 - » Trumenba: 3 doses series at 0, 1-2, & 6 months

CDC. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger. Available at CDC.gov
 McNamara LA, et al. MMWR 2017;66:734-7.

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COVID-19 Vaccination <18 years

- Recommended for healthy children 5-17 years as of May 2022
 - Pfizer-BioNTech Series
 - 5-11 Years (10 mcg dose)
 - 2 Doses separated by at least 3 weeks; booster 5 months after 2nd dose
 - 12-17 years (30 mcg dose)
 - 2 doses separated by 3-8 weeks; booster 5 months after 2nd dose
 - Adverse effects rare (~1 in 1000) and mostly non-severe
 - Severe adverse effects 2.4-9.3%

CDC. COVID-19 Vaccine. Available at CDC.gov
 Graff K, et al. Pediatr Infect Dis J 2021;40(4):e137-45
 Hause AM, et al. MMWR Morb Mortal Wkly Rep 2021;70(51-52):1755-60.
 Hause AM, et al. MMWR Morb Mortal Wkly Rep 2021;70(31):1053-8.

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COVID-19 Vaccination in Immunocompromised Children and Adolescents

- Recommended for immunocompromised children 5-17 years as of May 2022
 - Pfizer-BioNTech Series
 - 5-11 Years (10 mcg dose)
 - 3 dose primary series:
 - » 3 weeks between dose 1 & 2
 - » 4 weeks between dose 2 & 3
 - 1 booster at least 3 months after 3rd dose
 - 12-17 years (30 mcg dose)
 - 3 dose primary series:
 - » 3 weeks between dose 1 & 2
 - » 4 weeks between dose 2 & 3
 - Booster #1 at least 3 months after 3rd dose
 - 2nd booster 4 months after 4th dose

CDC. COVID-19 Vaccine. Available at CDC.gov

Graff K, et al *Pediatr Infect Dis J* 2021;40(4):e137-45

Hause AM, et al. *MMWR Morb Mortal Wkly Rep* 2021;70(51-52):1755-60.

Hause AM, et al. *MMWR Morb Mortal Wkly Rep* 2021;70(31):1053-8.

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Live Vaccinations

- Measles, mumps, rubella
 - General recommendation: 2 dose series (12-15 months, 4-6 years)
 - Minimum age is 6 months
 - Dose 2 can be given as soon as 4 weeks after dose 1
 - Evaluate for serologic response
- Varicella
 - General recommendation: 2 dose series (12-15 months, 4-6 years)
 - Minimum age is 9 months
 - Dose 2 can be given as soon as 4 weeks, 12 weeks is recommended by CDC
 - Evaluate for serologic response

CDC. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger. Available at CDC.gov

Danziger-Isakov L, et al. *Clin Transplant*. 2019:e13563.

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Question 5: A 22-month old male with dilated cardiomyopathy and heart failure is implanted with a Berlin EXCOR VAD and listed status 1A for heart transplant. Which immunizations do you recommend now based on his current immunization record and to avoid any unnecessary inactive periods due to the high stroke risk of the device?

Current Immunizations

- DTaP-IPV/HiB: 7/3/2018, 9/11/2018, 11/6/2018
- DTaP: 5/8/2019
- HepA: 5/8/2019, 11/22/2019
- HepB: 5/2/2018, 7/3/2018, 11/6/2018
- Influenza: 11/6/2018, 12/28/2018, 9/19/2019
- MCV4: 2/17/2020
- MMR: 5/8/2019
- PCV13: 7/3/2018, 9/11/2018, 11/6/2018
- RV5: 7/3/2018, 9/11/2018, 11/6/2018
- Varicella: 5/8/2019

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Question 5: Answer Options

- A. 4th dose PCV13
- B. 1st dose PPSV23
- C. 2nd dose MMR
- D. 1st dose of Meningococcal B

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Question 5: Correct Answer

- A. 4th dose PCV13
- B. 1st dose PPSV23
- C. 2nd dose MMR
- D. 1st dose of Meningococcal B

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Key Takeaways

- Immunosuppressants in children have distinct pharmacokinetics, therefore drug monitoring should be performed to determine appropriate dosing regimen
- The consequences of organ failure and the associated etiology result in a different variety of post-transplant complications and immunosuppressant strategies
- Immunizations provide the core foundation of infectious disease prophylaxis pediatric SOT recipients

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Special Considerations in Pediatric Transplant Populations

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Special Considerations in Geriatric Transplant Populations

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University of Maryland Medical Center
Baltimore, Maryland



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Disclosures

- I have no relevant financial relationships or commercial interests to disclose for this presentation.



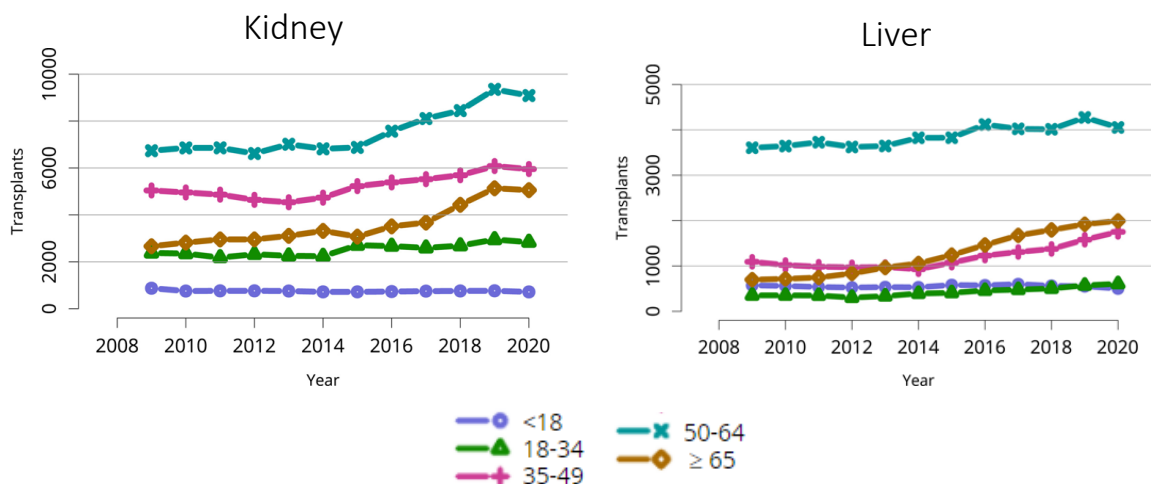
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Learning Objectives

1. Compare outcomes of transplant recipients by age group.
2. Evaluate geriatric candidates for transplant based on guideline recommendations.
3. Distinguish pharmacokinetic differences among geriatric transplant recipients.
4. Design an immunosuppression regimen for a geriatric transplant recipient.

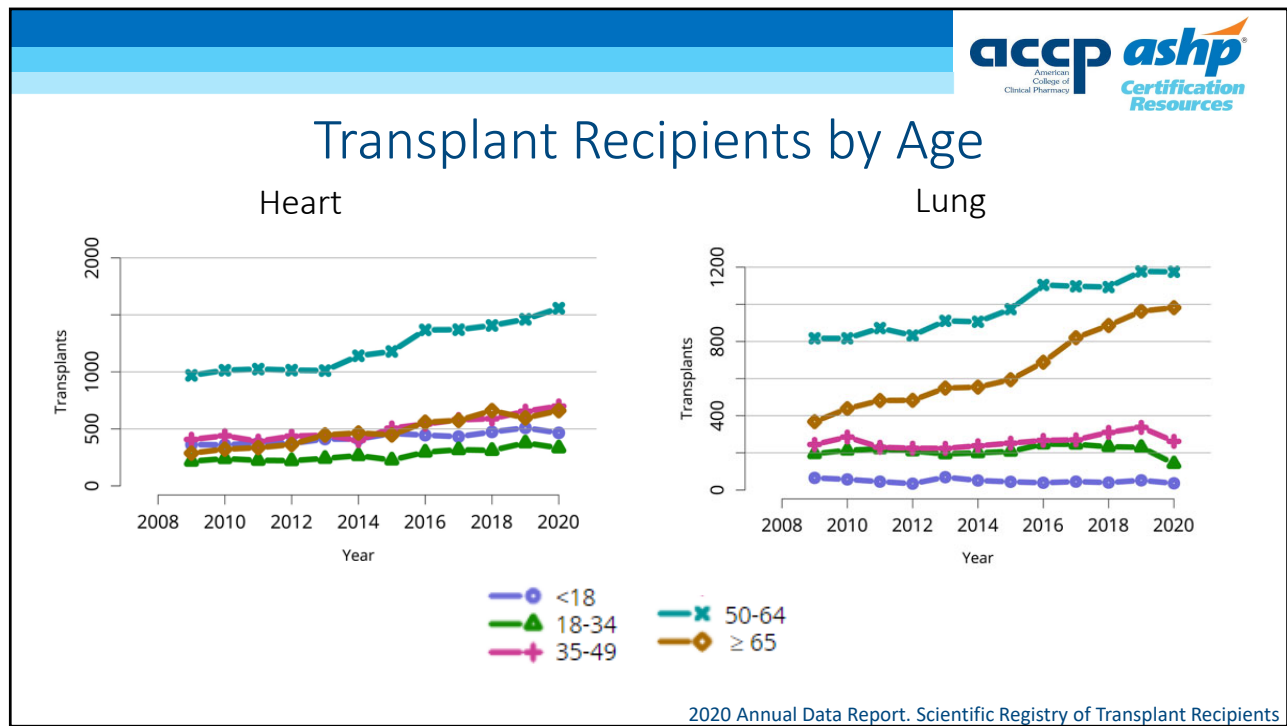
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Transplant Recipients by Age

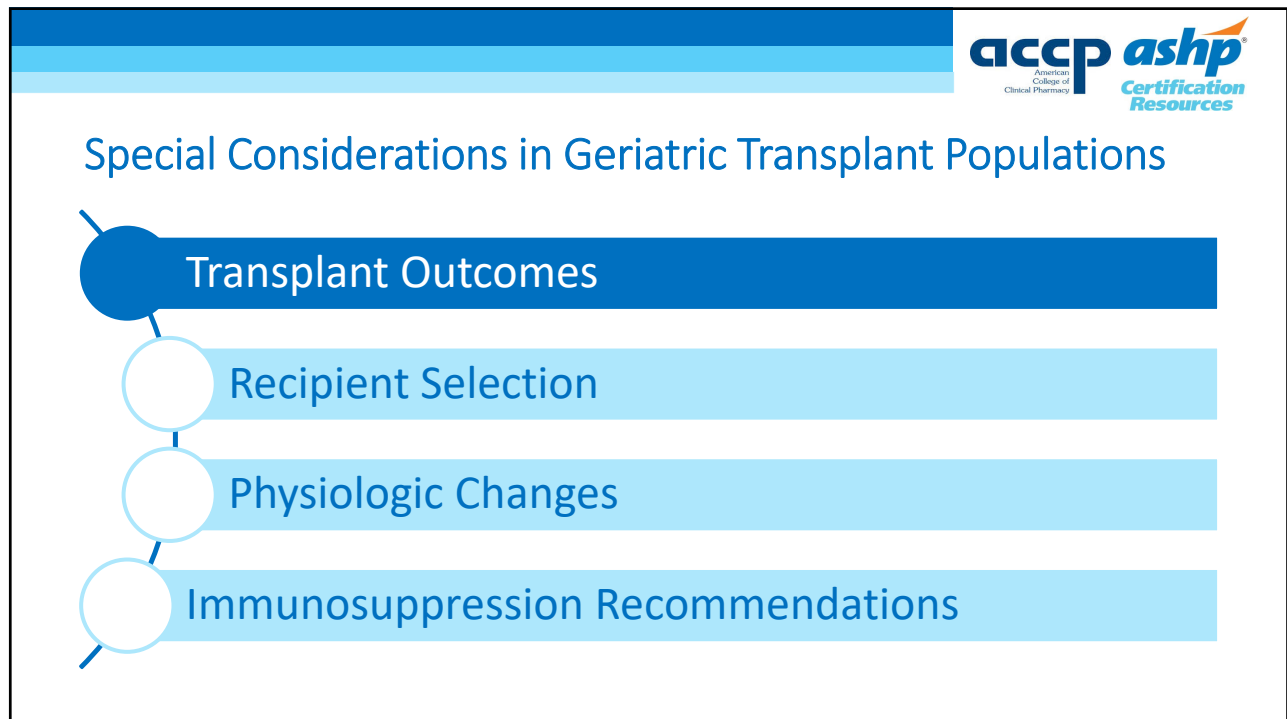


2020 Annual Data Report. Scientific Registry of Transplant Recipients

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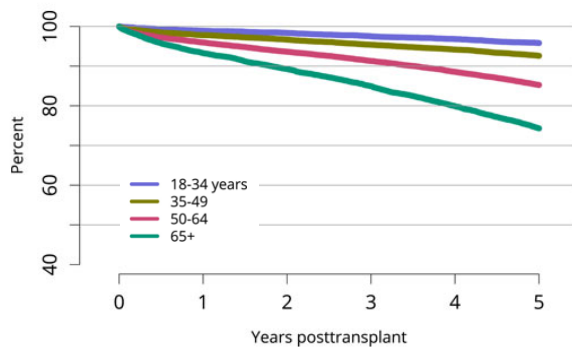
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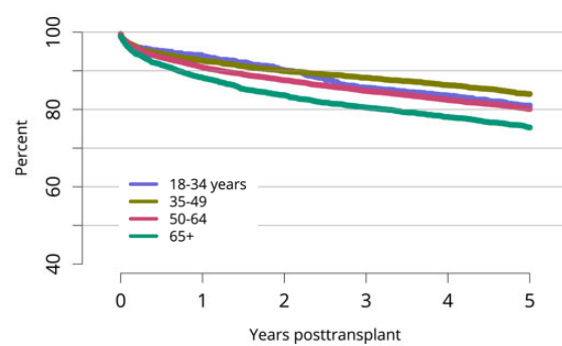
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Patient Survival

Patient survival among deceased donor kidney recipients (2013-2015)



Patient survival among deceased donor liver recipients (2011-2013)



2020 Annual Data Report. Scientific Registry of Transplant Recipients

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Survival Benefit of Kidney Transplant

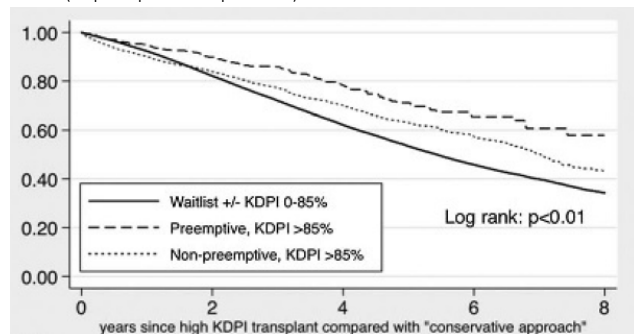
Mortality for kidney transplant recipients versus waitlisted dialysis patients

Time since transplant	Day 45	Day 125	Day 183	1 year	>1.5 years
Mortality Relative Risk	2.26*	0	0.73	0.49*	0.44*

Cumulative survival	Transplant recipients	Dialysis patients
4 years*	66%	51%

*Statistically significant

Patient survival for preemptive and non-preemptive KDPI >85% kidney transplant
(Graphic reprinted with permission)



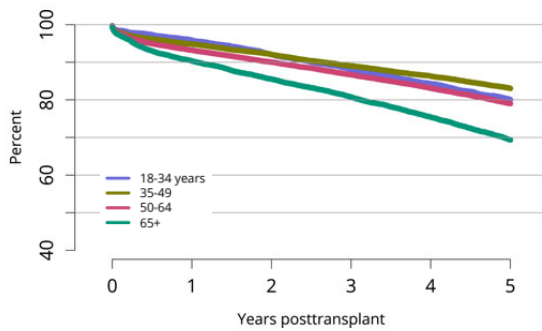
Transplantation 2007;83:1069-74.

Transplantation 2017;101:867-72.

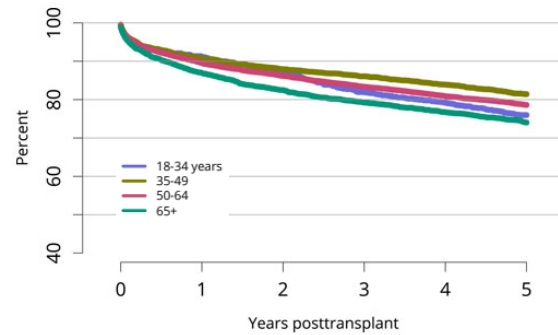
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Graft Survival

Graft survival among deceased donor
kidney recipients (2013-2015)



Graft survival among deceased donor
liver recipients (2013-2015)



2020 Annual Data Report. Scientific Registry of Transplant Recipients

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Outcomes

Kidney Int 2001;59:1539–43., JAMA 2011;306:1891–1901., Am J Transplant 2001;1:3–95.,
Transplantation 2005;80:989–92, 2019 Annual Data Report. Scientific Registry of Transplant Recipients

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Question 1: Patient JD is a 68 yom with a PMH of ESRD due to HTN and T2DM, which of the following is true?

- A. His best option to maximize life expectancy is to remain on dialysis
- B. A kidney transplant even with a high KDPI donor will improve his survival
- C. He is at decreased risk of infection and malignancy after transplant
- D. He is at increased risk of rejection and will require higher levels of immunosuppression post-transplant

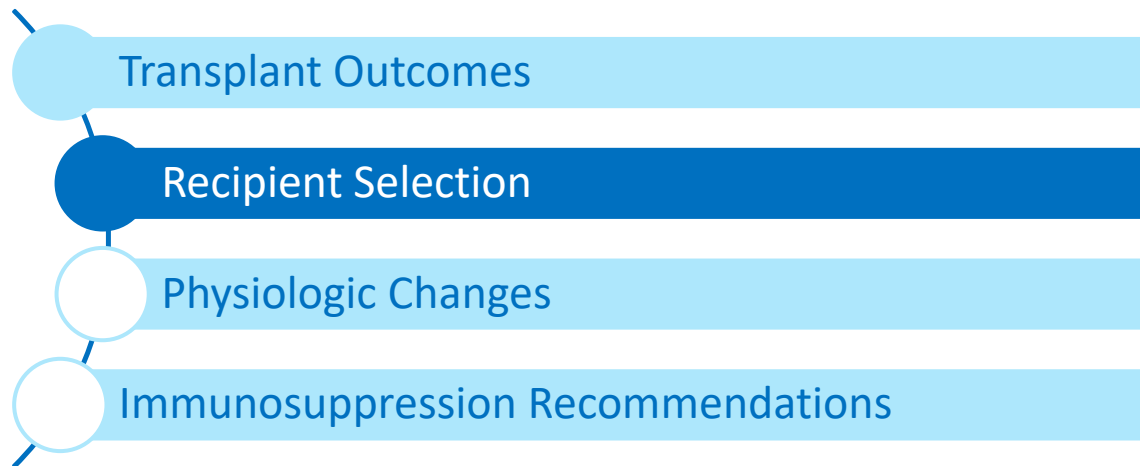
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Special Considerations in Geriatric Transplant Populations



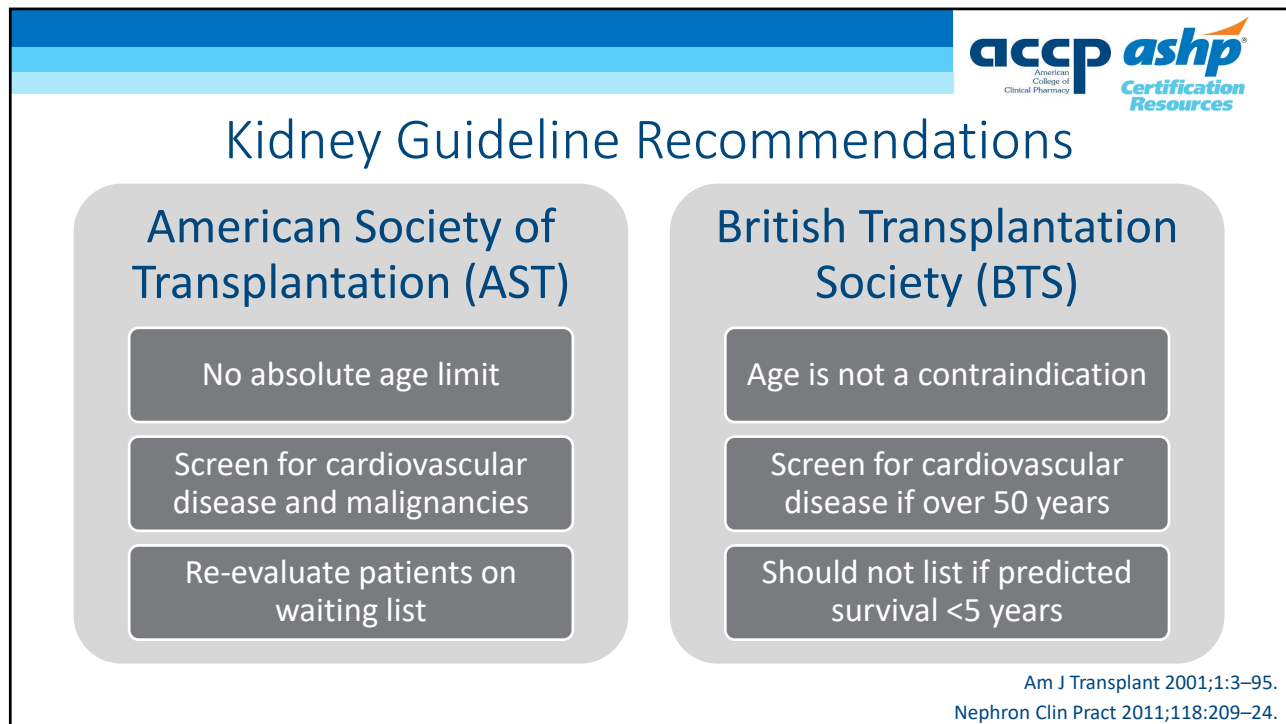
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Evaluation Based on Age

- Age alone should not prevent listing for transplant
- Patients with short life expectancy should not be listed
- Consider objective assessments of fitness:
 - Lean trunk muscle size
 - Six minute walk test
 - Frailty assessment

Am J Transplant 2012;12:2608–22.

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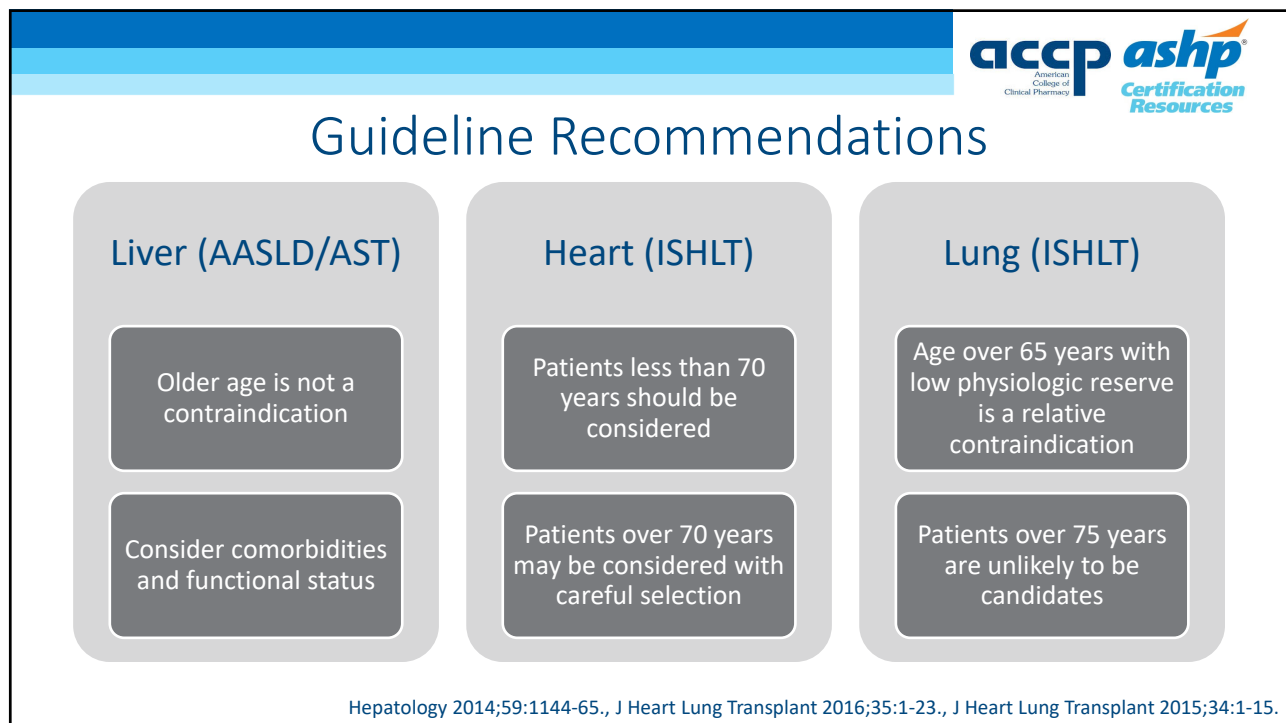
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Kidney Guideline Recommendations

American Society of Transplantation (AST)	British Transplantation Society (BTS)
No absolute age limit	Age is not a contraindication
Screen for cardiovascular disease and malignancies	Screen for cardiovascular disease if over 50 years
Re-evaluate patients on waiting list	Should not list if predicted survival <5 years

Am J Transplant 2001;1:3-95.
Nephron Clin Pract 2011;118:209-24.

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Guideline Recommendations

Liver (AASLD/AST)	Heart (ISHLT)	Lung (ISHLT)
Older age is not a contraindication	Patients less than 70 years should be considered	Age over 65 years with low physiologic reserve is a relative contraindication
Consider comorbidities and functional status	Patients over 70 years may be considered with careful selection	Patients over 75 years are unlikely to be candidates

Hepatology 2014;59:1144-65., J Heart Lung Transplant 2016;35:1-23., J Heart Lung Transplant 2015;34:1-15.

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Pre-Transplant Screenings

- Cardiovascular Disease
 - AHA/ACCF recommends a non-invasive stress test for:
 - Patients over 60 years with no active cardiac conditions and at least 2 risk factors for coronary artery disease
- Malignancy
 - Colonoscopy -> patients over 50 years
 - Mammogram -> female patients over 40 years
 - Prostate-specific antigen -> male patients over 50 years

J Am Coll Cardiol. 2012;60:434–80.

Am J Transplant 2001;1:3–95

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Question 2: Patient JD is a 68 yom with a PMH of ESRD due to HTN and T2DM, his stress test is negative and he has no family history of malignancy, is he an appropriate candidate for kidney transplant?

- A. Yes, his stress test is negative and he should be listed
- B. No, he is at high risk for cardiovascular disease given HTN and T2DM
- C. No, he is older than the recommended age of less than 65 years
- D. Yes, he may be pending colonoscopy and prostate specific antigen testing

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Question 2: Patient JD is a 68 yom with a PMH of ESRD due to HTN and T2DM, his stress test is negative and he has no family history of malignancy, is he an appropriate candidate for kidney transplant?

- A. Yes, his stress test is negative and he should be listed
- B. No, he is at high risk for cardiovascular disease given HTN and T2DM
- C. No, he is older than the recommended age of less than 65 years
- D. Yes, he may be pending colonoscopy and prostate specific antigen testing

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Special Considerations in Geriatric Transplant Populations

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Immune System Changes

Am J Transplant 2012;12:2608–22.
J Clin Invest 2017;127:2523–9.

97

Frailty

- Loss of physiologic reserve and increased vulnerability to stressors
 - Poor caloric intake, low physical activity, muscle depletion
- Difficult to assess
 - No single definition or criteria
 - Overlaps with aging, comorbidities, and organ failure
- Multiple assessment tools
 - Fried Frailty Phenotype
 - Liver Frailty Index

Am J Transplant 2019;19:984–94

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2019 AST Report on Frailty in SOT

- Frailty is common pre and post transplant
- Associated with worse outcomes
 - Increased mortality among all organ groups
 - Increased risk delayed graft function, readmission, immunosuppression intolerance, and mortality for kidney recipients
- No consensus on how to best address frailty
 - Should be evaluated during listing for transplant

Am J Transplant 2019;19:984-94

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Pharmacokinetic Changes with Aging

Merck Manuals Professional Edition: Pharmacokinetics in older adults.

100

Tacrolimus Pharmacokinetics

Time post transplant	Dose (mcg/kg/day)			Adjusted AUC (ng*hr*kg/mL/mg)		
	Elderly	Controls	P-value	Elderly	Controls	P-value
Day 7	79 ± 27	119 ± 35	<0.01	2286 ± 1372	1369 ± 582	0.001
Day 30	67 ± 38	105 ± 51	<0.001	2513 ± 1626	2167 ± 1852	NS
Day 60	53 ± 31	95 ± 51	<0.001	3172 ± 1869	2041 ± 1124	0.019
Day 180	33 ± 15	64 ± 43	<0.001	3186 ± 2333	1673 ± 1041	0.033
Overall	64 ± 34	101 ± 48	0.000	2652 ± 1730	1793 ± 1253	0.000

Older patients have decreased tacrolimus dose requirements

Transplantation 2017;101:1365–72.

101

Mycophenolate Pharmacokinetics

- Prospective study of 26 elderly kidney recipients
 - Average age 44 years vs 66 years
 - Received mycophenolate mofetil 1000 mg PO BID
- Results:
 - No difference in mycophenolic acid AUC
 - No difference in IMPDH activity

Age does not significantly affect mycophenolate exposure

Br J Clin Pharmacol 2017;83:812–22.

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Question 3: Which of the following is true about geriatric transplant recipients?

- A. Tacrolimus absorption is decreased
- B. Mycophenolate metabolism is increased
- C. Tacrolimus clearance is decreased
- D. Mycophenolate exposure is increased

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Question 3: Which of the following is true about geriatric transplant recipients?

- A. Tacrolimus absorption is decreased
- B. Mycophenolate metabolism is increased
- C. Tacrolimus clearance is decreased
- D. Mycophenolate exposure is increased

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Special Considerations in Geriatric Transplant Populations

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AST Workshop Statement

- Immunosuppression protocols must account for age
 - Pharmacokinetic and pharmacodynamics changes
 - High risk of adverse drug events
- May be a role for calcineurin inhibitor avoidance and mycophenolic acid withdrawal
- Unknown if steroid avoidance provides benefit

Am J Transplant 2012;12:2608–22.

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Induction Immunosuppression

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Choice of induction agent

- Retrospective cohort study
 - 14,907 kidney recipients ≥ 65 years
 - 6.7% received alemtuzumab
- Factors that increased risk of graft loss:
 - Older age, male sex, diabetes
 - Delayed graft function, expanded criteria donor, deceased donor
 - Use of Alemtuzumab

Alemtuzumab increased risk of graft loss and death

Age group	Adjusted Hazards Ratio (95% CI)	P-value
Alemtuzumab		
> 60 years	1.16 (1.03-1.31)	0.014
≥ 65 years	1.26 (1.08-1.48)	0.004
≥ 70 years	1.42 (1.13-1.81)	0.003
≥ 75 years	1.68 (1.07-2.63)	0.024
Thymoglobulin		
≥ 65 years	1.03 (0.94-1.13)	0.520

Am J Nephrol 2011;34:534–541

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Choice of induction agent

- Retrospective study of OPTN/UNOS data
 - 14,820 deceased donor kidney recipients ≥ 60 years
 - High risk recipient: PRA $>20\%$, prior transplant, black race
 - High risk donor: ECD, DCD, CIT >24 hours
- Less acute rejection with rATG (7.3%, 10.5%, 11.4%)
- Better graft and patient survival with rATG for high risk donors
- No difference in graft or patient survival between rATG and IL2RA for low risk donors

rATG is preferred for elderly recipients of high risk donors

Clin J Am Soc Nephrol 2011; 6: 1168–1178.

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Safety and Efficacy of rATG

- Single center retrospective study
 - 413 deceased donor kidney recipients who received rATG
 - Compared outcomes in recipients ≥ 65 years to those < 65 years
- Recipients ≥ 65 years:
 - Received less rATG (5.4 vs 5.6 mg/kg, $p=0.04$)
 - Lower 3 year patient survival ($p=0.002$)
- No difference in graft survival, graft function, or acute rejection

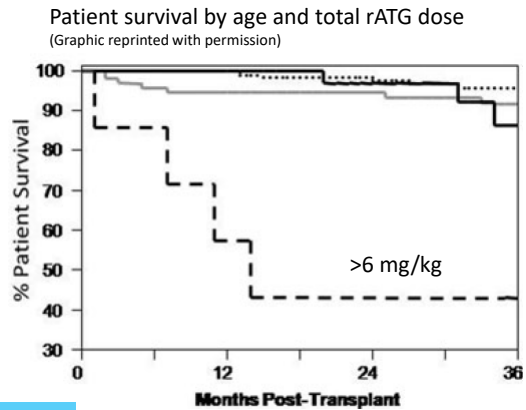
rATG 5-6 mg/kg is safe and effective for elderly patients compared to younger patients

Exp Clin Transplant 2013;11:222–8.

110

Impact of rATG dosing

- Retrospective review of 301 DDRT recipients
 - Compared outcomes by age and total rATG dose
- Recipients > 60 years:
 - Received less rATG (4.6 vs 5.1 mg/kg, $p < 0.01$)
 - Had less acute rejection (2% vs 16%, $p < 0.01$)
 - Lower patient survival (80% vs 95%, $p = 0.01$)
 - For patients who got >6 mg/kg rATG, 2 year survival was <50% ($p < 0.001$)



Lower doses of rATG may be preferred for elderly kidney recipients

Clin Transplant 2011;25:250-6.

111


Efficacy of Low Dose rATG

- Retrospective study of kidney recipients 2001-2009
 - Compared outcomes between recipients > 65 years to those <65 years
 - All patients received low dose rATG (2.96 and 3.2 mg/kg)
- No difference in graft or patient survival
 - 5 year patient survival: 82% vs 89%, $p = 0.4$
 - 5 year death censored graft survival: 88% vs 87%, $p = 0.9$
- No episodes of acute rejection in elderly group

Lower doses of rATG are effective for elderly kidney recipients


Transplant Proc 2011;43:466-8.

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Induction Immunosuppression

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Maintenance Immunosuppression

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CNI Avoidance

Transpl Int 2008;21:637–45.

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CNI Avoidance

Transplant Proc 2009;41:2529–32.

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Delayed CNI Introduction – SENIOR Study

	Delayed Tacrolimus Group (n=132)	Standard Tacrolimus Group (n=122)
Immunosuppression	Basiliximab Tacrolimus (started day 7) Mycophenolate mofetil Steroids (stopped by day 8)	Tacrolimus (started day 0) Mycophenolate mofetil Steroids (stopped by day 90)
CrCl at 6 months	45.7 ± 16.1 mL/min	45.0 ± 18.2 mL/min
BPAR, n (%)	25 (18.9%)	22 (18.0%)
Patient survival, %	96.1	99.2
Graft survival, %	90.0	87.6

Delayed CNI introduction did not improve renal function at 6 months

Transplantation 2009;88:1101-8

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CNI Minimization

Trial	Design	Outcomes
Everold (Transplant International. 2015; 28(Suppl 1):8.)	<ul style="list-style-type: none"> Randomized multicenter trial 307 renal recipients > 60 years Interventions: <ul style="list-style-type: none"> IL2RA/CsA/MMF IL2RA/EVL/MMF ATG/de novo EVL/MMF 	<ul style="list-style-type: none"> No difference in 1 year patient survival, BPAR, or GFR Significantly less DGF in IL2RA/EVL/MMF group Higher rate of discontinuation due to adverse effects in EVL groups
nEverOld Study (Am J Transplant. 2019; 19 (suppl 3))	<ul style="list-style-type: none"> 5-year prospective randomized, single-center, parallel group trial 100 renal recipients ≥ 60 years Interventions: <ul style="list-style-type: none"> EVL/low-TAC MPS/TAC 	<ul style="list-style-type: none"> No difference in composite of graft loss, death, and GFR <50 mL/min Differences in adverse events

Transplant International. 2015; 28(Suppl 1):8

Am J Transplant. 2019; 19 (suppl 3).

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CNI Minimization

Trial	Design	Outcomes
(Exp Clin Transplant 2018;3:301-6)	<ul style="list-style-type: none"> Prospective, randomized single center trial 44 renal recipients > 65 years Interventions: <ul style="list-style-type: none"> TAC/SRL TAC/MMF 	<ul style="list-style-type: none"> No difference in GFR, BPAR, patient survival, or DGF Higher incidence of CMV in MMF group Higher total cholesterol in SRL group
SENATOR (PLoS One. 2019; 14(9): e0222730.)	<ul style="list-style-type: none"> Prospective, randomized, multicenter study 75 renal recipients > 65 years Interventions: <ul style="list-style-type: none"> CsA/MPA MPA/EVL/basiliximab 	<ul style="list-style-type: none"> No difference in GFR Higher rate of discontinuation due to adverse effects in EVL group

Exp Clin Transplant 2018;3:301-6.

PLoS One. 2019; 14(9): e0222730.

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Reduced Immunosuppression

	Control Tacrolimus Group (n=101)	Reduced Tacrolimus Group (n=88)
Immunosuppression	Tacrolimus (goal 10-12 ng/mL) Mycophenolate mofetil 2 g/day Steroid taper	Tacrolimus (goal 8-10 ng/mL) Mycophenolate mofetil 1 g/day Steroid taper
Graft survival, %	74 (73.3%)	80 (90.9%)
Patient survival, %	82 (81.2%)	81 (92%)
BPAR, n (%)	16 (15.8%)	18 (20.5%)
eGFR at 12 months	49.4 ± 19.1 mL/min	47.9 ± 19.7 mL/min

Reduced immunosuppression in elderly patients improved graft survival.

Clin Transplant 2009;23:930-7.


120



Early steroid withdrawal

Transplantation 2014;98:144–5.

121



Maintenance Immunosuppression

122

Expert Consensus

- Optimal immunosuppression regimen is unclear
 - Evidence is limited
- Maintenance with a CNI is preferred
 - Patients will likely require lower doses
- Consider overall reduction in immunosuppression
 - Lower risk for rejection and higher risk for infection

Transplantation 2015;99:2258–68.
 Transplant Rev 2016;30:144–53.
 Transplant Rev. 2020;34:100529.

123

Question 4: Patient JD is a 68 yom with HTN and T2DM presenting for DDRT, which immunosuppression regimen would be best for JD?

- A. rATG 4 mg/kg + MMF 1000 mg BID + steroid taper
- B. Alemtuzumab 30 mg + tacrolimus goal 7-9 ng/mL + MMF 500 mg BID
- C. rATG 3 mg/kg + tacrolimus goal 8-10 ng/mL + MMF 500 mg BID
- D. rATG 7 mg/kg + everolimus goal 6-8 ng/mL + steroid taper

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Question 4: Patient JD is a 68 yom with HTN and T2DM presenting for DDRT, which immunosuppression regimen would be best for JD?

- A. rATG 4 mg/kg + MMF 1000 mg BID + steroid taper
- B. Alemtuzumab 30 mg + tacrolimus goal 7-9 ng/mL + MMF 500 mg BID
- C. rATG 3 mg/kg + tacrolimus goal 8-10 ng/mL + MMF 500 mg BID
- D. rATG 7 mg/kg + everolimus goal 6-8 ng/mL + steroid taper

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Key Takeaways

- Transplant improves survival for elderly patients on dialysis
- Elderly transplant recipients have decreased risk of rejection and increased risk of infection
- Age should not be used alone during transplant evaluation
- Elderly patients often require lower tacrolimus doses
- More research is needed to optimize immunosuppression regimens for elderly patients

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