

# Induction and Management of Acute Cellular Rejection

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## Disclosures

- Advisory Board Merck (ended September 2021)
- I will discuss off label use of medications.



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## Learning Objectives

- Outline the principles of induction immunosuppression and how these agents can be used for different organs.
- Compare and contrast the available induction agents; specifically focusing on mechanism of action, ease of administration, adverse events and economic impact.
- Evaluate the efficacy of induction therapy among the different organs.
- Design an evidence-based induction regimen centered on donor, recipient and transplant characteristics.
- Compare and contrast the agents available for the treatment of acute cellular rejection.
- Assess the optimal therapeutic options for management of acute cellular rejection.

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## History of Use of Induction Therapy

- Goals of induction therapy have evolved from preventing acute rejection, to facilitating minimization protocols and now towards inducing T-cell non-responsiveness
- The benefits of antilymphocyte serum were first demonstrated in humans in the mid 1960's
- Prior to available commercial preparations, many centers used home grown anti-lymphocyte serums
- Horse antithymocyte globulin was the first commercially available ATG (late 1980's), followed by rabbit antithymocyte globulin in Europe in 1984 and the US in 1999
- The IL-2 receptor antagonists were approved as induction agents in the late 1990's
  - Use primarily reserved for low risk population
- Popularity of alemtuzumab as an induction agent rose in the early 2000's due to favorable cost, ease of administration and ability to facilitate steroid withdrawal

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## Cellular Rejection and Expanded Use of Induction Therapy

Elimination of acute rejection would be ideal (if there were no side-effects)

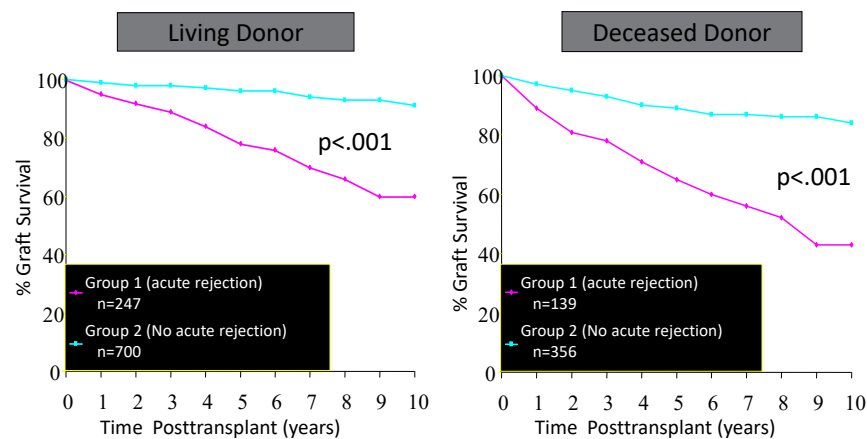
Humar, et al.

- Studied long-term outcome (rejection vs. no rejection) of renal transplant recipients at a single center from 1984-1998
- Immunosuppression – cyclosporine, prednisone, azathioprine
- Excluded graft loss to technical failure, primary nonfunction, death, recurrent disease

Humar A, et al. *Transplantation* 1999;68:1842-6

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## 10-Year Death-Censored Allograft Survival Rates



Humar A, et al. *Transplantation* 1999;68:1842-6

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## Induction Therapy

### Goals of induction therapy

- To decrease the rate of acute rejection
- To permit delayed initiation, minimization or avoidance of some of the maintenance agents (i.e. calcineurin inhibitors [CNI], corticosteroids)

### Available agents

1. Monoclonal antibodies that react with a single antigen receptor on the lymphocyte
  - Basiliximab (Simulect®) - CD25 or IL-2 R
  - Alemtuzumab (Campath®) - CD52
2. Polyclonal antibodies: react with multiple antigen receptors
  - Equine antithymocyte globulin (eATG; ATGAM®)
  - Rabbit antithymocyte globulin (rATG; Thymoglobulin®)

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Question 1: The only induction agent known to have a long-term impact on CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> regulatory T-cells is?

- Alemtuzumab
- Basiliximab
- eATG
- rATG

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Question 2: The induction agent with the shortest duration of activity (based on recommended doses) is?

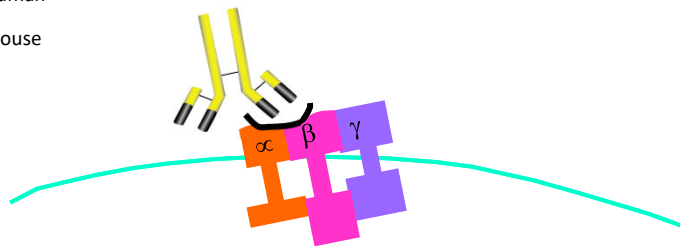
- Alemtuzumab
- Basiliximab
- eATG
- rATG

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## Non-Depleting Proteins: Basiliximab

- A chimeric monoclonal antibody that competitively inhibits the activation of lymphocytes by IL-2
- This agent has low immunogenicity potential because of the incorporation of human protein sequences.

 Human  
 Mouse



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## Basiliximab

Points of Discussion	Basiliximab Characteristics
Formulation	- Reconstituted (preservative free) 10 and 20 mg vials
Dosing	- 20 mg given 2 hours prior to transplant, then 20 mg on post-op day 4 - In patients weighing less than 35 kg (adults/pediatrics), 10 mg doses are utilized with the same dosing schedule
Administration	- IV infusion over 20-30 minutes via central or peripheral line - Premedication with diphenhydramine and/or acetaminophen is not recommended as infusion-related reactions are rare (<1%)

Simulect (basiliximab) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018

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## Basiliximab

Points of Discussion	Basiliximab Characteristics
Monitoring	- No Therapeutic Drug Monitoring (TDM) - Clinical Monitoring: <ul style="list-style-type: none"> <li>- Hypersensitivity reactions: severe, acute (onset within 24 hours) hypersensitivity reactions are rare, but have been observed</li> <li>- Hypotension, tachycardia, cardiac failure, dyspnea, wheezing, bronchospasm, pulmonary edema, respiratory failure, urticaria, rash, pruritus, or sneezing.</li> </ul>
Pharmacokinetic Considerations	- Distribution = $8.6 \pm 4.1$ L - Total body clearance = $41 \pm 19$ mL/hr - Terminal elimination half-life ( $t_{1/2}$ ) = $7.2 \pm 3.2$ days

Simulect (basiliximab) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018

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## Basiliximab

Points of Discussion	Basiliximab Characteristics
Duration of Activity	<ul style="list-style-type: none"> <li>- Basiliximab concentrations of 0.2 mg/L or more provide significant IL-2 receptor saturation.</li> <li>- Total basiliximab doses from 20 to 60 mg yield receptor-saturating concentrations for up to 8 weeks post-transplant.</li> <li>- A cumulative dose of 40 mg offers the best balance between receptor suppression (up to 45 days) while avoiding pronounced potential for prolonged suppression.</li> </ul>

Simulect (basiliximab) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018; Onrust SV, et al. *Drugs* 1999;57:207-13; Mentre F, et al. *J Pharmacokinet Biopharm* 1999;27:213-30; Kovarik J, et al. *Transplantation* 1997;64:1701-5.

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Question 3: Some clinicians choose to monitor the clinical efficacy of the antilymphocyte antibodies by monitoring:

- CD3<sup>+</sup> cells
- CD25<sup>+</sup> cells
- Platelets
- Promyelocytes

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## Depleting Proteins: Antithymocyte Globulins (Horse and Rabbit)

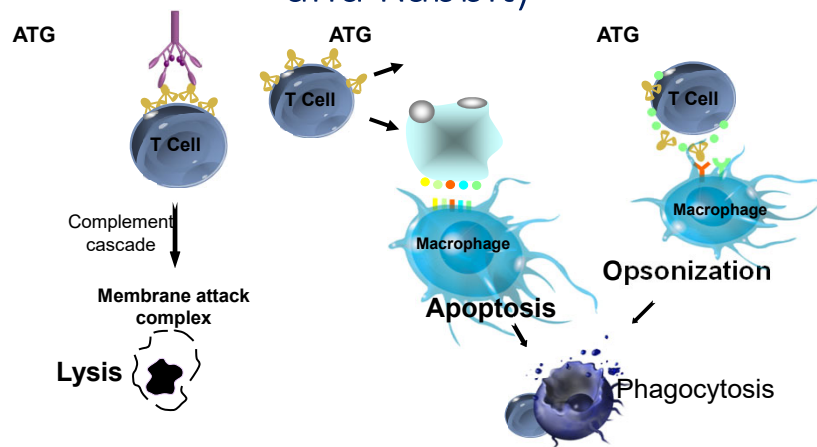
- The antithymocyte globulins (ATG) are purified gamma globulin obtained by immunizing an animal w/ human lymphocytes.
  - Cytotoxic antibodies directed against a broad array of surface antigens expressed on T- and B-cells

Immune Response Antigens		Adhesion & Cell Trafficking	Heterogeneous Pathways
CD1a	CD28*	CD6	CD2
CD3/TCR	CD30	CD11a/CD18 (LFA-1)	CD5
CD4	CD32	CD44	CD11b
CD6	CD40	CD49/CD29 (VLA-4)	CD29
CD7	CD80*	CD50 (ICAM-3)	CD38
CD8	CD86	CD51/61	CD40
CD16	CD152 (CTLA-4)	CD54 (ICAM-1)	CD45
CD19	HLA class I	CD56*	CD52
CD20*	HLA DR	CD58 (LFA-3)	CD95
CD25*	$\beta$ 2-M	LPAM-1( $\alpha$ 4 $\beta$ 7)	CD126
		CD102 (ICAM-2)	CD138
		CD195 (CCR5)	
		CD197 (CCR7)	
		CD184 (CXCR4)	

Ankersmit HJ, et al. *Am J Transplant*. 2003;3:743. Bourdage JS, et al. *Transplantation*. 1995;59:1194. Michallet M-C, et al. *Transplantation*. 2003;75:657. Monti P, et al. *Int Immunopharmacol*. 2003;3:189. Pistillo MP, et al. *Transplantation*. 2002;73:1295. Prévile X, et al. *Transplantation*. 2001;71:460. Rebellato LM, et al. *Transplantation*. 1994;57:685. Tsuge I, et al. *Curr Ther Res*. 1995;56:671. Zand M, et al. *Transplantation*. 2005;79:1507. Zand MS, et al. *Blood*. 2006;107:2895.

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## Depleting Proteins: Antithymocyte Globulins (Horse and Rabbit)



Genestier L, et al. *Blood*. 1998;91:2360. Prévile X, et al. *Transplantation*. 2001;71:460

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## Antithymocyte Globulins (Horse and Rabbit)

Adhesion & Cell Trafficking Target Antigens		B cell Target Antigens	
CD11a/CD18 (LFA-1)	CD195 (CCR5)	HLA DR	CD32
CD44	CD197 (CCR7)	CD5	CD38
CD49/CD29 (VLA-4)	CD184 (CXCR4)	CD19	CD40
CD50 (ICAM-3)		CD20*	CD45
CD51/61		CD25*	CD52
CD54 (ICAM-1)		CD27	CD80*
CD56 *		CD30	CD86
CD58 (LFA-3)			CD95
LPAM-1 ( $\alpha 4\beta 7$ )			CD138
CD102 (ICAM-2)			

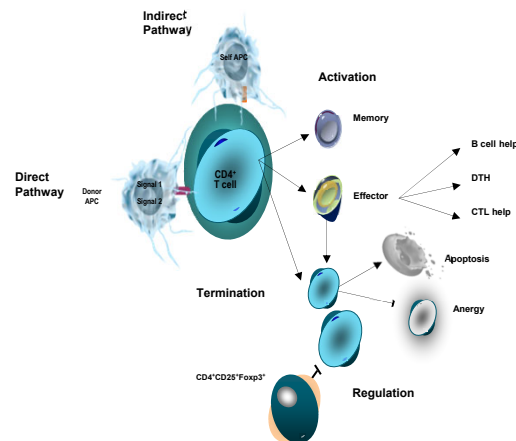
- Major Differences in Mechanism of Action
  - Antithymocyte globulin rabbit (rATG) not only causes cell depletion, but it also has some secondary mechanisms:
    - antibody-dependent cellular cytotoxicity
    - B-cell apoptosis
    - regulatory actions on adhesion molecules
    - dendritic cell depletion

Thymoglobulin (antithymocyte globulin [rabbit]) [package insert]. Cambridge, MA: Sanofi Aventis; 2017

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## Antithymocyte Globulins (Horse and Rabbit)

- Immunomodulation
  - Immune reconstitution generally occurs within 2-4 months following ATG induction, but in some patients it may persist for years.
  - rATG-mediated immunosuppression also appears to be attributable in part to immunologically specific actions involving the generation of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> regulatory T-cells.
  - In vitro, rATG has the unique ability to convert CD4<sup>+</sup>CD25<sup>-</sup> T-cells into CD4<sup>+</sup>CD25<sup>+</sup> T-cells within 24 hrs.



Lopez M, et al. *J Am Soc Nephrol* 2006; 17: 2844-53

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## Antithymocyte Globulins (Horse and Rabbit)

Points of Discussion	Rabbit ATG Characteristics	Horse ATG Characteristics
Formulation	- Reconstituted 25 mg vial	- Ampule 250 mg per 5 mL
Dosing	- Cumulative doses of 3-6 mg/kg, generally given in doses of 0.75-1.5 mg/kg/day x 1-8 doses	- 5-15 mg/kg/day for 3 days

Thymoglobulin (antithymocyte globulin [rabbit]) [package insert]. Cambridge, MA: Sanofi Aventis; 2017; ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) [package insert]. New York, NY: Pfizer; 2018

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## Antithymocyte Globulins (Horse and Rabbit)

Points of Discussion	Rabbit ATG Characteristics	Horse ATG Characteristics
Administration	<ul style="list-style-type: none"> <li>- IV via central or peripheral line</li> <li>- Peripheral administration: consider addition of heparin and hydrocortisone in a larger volume</li> <li>- Premedicate with steroids, diphenhydramine and acetaminophen</li> </ul>	<ul style="list-style-type: none"> <li>- IV via central or peripheral line (not recommended)</li> <li>- Premedicate with steroids, diphenhydramine and acetaminophen</li> <li>- An intradermal skin test (5 mcg or 0.1 mL) should be performed prior to administering infusion.</li> <li>- Observe patient q15-20 mins over the 1<sup>st</sup> hour.</li> <li>- Local reaction of <math>\geq 10</math> mm with a wheal or erythema (or both), with or without pseudopod formation and itching, or a marked local swelling is a positive test.</li> </ul>

Thymoglobulin (antithymocyte globulin [rabbit]) [package insert]. Cambridge, MA: Sanofi Aventis; 2017; 2017; ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) [package insert]. New York, NY: Pfizer; 2018

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## Rabbit Antithymocyte Globulin

- Timing of rATG in renal transplant recipients may impact delayed graft function (DGF)
  - Prospective, randomized study of rATG induction therapy in 58 adult deceased donor renal transplant recipients
  - Intraoperative rATG administration significantly reduced prevalence of DGF (15%) in comparison to postoperative rATG (36%) administration only.
  - Intraoperative rATG was also associated with a decreased length of stay post-transplant.

Goggins WC, et al. *Transplantation* 2003;76:798-802

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## Antithymocyte Globulins (Horse and Rabbit)

Points of Discussion	Rabbit ATG Characteristics	Horse ATG Characteristics
Contraindication	- Allergy to rabbit proteins or serum	- Allergy to horse proteins or serum

Thymoglobulin (antithymocyte globulin [rabbit]) [package insert]. Cambridge, MA: Sanofi Aventis; 2017; 2017; ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) [package insert]. New York, NY: Pfizer; 2018

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## Antithymocyte Globulins (Horse and Rabbit)

Points of Discussion	Rabbit ATG Characteristics	Horse ATG Characteristics
Monitoring	<ul style="list-style-type: none"> <li>- No TDM, but may monitor T-cell depletion</li> <li>- WBC (lymphocytes <math>&lt;200/\text{mm}^3</math>) or <math>\text{CD3}^+</math> T-cells (<math>&lt;20/\text{mm}^3</math>) performed daily or three times a week.</li> <li>- Clinical Monitoring: localized infusion site reactions (i.e., pain, swelling, erythema) and immune-mediated reactions (i.e., fever, chills, hypotension, tachycardia, edema, myalgia)</li> <li>- Myelosuppression: WBC <math>2,000\text{--}3,000\text{ cells}/\text{mm}^3 = \frac{1}{2}</math> dose; <math>&lt; 2,000 =</math> hold/discontinue; Platelets <math>50,000\text{--}75,000\text{ cells}/\text{mm}^3 = \frac{1}{2}</math> dose; <math>&lt;50,000 =</math> hold/discontinue</li> </ul>	<ul style="list-style-type: none"> <li>- No TDM</li> <li>- Clinical Monitoring: stop infusion if a systemic reaction (i.e., dyspnea, tachycardia, hypotension, skin reaction) or anaphylaxis occurs.</li> <li>- Myelosuppression</li> </ul>

Thymoglobulin (antithymocyte globulin [rabbit]) [package insert]. Cambridge, MA: Sanofi Aventis; 2017; 2017; ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) [package insert]. New York, NY: Pfizer; 2018

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## Antithymocyte Globulins (Horse and Rabbit)

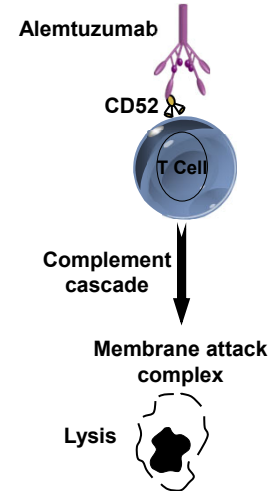
Points of Discussion	Rabbit ATG Characteristics	Horse ATG Characteristics
Pharmacokinetic Considerations	<ul style="list-style-type: none"> <li>- The terminal <math>t_{1/2}</math> was found to be highly variable as elimination is dependent on the individual patients' elimination of the foreign protein</li> <li>- Mean plasma <math>t_{1/2} = 2\text{--}3</math> days</li> </ul>	<ul style="list-style-type: none"> <li>- Terminal elimination <math>t_{1/2} = 5.7 \pm 3</math> days</li> </ul>

Thymoglobulin (antithymocyte globulin [rabbit]) [package insert]. Cambridge, MA: Sanofi Aventis; 2017; 2017; ATGAM (lymphocyte immune globulin, anti-thymocyte globulin [equine]) [package insert]. New York, NY: Pfizer; 2018

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## Depleting Proteins: Alemtuzumab

- Alemtuzumab is an anti-CD52 humanized, monoclonal antibody that has an FDA indication for use in B-cell chronic lymphocytic leukemia and multiple sclerosis.
- CD52 is present on virtually all B- and T-cells, as well as macrophages, NK cells and some granulocytes.
- The alemtuzumab-CD52 complex triggers antibody-dependent lysis.



Campath (alemtuzumab) [package insert]. Cambridge, MA: Sanofi Aventis; 2015

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## Alemtuzumab

Points of Discussion	Alemtuzumab Characteristics
Formulation	- Vial (preservative free) 30 mg/mL ; 1 mL vial
Dosing	- 20-30 mg given as a single dose intraoperatively
Administration	- IV infusion over 2 hours via a peripheral or central line <ul style="list-style-type: none"> <li>- Premedicate with diphenhydramine and acetaminophen 30 minutes prior to infusion. If patient is receiving corticosteroids, it is appropriate to administer prior to an alemtuzumab infusion.</li> </ul>
	- SC administration less commonly causes chills or infusion-related reactions, but may cause injection site reactions that warrant premedication

Campath (alemtuzumab) [package insert]. Cambridge, MA: Sanofi Aventis; 2015

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## Alemtuzumab

Points of Discussion	Alemtuzumab Characteristics
Monitoring	<ul style="list-style-type: none"> <li>- No TDM, but some centers will monitor the long-term effects of Alemtuzumab by monitoring CD4<sup>+</sup> counts</li> <li>- Clinical Monitoring: <ul style="list-style-type: none"> <li>- Infusion-related reactions (i.e., nausea, vomiting, diarrhea, headache, dysesthesias and dizziness)</li> <li>- Immune-mediated reactions (i.e., fever, chills, hypotension, tachycardia, edema, myalgia)</li> <li>- Myelosuppression</li> </ul> </li> </ul>
Pharmacokinetic Considerations	<ul style="list-style-type: none"> <li>- Based on multi-dose CLL studies <ul style="list-style-type: none"> <li>- Volume of Distribution (Vd) = 0.18 L/kg</li> <li>- Terminal elimination half-life <math>t_{1/2}</math> = 11 hours (single-dose data)</li> </ul> </li> </ul>

Campath (alemtuzumab) [package insert]. Cambridge, MA: Sanofi Aventis; 2015

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## Alemtuzumab

Points of Discussion	Alemtuzumab Characteristics
Duration of Activity	<ul style="list-style-type: none"> <li>- The depletion of lymphocytes is so marked that it takes several months, in some cases more than one year, post-administration for a patient's immune system to be fully reconstituted.</li> </ul>

Todeschini M, et al. *J Immunol* 2013;191:2818-28

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## Alemtuzumab

Points of Discussion	Alemtuzumab Characteristics
Special Considerations	<ul style="list-style-type: none"> <li>- Clinical Considerations               <ul style="list-style-type: none"> <li>- There is a significant IL-21-driven autoimmune response during immune-reconstitution following alemtuzumab use. In a single-center, retrospective analysis, Noureldeen, et al found a higher rate of AMR in patients induced with alemtuzumab compared to those that received rATG.</li> </ul> </li> <li>- Distribution               <ul style="list-style-type: none"> <li>- As of September 4, 2012, Alemtuzumab is no longer commercially available, but is provided through the Campath Distribution Program free of charge.</li> <li>- In order to receive Alemtuzumab, the healthcare provider is required to document and comply with certain requirements (<a href="https://www.clinigengroup.com/direct/en/products/detail/087dd185-campath/">https://www.clinigengroup.com/direct/en/products/detail/087dd185-campath/</a>)</li> </ul> </li> </ul>

Willcombe M, et al. *Transplantation* 2011;92(2):176-82. ; Noureldeen T, et al. *Transplant Proc* 2014;46(10):3405-7.

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Question 1: The only induction agent known to have a long-term impact on CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> regulatory T-cells is?

- Alemtuzumab
- Basiliximab
- eATG
- rATG

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Question 2: The induction agent with the shortest duration of activity (based on recommended doses) is?

- Alemtuzumab
- **Basiliximab**
- eATG
- rATG

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Question 3: Some clinicians choose to monitor the clinical efficacy of the antilymphocyte antibodies by monitoring:

- CD3<sup>+</sup> cells
- CD25<sup>+</sup> cells
- Platelets
- Promyelocytes

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Question 4: Refer to the case and choose the appropriate starting dose of corticosteroids to initiate immunosuppression (in the OR):

- A 48 y/o male w/ IgA nephropathy presents for living donor (related) renal transplant. His past medical history is significant for hypertension, hyperlipidemia, IgA nephropathy (biopsy in 2015) and gout. The patient has a non-contributory social history and vitals are within normal limits on presentation to the hospital. The patient weighs 218 lbs. and has a BMI of 31.8. Both the patient and donor are EBV positive, the recipient is CMV negative, but the donor is CMV positive. All hepatitis and HIV serologies are negative.
- Prednisone 100 mg
- Dexamethasone 250 mg
- Hydrocortisone 1000 mg
- Methylprednisolone 500 mg

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## Corticosteroids

- The exact MOA is still not fully understood. Some believe...
  - High dose: > 100 mg of prednisone equivalents, the MOA = directly toxic to T cells
  - Low dose: < 100 mg of prednisone equivalents, the MOA is inhibit IL-1, IL-2, IL-3, IL-6, IL-15, TNF-alpha and INF-gamma.
    - Decreased activation of T cells.
  - Blockade of Cytokine Gene Expression
    - ↓ T-cell and APC cytokine expression
      - Bind to heat shock protein → translocates to nucleus → binds to GRE → inhibition of IL-1, IL-2, IL-3, IL-6, INF-γ, and TNF-α
    - ↓ cytokine-receptor expression
  - Nonspecific Effects
    - Anti-inflammatory effects

Barshes NR, et al. *Front Biosci* 2004;9:411-20.

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## Corticosteroids

Points of Discussion	Corticosteroid Characteristics
Formulation	<ul style="list-style-type: none"> <li>- Methylprednisolone:               <ul style="list-style-type: none"> <li>- Available in 40 mg, 125 mg, 500 mg, 1000 mg and 2000 mg vials for reconstitution and IV administration.</li> <li>- Several IV dosage forms may contain benzyl alcohol.</li> </ul> </li> <li>- Prednisone:               <ul style="list-style-type: none"> <li>- Available in an oral solution (5 mg/ml) and tablets (1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg)</li> </ul> </li> </ul>
Dosing	<ul style="list-style-type: none"> <li>- Dosing is dependent on organ, but in general high doses of methylprednisolone are given at the time of transplant (250-1000 mg x 1) followed by tapered doses thereafter.</li> <li>- Oral prednisone tapers may take place following IV administration</li> </ul>

Lee RA, Gabardi S. *Am J Health Syst Pharm* 2012;69(22):1961-75

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## Corticosteroids

Points of Discussion	Corticosteroid Characteristics
Administration	<ul style="list-style-type: none"> <li>- General infusion guidelines are based on the dose               <ul style="list-style-type: none"> <li>- 125-249 mg = IV push over 3-15 minutes</li> <li>- 250-499 mg = IV infusion over 15-30 minutes</li> <li>- 500-999 mg = IV infusion over <math>\geq</math> 30 minutes</li> <li>- <math>\geq</math>1000 mg = IV infusion over 1 hour</li> </ul> </li> </ul>
Monitoring	<ul style="list-style-type: none"> <li>- No TDM</li> <li>- Clinical Monitoring:               <ul style="list-style-type: none"> <li>- Blood sugar (consider finger-stick monitoring even in non-diabetics); Fluid retention; Hypertension; Neurologic adverse events (changes in mental status, agitation, insomnia, mood swings)</li> </ul> </li> </ul>

Lee RA, Gabardi S. *Am J Health Syst Pharm* 2012;69(22):1961-75

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## Corticosteroids

Points of Discussion	Corticosteroid Characteristics
Pharmacokinetic Considerations	<ul style="list-style-type: none"> <li>- Vd = 1.5 L/kg</li> <li>- Metabolism = hepatic by oxidation</li> <li>- Excretion = primarily through the kidneys (feces = minor)</li> <li>- Total body clearance = 16-21 L/hr</li> <li>- Terminal t<sub>1/2</sub> = 2-3 hours</li> </ul>

Lee RA, Gabardi S. *Am J Health Syst Pharm* 2012;69(22):1961-75

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Question 4: Refer to the case and choose the appropriate starting dose of corticosteroids to initiate immunosuppression (in the OR):

- A 48 y/o male w/ IgA nephropathy presents for living donor (related) renal transplant. His past medical history is significant for hypertension, hyperlipidemia, IgA nephropathy (biopsy in 2015) and gout. The patient has a non-contributory social history and vitals are within normal limits on presentation to the hospital. The patient weighs 218 lbs. and has a BMI of 31.8. Both the patient and donor are EBV positive, the recipient is CMV negative, but the donor is CMV positive. All hepatitis and HIV serologies are negative.
- Prednisone 100 mg
- Dexamethasone 250 mg
- Hydrocortisone 1000 mg
- Methylprednisolone 500 mg

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## Induction Therapy Use Among Different Organs

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### Question 5: Refer to the case and choose the appropriate induction agent for this patient:

- A 48 y/o male w/ IgA nephropathy presents for living related renal transplant. His past medical history is significant for HTN, hyperlipidemia, IgA nephropathy and gout. The patient has a non-contributory social history and vitals are within normal limits. The patient weighs 218 lbs. and BMI is 31.8. Both patient/donor are EBV positive, the recipient is CMV negative, but donor is CMV positive. All other serologies are negative.
- Long-term immunosuppression will consist of Tacrolimus, Mycophenolate and a rapid corticosteroid withdrawal
- Basiliximab 20 mg x 2 (pod 0 and 4)
- rATG 1.5 mg/kg x 4 days
- eATG 15 mg/kg x 7 days
- Alemtuzumab 30 mg x 2 (pod 0 and 1)

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### Question 5: Refer to the case and choose the appropriate induction agent for this patient:

- A 48 y/o male w/ IgA nephropathy presents for living related renal transplant. His past medical history is significant for HTN, hyperlipidemia, IgA nephropathy and gout. The patient has a non-contributory social history and vitals are within normal limits. The patient weighs 218 lbs. and BMI is 31.8. Both patient/donor are EBV positive, the recipient is CMV negative, but donor is CMV positive. All other serologies are negative.
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- Alemtuzumab 30 mg x 2 (pod 0 and 1)

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### United States OPTN Data for use of Induction Therapies Among Kidney Transplant Recipients

- Induction therapy is commonplace among renal transplant recipients:
  - Induction therapy was used in 91.0% of renal transplants, a slight decrease from 92.1% in 2019
  - The majority of patients treated in the US receive a T-cell depleting agent.
  - 2019: Acute rejection at 1 year:
    - IL-2 RA = 8.4%
    - Antilymphocyte antibody = 6.9%
    - No induction = 6.6%

Lentine KL, et al. *Am J Transplant* 2022;22 Suppl s2:21-136; Hart A, et al. *Am J Transplant* 2021;21 Suppl s2:21-137

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## Clinical Data – Kidney Transplant

- eATG vs. rATG<sup>1-3</sup>
  - Efficacy: Significantly lower rates of BPAR and improved allograft/patient survival with rATG at 1-, 5- and 10-years
  - Safety: Significantly lower rates of CMV infection with rATG, despite higher early rates of leukopenia. Similar rates of PTLD.

1. Brennan DC, et al. *Transplantation* 1999;67:1011-8. 2. Hardinger KL, et al. *Transplantation* 2004;78:136-41. 3. Hardinger KL, et al. *Transplantation* 2008;86:947-52.

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## Clinical Data – Kidney Transplant

- Basiliximab vs. rATG (high risk recipients)
  - Efficacy: Similar composite end point of BPAR, DGF, allograft/patient survival
    - Significantly lower rates of BPAR associated with rATG
  - Safety: Significantly higher rates of myelosuppression and overall infections seen with rATG
    - Significantly fewer cases of CMV infection seen with rATG, despite higher early rates of leukopenia.

Brennan DC, et al. *N Engl J Med* 2006;355:1967-77

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## Clinical Data – Kidney Transplant

- Alemtuzumab vs. Basiliximab (low-risk); vs. rATG (high-risk)
  - Efficacy vs. Basiliximab: the incidence of BPAR was lower in the alemtuzumab group in comparison to the basiliximab group at 6-, 12- and 36-months post-transplant (2% vs. 18%, 3% vs. 20%, and 10% vs. 22%, respectively).
    - The composite endpoint of freedom from rejection, graft loss or death was significantly better at 3-years with alemtuzumab.
    - Late rejection, which the authors defined as BPAR occurring between months 12 and 36 in patients who did not have BPAR within the first 12 months, occurred in numerically higher rates in patients induced with alemtuzumab (8% vs. 3%, respectively), but, did not reach statistic significance.
    - SAFETY: lower rates of serious infectious complications seen with basiliximab.
  - Efficacy vs. rATG: BPAR was similar between alemtuzumab and rATG at 6-, 12- and 36-months post-transplant (6% vs. 9%, 10% vs. 13%, and 18% vs. 15%, respectively).
    - Late acute rejection was numerically more common with alemtuzumab (10% vs. 2%; p=NS)
    - The composite endpoint of freedom from rejection, graft loss or death was similar between both agents.
    - SAFETY: overall, more infectious disease seen with rATG, but similar rates of serious infectious complications.
  - This study was likely underpowered to detect a difference in late rejection among the individual groups.

Hanaway MJ, et al. *N Engl J Med* 2011;364:1909-19

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## United States OPTN Data for use of Induction Therapies Among Pancreas Transplant Recipients

- Induction therapy is also common among pancreas transplant recipients and have not changed much over the previous 5 years.
- Compared to kidney, there is a larger reliance on antilymphocyte therapies in pancreas transplant given the higher rejection rates seen with T-cell depleting therapies were avoided.
  - 90% of pancreas transplant recipients receive induction with a T-cell depleting agent.

Kandaswamy R, et al. *Am J Transplant* 2022;22 Suppl s2:137-203

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## Clinical Data – Pancreas Transplant

- Prospective, randomized single-center trial comparing alemtuzumab and rATG induction in adult kidney and pancreas transplantation.
- 222 patients: Alemtuzumab (n=113) vs. rATG (n=109)
  - Kidney alone (n=180), SPK (n=38), PAK (n=4)
  - Survival, initial length of stay, and maintenance immunosuppression (including early steroid elimination) were similar between alemtuzumab and rATG groups, but BPAR occurred in 16 (14%) alemtuzumab patients compared with 28 (26%) rATG patients (P=0.02).
  - Late BPAR (>12 months after transplant) occurred in 1 (8%) alemtuzumab patient and 3 (11%) rATG patients (P=NS).
  - Infections and malignancy were similar between the two induction arms.

Farney AC, et al. *Transplantation* 2009;88(6):810-9

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## United States OPTN Data for use of Induction Therapies Among Liver Transplant Recipients

- The majority (72%) of liver transplant recipients did not receive induction therapy in 2020.
- 2019: If induction therapy was utilized, an IL2-receptor antagonist was the preferred agent.
  - Antilymphocyte induction therapy was used in less than 10% of liver transplant recipients.

Kwong A, et al. *Am J Transplant* 2022;22 Suppl s2:204-309; Kwong A, et al. *Am J Transplant* 2021;21 Suppl s2:208-315

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## Clinical Data – Liver Transplant

- 19 randomized clinical trials (n=2067)
  - 16 trials were two-arm trials and 3 trials were three-arm trials
- Overall, no difference in mortality (RR 0.91; 95% CI 0.64 to 1.28; low-quality of evidence), graft loss (RR 0.92; 95% CI 0.71 to 1.19; low-quality of evidence), and adverse events (RR 0.97; 95% CI 0.93 to 1.02; low-quality evidence) outcomes was observed between induction and no induction
- Acute rejection seemed to be reduced with induction when compared with no induction (RR 0.85, 95% CI 0.75 to 0.96; moderate-quality evidence)
- Serum creatinine was statistically significantly higher when T-cell specific antibody induction was utilized compared with no induction
- No difference seen in infection or malignancy
- No differences in efficacy noted between IL-2RA and antilymphocyte antibodies (ALAs), but a higher degree of adverse events associated with ALAs

Penninga, et al. Cochrane Database Syst Rev 2014(6):CD010253

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## United States OPTN Data for use of Induction Therapies Among Heart Transplant Recipients

- Use of induction therapy in heart transplantation has changed little since 2007.
- In 2020, there was nearly an even split between the use of no induction therapy and any induction agent.
- In 2019, it was shown that IL2-RA are slightly preferred over T-cell depleting therapies in those centers utilizing induction therapy.

Colvin M, et al. *Am J Transplant* 2022;22 Suppl s2:350-437; Colvin M, et al. *Am J Transplant* 2021;21 Suppl s2:356-440

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## Clinical Data – Heart Transplant

- 11 (8 RCTs and 3 observational case-control studies) studies included in this analysis.
- Overall, patients receiving induction therapy with any agent had similar risk of moderate-to-severe rejection, all-cause death, infection, and cancer compared with patients who did not receive induction.
- The use of IL2RA was associated with significantly higher risk of moderate-to-severe rejection than ATG (OR 3.4; 95% CI 1.4 to 8.1), but similar risk of death, infections, and cancer.
- The use of induction was not associated with any benefits or harms compared with no induction therapy.

Briasoulis A, et al. *Heart Fail Rev* 2018;23(5):641-649

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## Clinical Data – Heart Transplant

- UNOS database evaluation of 34,361 adult heart transplant recipients (2000-2017).
- Induction therapy consisted of:
  - No Induction = 52%
  - IL2RA = 27%
  - ALA = 21%
- Population Characteristics:
  - Median age = 55 (IQR: 46-62) years.
  - 75% male
  - 39% were supported on LVAD at the time of transplantation.
  - Median follow-up = 4.2 (IQR: 1.1-8.5) years
- Multivariate analysis
  - ALA induction did not impact mortality (HR = 0.98, 95% CI 0.93-1.03, p = 0.48).
  - IL2RA was associated with a modest increase in risk for of all-cause mortality compared to no induction (HR = 1.06, 95% CI 1.01-1.11, p = 0.02).
  - Overall, 25% of patients were treated for rejection at one year
    - ALA induction was associated with reduced odds of rejection at one year (OR = 0.82, 95% CI 0.76-0.88, p < 0.001).
    - IL2RA was not found to have a significant impact (OR = 1.03, 95% CI 0.96-1.11, p = 0.36)

Bellumkonda L, et al. *J Heart Lung Transplant* 2022;41(4):482-491

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## United States OPTN Data for use of Induction Therapies Among Lung Transplant Recipients

- Use of induction therapy in lung transplantation has significantly increased in the past 10 years.
- In 2020, 80.9% of lung transplant recipients received induction therapy.
  - In the first posttransplant year, acute rejection occurred in 14.6% of lung transplant recipients
    - 19.6% of patient receiving no induction therapy
    - 18.4% of patients receiving an ALA
    - 13.0% of patients receiving an IL2RA

Valapour M, et al. *Am J Transplant* 2022;22 Suppl s2:428-518

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## Clinical Data – Lung Transplant

- 6 randomized clinical trials (n=278)
- Overall, no significant differences between different induction agents in terms of mortality, acute rejection, adverse effects, infectious complications, BOS or PTLD.
- None of the included analyses evaluated quality of life or kidney function.
- Superiority of one agent versus another regarding graft and recipient survival varies from one study to another, but use of an induction agent is generally considered to be superior to no induction.
- The current preference for IL2-RA among US transplant centers utilizing induction protocols is likely secondary to the belief that basiliximab has a favorable safety profile (as opposed to proven superior efficacy).

Penninga, et al. *Cochrane Database Syst Rev* 2013(11):CD008927

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## Clinical Data – Lung Transplant

- Single-center, retrospective cohort study of 721 lung transplant recipients (1/2008-6/2019) receiving alemtuzumab induction followed by a low-dose maintenance immunosuppression.
  - Freedom from higher-grade ACR (defined as definite CLAD stage 3 to 4, irrespective of phenotype) at 1, 5, and 10 years was 98%, 96%, and 96%, respectively.
  - AMR = 39 patients (5%)
  - High-grade (3a-5) CKD = 148 patients (21%)
  - Overall, 1488 infections were recorded.
    - 16% were diagnosed within the first 3 months.
  - Malignancy = 62 patients (9%) during follow-up
  - Freedom from CLAD at 1, 5, and 10 years was 94%, 72%, and 53%, respectively.
  - Overall survival rates at 1, 5, and 10 years were 85%, 71%, and 61%, respectively.
- Alemtuzumab induction combined with a low-dose tacrolimus/prednisone appears safe and is associated with low rates of acute and chronic rejection, with excellent long-term survival.

Benazzo A, et al. *Transpl Int* 2021;34(12):2633-2643

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## Induction Therapy - Economics

- Basiliximab 20 mg x 2 doses = \$8,947\*
- rATG 1.5 mg/kg<sup>†</sup> x 4 doses = \$20,155\*
- eATG 15 mg/kg<sup>†</sup> x 7 doses = \$70,342\*
- Alemtuzumab 30 mg x 1 dose = \$0<sup>††</sup>
- Methylprednisolone (variable dosing) price per 500 mg = \$27.74\*

<sup>†</sup>Based on 70 kg patient; <sup>††</sup>Based on current distribution program

\*Wholesale Acquisition Cost (WAC) per 2021 RedBook

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## Acute Cellular (T-cell Mediated) Rejection

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## Acute Cellular Rejection

- Acute cellular rejection is most common during the first 6 months post-transplant
  - Becomes substantially less common over time
- Most episodes are not accompanied by specific symptoms but present with a deterioration in organ function
- Because treatment is associated with significant side-effects, most suspected acute rejection episodes are confirmed through biopsy

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### Question 6: Refer to the case and choose the appropriate treatment option for this patient's rejection episode:

- Our 48 y/o male living related renal transplant: 2 months post-transplant nadir SCr is only 1.93 mg/dl.
- Renal biopsy reveals donor arteriosclerosis, which might explain kidney function.
- Patient is converted to belatacept with a 4 week taper off tacrolimus (maintained on belatacept and mycophenolate only) and has a decrease in SCr to 1.33 mg/dl within 30 days of the conversion.
- Two months post-conversion, SCr increases to 2.11 mg/dl and biopsy reveals BANFF IA cellular rejection.
- Methylprednisolone 250 mg/day x 3 doses
- rATG 1.5 mg/kg x 4-7 days
- eATG 15 mg/kg x 7-10 days
- Alemtuzumab 30 mg x 1

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## Treating Acute Cellular Rejection

Agent	Dosage
Corticosteroids	<ul style="list-style-type: none"> <li>– Intravenous methylprednisolone</li> <li>– 125-1000 mg/day x 3-5 days</li> <li>– 3 to 5 mg/kg x 3-5 days</li> </ul>
rATG	– 1.5 mg/kg/day x 4-14 days
Alemtuzumab	– 30 mg IV or SC x 1 dose

- First-line therapy is high-dose pulse corticosteroids.
- Antilymphocyte antibodies are generally reserved for corticosteroid-resistant rejection.
  - However, antibodies are sometimes used as first-line treatment for patients with histologically or clinically severe rejection.
- Administration of these agents may be done in conjunction with an intensification of maintenance immunosuppression

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- eATG 15 mg/kg x 7-10 days
- Alemtuzumab 30 mg x 1

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### Key Takeaways

- Great strides have been made at reducing cellular rejection rates with induction therapy over the last 2 decades.
- Protocols utilizing induction therapies have been able to take advantage of their potency by combining them with immunosuppressive-avoidance or elimination protocols.
- Despite the lack of newer therapies, current treatment options for acute cellular rejection episodes provide sufficient efficacy at reversing T-cell mediated events.

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## Induction and Management of Acute Cellular Rejection

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