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Evaluation of Baseline Immunophenotype in Pediatric Cardiac Transplant:

Improving Decisions in Long term Immunosuppression

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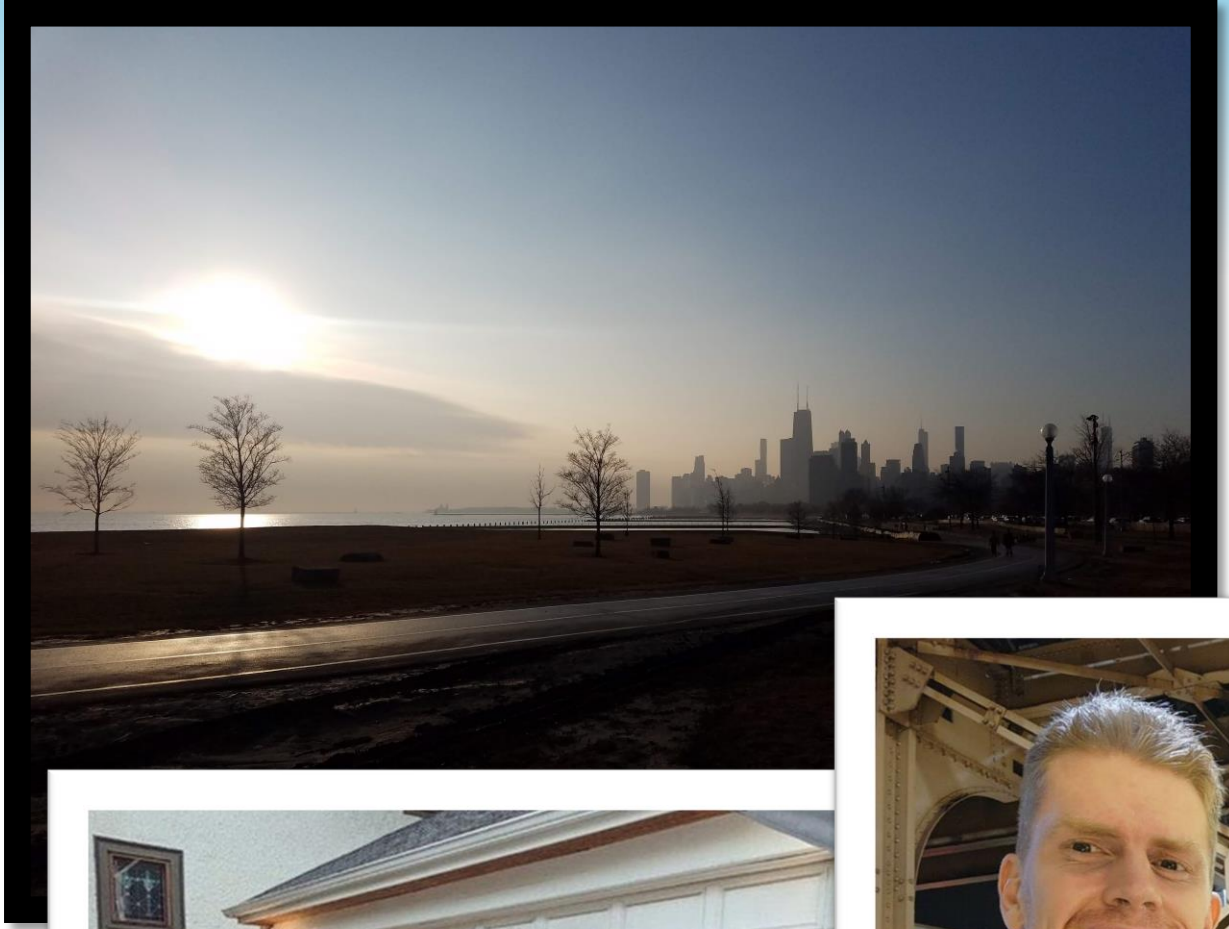
BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 10 SPECIALTIES 2019-20

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

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Disclosures

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- No other disclosures

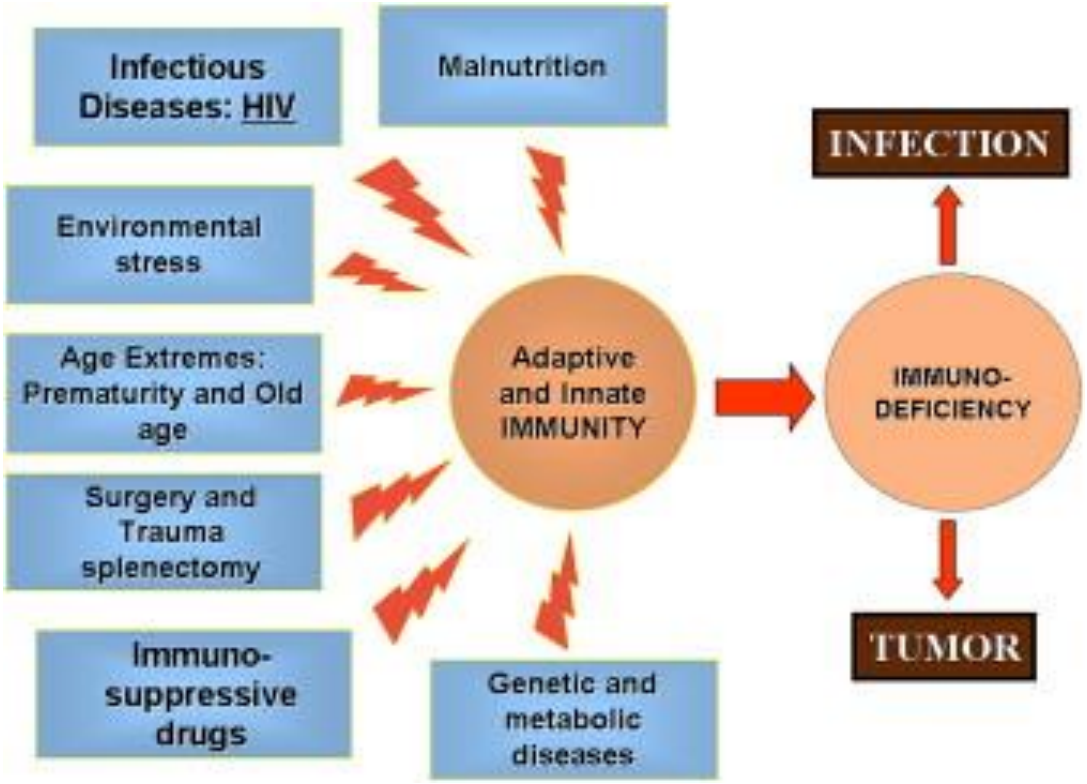
Outline

1. Background
2. Immune related complications before and after cardiac transplant
3. Project outline
4. Results
5. Limitations
6. Future directions

Background

Secondary immunodeficiency is a growing product of our environment:

- Resource poor countries
- Increased monoclonal directed therapies
- Increased rates of malignancy and autoimmunity

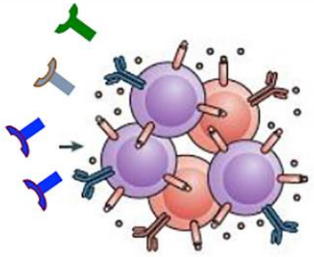


Chinen, Javier, and William T Shearer. "Secondary immunodeficiencies, including HIV infection." The Journal of allergy and clinical immunology vol. 125,2 Suppl 2 (2010): S195-203.

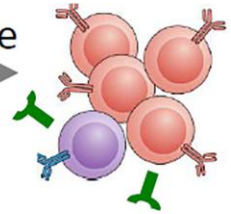
Background

Primary	Secondary
- (VEO-IBD) such as FOXP3, IL10RA, and XIAP - loss-of-function mutations in SLCO2A1, CD55, and DGAT1	Protein-Losing Conditions
- X-linked agammaglobulinemia	B-cell aplasia: CAR T therapy Rituximab
- Severe Combined Immunodeficiency (SCID) - Athymia (complete DiGeorge, Jacobson, CHARGE)	T cell deficiencies: Thymoglobulin HIV

Background



Hyperimmune → Hypoimmune



Rituximab or other B cell depleting therapies

Clinical state	Autoimmune disease → Risk of infections		
Immune phenotype	Normal B cell counts Normal IgG level	Increased risk*	B cell lymphopenia Hypogammaglobulinemia
Risk assessment	• Clinical and family Hx • Immunizations • Basic immune evaluation		• IgRT, antibiotic therapy • Genetic evaluation for PID • Mechanism-based tx

*Patients at risk for PH, infections and refractory AI
Pediatric age
AIHA / Evans syndrome
Underlying PID

Clinical improvement

Ballow, Mark et al. "Secondary Immune Deficiency and Primary Immune Deficiency Crossovers: Hematological Malignancies and Autoimmune Diseases." *Frontiers in immunology* vol. 13 928062. 18 Jul. 2022,

Immune Related Complications Before and After Cardiac Transplant

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1) **Hypogammaglobulinemia**:

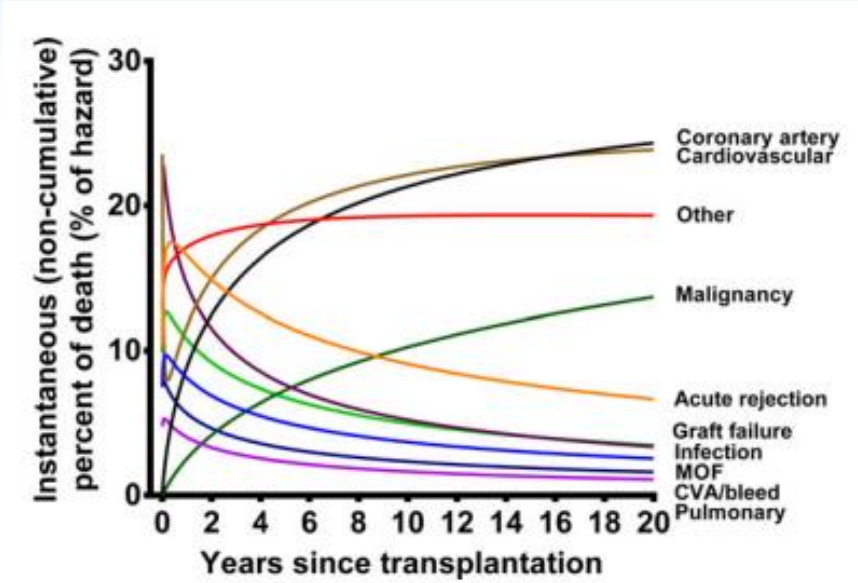
- Appears largely iatrogenic in nature due to immunosuppression.
- Additional contribution of protein losses coming into play (protein-losing enteropathy).

2) **T cell deficiencies:**

- Due to ongoing immunosuppression needs
- Goal of preventing graft vs host disease.

3) **Rejection:**

- Development of DSAs (Donor-specific antibodies
- Inefficient targeting of the implicated antibody-producing cells



4.) **Recurrent infections:**

- Persistent viral infections
- Complications from usual infections
- Unusual organisms (Nocardia)

5.) **Autoimmunity:**

- Post-transplant lymphoproliferative disorders (PTLD)
- New allergies?
- Enteropathy
- Malignancy

Mouledoux, Jessica H et al. "Clinical predictors of autoimmune and severe atopic disease in pediatric heart transplant recipients." Pediatric transplantation vol. 18,2 (2014): 197-203.

Immune Related Complications Before and After Cardiac Transplant

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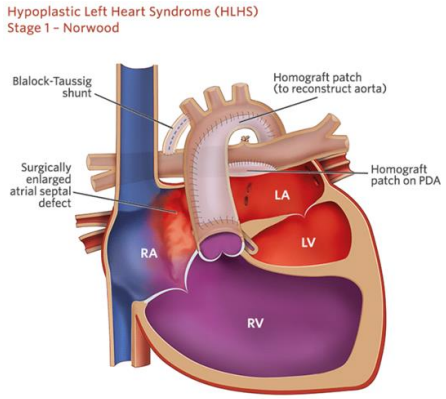
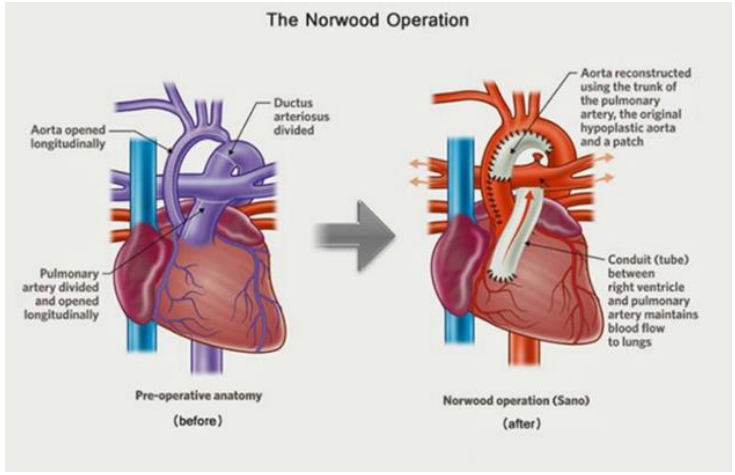
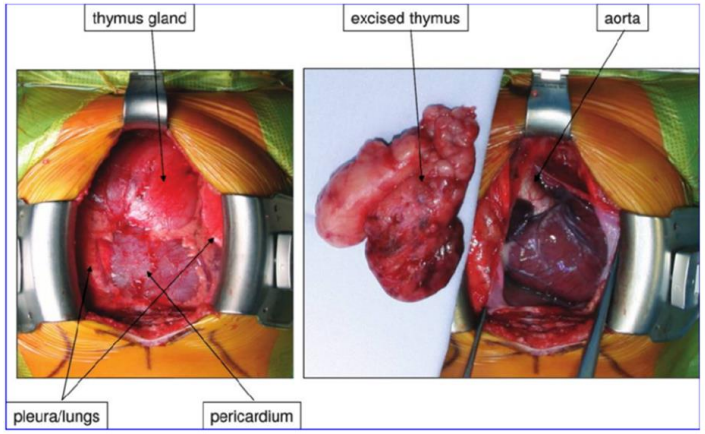
Figure 1 A.







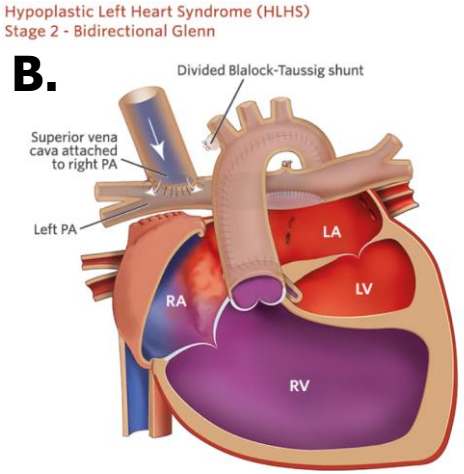
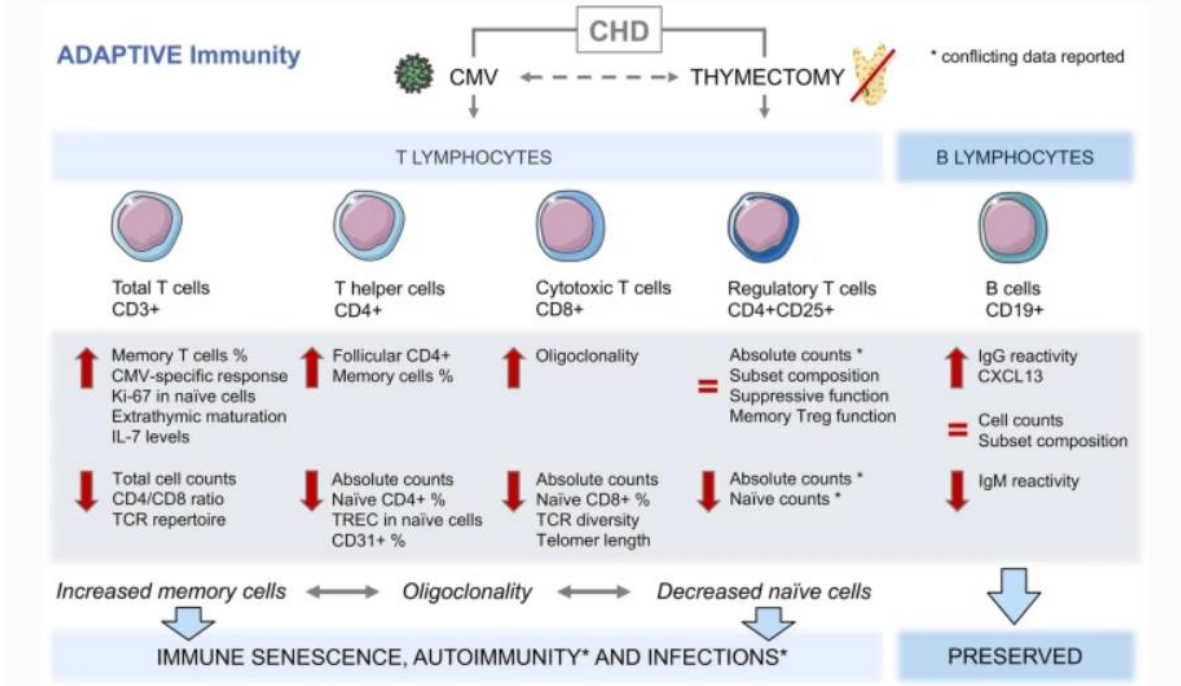


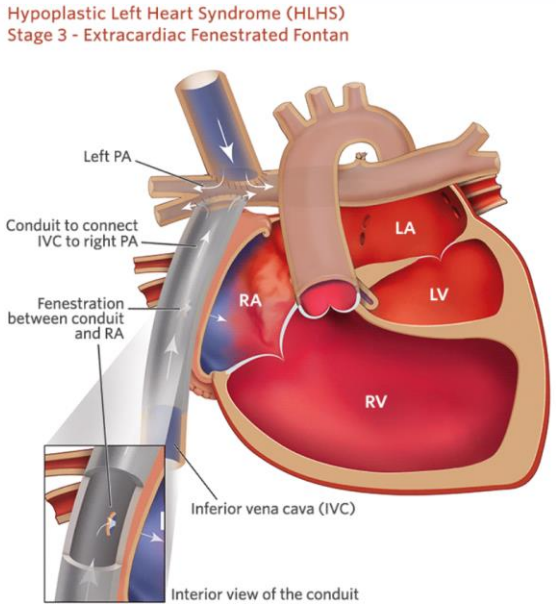
Fig. 2

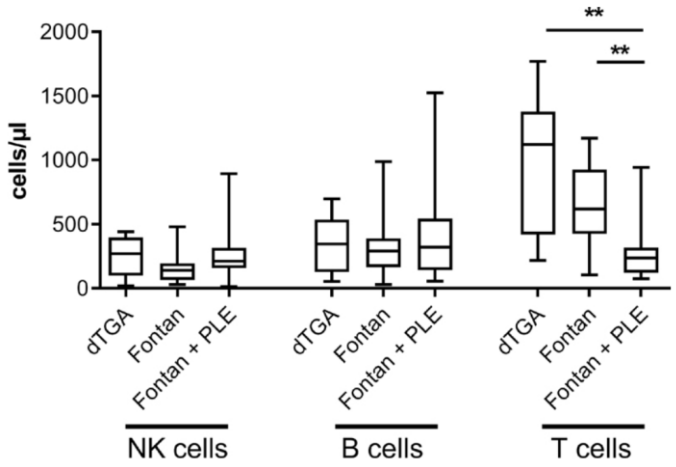


https://www.chop.edu/treatments/staged-reconstruction-heart-surgery

Wienecke, L.M., Cohen, S., Bauersachs, J. *et al.* Immunity and inflammation: the neglected key players in congenital heart disease?. *Heart Fail Rev* **27**, 1957–1971 (2022).

Immune Related Complications Before and After Cardiac Transplant





- What do we know?
  - Fontan-related hemodynamic changes:
    - increased central venous pressure (CVP) called "Fontan circulation"
  - Patients with Fontan without PLE were evaluated for lymphopenia (<1000 cells/uL)
    - 18.75% of the 48 patients had asymptomatic lymphopenia
  - Chronic low level lymphocyte loss?
    - Enteric lymphatic congestion
    - Intestinal spillage
  - Other issues develop:
    - Fontan associated liver disease (FALD), often silent

Moosmann, Jet al (2021). Lymphocyte Immune Response and T Cell Differentiation in Fontan Patients with protein-losing enteropathy. *The Thoracic and cardiovascular surgeon*, *69*(S 03), e10–e20.

Immune Related Complications Before and After Cardiac Transplant

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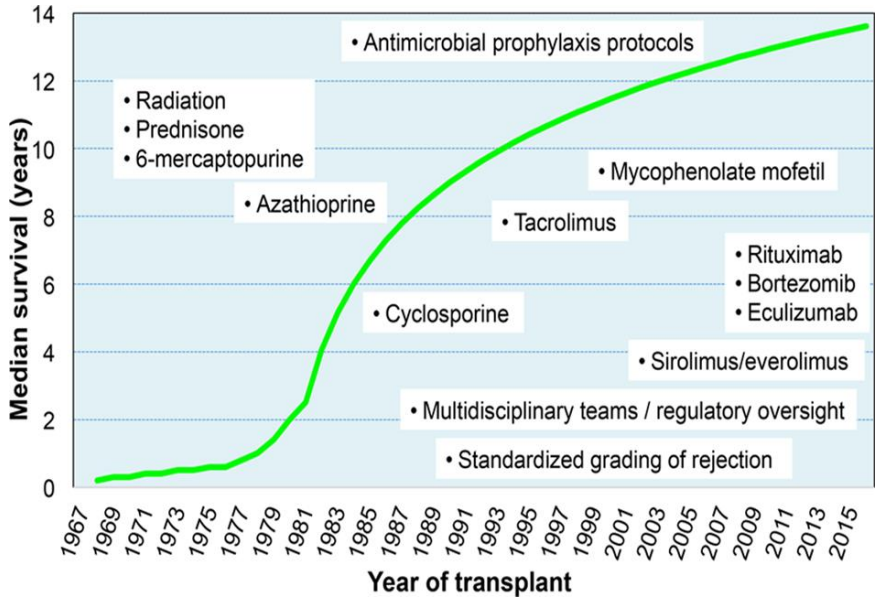
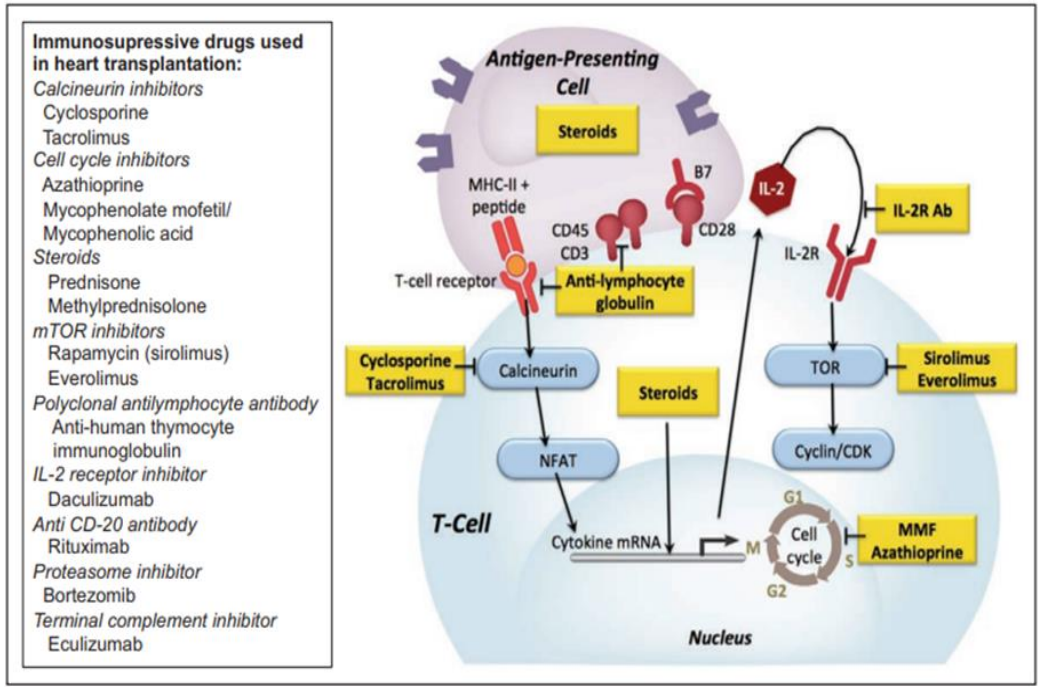
- Rejection:
  - T cell–mediated response presenting as acute cellular rejection
  - Hyperacute rejection and antibody-mediated rejection (AMR) are caused by preformed antibodies against ABO blood group antigens or HLA antigens on the allograft.



- Induction Medications:
  - Anti-thymoglobulin (ATG)
  - Anti-IL2Ra
  - Often paired with steroids until they can be weaned and tacrolimus started



	Medications	notes	MOA	Side effects
Calcineurin inhibitors	Cyclosporine		Preferred as they leave macrophages and neutrophils alone, but lead to T cell adverse effects and increased viral infections.	Increased viral infections
	Tacrolimus			
	Pimecrolimus			
MTOR inhibitors	Rapamycin/Sirolimus		Both T and B cell effects.	Mouth sores, cytopenias
Cytotoxic agents	Cyclophosphamide	Alkylating agent	Interfere with the synthesis of DNA, arresting the cell cycle and inducing apoptosis.	- Inhibit both T- and B-cell proliferation and therefore any new immune responses. - Depending on the dose used, they inhibit cellular and antibody responses resulting from previous sensitizations. Major limitations: - toxicity to other hematopoietic and nonhema-topoietic cells, with development of cytopenias, gastrointestinal, and skin deterioration. These cytopenias contribute to the state of secondary immunodeficiency and susceptibility to infections
	Mycophenolate	Anti-metabolites		
	Azathioprine	Anti-metabolites		

Immune Related Complications Before and After Cardiac Transplant

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Recurrent Infections:

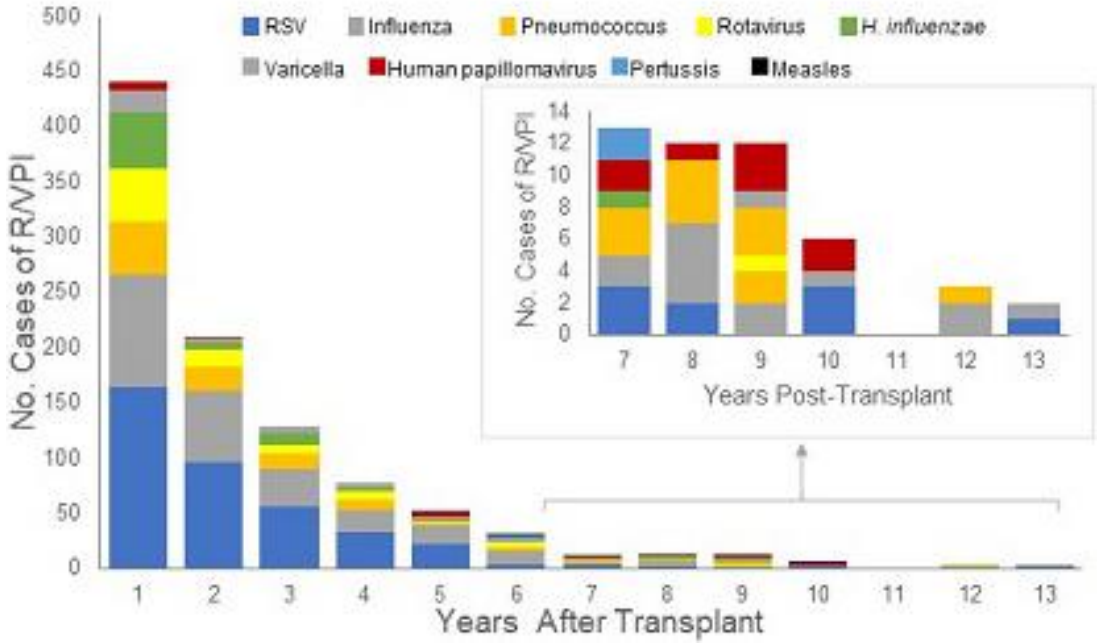
1.) Many studies have been completed on early thymectomy in infants with CHD

- Decreased repertoire of B and T cells, increased memory phenotype
- Well documented lymphopenia

2.) Heart transplant itself leads to infections post-transplant

- Immunosuppression
- Lymphatic damage

Figure: Distribution of cases of Respiratory Syncytial Virus/Vaccine-Preventable Infection (R/VPIs) over the post-transplant period among pediatric heart transplant recipients, 2003 – 2018.



Circulation. 2020;142:A14040

Immune Related Complications Before and After Cardiac Transplant

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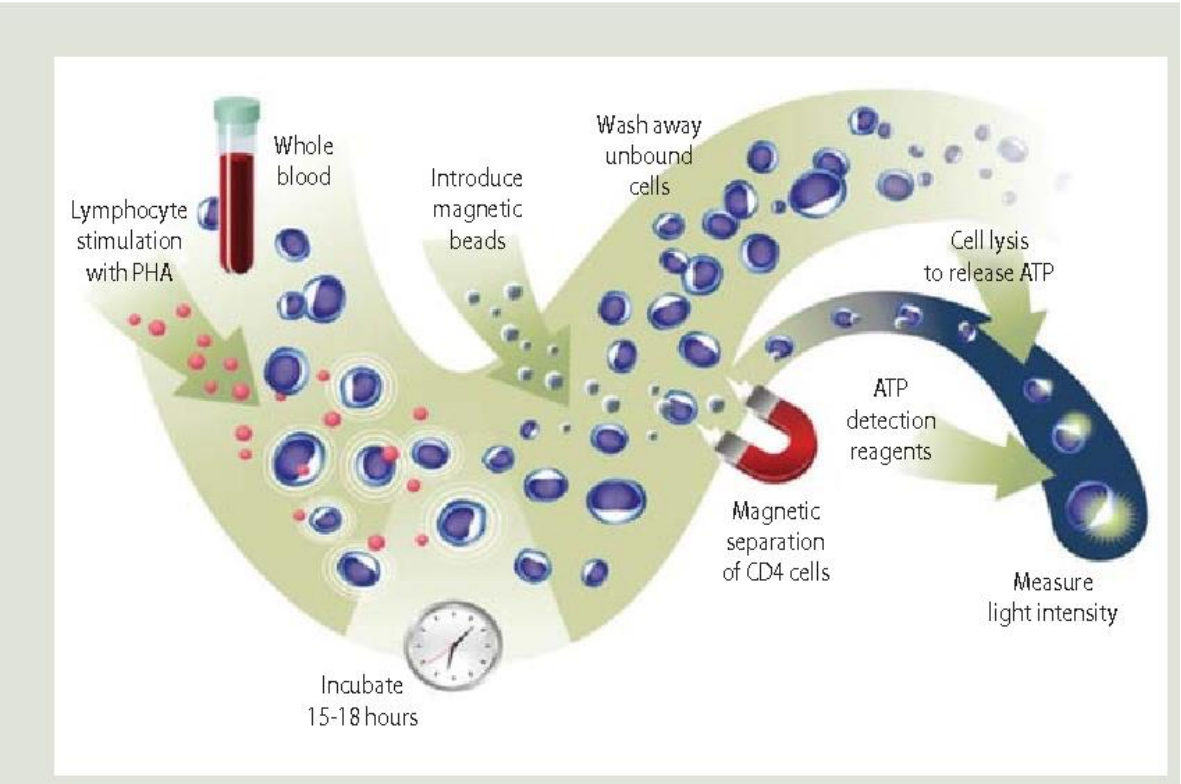
- ImmuKnow:
  - Advertised as an immune cell functional assay that detects cell-mediated immunity in an immunosuppressed population.



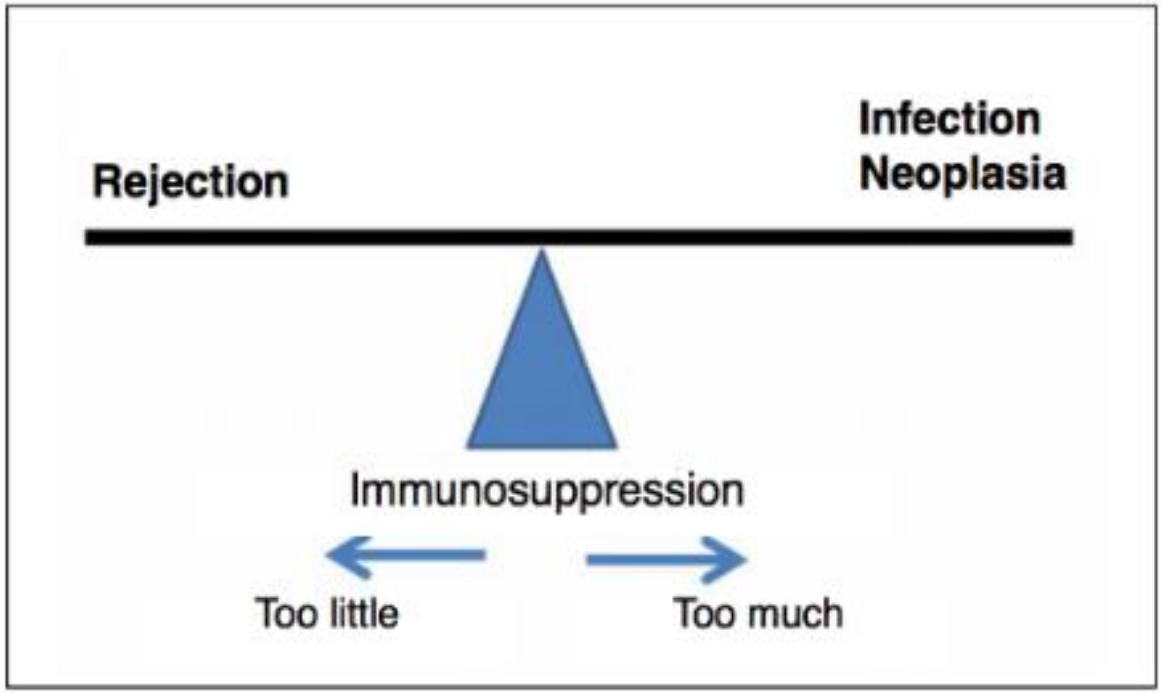
Stewart, B.L. (2012). ImmuKnow ® as an immune monitoring tool following organ transplantation ImmuKnow ® : biomarqueur de l ' immunité cellulaire après transplantation d ' organe.

Project Outline

The Research Question:

- In pediatric cardiac transplant patients referred to Lurie Children's hospital, do immune phenotype-based adjustments in immunosuppression improve transplant outcomes?

- **Outcomes**:
  - infection
  - graft vs host disease
  - rejection
  - graft failure
  - cardiac allograft vasculopathy (CAV)



https://www.niakoro.com/courses/basics-in-pediatric-heart-failure-and-heart-transplantation

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Project Outline

Goals of the Project:

- First Step:
  - Describe the population of children referred for cardiac transplant to Lurie Children's Hospital
  - Include baseline immunophenotyping
- Second Step:
  - Begin evaluation of the patients who completed transplant; specifically, those who are 12 months post-transplant

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Project Outline

Methods:

- Lurie Children's Cardiac Transplant referral database
- From 1/1/2020 to 6/30/2022, 51 patients were referred to Lurie for cardiac transplant evaluation.

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Results

- Demographics:

	Patients (n=51)	**Percentage** (rounded to nearest whole)
Gender		
Male	33	65%
Female	18	35%
Age at Eval. (years)		
0-10	29	56%
>10	22	43%
Ethnicity		
Asian	3	6%
Black	15	29%
Latino	12	24%
White	19	37%
Other	2	4%

Results

- Cardiac History:

	Patients (n=51)	**Percentage** (rounded to the nearest whole)
Heart Condition		
Congenital Heart Disease (CHD)	33	65%
Cardiomyopathy	12	24%
Cardiac allograft vasculopathy (CAV)	6	12%
Prior Cardiac Surgery		
Yes	43	83%
No	8	16%
Age at first Cardiac Surgery		
<12 months	36	84%
>12 months	7	16%
Norwood/Glenn		
Yes	25	49%
No	26	51%
Fontan		
Yes	12	24%
No	39	76%

Results

- Cardiac History/Genetics:

	Patients (n=51)	**Percentage** (rounded to the nearest whole)
Genetic Complications		
22q11.2 deletion	3	6%
Cardiac genetic testing*	16	31%
Heterotaxy +/dextrocardia	7	14%

* Includes dilated cardiomyopathy panels, chromosomal abnormalities, known genetic syndromes (VACTERL, NONO syndrome)

Results

Immune Phenotyping:

- All 51 patients were reviewed for baseline immune evaluation
  - TRECs
  - T/B/NK cell enumeration
  - Available subsets of T and B cells
  - Quantitative immunoglobulins
  - Vaccine responses**
  - Limitations: few had T cell functional testing completed, rarely were TCR-V beta assessed

	Patients (n=51)	**Percentage** (rounded to the nearest whole)
TRECs		
Low	3	6%
Normal	20	39%
Unknown	28	55%
CD3+ T cells (cells/mm^3)	**n=45**	
<1000**	24	53%
>/=1000	21	47%
IgG levels (mg/dL)	**n=31**	
<600	8	26%
>/=600	23	74%

*All patients had protective Strep and Tetanus

**6 patients had <200 CD3+ T cells

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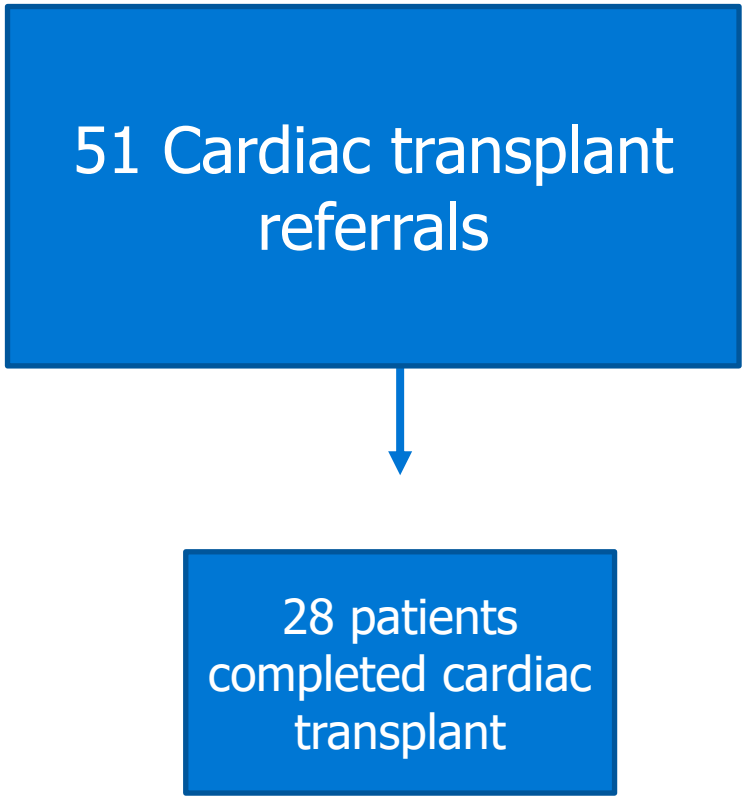
Results

Who made it to transplant?



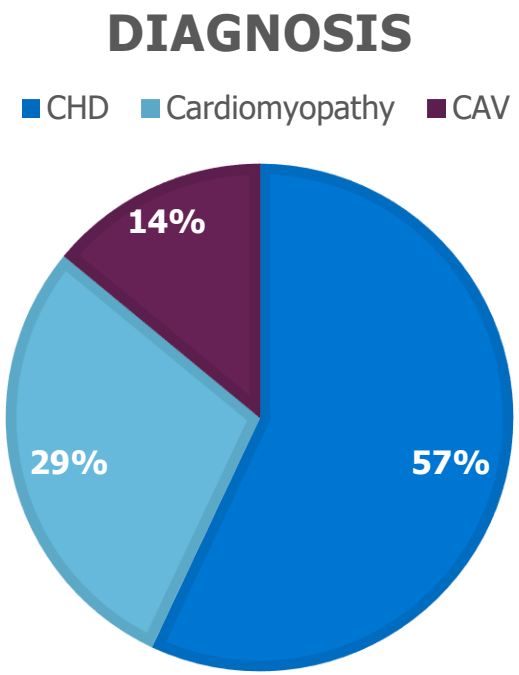
Results

Outcome Evaluation:

- Does baseline immune phenotype or age of thymic disruption affect rate of:
  - Infections
  - Rejection
  - Autoimmunity/lymphoproliferation (limited by follow up time)

Results

- Transplanted patients:



Sex	n=28	% total (rounded to the nearest whole)
Male	19	68%
Female	9	32%

Baseline CD3+ T cells	n=28	% total
<200	3	11%
200-500	5	18%
501-1000	10	36%
1001-1500	4	14%
1501-2000	4	14%
Unknown	2	7%

Results

- Transplanted patients:

Age at Transplant (yrs)	**Patients** n=28	**% total** (rounded to nearest whole)
<1	4	15%
1-5	8	31%
6-10	1	4%
11-15	4	15%
16-20	9	35%

Immunosuppressive Regiment	**Patients** n=26	**% total**
Tacro + MMF	15	58%
Tacro + Sirolimus	8	31%
Tacro + Azathioprine	1	4%
CyA + MMF	1	4%
Tacro only	1	4%

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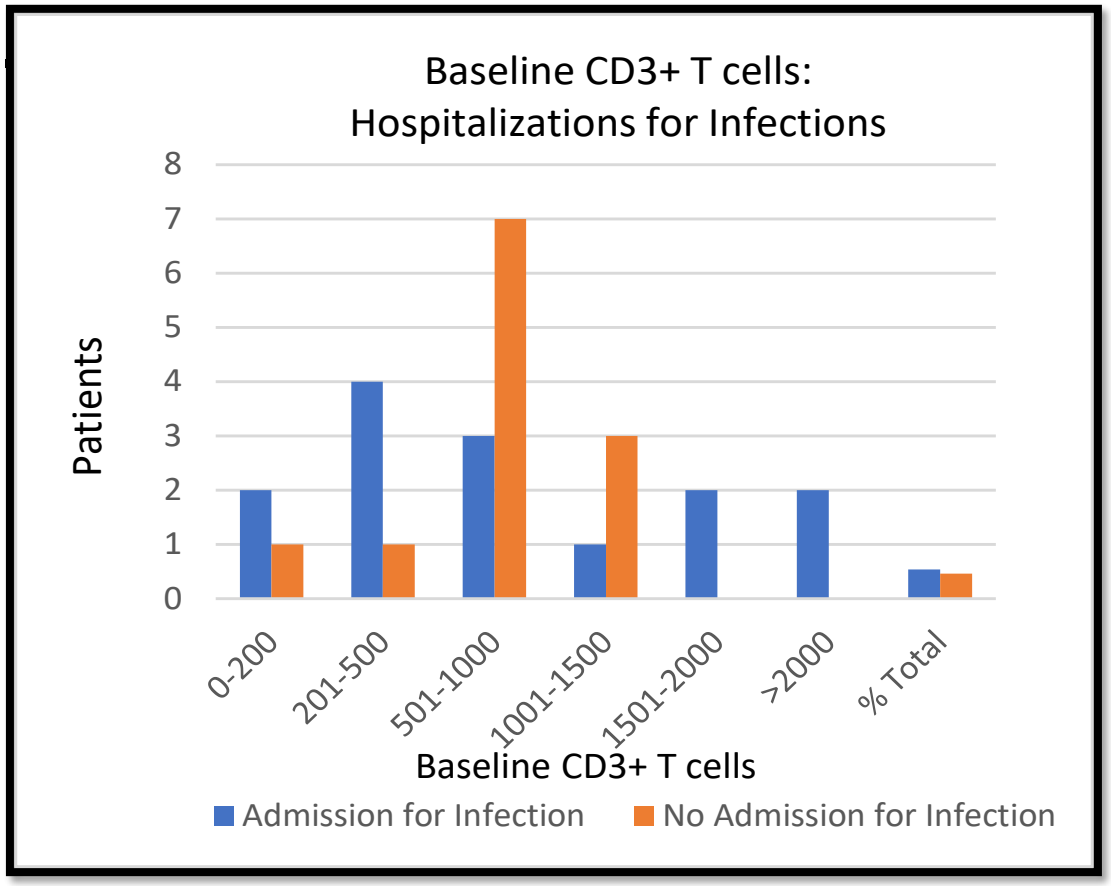
Results

When considering baseline CD3+ T cells, what impact did this have on infections post-transplant?

A.



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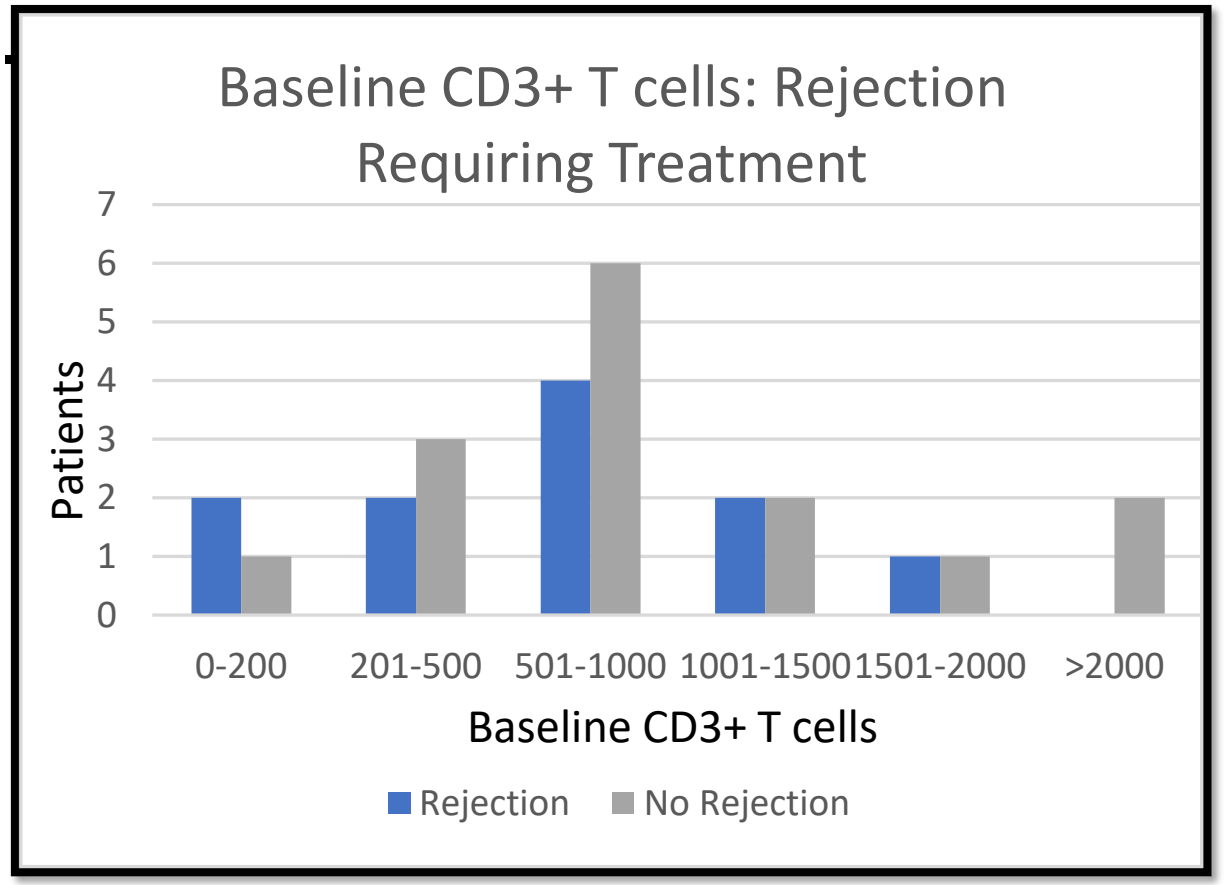
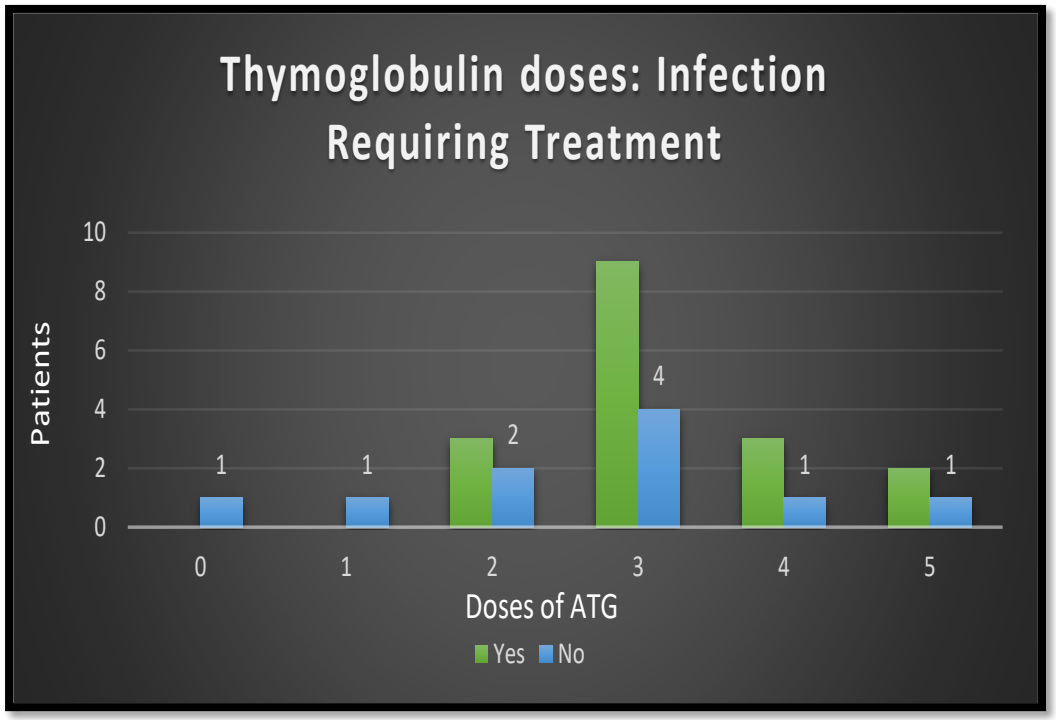
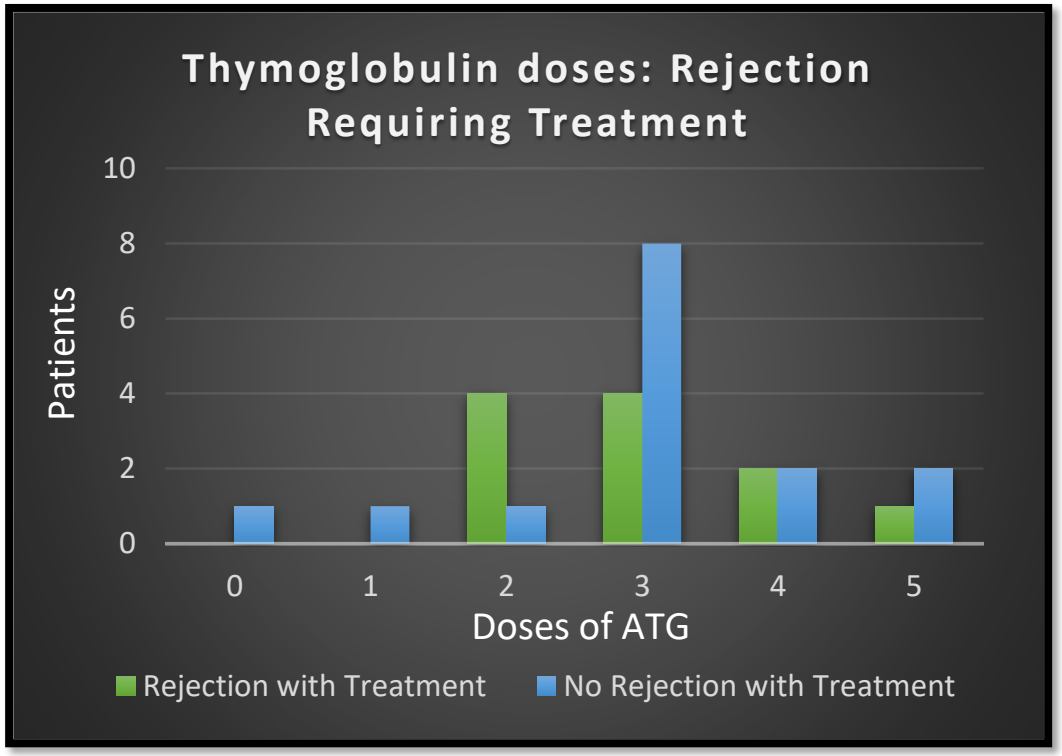


Results

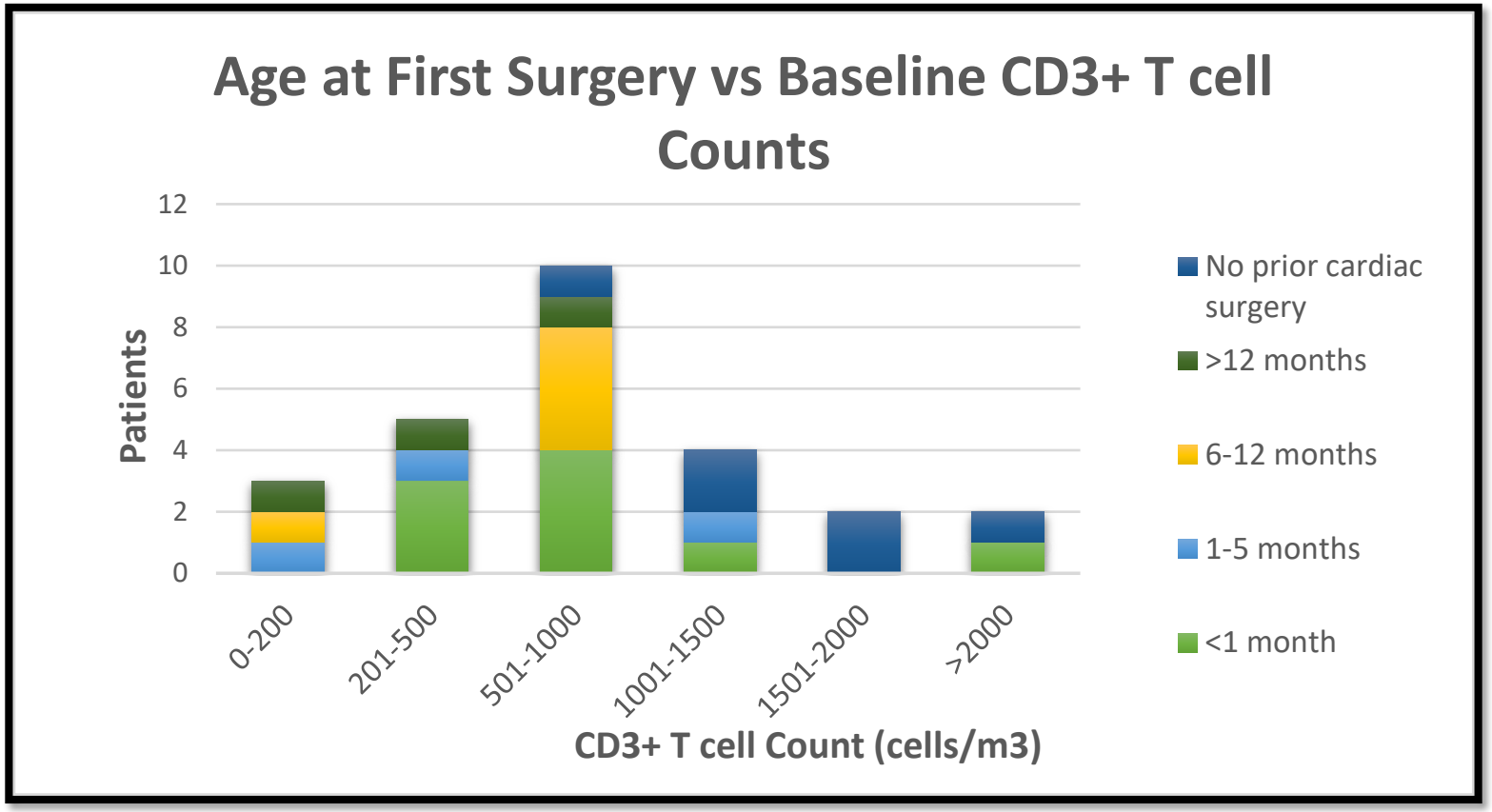
How is induction immunosuppression impacting infections and rejection?





Results

- Secondary questions:



Results

Analysis Plans:

- Multivariable analysis to answer the following questions:
  - Primary Question:
    - Can we reduce immunosuppression in cardiac transplant patients who are immunosuppressed at baseline to decrease infections while maintaining protection from rejection?
  - Secondary Question:
    - Can we redemonstrate CD3+ lymphopenia based on timing of first cardiac transplant/thymectomy?

Limitations

- Small sample size
- Retrospective – missing data cannot be changed such as labs collected, functional testing.
- Apart from vaccines, T cell functional testing was not completed pre-transplant in the majority of patients.

Future Directions

- Partnership with infectious disease
  - Optimizing prophylaxis and pre-transplant vaccination safely
- Etiology of infections post-transplant
  - Immune suppression vs a combined picture
- Informed and new targeting of B-cell producing cells
  - Continued rejection despite plasma cell targeting and B cell depletion

Thank you!

- Dr. Aisha Ahmed,
  Department of Allergy and Immunology
- Dr. Brian Madden,
  Department of Pediatric Cardiology

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