Immune Function and Infection Risk after Pediatric Cardiac Surgery

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Introduction/Background

Congenital Heart Disease

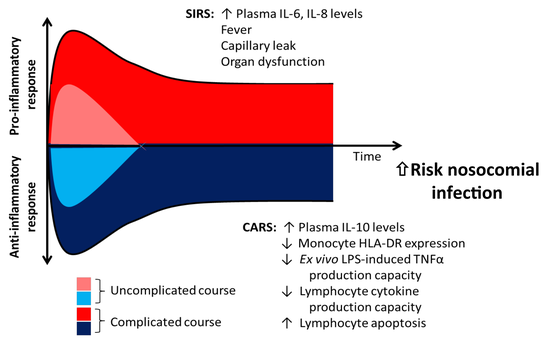
- Congenital heart disease (CHD) comprises structural abnormalities of the heart and/or great vessels
- Most common congenital condition diagnosed in neonates
- Comprises ~ 1% of births in US per year
- More complex surgeries required at younger age confers greatest risk for morbidity and mortality

Infection Risk after Cardiac Surgery

- Nosocomial infections after CHD surgery are a significant *additional* source of morbidity
  - ➢Re-operation
  - ➢Prolonged hospital and ICU stays
  - ➢Longer mechanical ventilation
  - ➢Longer need for inotropic support

Major *host* factor related to risk for infection: **Post-operative systemic inflammation**

SIRS/CARS

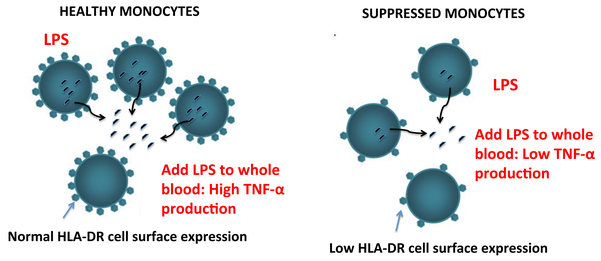


K. C. Greathouse and M. W. Hall, 2016, *American Journal of Critical Care, 25*(1), p. 88.

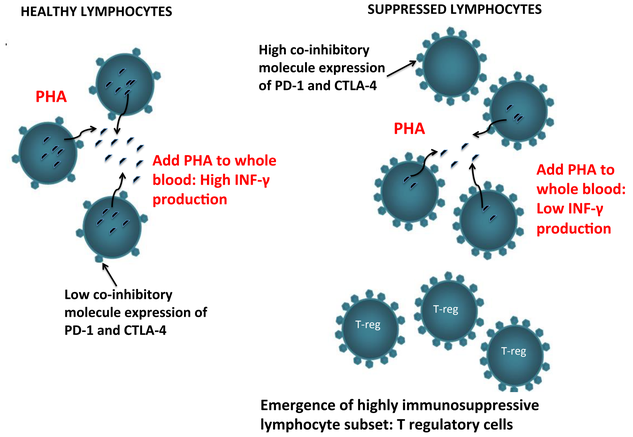
- Predominance of an *anti-inflammatory* response leads to an *acquired* immune suppressed state.

Determination of immune suppression

Innate immune function

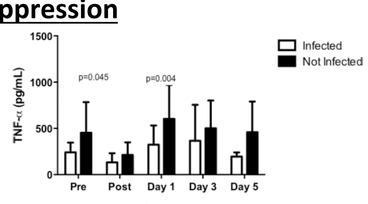


Adaptive immune function

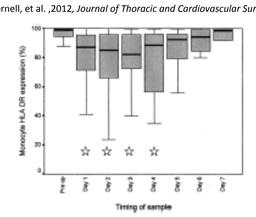


Evidence for post cardiac innate immune suppression

- Both TNF-α production and HLA-DR expression suppressed early after pediatric cardiac surgery
- To date, adaptive immune suppression has not been evaluated



Cornell, et al. ,2012, *Journal of Thoracic and Cardiovascular Surgery, 32*(6)



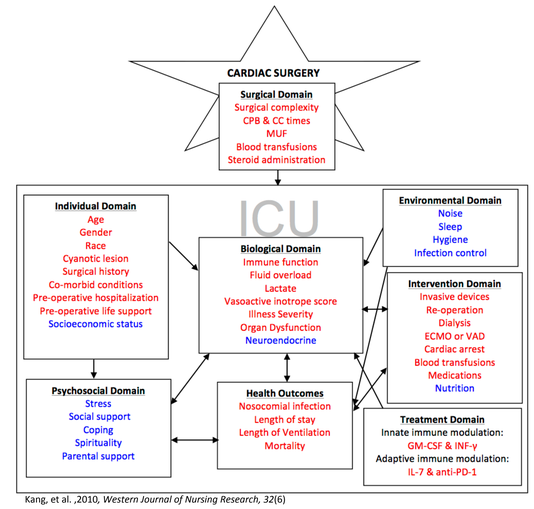
Allen, et al. ,2002, *Critical Care Medicine, 30*(5)

Aims/Purpose

- Quantitate changes in innate *and* adaptive immune function over time in children undergoing surgery for congenital heart defects and determine its relationship with development of nosocomial infection.

Theoretical Framework

Modified Expanded Biobehavioral Model



Kang, et al. ,2010, *Western Journal of Nursing Research, 32*(6)

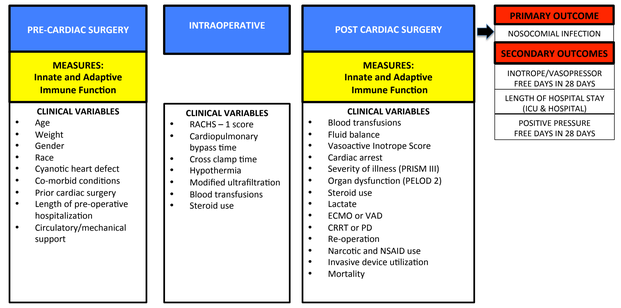
Red: Variables that will be measured in this study; **Blue**: Focus of future aims

Methods/Measurements

- **Inclusion criteria:** Any child < 18 years of age undergoing cardiac surgery at NCH
- **Exclusion criteria:**

1) Age ≥ 18 years old
2) Limitation of care order
3) History of immunodeficiency disorder or receiving medications for the purposes of immune suppression
4) Heart or heart/lung transplantation

Study Design



Innate & Adaptive Immune Function Measures

PRE-CARDIAC SURGERY Pre-admission testing or In-hospital pre-op bloodwork → ***POST-OPERATIVE WEEK 1** Post Op Day 1 & Day 3 → ***POST-OPERATIVE WEEKS 2 – 4** x2 weekly Cytokine Measures x1 weekly Flow Cytometry

CYTOKINE MEASURES	

Stimulated cytokine production
• Whole blood *ex vivo* LPS induced cytokine production
  ○ Primary biomarker: **TNF-α production capacity**
• Whole blood *ex vivo* PHA induced cytokine production
  ○ Primary biomarkers: **INF-γ, IL-2 and IL-10 production capacity**
	Plasma cytokine evaluation
	• Plasma cytokine evaluation from supernatants of non-stimulated whole blood samples: **IL-10 and IL-6**

FLOW CYTOMETRY MEASURES	

Monocyte flow cytometry
• **HLA-DR expression**
  ○ Percent positive
  ○ **PD – 1 ligand (PD-L1 &PD-L2) and CLTA-4 ligand (CD80 & CD86) expression**
	Lymphocyte flow cytometry
	• **CTLA-4 & PD-1 expression**
	  ○ Percent positive
	• **Percentage of T regulatory cells**

ABSOLUTE LYMPHOCYTE COUNTS	
• **Complete blood counts (when available)** • **Enumeration of lymphocyte subsets via flow cytometry**	

*Bloodwork to perform immune function measures will be obtained post-op in the ICU and limited to 28 days if they remain in the ICU

Summary

- Goal of this study is to determine the incidence of cardiac surgery induced immune suppression and its relationship with development of post-operative infection
- First study to evaluate *both* innate and adaptive immune function in pediatric cardiac patients and its relevance to post-surgical outcomes

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