Stanford MEDICINE | Pediatric Infectious Diseases Program for Immunocompromised Hosts

Stanford Children's Health | Lucile Packard Children's Hospital Stanford


# Optimizing CMV Prevention

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# What is the optimal CMV prevention strategy for pediatric solid organ transplant patients?

# Main prevention strategies

| Strategy | Characteristic |
|---|---|
| Prophylaxis | Continuous anti-viral |
| Preemptive | Trigger used to start anti-viral |
| Hybrid | Mix use dependent on time |

# 1. Need a better idea of the risk factors

# What are the issues for identifying risk factors?

Epidemiology for CMV disease is not well-delineated.

- Small sample size
- Focus on one organ
- Institution-specific

Green M. Am J Transpl 2006, 6:1906
Bueno J. Clin Infect Dis 1997, 25:1078
Nayyar N. Semin Pediatr Surg 2010, 19:64

Kranz B. Pediatr Transpl 2008, 12:474
Smith JM. J Am Soc Nephrol 2010, 21:1579
Danziger-Isakov LA. Transpl 2003, 75:1538
Danziger-Isakov LA. Transpl 2009, 87:1541

# What are the issues for identifying risk factors?

Epidemiology for CMV infection is also not well-delineated.

- Definition for CMV infection, CMV syndrome, CMV disease is not standardized.
- Threshold for CMV quantitative nucleic acid testing (QNAT) is not known.
- Is the rate of rise of CMV QNAT (viral load) predictive for CMV disease?

# Risk factors

- Donor/Recipient CMV serostatus
- Age
- CMV QNAT (viral load) and rate of rise
- Primary CMV infection
- Immunosuppression intensity
  - Induction
  - Allograft rejection
  - Type of organ
  - Time from transplant
- Other infections

2.Need a better idea of outcomes with each prevention strategy.

# Clinical Outcomes?

For prophylaxis vs. preemptive vs. hybrid:

- CMV disease, CMV syndrome, CMV infection
- Death
- Allograft rejection
- Other infections

# Our approach

Developed a database of our SOT patients at LPCH

- Clinical data warehouse (STRIDE) – 2005
- Extract risk factors and outcomes (as outlined before)

# Our Proposal

- Systematic analysis through the Collaborative/Network to start identifying potential optimal CMV prevention strategies.
- Extract the risk factors and outcomes from each multiple institutions.
- Assumption: variability of prevention strategies, risk factors, and clinical outcomes at the different institutions.

# Our Future

- Conduct comparative effectiveness trial of the different CMV prevention strategies.
- Incorporate immune-monitoring to the prevention strategies (i.e. CMV-specific T-cells).
- Incorporate adoptive transfer of CMV-specific T-cells to prevention strategies.

# Things to discuss

- Risk factors
- Clinical Outcomes
- Database strategy for the Collaborative/Network
- Funding strategy for the Collaborative/Network

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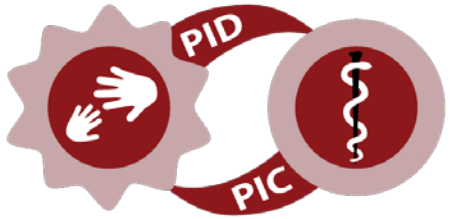


# In search of Evidence-based Guidelines for Management of Epstein Barr Virus in Pediatric Transplant Patients

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# Background

- EBV Particularly problematic for pediatric organ recipients
  - Large number experience primary EBV infection post transplant
- The most important long term outcome is Post-transplantation Lymphoproliferative Disease (PTLD)
  - Occurs in 1-15% of liver/renal and up to 6-20% in lung /intestinal/heart
  - Outcomes of PTLD are variable to institutions and are organ-specific
    - Overall ~14%
    - 44% intestinal
    - 31% heart
    - 30% lung
    - 22% liver
    - ~0% renal
  - Prevention is key but early diagnosis is associated with better outcomes, low threshold of suspicion for disease

# Data From UNOS-Stanford

## Summary Stats 1988-2014 CASU + 2009-2014 CAPC

| Organ | Total | PTLD | Percent PTLD | Percent PTLD in Literature |
|---|---|---|---|---|
| Heart | 294 | 21 | 7 | 3-9 |
| Heart-Lung | 34 | 3 | 9 | 16 |
| Intestine | 42 | 7 | 17 | 10-45 |
| | | | | |

## Summary Stats 1995-2014 CAPC

| Organ | Total | PTLD | Percent PTLD | Percent PTLD in Literature |
|---|---|---|---|---|
| Kidney | 426 | 7 | 2 | 2-4 |

# PTLD Risk Factors from Literature

- Pre-transplant
  - Seronegative
- Time of transplant
  - Use of T cell suppressive therapy
  - <24 months of age
  - Circulating virus
  - Viral co-infections (?)
- Post-transplant
  - EBV DNAemia
  - Persistent low levels of DNAemia
  - Use of T cell suppressive therapy
  - Use of steroids
  - < 5 years old at time of EBV DNAemia

# What is known

- Pre-emption
  - No established cut-offs signifying PTLD disease or risk but usually detection in more than one sample prompts action
  - Only decreasing immunosuppression as preemptive therapy has been shown to be effective in reducing EBV disease including PTLD
  - Older studies supported IVIg, but newer ones did not
- Treatment
  - IVIg including CMV-IVIg has been shown in vitro to be effective in controlling EBV infected cells
  - Rituximab or anti-CD20 monoclonal antibody is effective and should be used for PTLD that has a strong CD20 phenotype which is not routinely the case
  - Role for T cells in viral control has been established

# Knowledge Gaps

- Organ specific risk factors
  - Immunosuppression regimens
  - rejection
- Host specific risk factors
  - Age
  - Viral-specific immunity
- Virus specific risk factors
  - Monitoring strategies
    - When, how frequently, with what assay
  - Thresholds requiring interventions
    - Links to disease states
- Interventions
  - What, when, how long
- Treatments
  - Effective therapies
    - Viral specific
    - Immune specific

-Can we effectively risk stratify
-Is there a strategy for screening that is based on viral and host interactions
-Are there viral copy thresholds below which no disease or PTLD develops
-Is this also determined by host immunity
-What known interventions work, don't work
-What known treatments work, don't work

# Proposal

- Consortium of pediatric transplant centers
  - Leverage institutional variation
    - Numbers alone not sufficient to develop universal guidelines but together are
    - Institutional variation in screening, interventions, treatment will allow for comparisons
- Data-base informatics to extract clinical information
  - Phase 1: Retrospective data collection
    - Goal:
      - Generate evidence-based universal guidelines
  - Phase 2; Prospective surveillance
    - Goals:
      - Continue to generate information to inform guidelines
      - Monitor outcomes if institutional variation continues
      - Add host-specific and viral-specific immunological surveillance
      - Add tissue  specific information, what compartment is most important, how to monitor
      - Add new treatments as they become available

# Data Extraction

- Use of clinical informatics to extract research specific clinical data from EMR
  - Stanford Clinical data warehouse
- Extracted data will be coupled with manual chart extraction for missing data points
- Entered into cloud based data storage, ie Research Electronic Data Capture
- Data pooled and analyzed by lead institution and shared back