Optimizing CMV Prevention

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February 19, 2015
What is the optimal CMV prevention strategy for pediatric solid organ transplant patients?
### Main prevention strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>Continuous anti-viral</td>
</tr>
<tr>
<td>Preemptive</td>
<td>Trigger used to start anti-viral</td>
</tr>
<tr>
<td>Hybrid</td>
<td>Mix use dependent on time</td>
</tr>
</tbody>
</table>
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

Nayyar N. Semin Pediatr Surg 2010, 19:64
Kranz B. Pediatr Transpl 2008, 12:474
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
In search of Evidence-based Guidelines for Management of Epstein Barr Virus in Pediatric Transplant Patients

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February 19, 2015
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

<table>
<thead>
<tr>
<th>Organ</th>
<th>Total</th>
<th>PTLD</th>
<th>Percent PTLD</th>
<th>Percent PTLD in Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>294</td>
<td>21</td>
<td>7</td>
<td>3-9</td>
</tr>
<tr>
<td>Heart-Lung</td>
<td>34</td>
<td>3</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Intestine</td>
<td>42</td>
<td>7</td>
<td>17</td>
<td>10-45</td>
</tr>
</tbody>
</table>

#### Summary Stats 1995-2014 CAPC

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</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>426</td>
<td>7</td>
<td>2</td>
<td>2-4</td>
</tr>
</tbody>
</table>
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