Cytomegalovirus in the immunocompetent: Prevent, Treat, or Ignore?

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Cytomegalovirus

- Double stranded DNA virus (HSV, VZV, EBV)
- CMV acquired by 80% by age 70
- Mother-child and any close contact are routes
- After primary infection remains latent in mononuclear cells
- With acquired immune deficiency, replication and tissue invasion: lungs, GI, retina, heart
CMV cycle

Primary Infection (seroconversion)

Latency in mononuclear cells (seropositive no tissue invasion)

Immunosuppression (organ transplant, HIV, blood transfusion)

Reactivation (CMV viral replication no tissue invasion)

CMV Disease Lung + GI tract (CMV viral replication with tissue invasion + symptoms)

Viral load, degree of immune suppression
CMV well recognized pathogen in immune compromised patient
CMV in “immune competent” critically ill

- In “immune competent” critically ill patients:
  - Is there evidence of CMV viral replication?
  - Is CMV viral replication associated with outcome?
  - Is CMV viral replication causally associated with outcome?
  - Should CMV replication be prevented or treated?
In “immune competent” critically ill patients
Is there evidence of CMV replication?

31% of CMV sero-positive immune competent ICU patients show viral replication
36% if restricted to studies using PCR instead of culture
Timing and prevalence of CMV replication by risk factor

Limaye, A. P. et al. JAMA 2008;300:413-422.
In “immune competent” critically ill patients is CMV viral replication associated with outcome?

CMV replication associated with crude doubling of mortality

CMV viral replication is independently and dose associated with death or prolonged hospitalization.

<table>
<thead>
<tr>
<th>Hospital stay variables</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Major infection</td>
<td>No</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3.0 (1.1-8.4)$^d$</td>
</tr>
<tr>
<td>CMV viremia at any level</td>
<td>No</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4.3 (1.6-11.9)$^d$</td>
</tr>
<tr>
<td>CMV viremia at &gt;1000 copies/mL</td>
<td>No</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>13.9 (3.2-60.9)$^d$</td>
</tr>
<tr>
<td>Maximum CMV load, log$_{10}$ copies/mL</td>
<td>1.8 (1.3-2.4)$^d$</td>
<td>&lt;.001</td>
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<tr>
<td>Average CMV AUC, log$_{10}$ copies/mL</td>
<td>2.1 (1.4-3.2)$^d$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Transfusion days (10% increments)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator days (10% increments)</td>
<td>1.3 (1.1-1.7)$^d$</td>
<td>.01</td>
</tr>
</tbody>
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JAMA. 2008;300(4):413-422
The phenomenon is not unique to CMV

Herpes simplex virus in the respiratory tract of critical care patients: a prospective study

Lancet 2003; 362: 1536–41

- HSV replication noted in oral and BAL samples in critically ill patients
- Risk factors for HSV replication: severity of illness, duration of critical illness, ARDS, intubation
- Associated with mortality, increased organ failure, and length of stay
In “immune competent” critically ill patients
Is CMV viral replication associated with outcome?

- Problems with association studies
  - CMV replication associated with severity of illness
  - CMV replication associated with duration of critical illness
  - CMV replication associated with sepsis

CMV replication may merely be a **marker** of immune suppression
In “immune competent” critically ill patients
Is CMV viral replication associated with outcome?

or ... CMV replication causes death

Severity of illness ➔ Immune Suppression ➔ CMV Replication ➔ Death

Severity of illness ➔ CMV Replication ➔ Infects lungs - ALI ➔ Death

Infects lungs - ALI ➔ Inflammation ➔ CMV Replication ➔ Death

Nosocomial Infection ➔ CMV Replication ➔ Death
In “immune competent” critically ill patients
Is CMV viral replication causally associated with outcome?

• Mechanisms for CMV to increase mortality and length of stay in critically ill patients:
  – Organ (lung) infection
  – Unique ability of CMV to Amplify inflammatory pathways
  – Unique ability of CMV to Suppress immune function
Is CMV viral replication causally associated with outcome? Evidence for CMV tissue infection in ICU

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Number of patients</th>
<th>CMV IgG&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time of histologic examination, day</th>
<th>Methods</th>
<th>Rate&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>[31]</td>
<td>ICU, acute respiratory failure or VAP, negative BAL cultures</td>
<td>86</td>
<td>13/18 (72)</td>
<td>18 (10–40)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Autopsy or open-lung biopsy</td>
<td>25/86 (29)</td>
</tr>
<tr>
<td>[30]</td>
<td>ICU, ≥ 5 days of evolution of ARDS, negative microbiological cultures</td>
<td>36</td>
<td>ND</td>
<td>10 (5–55)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Open-lung biopsy</td>
<td>18/36 (50)</td>
</tr>
<tr>
<td>[29]</td>
<td>ICU, ≥ 5 days of evolution of ARDS, negative microbiological cultures</td>
<td>100&lt;sup&gt;d&lt;/sup&gt;</td>
<td>ND</td>
<td>7 (6–13.5)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Open-lung biopsy</td>
<td>30/100 (30)</td>
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At least **some** evidence of tissue infection by CMV

Does CMV cause ICU acquired ALI?

Osawa & Singh Crit Care 2009
Is CMV viral replication causally associated with outcome? CMV replication causes amplification of inflammation

- CMV replication associated with autoimmune diseases
- TNF levels correlate with CMV in sepsis
- Direction of causal arrow unclear

Mechanisms of CMV induced inflammation

- Translocation of NF-κB to nucleus
- ↑ TNF-α production
- ↑ smooth muscle cell proliferation
- ↑ Adhesion molecule expression
- ↑ IL-8 and chemokine secretion

American Journal of Transplantation 9: 2453–2458
Is CMV viral replication causally associated with outcome? CMV replication causes amplification of inflammation.

- CMV associated with increased IL-6/8 production in ALI patients (Limaye)
Is CMV viral replication causally associated with outcome? CMV replication causes immune suppression

- Evolutionary adaptation by virus to evade immune system?
- Increased rates of fungal and bacterial infections in viremic transplant recipients

Mechanisms of CMV Immune Suppression
- ↓ HLA expression
- HLA class I homologue
- ↓ Antigen presentation
- ↓ T-cell proliferation
- ↓ Production of IL-2, INF-γ, PD-1
- ↑ Fc receptor expression
- Fc receptor homologue
- ↑ Complement inhibitors
- ↓ Macrophage migration

In “immune competent” critically ill patients
Should CMV replication be prevented or treated?

• Current evidence does not support screening for or routine evaluation for CMV in immune competent ICU
• Current evidence does not support prophylactic therapy for CMV IgG positive
• Current evidence does not support treatment for recovery of CMV (culture or PCR) in blood or BAL in immune competent ICU without evidence of tissue invasive disease
A Randomized Double-Blind Placebo-Controlled Trial of
Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Lung Injury

- Phase II trial, 160 patients
- Inclusion: CMV IgG+, sepsis-ALI
- Exclusion: Immune-compromised patients who might merit screening for and treatment of CMV, expected mortality, expected short duration of mechanical ventilation
- Intervention: ganciclovir/valganciclovir x 28 days
# Screen and prophylaxis or Test and treat

<table>
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<tr>
<th>Pros</th>
<th>Treatment</th>
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<tr>
<td><strong>Prophylactic</strong></td>
<td><strong>Treatment</strong></td>
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<tr>
<td>• Conceptually more attractive (prevention rather than treatment) as it prevents all CMV reactivation at any site (including lung) before CMV-associated effects begin</td>
<td>• Minimizes drug exposure and toxicity by targeting only patients with documented CMV reactivation</td>
</tr>
<tr>
<td>• Logistically simpler</td>
<td></td>
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<tr>
<td>• Best opportunity to intervene before CMV-associated effects begin</td>
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<td>• Standard of care for other populations where CMV is a clinical problem</td>
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<tr>
<td>• Best experimental and clinical data for preventing CMV effects</td>
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<tr>
<td><strong>Cons</strong></td>
<td></td>
</tr>
<tr>
<td>• Effect “diluted” by high proportion of non-reactivators</td>
<td>• Logistically complicated</td>
</tr>
<tr>
<td>• Relative “over-treatment” with risk for drug toxicity</td>
<td>• May be too late to see any benefit of intervention (CMV-mediated effect cascade already initiated)</td>
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<td></td>
<td>• Plasma CMV PCR is an insensitive marker of CMV reactivation (preferentially local reactivation in lung)</td>
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Prophylactic regimen

• Ganciclovir 5 mg/kg BID x 5 days then
• Ganciclovir 5 mg/kg QD until tolerating oral
• Valganciclovir 900 mg orally until day 28
  – This is a higher dose than the current “low dose” regimens taken for longer periods in solid organ transplant
A Randomized Double-Blind Placebo-Controlled Trial of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Lung Injury

- **Primary Endpoint:** Change in blood IL6
- **Secondary endpoints (mechanistic)**
  - Immune modulatory cytokines in BAL and serum
  - CMV viral load (blood, throat BAL)
- **Secondary endpoints (clinical) - underpowered**
  - Organ failure
  - Nosocomial infection
  - Duration of mechanical ventilation
  - Mortality
  - Safety
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or fellowship inquiries