Opportunistic pathogens in the intensive care unit

David Ong, MD, PharmD, PhD
10 februari 2017
NVIC Intensivistendagen 2017
Cytomegalovirus reactivation in ICU patients

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## Disclosure belangen spreker

<table>
<thead>
<tr>
<th>(potentiële) belangenverstrengeling</th>
<th>Geen</th>
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<tbody>
<tr>
<td>Voor bijeenkomst mogelijk relevante relaties met bedrijven</td>
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<tr>
<td>- Sponsoring of onderzoeksgeld</td>
<td>GEEN</td>
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<td>- Honorarium of andere (financiële) vergoeding</td>
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<td>- Aandeelhouder</td>
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<td>- Andere relatie, namelijk …</td>
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Introduction

After primary infection cytomegalovirus (CMV) remain latent under control of cellular and immune surveillance mechanisms.

Impaired immune system $\rightarrow$ viral replication

CMV infection associated with increased morbidity and mortality in immunocompromised patients (e.g. transplant patients, HIV patients).

Reactivation of (especially) CMV in intensive care unit (ICU) patients without known prior immune deficiency.

Osawa 2011 Crit Care
Effects of cytomegalovirus (CMV) on outcome

Three possible mechanisms:
1. Direct cytopathologic effect on organs
   • “CMV disease”, e.g. CMV pneumonitis, colitis, hepatitis
   • Histopathological evidence of CMV pneumonia in 30% of open-lung biopsies in ARDS patients with negative cultures and no respiratory improvement

Effects of cytomegalovirus (CMV) on outcome

Three possible mechanisms:

1. Direct cytopathologic effect on organs
2. Immunopathologic effect (excessive immune response)
   • CMV reactivation \(\rightarrow\) abnormal pulmonary cytokine/chemokine expression \(\rightarrow\) pulmonary fibrosis

Cook 2006 Crit Care Med
Effects of cytomegalovirus (CMV) on outcome

Three possible mechanisms:

1. Direct cytopathologic effect on organs
2. Immunopathologic effect (excessive immune response)
   • CMV reactivation → abnormal pulmonary cytokine/chemokine expression → pulmonary fibrosis
3. Alteration of immune defenses
   • CMV = immunosuppressive effect in animal models
   • Clinical studies in transplant patients: less bacterial (super)infections in ganciclovir group
Prophylactic treatment against CMV

Proven effectiveness of prophylactic/pre-emptive antiviral treatment in:
- Solid organ transplant patients
- Hematopoietic stem cell transplantation patients

How about previously immunocompetent ICU patients with:
- Acute respiratory distress syndrome (ARDS) patients?
- Severe sepsis or septic shock?

Overview studies assessing the impact of CMV reactivation on mortality (with adjusted analyses)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Patient study population</th>
<th>Increased mortality</th>
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<tbody>
<tr>
<td>Jaber 2005 Chest</td>
<td>Blood (pp65)</td>
<td>237 patients with fever for &gt;72 and without proven infection</td>
<td>No</td>
</tr>
<tr>
<td>Limaye 2008 JAMA</td>
<td>Blood (PCR)</td>
<td>120 newly admitted ICU seropositive patients</td>
<td>Yes</td>
</tr>
<tr>
<td>Heininger 2011 Crit Care</td>
<td>Blood + respiratory tract (PCR)</td>
<td>86 with severe sepsis or septic shock</td>
<td>No</td>
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<tr>
<td>Coisel 2012 Plos One</td>
<td>Blood + respiratory tract (PCR)</td>
<td>93 with suspected pneumonia</td>
<td>Yes</td>
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<tr>
<td>Frantzeskaki 2014 J Crit Care</td>
<td>Blood (PCR)</td>
<td>80 mechanically ventilated CMV-seropositive patients</td>
<td>No</td>
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<tr>
<td>Lopez Roa 2015 Plos One</td>
<td>Blood (PCR)</td>
<td>133 CMV seropositive ICU patients that have undergone major heart surgery</td>
<td>Yes</td>
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<tr>
<td>Lopez Roa 2015 Crit Care Med</td>
<td>Blood (PCR)</td>
<td>115 CMV seropositive patients</td>
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Marker or true pathogen?

Most studies do not account for:
- Time dependent occurrence of CMV reactivation
- Competing risks / informative censoring
Study population

ARDS + ≥4 MV + immuno-competent + CMV seropositive

reactivation (viral load >100 IU/mL)

no reactivation

attributable mortality?
January 2011 – December 2013 mixed ICUs of two tertiary care centers

544 ARDS patients with ventilation > 4 days

Immunocompromised and/or antiviral treatment (n=145)

399 patients

128 seronegative

271 seropositive

197 no CMV reactivation (73%)

74 CMV reactivation (27%)

Median time to reactivation:
8.5 days (IQR 4 – 11 days)

Ong et al, 2016 Intensive Care Med
# CMV reactivation and ICU mortality

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<td>Adjusted (baseline and time-varying confounders *)</td>
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* Marginal structural modelling including:
  - daily RIFLE score from the previous day
  - daily SOFA score from the previous day
  - presence of septic shock on the previous day
  - receipt of at least 2 days of high dose corticosteroids during any previous days in the ICU
Results

Observed mortality 19%
Mortality difference 4%
(95% CI 1% - 8%)
Discussion

Observational studies cannot provide definite proof of CMV pathogenicity in ICU patients

Prophylactic approach:
- Reactivation rate 27% in CMV seropositive ARDS patients
- Adverse effects

Pre-emptive approach:
- Very frequent viral load monitoring
- Likely reduced effectiveness
Take-home messages:

CMV reactivation in ¼ of ICU patients with ARDS ➔ Independently associated with increased risk of dying in the ICU

Several possible mechanisms of pathogenicity:
1. Direct cytopathologic effect (“CMV disease”)
2. Immunopathologic effect (pro-inflammatory immune response)
3. Immunosuppressive effect

It remains to be determined whether antiviral prophylaxis or pre-emptive treatment will be effective in ICU patients.
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