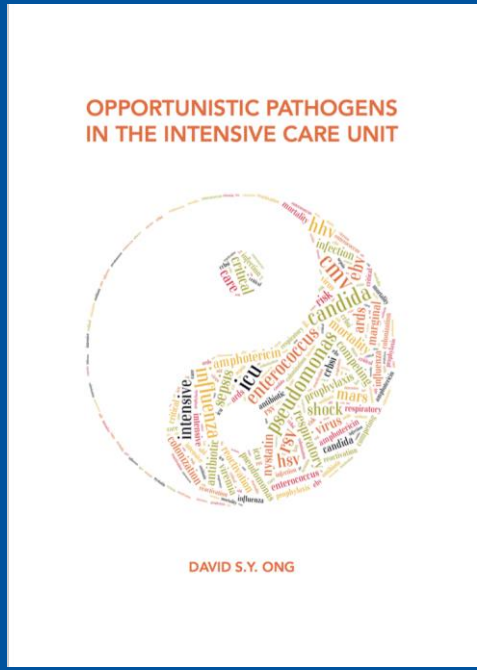
UMC Utrecht

Opportunistic pathogens in the intensive care unit

David Ong, MD, PharmD, PhD

10 februari 2017

NVIC Intensivistendagen 2017



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Cytomegalovirus reactivation in ICU patients

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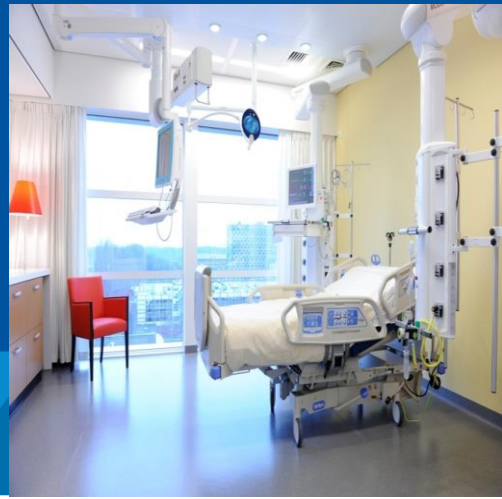


Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	GEEN

Introduction

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

Impaired immune system → viral replication

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

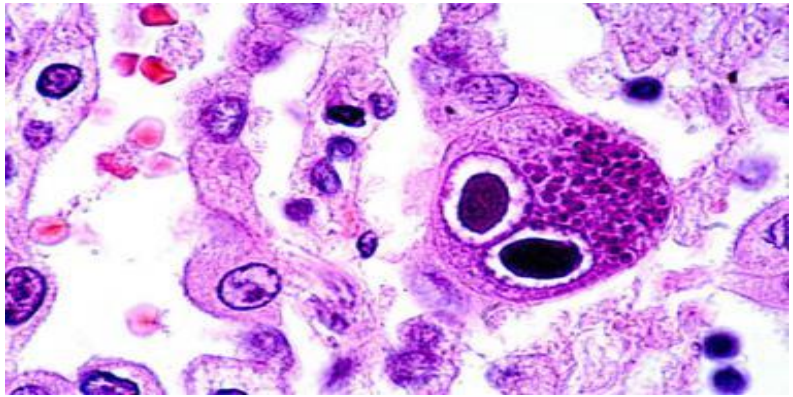
Reactivation of (especially) CMV in intensive care unit (ICU) patients without known prior immune deficiency

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



Papazian 2007 Crit Care Med, Luyt 2011 Presse Med, Papazian 2015 Intensive 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

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?

Owers 2013 Cochrane Database Sys Rev, Hodson 2013 Cochrane, Goodrich 1991 N Engl J Med, Mandell 2015 8th Edition, Medscape from WebMD

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

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

Marker or true pathogen?

Most studies do not account for:

- Time dependent occurrence of CMV reactivation
- Competing risks / informative censoring

Study population

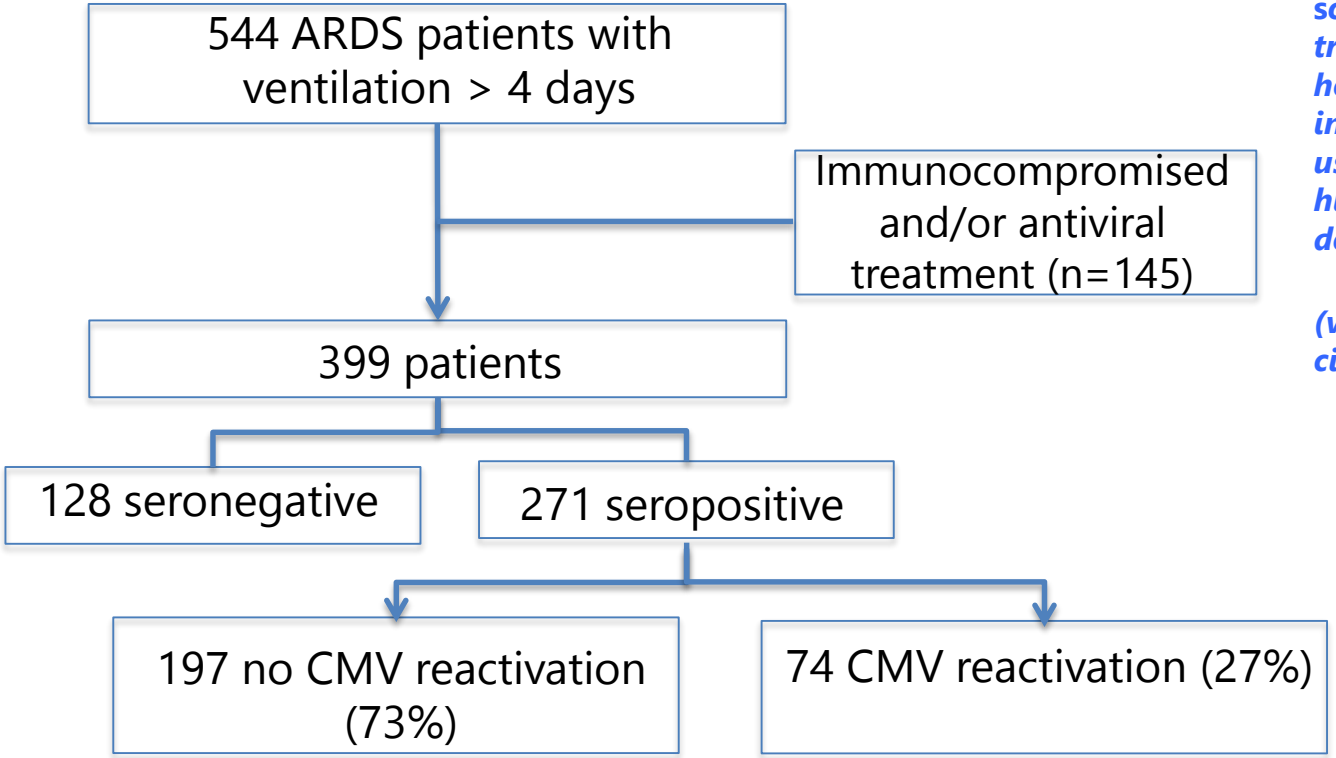
ARDS
+
≥4 MV
+
immuno-competent
+
CMV seropositive

reactivation (viral load >100 IU/mL)

no reactivation

attributable mortality?

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



solid organ or stem cell transplantation, HIV, hematological malignancy, immunosuppressive medication use, chemotherapy/radiotherapy, humeral or cellular immune deficiency

(val)ganciclovir, (val)aciclovir, cidofovir and foscarnet

enzyme immuno assay

CMV-DNA PCR

reactivation ≥ 100 IU/mL

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

Ong et al, 2016 Intensive Care Med

CMV reactivation and ICU mortality

Time-dependent Cox Regression Model	Mortality - SHR (95% CI)
Crude	3.39 (1.96-5.87)

CMV reactivation and ICU mortality

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Adjusted (baseline confounders)	2.74 (1.51-4.97)

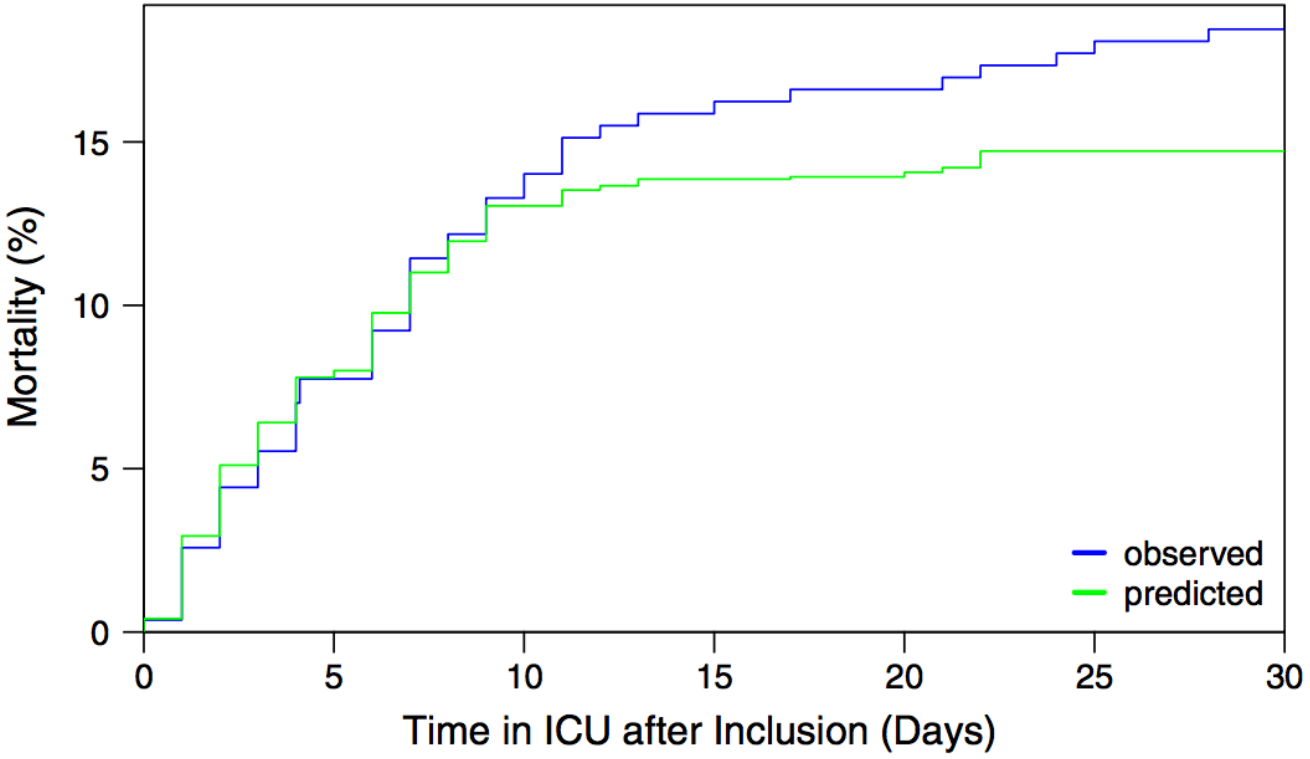
CMV reactivation and ICU mortality

Time-dependent Cox Regression Model	Mortality - SHR (95% CI)
Crude	3.39 (1.96-5.87)
Adjusted (baseline confounders)	2.74 (1.51-4.97)
Adjusted (baseline and time-varying confounders *)	2.48 (1.32-4.66)

** 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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