Journal Club

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Cytomegalovirus infection in critically ill immunocompetent hosts

Introduction

- A significant number of immunocompetent people suffer critical illness each year
- Many of these individuals experience CMV reactivation during their critical illness
- Associated with increased morbidity and mortality

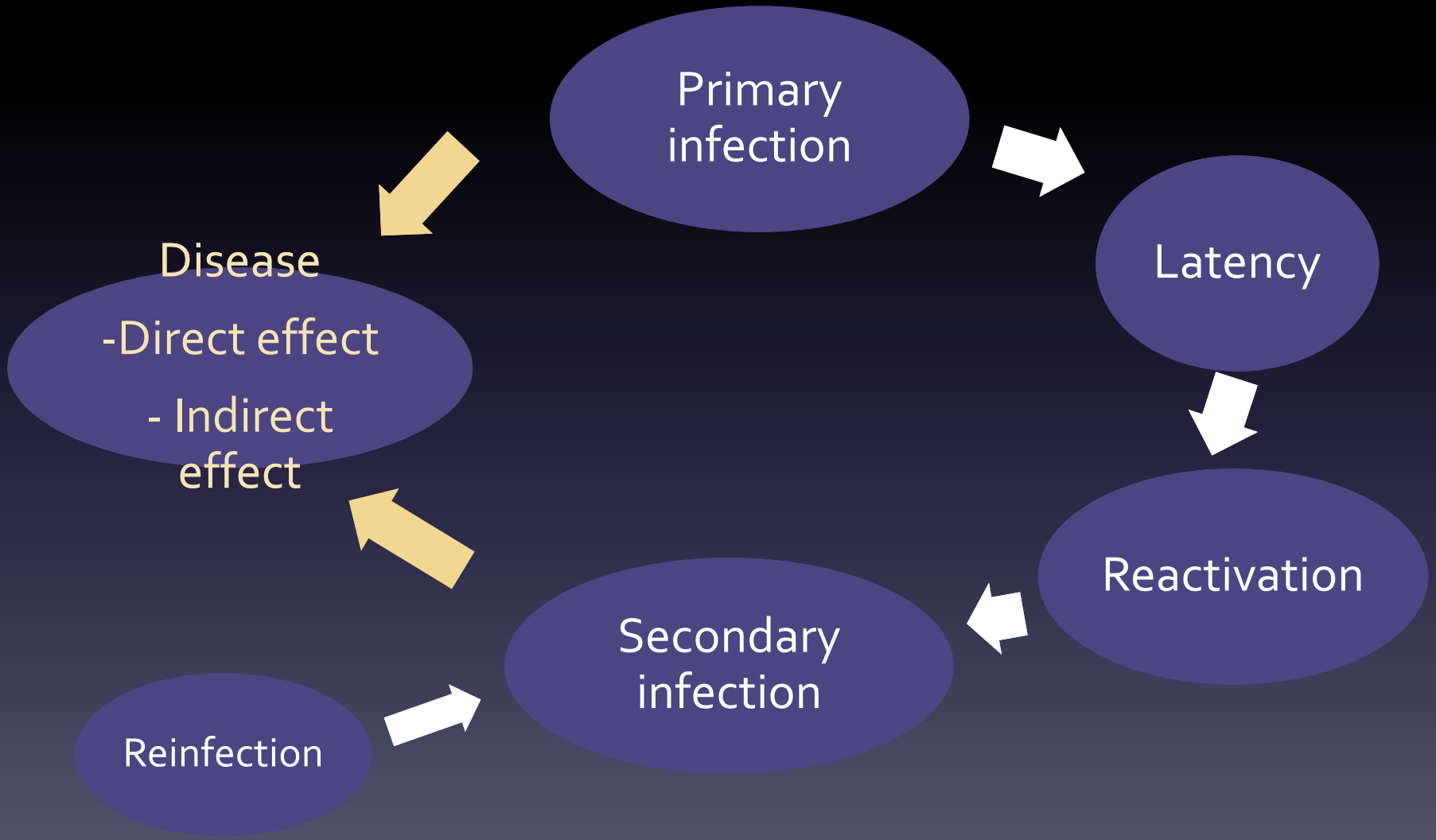
CMV

- An enveloped double stranded DNA virus
- Classified as a β-herpesvirus
- Latency
  - Following primary infection, can become latent in
    - Monocyte lineage and other leucocytes
    - Endothelial vascular cells
    - Others

Disease vs. infection

- INFECTION
  - Evidence of replication regardless of symptoms and signs
- DISEASE
  - Evidence of infection PLUS attributable symptoms and signs

Disease vs. infection



How do we know there is CMV infection?

- Positive viral cultures
- CMV antigenaemia quantification (pp65)
- CMV DNA quantification by PCR in blood/ clinical specimen e.g. BAL

Reactivation vs. Reinfection

- Most were reactivation rather than reinfection
  - Majority of patients with documented CMV activity during critical illness were CMV-IgG positive to begin with
  - Chance of getting a new CMV strain infection through blood transfusion was not high

Immunocompetent = NOT immunosuppressed

- NOT solid organ or HSCT recipients
- NOT infected with HIV
- NOT having a primary immunodeficiency disorder
- NOT recipients of immunosuppressive agents such as calcineurin-inhihibitors, antiTNFα drugs, antilymphocte antibodies or chemotherapeutic agents for treating cancers
- Patients on corticosteroids *not excluded (considered 'immunocompetent')*
- Do acknowledge that critical illness can induce transient immune compromise

CMV infection - How common? When? Who?

- Confounders
  - Monitoring methodology
    - PCR vs. pp65 vs. Culture (conventional/ shell vial)
    - Samples e.g. blood, BAL
    - Frequency/ timing of sampling
  - Patient groups e.g. different etiologies of one's critical illness

CMV infection *rate* and *timing*

- Overall rate
  - Up to 36%
- Time to onset
  - Usually 1 -3 weeks after the onset of critical illness
  - PCR assays seems to help diagnose earlier than antigenaemia assay

Risk factors for CMV infection

- Factors that seem associated
  - Burn and trauma patients
  - Mechanical ventilation at admission
  - Bacterial pneumonia
  - Sepsis
  - Steroid use
  - Transfusion within 24 hours of admission
- Factors that seem NOT associated
  - Age, sex
  - Disease severity scores e.g. APACHE, SOFA

Risk factors for CMV infection

- *Note: Despite exhaustive analyses of multiple available data sets, it has been impossible to narrow the group at risk for reactivation beyond ~ 1/3*

CMV infection is associated with poorer outcomes

- Higher mortality rate
- Longer ICU stay
- Longer period of mechanical ventilation
- Increased rate of nosocomial infections
- Higher incidence of organ dysfunction e.g. ARDS, renal failure, hepatic dysfunction

CMV ? Pathogenic role ? Merely bystander

- The causative role is not clear in human
- However, a pathogenic role in mice has been demonstrated

Animal model

- Murine CMV and human CMV share significant genetic and functional similarities
- Murine CMV is considered as an excellent model for human CMV infection, latency and reactivation
- Mice with CMV reactivation have higher levels of proinflammatory cytokines when compared to those without

Mice with CMV reactivation have higher levels of proinflammatory cytokines

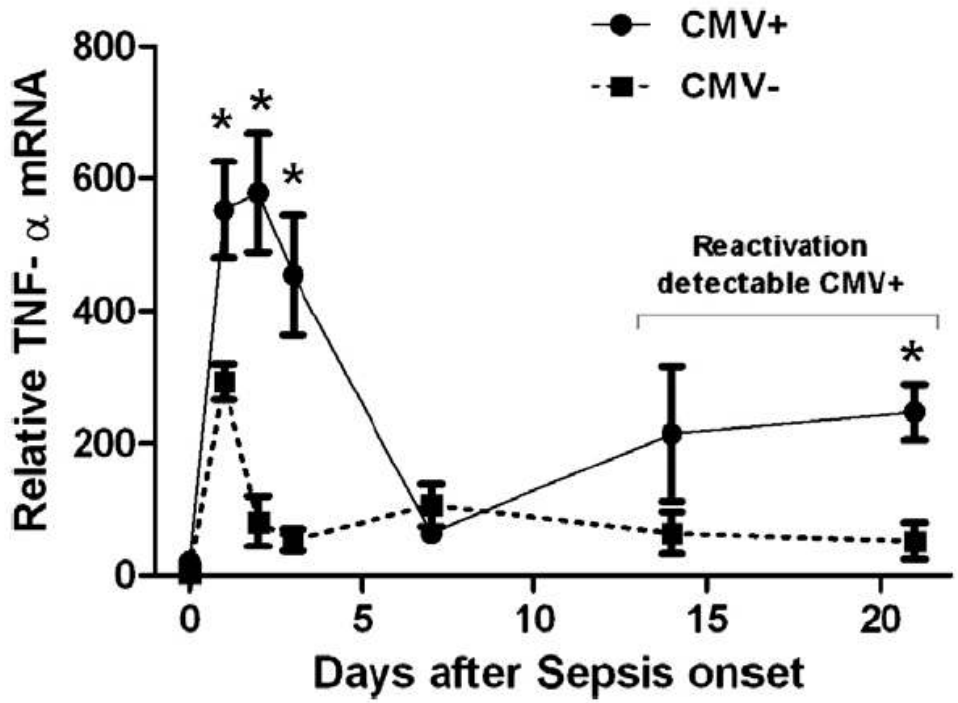


Fig. 1. Influence of previous cytomegalovirus infection on pulmonary TNF-α response to sepsis. BALB/c mice latently infected with 10^6 pfu Smith murine cytomegalovirus (CMV+) or naïve (CMV−) underwent sepsis by cecal ligation and puncture. Lung homogenates from cohorts ($n = 3–5$) were evaluated for TNF-α and β-actin mRNA 1, 2, 3, 7, 14 and 21 days after sepsis. TNF-α mRNA are expressed relative to β-actin and ∗ indicates significant difference from CMV- mice (two-tailed Student's t-test $p < 0.05$). Figure produced from previously published data (Cook et al., 2006b).

Antivirals prevented sepsis induced CMV reactivation and reduced the degree of pulmonary fibrosis in mice

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Antiviral prevention of sepsis induced cytomegalovirus reactivation in immunocompetent mice

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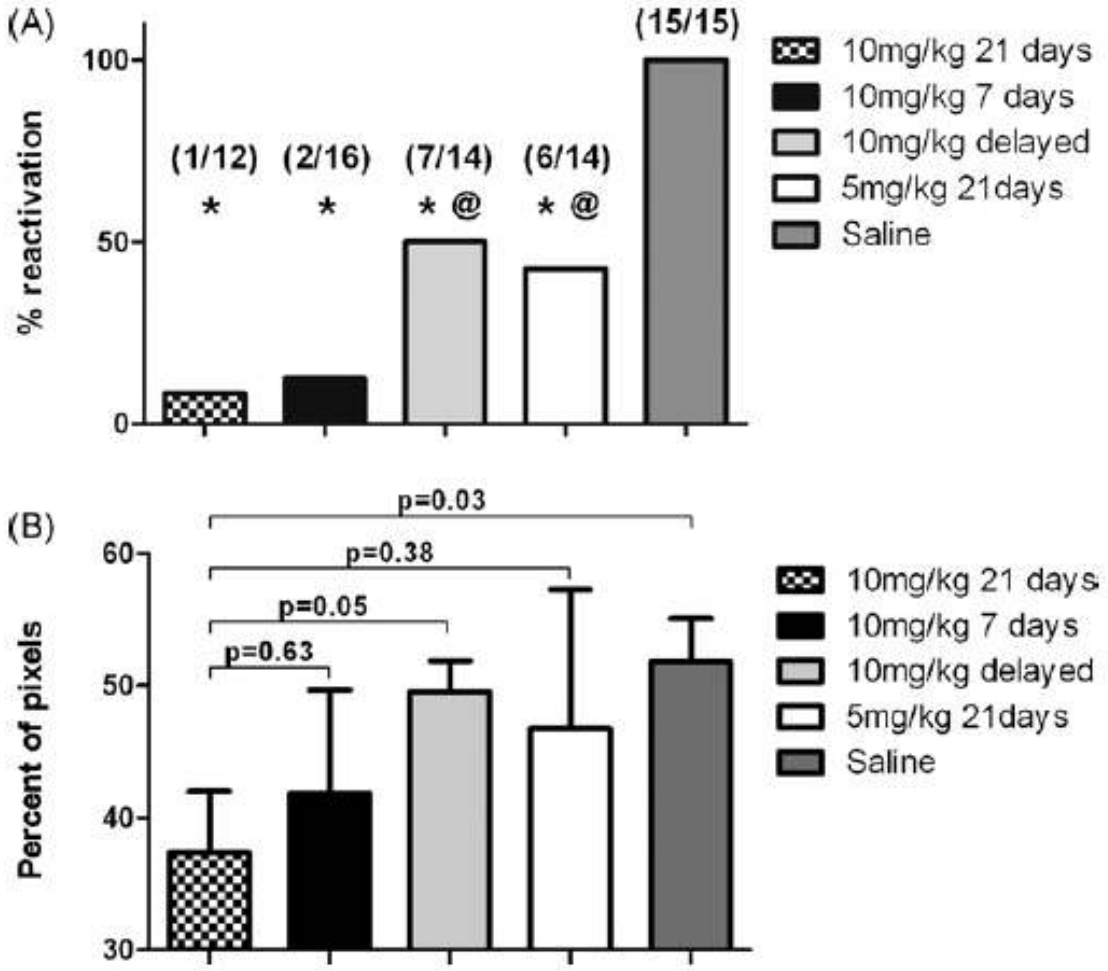
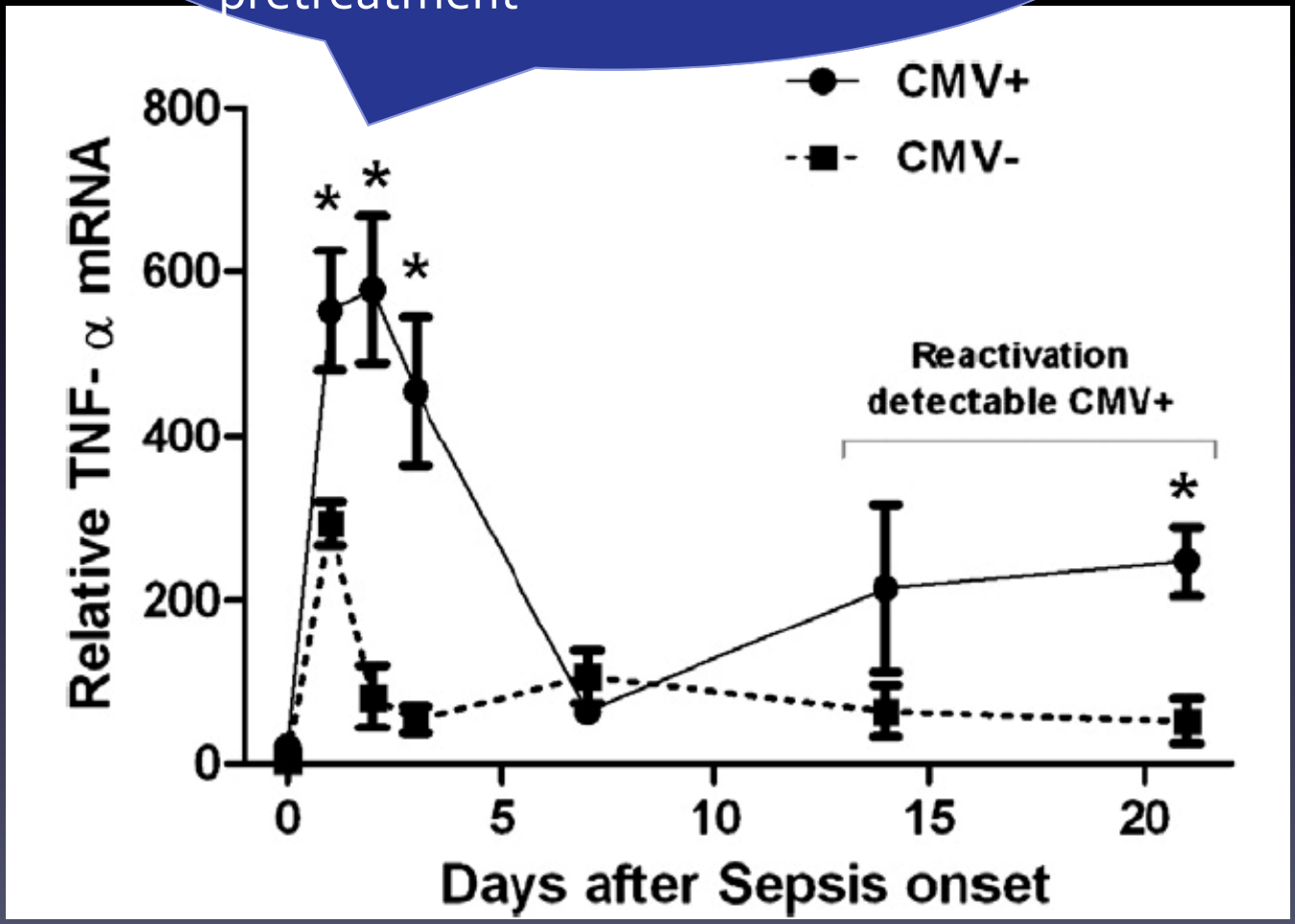
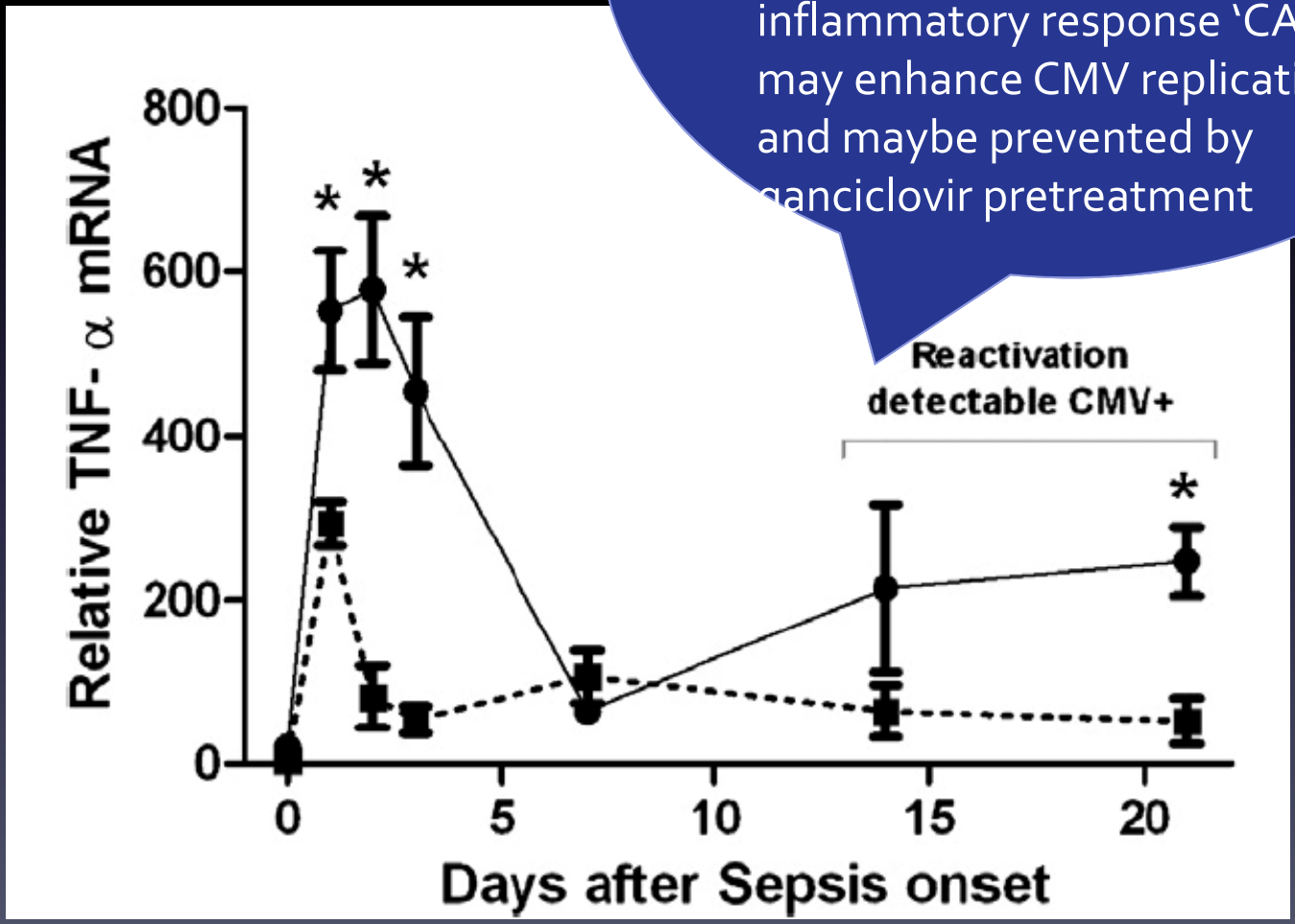


Fig. 2. Ganciclovir treatment influences reactivation and pulmonary injury. Mice latently infected with murine cytomegalovirus (MCMV) had bacterial sepsis induced and received one of the listed ganciclovir regimens or saline (control). (A) Three weeks later lungs from surviving mice were evaluated for MCMV transcriptional reactivation. Each bar represents the percentage reactivation (# reactivation/n) for each treatment group. *Significant difference from saline controls ($p < 0.05$), and @significant difference from 10 mg/kg 21 days group ($p < 0.05$). All evaluations were performed in triplicate. (B) Surviving mice were also evaluated for pulmonary fibrosis. Lungs were fixed, embedded, sectioned, and stained with Gomori's trichrome. Images were acquired, color segmented, and fibrosis quantitated as percent of pixels. Each bar represents the mean ± standard error for 5–7 mice.

Early exaggerated inflammatory response ? related to CMV specific T cell activation and is not prevented by ganciclovir pretreatment



Later phase of sepsis is characterized by generation of immunosuppressive cytokines e.g. IL10 and IL4 (Compensatory anti-inflammatory response 'CARS') may enhance CMV replication and maybe prevented by ganciclovir pretreatment



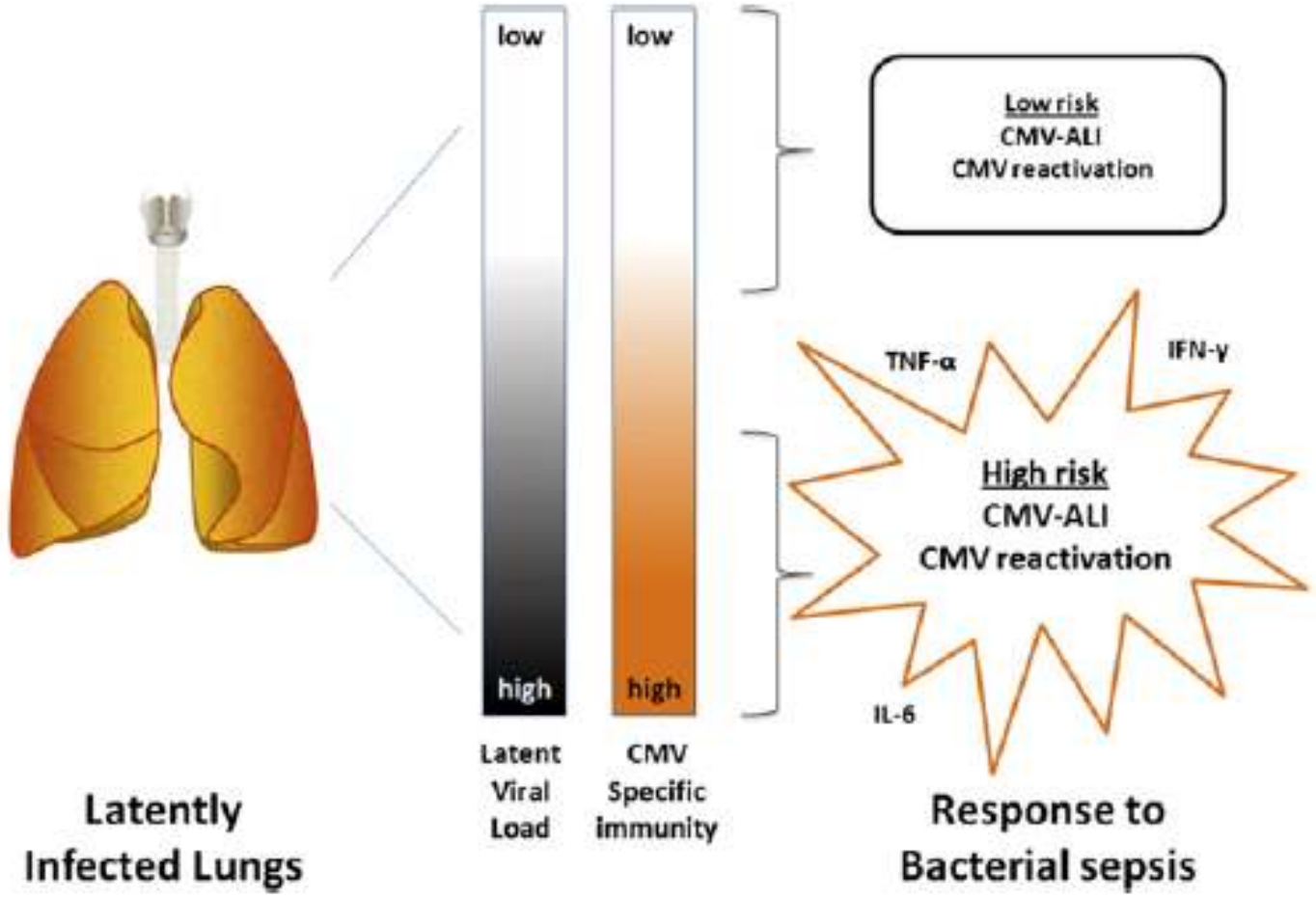


Fig. 2. Model for immunopathogenesis after cytomegalovirus infection. Following primary infection, cytomegalovirus (CMV) becomes latent in the lungs of the infected host. The conditions of the original infection determine lung latent viral load (Reddehase et al., 1994) as well as CMV-specific immunity, with high viral loads inducing "inflated" CMV-specific immunity (Thomas et al., 2010). During a bacterial septic challenge there is activation of CMV-specific immunity (Forster et al., 2010). In this model, hosts with heavy latent viral load and inflated immunity are prone to CMV reactivation and an exaggerated pulmonary inflammatory response (Cook et al., 2006b), leading to CMV-associated lung injury (CMV-ALI).

Human studies

- Two retrospective studies where small subsets of ICU patients received antiviral agents for CMV infection have yielded inconclusive results
- A randomized trial is ongoing to see if antiviral prophylaxis for CMV reactivation is beneficial
  - 2010 to 15, NIH/NHLBI: "A Randomized Double-Blind Placebo-Controlled Trial of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung"; 1U01HL102547-01 (PIs - Limaye, Boeckh; Seattle, WA) ClinicalTrials.gov Identifier: NCT01335932

Summary

- CMV reactivation occur in up to ~ 1/3 of critically ill immunocompetent hosts
- No good prediction rules who would get the CMV reactivation
- Associated with worse ICU outcomes

Summary

- Pathogenic role rather than bystander and prophylatic treatment rather than pre-emptive treatment is needed from animal studies
- Human trial is ongoing
- Better understanding of the pathophysiology and newer, better tolerated antivirals are needed