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Review

Cytomegalovirus reactivation in critically ill immunocompetent hosts: A decade of progress and remaining challenges

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ABSTRACT

Human cytomegalovirus (HCMV) is an undisputed pathogen in humans with severe immune compromise, which has historically been thought to carry little consequence in immunocompetent hosts. During the past decade, however, accumulating data suggest that significant numbers of immunocompetent humans reactivate HCMV during critical illness, and that these reactivation episodes are associated with worsened outcomes. Because most people are infected with this ubiquitous virus by adulthood, confirming pathogenicity has now become a clinical priority. In this article, we will review the incidence and implications of reactivation, the relevant immune responses and reactivation triggers relevant to the immunocompetent host. We will summarize the progress made during the past ten years, outline the work ongoing in this field, and identify the major gaps remaining in our emerging understanding of this phenomenon.

Contents

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1. Introduction

Millions of immunocompetent people suffer critical illness each year (Halpern and Pastores, 2010). Since our interest in cytomegalovirus (CMV) in this population began in the nineties (Cook et al., 1998), it has become increasingly clear that many of these individuals experience CMV reactivation during their critical illness. This finding has now been reproduced independently by eight different groups (Chiche et al., 2009; Chilet et al., 2010; Heininger et al., 2001; Jaber et al., 2005; Kutza et al., 1998; Limaye et al., 2008; von Muller et al., 2006; Ziemann et al., 2008). More importantly, these clinical data have shown that CMV reactivation during critical illness is associated with increased morbidity and mortality. In this review, we will discuss the incidence, causes, and potential consequences of CMV reactivation in non-immunosuppressed critically ill hosts. We will also highlight contemporary challenges facing researchers and clinicians in this field. Because the terms non-immunosuppressed and immunocompetent are both used frequently by different authors, we will use these terms interchangeably to distinguish patients as not receiving canonical immune suppression and not having immune compromise from HIV/AIDS. We do this understanding that critical illness can induce transient immune compromise.

2. Primary infection and latency

Cytomegaloviruses for all species are ubiquitous and have classic beta-herpes virus characteristics. Following host control of primary lytic infection, CMV establishes life-long infection, becoming dormant in multiple end organs, a state also referred to as latency. Previous infection is most often confirmed by the presence of CMV-specific IgG responses. Roughly 50–70% of school aged adolescents in the US are human CMV (HCMV) seropositive (Stadler et al., 2010; Stanberry et al., 2004; Staras et al., 2006), and this percentage increases to >80% with age (Musiani et al., 1988). Thus significant numbers of immunocompetent patients harbor latent virus, making them "at risk" for reactivation during critical illness.

3. Reactivation from latency

Defining viral reactivation must begin with the definition of latency. Although a full discussion of latency is beyond the scope of this review, most authors use some variation of an operational definition that requires the presence of viral DNA in tissues without transcription or translation of lytic or "late" gene RNAs to protein and thereby the absence of lytic virus (for review see (Reeves and Sinclair, 2008)). Thus from a purist point of view, viral reactivation can be defined as recovery of infectious virus following some period of viral latency. Importantly we have confirmed that recovery of lytic virus is possible from immunocompetent patients during critical illness (Cook et al., 2003). Nonetheless isolation of lytic virus appears to be less sensitive for detecting CMV reactivation in immunocompetent patients than molecular methods (Kalil and Florescu, 2009) just as it is in immunosuppressed patients (Weinberg et al., 2000). This insensitivity is complicated by the fact that immunocompetent patients manifest mostly non-specific signs and symptoms during primary infection or reactivation episodes, making these events frequently "occult" (Adler, 2008; Cook et al., 1998). In addition, immunocompetent patients have narrower windows of diagnostic opportunity given their ability to ultimately control reactivation episodes (Chilet et al., 2010; Limaye et al., 2008; von Muller et al., 2007).

The lower sensitivity of culture for detecting HCMV reactivation in humans has led to the development of newer and more sensitive methods, which are all byproducts of advances in monitoring immunosuppressed patients. Historically, elevations in anti-CMV IgG titers were used to diagnose reactivation in latently infected hosts (Nagington, 1971), but antibody titer fluctuations lacked specificity leading to abandonment of this method. Although recovery of lytic virus appears to correlate better with symptomatic CMV reactivation, its lower sensitivity has led to its disuse (Hebart and Einsele, 1998). Currently, molecular methods that quantitate CMV DNAemia or antigenemia are considered by most to be the most sensitive and, therefore, the most widely used for immunosuppressed patients (Weinberg et al., 2000), and these also appear to be the most sensitive for immunocompetent patients (Kalil and Florescu, 2009). Increasing sensitivity in detecting CMV reactivation has come at a price, requiring distinction between "CMV disease" and "viral shedding" in immunosuppressed patients, because not all positive patients with reactivation show disease manifestations. We suspect that this phenomenon might also be true for immunocompetent patients, and that some reactivation episodes could be trivial while others are not. Indeed, the scant data available to date suggest that higher viral loads during reactivation are associated with worse outcomes (Limaye et al., 2008), and this topic will require keen attention in future clinical trials.

4. Reactivation incidence

Trying to pin down the actual incidence of CMV reactivation during critical illness has been confounded by several factors. One is the monitoring methodology chosen as previously discussed. When only CMV IgG positive patients are analyzed, reactivation incidence is observed in 22–42% (Kalil and Florescu, 2009). Timing of monitoring also influences detection because reactivation does not occur immediately. As shown by recent studies, reactivation typically occurs between 1 and 3 weeks after critical illness begins (Chilet et al., 2010; Cook et al., 2003; Limaye et al., 2008). Thus if testing is done too early, the incidence of reactivation is grossly underestimated, as highlighted by the two studies monitoring for reactivation within 4 days of admission (Desachy et al., 2001; Razonable et al., 2002). The etiology of one's critical illness also appears to influence reactivation rates, with burn and trauma patients possibly at higher risk than cardiac or medical ICU patients (Limaye et al., 2008). Finally, a recent study that evaluated bronchoalveolar lavage fluid suggested even higher rates of reactivation (42%) than those seen from peripheral blood (Chilet et al., 2010), suggesting that the site of testing can influence detection. Taken together, if one excludes studies with very early monitoring and monitors only those with latent CMV, a reasonable estimate of reactivation appears to be one in three non-immunosuppressed critically ill patients.

5. Reactivation implications

Despite the incontrovertible evidence that HCMV reactivates in non-immunosuppressed patients during critical illness, the question remains over the clinical consequence. It is relevant to note that this is the same conundrum that faced transplant surgeons almost 40 years ago (Lopez et al., 1974). During the subsequent decades, HCMV reactivation has become recognized as a pathogen in those without fully functional immune systems (Gaytant et al., 2002; Gor et al., 1998; Simmons et al., 1977; Steininger, 2007). Intensivists are now facing the same question in patients who were immunocompetent before they became critically ill? Is reactivated HCMV a pathogen in these patients, or an innocent bystander identifying those with transient immune suppression or immunological insult?

The preponderance of recent clinical data supports the hypothesis that HCMV is a pathogen during critical illness. Studies to date have demonstrated consistent morbidity in these patients,