

Antiviral prophylaxis of cytomegalovirus reactivation in immune competent patients—the jury remains out

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Cytomegalovirus (CMV) has been recognized as a pathogen in immunosuppressed patients for many years, with viral reactivation after transplantation continuing to plague many patients. During the last two decades, it has become increasingly recognized that CMV can also reactivate in previously immune competent patients suffering critical illness. A recent review suggests that when sensitive detection methods are used, approximately 1 of 3 immune-competent patients with latent CMV will reactivate CMV during their critical illness (1).

The consequences of CMV reactivation in immune competent hosts remain unclear. The pathogenic potential of CMV reactivation was widely recognized during the early transplant era, before the advent of ganciclovir, when patients with reactivation frequently lost their grafts or even their lives. For immune competent hosts, however, CMV reactivation has generally been thought to be of little consequence. Recent data have called this assumption into question, associating CMV reactivation during critical illness with roughly doubled mortality, duration of mechanical ventilation, and days in the intensive care unit (1,2).

The association between CMV reactivation in immunocompetent hosts and worsened outcomes is not proof of causality. While CMV might act as a pathogen just as it does in transplant patients, it might just as easily be a bystander that indicates transient immune-

compromise and severity of illness. There are limited data in humans and mice that suggest that CMV is a pulmonary pathogen during critical illness (3-5), but these data are circumstantial. The central question therefore remains—is CMV reactivation in immune competent hosts during critical illness pathogenic?

The simplest way to answer the pathogenicity question is to study antiviral treatment in immune competent patients at risk for reactivation. Such studies should demonstrate whether CMV reactivation can be prevented in humans as it can in immune competent mice (6). If these animal data are reflective, then prophylaxis of at risk patients would maximize chances of showing treatment effect. Great care must be taken, however, because 2 of 3 patients in this approach will be exposed unnecessarily to the side effects of antiviral medications during their critical illness. Therefore, the pathogenicity question must be answered in the context of carefully conducted clinical trials designed that address these central questions:

- (I) Is treatment effective at preventing reactivation?
- (II) Is antiviral treatment harmful during critical illness?
- (III) Assuming that treatment is effective and not harmful, does it improve outcomes?

Cowley *et al.* are the first to report the results of such a trial (7). In this open label randomized prospective trial,

patients at risk for reactivation receiving valacyclovir or valganciclovir were compared to patients receiving no antiviral therapy. The primary outcome measure was time to first reactivation of CMV in blood from initiation of the study drug until day 28. Viral reactivation in blood occurred in 12 of 44 control patients, compared with only 2 of 34 receiving valacyclovir and 1 of 46 receiving valganciclovir (HR 0.14; 95% CI, 0.04–0.50; $P=0.002$ for combined treatment group *vs.* control). Thus for central question #1, their results suggest that antiviral prophylaxis is highly effective at preventing CMV reactivation in immunocompetent patients.

This study also begins to address question #2—safety of antiviral therapy. Recruitment was stopped in the valacyclovir arm due to significantly worsened mortality compared with controls, although review of the deaths by independent intensivists determined them to be due to underlying disease processes. Adverse events were reported more frequently following prophylaxis, but the open label design may have allowed reporting bias. Importantly there was no difference in bone marrow suppression or renal failure, two well described side-effects of these antiviral medications. Most importantly, this study is underpowered to detect small differences in complication risks of antiviral therapy, making it imperative that safety continues to receive careful attention in future studies.

For central question #3, the jury is still out. Because CMV reactivation is unlikely the sole cause of all that ails the critically ill patient, it is anticipated that any potential survival benefits conferred by prevention of CMV reactivation may be modest. “Proof” will therefore require large numbers of patients, and the Cowley study was certainly underpowered to determine survival benefit. This lack of power was further weakened by having two treatment groups. Until the causality question is answered, future studies should ideally focus on a single treatment regimen of ganciclovir/valganciclovir given the efficacy of prevention shown in this first trial.

Fortunately, there are two additional clinical trials that should help to address these questions. First is a reactivation prevention trial NCT01335932 that has just closed (personal communication Michael Boeckh and Ajit Limaye) that compares ganciclovir to placebo in patients with ARDS. The second trial NCT02152358 is still ongoing, evaluating preemptive therapy with ganciclovir for immune competent patients with CMV reactivation and is likely more than 1 year away from completion (personal communication Laurent Papazian). While we eagerly await conclusions

from these trials, assuming that the therapy proves to be safe, it seems likely that these trials may also be insufficient to confirm causality, and that much larger prevention trials may be necessary.

For clinicians, the question is whether the Cowley trial should be used to inform treatment to prevent CMV reactivation in immune competent patients during critical illness. Our suggestion is “not yet”. While this exciting study suggests that CMV reactivation can be effectively prevented with antiviral prophylaxis, it also reminds us that antiviral therapy during critical illness is not innocuous, and that critical questions about safety remain. Moreover, until mortality causality and prevention is answered, the benefit of placing patients at such risk is undefined. We therefore strongly recommend that until these critical questions are answered, that antiviral treatment to prevent CMV reactivation should occur only under the auspices of a clinical trial.

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Footnote

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