Published in final edited form as:

Crit Care Med. 2009 June ; 37(6): 2095–2096. doi:10.1097/CCM.0b013e3181a5e725.

CMV in the ICU: Pathogen or passenger?

Jeffrey I. Cohen, M.D.

Medical Virology Section, Laboratory of Clinical Infectious Diseases, Bldg. 10, Room 11N234,
National Institutes of Health, 10 Center Drive, Bethesda, MD 20892

Keywords

cytomegalovirus; reactivation; intensive care unit; herpesvirus; prophylaxis

Several herpesviruses have been reported to reactivate in non-immunocompromised patients in the intensive care unit (ICU) including herpes simplex virus (HSV), human herpesvirus 6, and cytomegalovirus (CMV). Shedding of HSV has been associated with reduced survival in non-immunocompromised patients on ventilators in some studies [1]; however, at present it is not known whether this is due to a general impairment in host defense mechanisms that occurs in patients in the ICU or whether the virus is a direct cause of morbidity and mortality. Human herpesvirus 6 has also been reported to reactivate in non-immunocompromised patients admitted to the ICU; however, the virus was not been associated with increased severity of disease or mortality in these patients [2].

About 40% to 70% of adults in the United States are seropositive for CMV. CMV is usually acquired during childhood, and adults with latent infection are asymptomatic. Primary infection of healthy adults with CMV is a cause of infectious mononucleosis. The virus can reactivate and cause severe disease in persons who are immunosuppressed such as those receiving organ or hematopoietic cell transplants or those with AIDS. In these patients the virus can cause severe retinitis, pneumonia, colitis, or hepatitis.

Several studies have evaluated the outcomes of patients admitted to ICUs who were not immunocompromised, based on whether the patients developed CMV infection [3-12]. In the majority of cases no evidence of CMV clinical disease was noted. Studies in patients whose CMV serostatus was tested and in whom tests were performed to look for CMV infection are shown in Table 1. Infection with the virus was defined by detection of infectious virus, virus pp65 antigen, or virus DNA by PCR in blood, urine, or respiratory secretions. Rates of CMV infection ranged from 0% to 36% and most studies found a significant correlation of CMV infection with increased time in the ICU, but a non-significant correlation of infection with mortality. In nearly all cases infection was thought to be due to virus reactivation, rather than primary infection in the ICU, since most infections occurred in persons previously seropositive for CMV.

The study of Chiche et al in this issue [12] is the largest prospective study of nonimmunocompromised patients in a medical ICU. Like most of the other studies, the authors found that patients with CMV infection had prolonged hospitalization in the ICU compared to patients without infection, and an increased (but not statistically significant) rate of ICU and in-hospital mortality. CMV infection was associated with a statistically significant increase in days on a ventilator, nosocomial bacterial infection, bacteremia, and renal failure. Older

persons, recent corticosteroid use before ICU admission, blood transfusions, and prior admissions on other wards were all associated with CMV infection. The authors appropriately excluded patients who were immunosuppressed, i.e. transplant recipients, persons with solid or hematologic malignancies with prior chemotherapy, and patients who received corticosteroids or other immunosuppressive agents for more than a month before ICU admission. In addition, unlike some recent studies, the authors tracked which patients received steroids in their study. The authors did not distinguish between the possibility of new CMV infections (in previously seronegative persons) and reactivation (CMV infection in previously seropositive persons) in their analysis. However, 89% of persons with CMV infection were seropositive for CMV at admission indicating that most of the infections observed were due to reactivation of virus. One concern about the study is that healthcare workers were not blinded to the results of CMV testing and therefore clinical assessments might have been biased; in fact, more persons in the CMV-positive group received ganciclovir than those in the CMV-negative group. In addition, the level of CMV infection was not quantified, and patients with high or low levels of CMV in blood (or respiratory fluids) were not analyzed separately. CMV antigenemia rather than CMV PCR in the blood was used; the latter is now more commonly used in the United States and becomes positive earlier with infection than the antigen test.

This and other studies do not indicate whether CMV is a pathogen that causes increased morbidity and mortality, or if it is a passenger that reactivates and functions as a surrogate marker of impaired immunity and prolonged hospitalization. The observation that CMV infection did not correlate with ARDS or shock in the present study [12] suggests that severe lung or systemic disease may not alone cause reactivation of CMV. The finding that HSV also reactivates in ICU patients [1] and that levels of Epstein-Barr virus in the blood are used by some transplant physicians as a guide to titrate immunosuppressive medication [13] suggests that reactivation of CMV, like reactivation of other herpesviruses, may simply be a marker of impaired immunity. On the other hand, CMV is known to have immunosuppressive activity [14] and has been associated with an increased risk of bacterial and fungal infections in transplant recipients [15].

The true role of CMV in ICU patients is likely only to be determined in clinical trials, in which CMV seropositive patients are randomized to receive antiviral prophylaxis or placebo. Alternatively, patients could be monitored for CMV DNA infection in the blood by PCR and patients that are positive could be randomized to receive preemptive antiviral therapy until CMV DNA is no longer detected. One precedent for such a trial was a study showing that mice infected with murine CMV had reduced virus reactivation and lung injury if they were given ganciclovir prophylaxis after cecal injury [16]. The currently available drugs for a trial of prophylaxis or preemptive therapy in ICU patients, ganciclovir, valganciclovir, and foscarnet have hematologic and renal side effects which can complicate patient care. These drugs also have potent activity against HSV which can make it difficult to ascribe the effects of the drug on CMV rather than on HSV. Maribavir, a new drug that is not associated with hematologic and renal side effects and is inactive against HSV, was effective in reducing CMV infection (defined by CMV DNA or pp65 antigen in the peripheral blood) in transplant patients [17]. The association of CMV with poorer outcomes in ICU patients, warrants that a randomized, placebo-controlled trial of antiviral prophylaxis or pre-emptive therapy for CMV be considered in these patients.

REFERENCES

1. Simoons-Smit AM, Kraan EM, Beishuizen A, et al. Herpes simplex virus type 1 and respiratory disease in critically-ill patients: Real pathogen or innocent bystander? *Clin Microbiol Infect* 2006;12:1050–9. [PubMed: 17002604]

2. Razonable RR, Fanning C, Brown RA, et al. Selective reactivation of human herpesvirus 6 variant a occurs in critically ill immunocompetent hosts. *J Infect Dis* 2002;185:110–3. [PubMed: 11756989]
3. Domart Y, Trouillet JL, Fagon JY, et al. Incidence and morbidity of cytomegaloviral infection in patients with mediastinitis following cardiac surgery. *Chest* 1990;97:18–22. [PubMed: 2153065]
4. Stéphan F, Méharzi D, Ricci S, et al. Evaluation by polymerase chain reaction of cytomegalovirus reactivation in intensive care patients under mechanical ventilation. *Intensive Care Med* 1996;22:1244–9. [PubMed: 9120120]
5. Kutza AS, Muhl E, Hackstein H, et al. High incidence of active cytomegalovirus infection among septic patients. *Clin Infect Dis* 1998;26:1076–82. [PubMed: 9597229]
6. Heininger A, Jahn G, Engel C, et al. Human cytomegalovirus infections in nonimmunosuppressed critically ill patients. *Crit Care Med* 2001;29:541–7. [PubMed: 11373417]
7. Cook CH, Martin LC, Yenchar JK, et al. Occult herpes family viral infections are endemic in critically ill surgical patients. *Crit Care Med* 2003;31:1923–9. [PubMed: 12847384]
8. Jaber S, Chanques G, Borry J, et al. Cytomegalovirus infection in critically ill patients: associated factors and consequences. *Chest* 2005;127:233–41. [PubMed: 15653989]
9. von Müller L, Klemm A, Weiss M, et al. Active cytomegalovirus infection in patients with septic shock. *Emerg Infect Dis* 2006;12:1517–22. [PubMed: 17176565]
10. Limaye AP, Kirby KA, Rubenfeld GD, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. *JAMA* 2008;300:413–22. [PubMed: 18647984]
11. Ziemann M, Sedemund-Adib B, Reiland P, et al. Increased mortality in long-term intensive care patients with active cytomegalovirus infection. *Crit Care Med* Dec;2008 36(12):3145–50. [PubMed: 18936696]
12. Chiche L, Forel J-M, Roch A, et al. Active cytomegalovirus infection is common in mechanically ventilated medical ICU patients. *Crit Care Med*. 2009in press
13. Bakker NA, Verschuuren EA, Erasmus ME, et al. Epstein-Barr virus-DNA load monitoring late after lung transplantation: a surrogate marker of the degree of immunosuppression and a safe guide to reduce immunosuppression. *Transplantation* 2007;83:433–8. [PubMed: 17318076]
14. van den Berg AP, Meygaard L, Otto SA, et al. Cytomegalovirus infection associated with a decreased proliferative capacity and increased rate of apoptosis and peripheral blood lymphocytes. *Transplant Proc* 1995;27:936–938. [PubMed: 7879239]
15. Kalil AC, Levitsky J, Lyden E, et al. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. *Ann Intern Med* 2005;143:870–80. [PubMed: 16365468]
16. Cook CH, Zhang Y, Sedmak DD, et al. Pulmonary cytomegalovirus reactivation causes pathology in immunocompetent mice. *Crit Care Med* 2006;34:842–9. [PubMed: 16521279]
17. Winston DJ, Young JA, Pullarkat V, et al. Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. *Blood* 2008;111:5403–10. [PubMed: 18285548]

Table 1

Studies of CMV Infection in Non-Immunocompromised Patients in Intensive Care Units

Year	Design	Number of patients	Sero-positivity for CMV	Site and method of CMV detection	Frequency of CMV infection	Duration in ICU	Mortality	Reference
						CMV vs. no CMV	CMV vs. no CMV	
1990 ^a	Pro	115	28%	Blood, urine; culture	25%	69d vs. 48d sig	55% vs. 37% NS	[3]
1996 ^b	Pro	23	100%	Blood, BAL; PCR, culture	0%	NR	NR	[4]
1998 ^c	Pro	34	94%	Blood; antigen, PCR	32%	NR	64% vs. 74% NS	[5]
2001	Pro	56	100%	Blood, resp; PCR, culture	36%	30d vs. 23d sig	55% vs. 36% NS	[6]
2003 ^c	Pro	104	73%	Blood, resp; culture	9.6%	41d vs. 19d sig	50% vs. 27% NS	[7]
2005	Retro	80	50%	Blood; antigen	17%	41d vs. 31d sig	50% vs. 28% sig	[8]
2006 ^c	Pro	25	100%	Blood, urine, resp; antigen, culture	32%	42d vs. 18d sig	63% vs. 35% NS	[9]
2008	Pro	120	100%	Blood; PCR	33%	NR sig ^d	NR sig ^d	[10]
2008	Retro	99	73%	Blood; PCR	35%	33d vs. 22d sig	29d vs. 11d sig	[11]
2009 ^e	Pro	242	75%	Blood, BAL; antigen, culture	16%	32d vs. 12d sig	54d vs. 37d NS	[12]

Pro=prospective, Retro=retrospective, BAL=bronchoalveolar lavage, sig=significant, NS=not significant, NR=not reported, resp=respiratory tract specimen

^a All patients had mediastinitis

^b All patients were on mechanical ventilation

^c All patients had sepsis or septic shock

^d CMV infection was significantly associated with continued hospitalization and death, but duration of ICU hospitalization and percent mortality were not reported

^e All patients were mechanically ventilated at least 2 days