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EDITORIAL

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Treating HSV and CMV reactivations in critically ill patients who are not immunocompromised: con

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Herpesvirus, especially cytomegalovirus (CMV) and herpes simplex virus-1 (HSV-1), are frequently detected in non-immunocompromised critically ill patients hospitalized in the intensive care unit (ICU). Although the exact seroprevalence of herpesvirus at the time of ICU admission is not known, it is often assumed that the production of viral particles is more likely to be determined by viral reactivation rather than by primary infection. This is because of high seroprevalence in the adult population, ranging from 50 to 100 % [1, 2], as well as a limited risk of virus transmission while in the ICU, especially since transfusion of filtered leukocyte-reduced blood products has become the norm [3]. In critically ill patients, the incidence of CMV reactivation during an ICU stay is up to one patient in three for CMV detected in blood samples [4, 5], and one patient in four for HSV-1 detected in upper airway samples [6]. Incidence rates depend highly on identification techniques (antigenaemia, polymerase chain reaction, viral culture) as well as inclusion criteria (systematic screening versus testing in selected patients with specific symptoms) [7]. Reactivation is often associated with a worse outcome in ICU patients [4, 5, 7, 8]. It has been suggested that the higher the reactivation is, the poorer the prognosis for both CMV [4] and HSV-1 [9]. Antiviral treatment is mandatory in case reactivation is associated with a real organ infection, i.e. organ damage due to the virus (curative treatment) but should be discussed when the case organ infection is not proven (pre-emptive treatment). It might also be relevant to avoid any reactivation by giving antiviral drugs even earlier (prophylactic treatment). If there is no doubt that curative treatment is mandatory, clinicians need to consider pre-emptive and prophylactic treatments (which concern most of the cases) with extreme caution, pending the results from ongoing randomised trials designed to answer these questions.

First and foremost, the exact mechanisms of herpesvirus reactivation are still not clear [10]. For example, since any signal activating NF-κB is capable of triggering CMV reactivation, proinflammatory cytokines, enzymes, receptors and adhesion molecules released during sepsis, burns, surgery, trauma, multiple organ failure syndrome and transfusions could stimulate CMV reactivation [11]. This does not mean that CMV reactivation is the disease but rather the surrogate marker of an associated concomitant disease. In patients with no clear organ or tissue involvement due to the virus, viral reactivation could more likely be a marker of the disease severity and/or immunosuppression associated with critical illness and therapeutics. These patients are at a higher risk of dying but they are more likely to die with the virus than because of the virus. Giving antiviral drugs to these patients should therefore be considered cautiously in terms of benefit–risk ratio. The potential benefit would be that viral reactivation is part of the pathological process associated with the worse outcome. Unfortunately, current

knowledge is only based on observational reports showing statistical evidence of association but not causality. On the other hand, there are a number of risks associated with antiviral drugs:

Drug-related side-effects

This is probably the most obvious risk associated with any treatment. The recommended medical practice is *primum non nocere* meaning that we, as physicians, should not harm our patients, especially if the benefits are not clear. Until new anti-herpes drugs with a better safety profile become available [12], intravenous ganciclovir is the recommended first-line treatment strategy for CMV diseases, while foscarnet and cidofovir are used in case of ganciclovir resistance.

Acyclovir and valacyclovir are used to treat HSV-1 infections. All these drugs, which are nucleoside analogues (acyclovir, ganciclovir and derivates), nucleotide analogues (cidofovir) or pyrophosphate analogues (foscarnet), result in a highly selective inhibition of viral DNA synthesis. However, these drugs are frequently associated with cytotoxicity. Ganciclovir demonstrates the most frequent incidence of haematologic complications (neutropenia, leukopenia, anaemia and thrombocytopenia) of up to 60 % in solid organ recipients [13]. Although there is no doubt that ganciclovir is associated with haematologic toxicity, haematologic complications can be attributed both to ganciclovir and to CMV infection (especially in case of CMV infection-associated haemophagocytic syndrome), as well as to other medications, such as mycophenolate, currently used in solid organ recipients. Haematologic complications are also common in ICU patients with an incidence up to 44 % for thrombopenia and 97 % for anaemia [14]. High illness severity, sepsis and organ dysfunction are correlated with cytopenia which is itself associated with an increased mortality rate. Therefore, haematologic toxicity of antiviral drugs should be carefully monitored because it can worsen "ICU cytopenia". Moreover, the risk of ganciclovir-related haematologic toxicity is increased by renal dysfunction, a common feature in ICU patients, and consecutive ganciclovir overdose [15]. If renal toxicity is a common complication of foscarnet occurring in one to two-thirds of patients [16], acyclovir-related renal toxicity is often underappreciated by clinicians. Aside nephritis and acute tubular necrosis, the most frequent acyclovir-related renal complication is a crystal-induced obstructive nephropathy, characterized by a decrease in renal function that develops within 24–48 h of acyclovir administration [17]. Careful correction of hypovolaemia, slow infusion of the drug (especially for acyclovir) and avoiding concomitant use of other nephrotoxic drugs are recommended to prevent renal toxicity. Acyclovir psychosis is also an underappreciated side-effect. This is a delirious state associated with acyclovir overdose, especially in patients with renal impairment [18, 19].

Optimisation of resource utilization

It is not possible to search for and treat all hypothetical causes associated with a worse outcome in all patients, in all ICUs, before evidence is sufficiently proven. Otherwise, this would impact on global resource utilization at different stages:

Drugs

An accurate calculation of drug-related cost-effectiveness should take into account any treatment of the multiple side-effects associated with the antiviral drugs mentioned above.

Nurses

In ICUs working with a high nurse to patients ratio and/or where nurses have to prepare drugs themselves in addition to starting and monitoring infusions, every drug order is time consuming. Although herpesvirus reactivation in ICU patients is statistically associated with poor outcome and increased duration of mechanical ventilation (MV) [4, 5], it should be pointed out that many simple procedures that have been more clearly demonstrated to decrease MV duration are still often poorly implemented (light or no sedation protocols, nurse driven sedation, analgesia-based sedation, daily interruption of sedation and spontaneous breathing trials or even simple head raising to decrease ventilator-associated pneumonia).

Doctors

Because viral reactivation does not mean viral-related disease, it would be dangerous to recommend systematic treatment of reactivation that could make the clinical picture even more confusing for doctors. We have to carefully check every cause of fever, colitis, pneumonia and not only focus on laboratory tests highlighting a viral reactivation that could just be a reflection of the overall clinical situation but not the cause.

In conclusion, systematic treatment of CMV and HSV-1 reactivation in non-immunocompromised ICU patients is absolutely not proven to date. High level

Table 1 Morbidity associated with herpes simplex virus replication and antiviral treatment

Organ or system	Viral damage	Adverse drug events	
	Herpes simplex virus (HSV-1)	Acyclovir 5 mg/kg × 3 per day, IV (normal renal function)	Valacyclovir 1,000 mg × 2 per day, orally (normal renal function)
Blood		Leukoneutropenia, thrombopenia: very rare	
Kidney		Crystal-induced nephropathy, acute tubular necrosis, nephritis	Renal injury: rare
Liver	Acute hepatitis	Increase of liver enzymes	
Heart	Myocarditis		
Lungs	Acute lung injury		
Nervous system	Encephalitis, polyradiculopathy	Delirium → coma	Headache
Digestive tract	Mouth ulcers, oesophagitis	Nausea, diarrhoea	
Inflammation and immunity	HSV might be cause and/or consequence	Anaphylaxis	
Outcome	Association with increased duration of mechanical ventilation and pneumonia	Unknown benefit for preventive treatment in critically ill patients	Unknown benefit for preventive treatment in critically ill patients

Table 2 Morbidity associated with cytomegalovirus replication and antiviral treatment

Organ or system	Viral damage	Adverse drug events	
	Cytomegalovirus (CMV)	Ganciclovir 5 mg/kg × 2 per day, IV (normal renal function)	Foscarnet 60 mg/kg x 3 per day, IV (normal renal function)
Blood	Leukopenia, thrombopenia, anaemia, haemophagocytic syndrom leukoneutropenia > thrombopenia, anaemia	Severe Anaemia > thrombopenia	
Kidney		Rare	Acute renal failure, diabetes insipidus
Liver	Acute hepatitis	Increase of liver enzymes	
Heart	Myocarditis	Rare: arrhythmia, hypo/hypertension	↑QT, arrhythmia
Lungs	Acute lung injury		
Nervous system	Encephalitis, polyradiculopathy	Delirium → coma, headache	
Digestive tract	Mouth ulcers, oesophagitis, colitis	Rare: Nausea, diarrhoea	Frequent: Nausea, diarrhea; Possible: pancreatitis
Homeostasis		Rare: hypoglycaemia	Frequent: hypo K^{+}, Mg^{2+}, Ca^{2+}, Fe^{2+}, Zn^{2+}, hypo or hyperphosphataemia
Inflammation and immunity	CMV might be cause and/or consequence	Anaphylaxis	
Outcome	Associated with increased duration of mechanical ventilation, length of stay in ICU and D30 mortality	Unknown benefit for preventive treatment in critically ill patients	Unknown benefit for preventive treatment in critically ill patients

reactivation should be carefully checked regarding any specific viral organ infection. Reciprocally, any organ impairment (especially of the lungs, digestive tract, liver, bone marrow) and/or undiagnosed fever requires screening for CMV and HSV-1 reactivation. Treatment should be considered regarding the benefit–risk ratio and carefully monitored for side-effects (see Tables 1, 2). In the future, in addition to better defining which ICU patients should benefit from anti-herpes virus treatment, the optimal dose will also need to be precisely known, especially in ICU patients with frequent renal dysfunction or dialysis. This is necessary to avoid both overdosing and ineffective dosing that could lead to drug resistance. In the same way misuse of antimicrobial drugs is associated with increased risk of drug resistance [12]. Therefore, the indication of anti-herpes virus treatment in critically ill patients should be supported by further evidence to avoid overexposure and development of drug resistance.

Conflicts of interest SJ and GC declare no conflicts of interest related to the work.

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