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Charles-Edouard Luyt, Guillaume Hékimian, Nicolas Bréchet, Jean Chastre. Viral Ventilator-Associated Pneumonia/Hospital-Acquired Pneumonia. *Seminars in Respiratory and Critical Care Medicine*, 2022, 10.1055/s-0041-1740981 . hal-03561317

HAL Id: hal-03561317

<https://hal.sorbonne-universite.fr/hal-03561317>

Submitted on 8 Feb 2022

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Viral Ventilator-Associated Pneumonia/Hospital-Acquired Pneumonia

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Word count (excluding abstract, references, tables and figures legends): 3619 words

Funding : None

ABSTRACT

Among the viruses possibly responsible for hospital-acquired and ventilator-associated pneumonia, herpes simplex virus (HSV) is probably the most often involved: HSV reactivation is frequent in ICU patients, and lung parenchymal infection (HSV bronchopneumonitis) has been well described, either using cytological signs of parenchymal involvement in cells obtained during bronchoalveolar lavage, or using HSV virus load in the lower respiratory tract. Whereas treating patients with HSV bronchopneumonitis may be recommended, based on expert opinion, prophylactic or pre-emptive treatment of HSV reactivation should be avoided. Ventilator-associated pneumonia due to cytomegalovirus (CMV) is less frequent than HSV bronchopneumonitis, and more difficult to diagnose. No data exists on the impact of antiviral treatment on CMV pneumonia. The involvement of respiratory viruses has been described in patients with healthcare-associated pneumonia and hospital-acquired pneumonia, but their role in ventilator-associated pneumonia is not clear.

Abstract word count: 137 words

Keywords: Viral Infection, Herpes Simplex Virus, Cytomegalovirus, Respiratory viruses, Mechanical Ventilation

INTRODUCTION

The role of viruses as causes of severe respiratory infections has been recognized far before the current coronavirus infectious disease-19 (COVID-19) pandemic. Indeed, viruses may be responsible for community-acquired pneumonia, either as the sole pathogen or as a bacterial-viral co-infection [1]. However, the role of viruses in hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) is less clear. The purpose of this article is to review the role of viruses in HAP/VAP in non-immunosuppressed intensive care unit (ICU) patients. We will first describe the role of latent viruses (herpesviridae) in HAP/VAP, then the role of respiratory viruses.

HERPESVIRIDAE IN ICU PATIENTS

Among the nearly 100 known herpesviruses, only the following 8 have been observed to be responsible for infection in human: Herpes simplex virus (HSV)-1 and 2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus (HHV) 6 and 7 (roseola infantum) and HHV-8 (Kaposi-sarcoma associated virus). All herpes viruses induce a lifelong latent infection in their natural host after a primary infection, with the virus remaining dormant in the body, usually in a specific cell type. However, because of immunoparalysis following the initial pro-inflammatory response to aggression, latent viruses such as herpesviridae may reactivate in ICU patients and induce bronchopneumonitis [2].

Herpes simplex virus (HSV), cytomegalovirus (CMV) but also Epstein-Barr virus (EBV) are frequently recovered in lung or blood of ICU patients (up to 50%, depending on the case-mix), their reactivation being associated with morbidity and mortality [3–8]. However, the exact meaning of these reactivations is debated: these viruses can have real pathogenicity and

lead to organ damage (for example the lung for HSV [3], the lung or bone marrow for CMV [9]), thus having a direct role in the morbidity-mortality observed with their reactivation; or they may be simple bystanders, their reactivation only being secondary to the severity of the disease or to a prolonged stay in the ICU. Unfortunately, the most recent studies have often only looked for the presence of HSV, CMV or EBV DNA in the blood of patients, making it difficult to assert the existence of a causal link between the detection of the virus in the patient blood and pneumonia [4–6].

We will therefore focus this chapter on the potential role of herpesviridae as a cause of HAP/VAP.

HSV as a cause of HAP/VAP

HSV-1 is isolated in the saliva of 1 -5 % of the general population. In the ICU, the frequency of viral reactivation is higher. A study found that 22% of ICU patients had HSV in the throat [9] while 41% of the patients manifested it after surgery [10]. In a study on 201 non-immunocompromised patients ventilated for at least 5 days, HSV was detected in the throat of 109 (54%) patients. Reactivation was asymptomatic in 56% of the patients, whereas it was associated with a herpetic ulceration of the lip or a gingivostomatitis in 48 out of the 109 patients (44%) with reactivation [3].

In the distal airways, frequency of HSV reactivation varies from one study to another (Table 1 displays the main studies having evaluated its frequency). These variations are mostly due to heterogeneity between studies: some were retrospective, some combined immunocompetent and immunocompromised patients, while others mixed different populations of ICU patients with different severity. In a large cohort of ICU patients, Bruynseels et al. detected HSV in the lower respiratory secretions of 16% of mechanically ventilated patients in whom the virus was detected in the throat [9]. Similarly, Ong et al.

detected HSV in 27% of their mechanically ventilated patients [11]. In contrast, this rate was much higher in Luyt's study, reaching 64%, probably because the patients included were much more severe and required much longer ventilation. [3].

More recently, data has emerged suggesting that HSV reactivation may be common in COVID-19 patients [13]. However, these data are preliminary and need to be confirmed.

Signification of Viral Reactivation

The detection of HSV in the lower respiratory tract does not necessarily mean herpetic pulmonary disease [12]. It is not known whether HSV isolation from lower respiratory tract samples of non-immunocompromised ventilated patients corresponds to viral contamination of the lower respiratory tract from mouth and/or throat secretions, a local tracheobronchial excretion of the virus due to its reactivation without parenchymal involvement, or real HSV bronchopneumonitis (corresponding to HSV infection of the lung parenchyma). Therefore, the exact role of HSV in ICU patients, i.e., as a marker of disease severity or true pathogen with its own morbidity/mortality, remains unclear.

It has been demonstrated that HSV bronchopneumonitis was frequently detected among non-immunocompromised patients with prolonged mechanical ventilation: in a monocentric study, Luyt et al. found that out of 201 patients suspected of having ventilator-associated pneumonia, 42 (21%) were diagnosed with HSV bronchopneumonitis. In this study, HSV bronchopneumonitis was defined as a clinical deterioration suggesting pneumonia and leading to fiberoptic bronchoscopy with bronchoalveolar lavage (BAL), associated with HSV detection in BAL (by PCR and/or culture) and HSV-specific nuclear inclusions in cells recovered during lavage or bronchial biopsies (Figure 1A). No pathogen other than HSV virus was isolated in 23 patients while concomitant bacterial infection was identified in 19 [3]. The precise disease mechanism of HSV bronchopneumonitis is not clearly understood. In most

patients, HSV bronchopneumonia is probably initiated by viral reactivation in the throat (possibly secondary to critical illness and local microtrauma caused by endotracheal and gastric tubes, and oropharyngeal cavity suctioning), with microaspirations around the endotracheal tube subsequently leading to colonization and infection of the distal compartment of the lung (descending infection). This hypothesis is supported by previously reported findings: based on autopsy series, Nash concluded that the anatomic distribution of HSV involvement in the tracheobronchial tree and the lungs suggests that aspiration or contiguous spread from the upper respiratory tract was the most likely dissemination pathway [13]. Moreover, Bruynseels et al. showed that for 72% of their patients with lower respiratory tract HSV-positive specimens, HSV was detected in the throat on the same day of, or before, the detection in the lower respiratory tract [9]. Luyt et al. found the same results: in their 23 patients with oral–labial lesions and HSV bronchopneumonitis, the lesions being detected before or on the same day as HSV-bronchopneumonitis diagnosis. Moreover, they found that oral–labial lesions and HSV detection in the throat were independent risk factors for HSV bronchopneumonitis. These data suggest that viral reactivation or infection in the oropharynx reaches the lower respiratory tract by aspiration [3]. Macroscopic bronchial lesions, possibly due to local microtrauma and/or preexisting acute lung injury with distal squamous cell metaplasia, might also have paved the way for distal infection. However, since the authors were unable to detect the virus in the throat of several patients with lower respiratory tract involvement, another mechanism, i.e. local distal reactivation and infection or hematogenous spread, cannot be definitively ruled out. Several mechanisms could even differ from one patient to another.

Diagnosis of HSV Bronchopneumonitis

Clinical symptoms of HSV bronchopneumonitis are not specific and frequently mimic bacterial pneumonia, with fever, hypoxemia and purulent tracheal secretions. ARDS can even occur. Herpetic ulceration of the lip and/or gingivostomatitis are frequently associated with HSV bronchopneumonitis. Such lesions in mechanically ventilated patients should raise suspicion of HSV bronchopneumonitis [3, 14].

Radiologic findings of HSV bronchopneumonia are nonspecific, ranging from localized to diffuse and generalized infiltrates, sometimes associated with atelectasis or pleural effusion [14]. Fiberoptic bronchoscopy may show mucosal erythema or non-specific ulcerations [3]. However, in most cases, the mucosa is normal or edematous [14].

PCR is the most sensitive test to detect virus in the respiratory tract specimen. However, it can be too sensitive and thus has an imperfect specificity. New diagnostic techniques, such as real-time PCR, have improved its sensitivity and specificity and may allow quantifying the viral load, which is more clinically relevant than only detecting viral genome by PCR (19). Cytological examination of cells collected with BAL in patients with HSV bronchopneumonitis frequently detects HSV-specific cytopathic effect, namely giant, polynuclear cells with specific nuclear inclusions (see Figure 1 A), confirming the diagnosis with a high specificity. However, this examination is cumbersome and requires experienced anatomic-pathologists. This is why it has been replaced in many centers by direct quantification of the virus load in BAL fluid [3, 14]. [3, 12]. In a study, virus load was significantly higher in patients with HSV bronchopneumonitis than in patients without it [3]. Moreover, a cutoff value of 8×10^4 copies of HSV per million of cells had 81% sensitivity (95% CI, 69–90%) and 83% specificity (95% CI, 71–91%) for diagnosing HSV bronchopneumonitis (Figure 3 and 4). To date, a HSV virus load $>10^5$ copies per million cells is used as a surrogate for diagnosing HSV bronchopneumonitis.

Prognosis of HSV reactivation/infection

Oropharyngeal and tracheobronchial HSV carriage has been associated with prolonged hospital stay and higher mortality [9, 11]. Several data argue in favor of a true HSV pathogenicity in non-immunocompromised patients. Tuxen et al. showed in 1982 that 30% of their ARDS patients had histology-confirmed HSV lung involvement, and that these patients with HSV tracheobronchitis had longer mechanical ventilation and hospital stay, as well as higher mortality rate [15]. Moreover, patients with HSV bronchopneumonitis or with high virus load ($>10^5$ copies/ml) in BAL fluid had poorer outcome than patients without HSV reactivation or with low ($<10^5$ copies/ml) virus load [3, 16]. This increased mortality in patients with HSV has been confirmed in a meta-analysis [7].

However, the exact significance of HSV detection in the lower respiratory tract is still on debate: is it only a marker of severity or does it have its own morbidity and/or mortality? Even in patients with HSV bronchopneumonitis, its relationship with outcome is not clear. Indeed, it remains very difficult to establish a direct and indisputable causal link between the presence of the virus in respiratory secretions and the worsening of the prognosis from purely observational studies. Only randomized studies with a sufficient number of patients demonstrating the effectiveness of a treatment specifically targeting the virus could confirm such a link.

Treatment of HSV reactivation/infection

Tuxen et al. performed in 1987 the only randomized, double-blind, placebo-controlled study evaluating acyclovir as a prophylactic treatment in ARDS patients. They showed that acyclovir could prevent herpetic reactivation in the lower respiratory tract, but without any impact on mortality and duration of mechanical ventilation (Table 2) [17]. Therefore,

prophylactic treatment with acyclovir cannot be recommended in ICU, non-immunocompromised patients, even in the most severe patients.

In their prospective observational study conducted to define the frequency, risk factors and relevance of HSV bronchopneumonitis, Luyt et al. reported that among 42 patients with HSV bronchopneumonitis, 19 were treated with acyclovir and 23 were not. MV duration, clinical course of HSV bronchopneumonitis and mortality were similar in acyclovir-treated and untreated patients. However, the study was not randomized and not designed to test acyclovir efficacy in this context [3]. Other observational studies evaluating the impact of acyclovir in patients with HSV lung reactivation/infection have been published to date, and the main results are reported in Table 2. Recently, a meta-analysis based on these studies revealed that patients with HSV reactivation/infection who were treated with acyclovir had lower mortality than untreated patients [18]. Although no formal conclusion can be drawn from these data, most experts in that field now recommend treating with acyclovir ICU mechanically ventilated patients with HSV bronchopneumonitis as diagnosed by a virus load in the BAL fluid $>10^5$ copies per million cells.

Since prophylactic treatment may expose patients to unnecessary risk of acyclovir, and curative treatment may be too late to have a true efficacy, pre-emptive treatment (namely treatment at HSV reactivation onset, before disease occurs) may be the best option. Unfortunately, the only randomized-controlled trial having tested this hypothesis was negative. In this double-blind study, 239 patients were randomized to receive either intravenous acyclovir, 5 mg / kg tid for 14 days, or a corresponding placebo [19]. On day 60, the median (IQR) numbers of ventilator-free days were 35 (0-53) for acyclovir recipients and 36 (0-50) for controls ($P = .17$ for between-group comparison). Among secondary outcomes, 26 patients (22%) and 39 patients (33%) had died at day 60 (risk difference, 0.11, 95%CI, -0.004 to 0.22 , $P = .06$). The adverse event frequency was similar for both groups (28% in the

acyclovir group and 23% in the placebo group, $P = .40$), particularly acute renal failure post randomization affecting 3 acyclovir recipients (3%) and 2 controls (2%) [19].

In summary, reactivation of HSV is common in non-immunocompromised ICU patients, including patients with COVID-19 ARDS, and is associated with mortality. In some patients, true HSV bronchopneumonitis occurs, which appears to be associated with a poor prognosis. Although prophylactic or preemptive treatment cannot be routinely recommended to date, curative treatment (acyclovir, 5 mg / kg tid for 10-15 days) may be warranted in patients with suspected VAP and high viral load ($> 10^5$ copies of HSV per million cells in BAL fluid).

CMV as a cause of HAP/VAP

During ICU stay, CMV may reactivate in the blood of roughly 30% of CMV-positive patients [4, 8]. However, the relationship between CMV blood reactivation and CMV disease (i.e, CMV-organ involvement) has never been described. Despite the correlation between CMV viral load and prognosis in ICU patients [4, 8], and the association between viral load and CMV disease in immunocompromised patients, no data regarding the relationship between viral load CMV and CMV disease does exist in ICU patients.

CMV was clearly recognized as a cause of pneumonia in ICU patients based on data provided by autopsy or surgical biopsy of the lung parenchyma [20, 21]. In these studies, the frequency of CMV pneumonia was approximately 30%, but these concerned a very specific group of patients who required prolonged MV or with unexplained ARDS. In another study, thirty-nine of the 242 ICU patients (16.1%, confidence interval 11.5% to 20.7%) developed an active CMV infection, as diagnosed by positive antigenemia (85%) and/or positive rapid viral culture in bronchoalveolar lavage (26%) [22]. Therefore, the exact frequency of CMV pneumonia in ICU patients is unknown. Table 3 summarizes the main studies having

evaluated CMV pneumonia. Presence of intranuclear inclusions on microscopic examination of cells collected by BAL (Figure 1B) could avoid performing a surgical lung biopsy, at least theoretically. However this technique is less sensitive than for HSV: in a study looking for CMV reactivation in the lung, only 1 patient among the 11 with CMV lung disease, as defined by the authors, had CMV-specific intranuclear inclusion [22]. The use of virus load as a surrogate of cytology/histology to diagnose CMV lung disease, although attractive, has never been evaluated in ICU patients.

The potential usefulness of an antiviral treatment targeting CMV has recently been evaluated in three randomized, placebo-controlled trials [25-27]. In the first one, Limaye et al. randomized 160 CMV-seropositive adults with either sepsis or trauma and respiratory failure to receive either ganciclovir (5 mg/kg twice daily until hospital discharge) or matching placebo to determine whether ganciclovir prophylaxis reduces plasma interleukin 6 (IL-6) levels [23]. Although CMV reactivation in plasma was significantly lower in the ganciclovir group (12% versus 39%), treatment with ganciclovir vs placebo did not significantly reduce plasma IL-6 levels (mean change from days 1 to 14, -0.79 and -0.79 log₁₀ units, respectively). However the patients treated with ganciclovir had a greater number of days alive without mechanical ventilation than the others, with no difference in mortality between the 2 groups [23]. The authors concluded that the use of ganciclovir as a prophylactic agent cannot be recommended, but more studies are needed. The second study evaluated the benefit of anti-CMV prophylaxis with valganciclovir or valacyclovir compared to placebo [24]. In this study, 124 patients were randomized to receive valganciclovir ($n = 46$), valacyclovir ($n = 34$) or placebo ($n = 44$). Enrollment of patients in the valacyclovir arm was halted prematurely due to excess mortality in that arm. Compared with placebo, treatment with valganciclovir reduced the number of viral reactivation, but without any effect on morbidity and mortality [24]. More recently, Papazian et al. tested the usefulness of pre-emptive ganciclovir in ICU

patients: they randomized 76 patients with CMV blood reactivation to receive ganciclovir 5 mg/kg tid for 14 days or a matching placebo [25]. The trial was stopped by the data safety monitoring board for futility, based on the results of an interim analysis that showed no difference between groups. The subdistribution hazard ratio for being alive and weaned from mechanical ventilation at day 60 for patients receiving ganciclovir (N = 39) compared with control patients (N = 37) was 1.14 (95% CI from 0.63 to 2.06; P = 0.66). The median [IQR] numbers of ventilator-free days for ganciclovir-treated patients and controls were 10 [0-51] and 0 [0-43] days, respectively (P = 0.46). Mortality at day 60 was 41% in patients in the ganciclovir group and 43% in the placebo group (P = 0.845). To date, no studies have evaluated the usefulness of ganciclovir (or another anti-CMV agent) in patients with CMV pneumonia.

In summary, the relationship between CMV reactivation in the blood and/or the lung and CMV pneumonia is highly probable, but has never been established. Unfortunately, there is a lack of studies that have sought to determine whether there is a threshold above which the viral load in the lungs predicted the onset of CMV pneumonia. Finally, whether or not a specific antiviral treatment may improve the outcome of patients with CMV pneumonia in the ICU remains to be determined.

Epstein-Barr virus as a cause of HAP/VAP

Recently, several authors have studied the frequency of detection of EBV DNA in BAL fluid [28] or in the blood of ICU patients using multiplex and real-time PCR [5, 6]. They found that EBV DNA detection was relatively common in ICU patients, and appeared to be associated with mortality [5, 6]. For example, in a study of 87 patients with ARDS of unknown etiology in which BALF samples were analyzed for reactivation of human herpes virus, Tachikawa et

al. identified 16 patients (18%) with EBV DNA in their BAL fluid. Again, the exact significance of the detection of EBV in BAL fluid of the ICU patient must be determined before specific treatment for EBV can be considered.

RESPIRATORY VIRUSES

The denomination “respiratory viruses” regroups several viruses that may cause upper and lower respiratory tract infection, and includes influenza, rhinovirus, respiratory syncytial virus (VRS), human metapneumovirus, parainfluenza, adenovirus and coronaviruses other than SARS-CoV-2 (coronavirus 229E, NL63 and OC43).

Respiratory viruses are responsible for nosocomial infections, particularly in immunocompromised patients [26–28]. However, data on viral nosocomial pneumonia are scarce, and the role of respiratory viruses as a cause of nosocomial pneumonia in non-immunosuppressed patients is probably limited.

To investigate the role of viral infection in adult patients with pneumonia requiring ICU admission, Choi et al. conducted a retrospective analysis of a cohort of 198 patients (64 with community-acquired pneumonia and 134 with healthcare-associated pneumonia). Seventy-one patients (35.9%) had a bacterial infection, and 72 patients (36.4%) had a viral infection. Rhinovirus was the most common identified virus (23.6%), followed by parainfluenza virus (20.8%), human metapneumovirus (18.1%), influenza virus (16.7%), and respiratory syncytial virus (13.9%). The mortalities of patients with bacterial infections, viral infections, and bacterial-viral coinfections were not significantly different (25.5, 26.5, and 33.3%, respectively; $P = 0.82$) [29]. A more recent study found that the prevalence of viral infection in patients with HCAP was lower than that in patients with CAP (13.8% vs 24.6%, $p = 0.004$), and resulted in a similar length of hospital stay and in-hospital mortality as viral-

bacterial coinfection and bacterial infection [30]. In that study, viruses deemed responsible for HCAP were also predominantly respiratory viruses, influenza A being the most frequent, followed by rhinovirus. In 2017, Loubet et al. found that 30/95 (32.5%) of their patients with hospital-acquired pneumonia (HAP) who underwent multiplex PCR testing for respiratory viruses, had a virus that was detected (mostly influenza, rhinovirus and VRS) [31]. However, this frequency was probably overestimated, since all HAP patients were not tested.

Data in mechanically ventilated patients are more scarce: Daubin *et al.*, in a prospective study on 139 mechanically ventilated patients, showed that only two out of the 39 patients suspected of having developed VAP had a respiratory sample (tracheal aspirate) positive for respiratory viruses (1 enterovirus and 1 influenza) [32]. Notably, in that study, 12 (31%) patients had a sample positive for HSV and one for CMV. No other study has been published on the topic to date.

In summary, respiratory viruses may be recovered from respiratory secretions of patients developing HCAP, HAP or VAP. However, the exact significance of viral detection remains to be determined: it can be a bystander, a true pathogen with its own morbidity as a single infecting agent, or a co-infecting agent.

CONCLUSION

Viruses are increasingly recognized as pathogens responsible for HAP/VAP, latent viruses (herpesviridae) being the most frequent. Among the herpesviridae, HSV, due to its tropism for upper airways, is the most frequent. The diagnosis of HSV bronchopneumonitis is based on a clinical suspicion of pneumonia associated with the detection of HSV DNA in BAL fluid with a high viral load ($>10^5$ copies of HSV per million cells). In that case, treatment with acyclovir is probably justified. While CMV reactivation is common in the blood, CMV pneumonia is

less common and we currently lack diagnostic criteria. When the diagnosis of CMV pneumonia can be made with confidence, treatment with ganciclovir may be justified, while prophylactic or preemptive ganciclovir for CMV blood reactivation are not recommended to date. The exact role of EBV in HAP/VAP remains to be determined. Although respiratory viruses may be recovered in patients with HAP, their role in VAP is not established and their pathogenicity in that condition remains to be determined.

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Figure legends

Figure 1. Specific inclusions in cells recovered during bronchoalveolar lavage in patients with herpes simplex virus (HSV) bronchopneumonitis (**A:** HSV-specific nuclear inclusions (arrow); Papanicolaou stain, magnification x 1000) and cytomegalovirus (CMV) pneumonia (**B:** CMV-specific nuclear inclusion (arrow) with a peripheral halo. May-Grunwald-Giemsa stain, magnification x 1000).

Figure 2. Box plots of virus loads of patients with or without HSV bronchopneumonitis. $p < 0.0001$ between groups. T-bars represent the 10th and 90th percentiles, the horizontal line in the box is the median; the lower and upper limits of the box are the 25th and 75th percentiles, respectively. Circles represent outliers.

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Figure 3. Receiver operating characteristics curve of the virus load, determined by real-time polymerase chain reaction, to predict HSV bronchopneumonitis. Area under the curve was 0.89 (95% CI, 0.84–0.93).

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Table 1 : Main studies having evaluated HSV reactivation in the respiratory tract of intensive care unit patients

Author, year	Population	Oropharyngeal reactivation N (%)	Lung reactivation	Virological method
Bruynseels, 2003 [9]	764 patients (361 on MV)	169 /764 (22%)	58/361 (19%)	Virus culture
Ong 2004 [11]	393 patients on MV	106 (27%)		PCR
Luyt 2007 [3]	201 patients with VAP suspicion, on MV>4 days	109 (54%)	129 (64%)	PCR, virus culture
Linssen 2008 [16]	260 patients with VAP suspicion	-	99 (32%)	PCR
Costa 2012 [33]	127 patients with VAP suspicion	-	38 (31%)	PCR

Abbreviations : HSV, herpes simplex virus. CMV, cytomegalovirus. MV, mechanical ventilation. PCR, polymerase chain reaction. VAP, ventilator-associated pneumonia. ARDS, acute respiratory distress syndrome.

Table 2. Main studies having evaluated acyclovir to prevent or treat HSV reactivation/infection in intensive care unit patients

Author, year	Methods	Population	Mortality rates	Other endpoints
Tuxen 1987 [17]	Randomized, double-blind, placebo-controlled trial Prophylaxis	38 ARDS patients randomized to receive acyclovir (n=17) or placebo (n=21)	47% for acyclovir patients 43% for placebo patients P = NS	Duration of MV 21±19 d for acyclovir patients, 15 ± 12 d for placebo patients (P = NS)
Camps 2002 [34]	Prospective observational study Curative treatment	64 with a positive HSV lung sample 28 received acyclovir	43% for acyclovir patients 53% for patients without treatment P =NS	
Luyt 2007 [3]	Prospective observational study Curative treatment	42 patients with HSV bronchopneumonitis 19 received acyclovir, 23 no treatment	37% for acyclovir patients 57% for patients without treatment P = NS	Adjusted OR for mortality 0.62 (IC 95%, 0.16-2.34) aciclovir vs. no treatment
Traen 2014 [35]	Retrospective observational study Curative treatment	212 patients with HSV reactivation 106 received acyclovir 106 no treatment	37.7% for acyclovir patients 52.8% for patients without treatment P = 0.038	The difference in mortality rates persists after adjusting using a propensity score

Luyt 2019 [19]	Randomized, double-blind, placebo-controlled trial Pre-emptive treatment	238 patients on MV with HSV oropharyngeal reactivation randomized to receive acyclovir (n=119) or placebo (n=119)	Day 60 mortality 22% acyclovir arm 33% placebo arm P = 0.06	Same number or VFD (main outcome criteria)
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Abbreviations : HSV, herpes simplex virus. MV, mechanical ventilation. PCR, polymerase chain reaction. ARDS, acute respiratory distress syndrome. OR, odds ratio. VFD, ventilator-free days.

Table 3. Main studies having evaluated lung CMV reactivation in the intensive care unit

Author, year	Population	Frequency of HSV reactivation	Clinical manifestation of CMV disease	Diagnostic method
Papazian 1996 [20]	86 patients with ARF or VAP	25/86 (29%)	Interstitial lung disease	Histology: autopsy in 60, open lung biopsy in 26
Heininger 2001 [36]	56 surgical patients with SAPS II score >40	7/56 (6%)	NA	Virus culture, PCR
Papazian 2007 [21]	100 patients with unexplained ARDS	30/100 (30%)	Pneumonia, fibrosis	Hystology: open-lung biopsy. CMV recovered from lung tissue by virus culture in 10/30
Chiche 2009 [22]	242 patients on MV ≥2 days	11/242	Pneumonia	Rapid shell-vial culture, virus culture,

Abbreviations: ARF, acute respiratory failure. CMV, cytomegalovirus. MV, mechanical ventilation. PCR, polymerase chain reaction. VAP, ventilator-associated pneumonia. SAPS, simplified acute physiology score. ARDS, acute respiratory distress syndrome





