

Viral-associated Ventilator-associated Pneumonia

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Introduction

Nosocomial pneumonia is the most commonly acquired infection in intensive care units (ICUs). Its frequency is approximately 10 cases/1000 admissions; however, the incidence may increase to 20 times that number in patients undergoing invasive mechanical ventilation [1–3]. The overall incidence of ventilator-associated pneumonia (VAP) may range between 15 % to 20 % [2–6]. This complication prolongs the length of hospital stay, increases healthcare costs and may increase mortality [4, 5, 7, 8].

Classically, the etiology of this entity has been assumed to be bacterial, although in a significant percentage of patients with clinically suspected VAP, no bacteria can be identified. In recent years, introduction of highly sensitive techniques for detecting viruses in the respiratory tract, such as nucleic acid amplification by polymerase chain reaction (PCR), has significantly improved the diagnostic yield of infections such as community-acquired pneumonia (CAP), increasing the isolation rate from less than 10 % (using traditional techniques) to 35 % when using PCR in CAP that requires hospital admission [9].

Recently, new evidence has shown that viral isolation in the respiratory tract of immunocompetent patients undergoing invasive mechanical ventilation is higher than previously thought [10–12]. However, there are several limitations when determining the role of viruses in VAP:

- Difficulty in establishing a causal relationship between the viral isolate in the respiratory tract and pneumonia;
- Lack of an accessible gold standard for establishing the diagnosis;
- Lack of evidence regarding the efficacy of antiviral therapy in the context of suspected viral pneumonia during mechanical ventilation.

Incidence

In critically ill immunocompetent patients undergoing invasive mechanical ventilation, two kinds of virus may cause viral nosocomial pneumonia: Herpesviridae or the ‘classic’ respiratory viruses (influenza A, parainfluenza, respiratory syncytial virus [RSV], rhinovirus, metapneumovirus, and adenovirus). Although many clinical studies have focused on a particular aspect of the role of viruses in the critically ill patient, few studies have determined the frequency of viral respiratory tract involvement in patients with risk factors or suspected VAP.

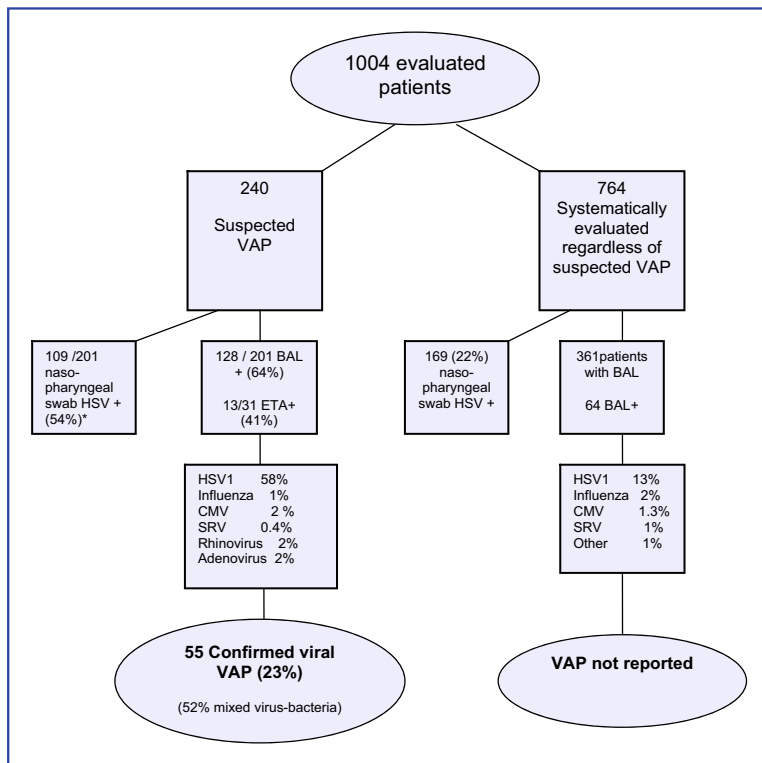


Fig. 1. Pooled analysis of studies evaluating viral infection of lower respiratory tract with more than one diagnostic test, including molecular testing or viral cultures on respiratory samples. BAL: bronchoalveolar lavage; ETA: endotracheal aspirate sample; CMV: cytomegalovirus; HSV1: herpes simplex type 1; SRV: syncytial respiratory virus. * 201 patients were evaluated with nasopharyngeal swab and BAL [12].

Ideally, a study to address this issue should have an appropriate design (prospective cohort), systematically evaluate samples from the upper and lower respiratory tract, explore a wide range of viruses, and include nucleic acid amplification (PCR) as diagnostic test. After an exhaustive review of the literature, only three studies meet most of these requirements [10, 12, 13]. **Figure 1** shows a pooled analysis of these studies.

Although the presence of viruses in respiratory samples was not always accompanied by a definitive diagnosis of viral VAP and not all these studies reported this final diagnosis, all the studies reported a very low incidence of the ‘classic’ respiratory viruses. Herpes simplex virus (HSV) and cytomegalovirus (CMV) were the most frequently isolated agents. For this reason, we will focus on the description of the most relevant aspects regarding respiratory tract infections associated with these viruses.

It should be clarified that because viral pneumonia due to HSV and CMV during mechanical ventilation in the majority of cases is assumed to be a reactivation from a previous infection acquired outside the hospital, the term VAP, which implies nosocomial acquisition of the infection, will not be used, instead we will refer to viral reactivated pneumonia.

Herpes Simplex Virus

Initial infection with HSV usually occurs during childhood and is asymptomatic in most cases. A small percentage of patients may present with gingivostomatitis or pharyngitis. HSV type 1 may be isolated in the saliva of between 1 % and 5 % of the healthy population. Several factors such as tissue trauma, radiation therapy, heat exposure and acute bacterial infections may cause reactivation of the infection from a latent state, causing lesions of the skin and mucous membrane [14].

Lower respiratory tract infection with HSV-1 was initially considered as an entity exclusive of immunocompromised patients; however, in the past two decades, different studies have indicated the potential role of HSV-1 in non-immunosuppressed patients who are critically ill.

Incidence and Risk Factors

HSV respiratory infection in non-immunosuppressed critically ill patients was first reported in patients with acute respiratory distress syndrome (ARDS) in 1983 [15]. The presence of HSV in the lower respiratory tract was previously thought to be exceptional. Four studies evaluated a necropsy series of unselected patients between 1966 and 1982 and reported an incidence of 42 cases per 8535 patients (0.5 %) with a very high mortality and mainly affecting patients with underlying malignancies and extensive burns [16]. It was, therefore, assumed that respiratory tract involvement of HSV was very unusual and associated with a poor prognosis. Findings of a high incidence of HSV in patients with ARDS sparked interest in the hypothesis that HSV reactivation may play a role in an unfavorable clinical outcome in non-immunosuppressed critically ill patients. This was reflected in the increased number of publications reporting the frequency of HSV.

The overall incidence reported thereafter ranges between 5 % and 64 % (10, 15, 17–26). The wide variability of the reported incidence of HSV is due to differences in study designs, study populations and the diagnostic tests used. Despite these differences, particularly susceptible populations, and various risk factors have been identified: Extensive burns, patients with ARDS, intubation and prolonged invasive mechanical ventilation, positive serology for HSV-1 (IgG), appearance of herpetic mucocutaneous lesions, advanced age, high severity scores at admission and use of systemic corticoid therapy during the ICU stay.

It should be noted that, despite the widely varying incidence reported in the literature, the best quality study (in terms of design, adequate number of studied patients, use of highly sensitivity diagnostic tests and consecutive evaluation of non-immunosuppressed critically ill patients) showed high incidences of HSV detection in the lower respiratory tract (64 %) and of HSV bronchopneumonitis (21 %) among patients undergoing mechanical ventilation for more than 5 days [12]. In this study, the presence of herpetic oral-labial lesions, positive pharyngeal swab and macroscopic bronchial lesions were predictors for herpetic bronchopneumonitis.

Table 1 shows a detailed summary of studies evaluating lower respiratory tract infection caused by HSV-1 in critically ill patients since 1982.

Table 1. Summary of studies of lower respiratory tract infections by herpes simplex virus (HSV) 1 in immunocompetent ICU patients.

Year [reference]	Design	Population	HSV 1 + (%)	Risk Factors	Outcomes (HSV+ vs HSV-)	Mortality (%)
1982 [15]	Prospective	ARDS	14/46 (30)	N.A	↑ Days on M.V. ↑ Mortality	57
1982 [16]	Prospective	Suspected VAP	37/308 (12)	Intubation/MV	NA	24
1992 [18]	Retrospective	Mixed	42/42	Intubation/MV	NA	57
1996 (20)	Retrospective	Burned critically ill	27/54 (50)	ARDS	¶	¶
1998 [21]	Retrospective	Sepsis postoperative	8/142 (6)	Thrombocytopenia	↑ Mortality ↑ Bacterial nosocomial infections	63
2000 [22]	Retrospective	Pulmonary infiltrates in trauma patients	4/74 (5)	NA	NA	NA
2003 [23]	Prospective	ICU-LOS > 5 days	11/104 (23)	None	No adverse outcomes	27
2003 [10]	Prospective	ICU-LOS > 3 days	58/361 (16)	HSV + in pharyngeal swabs SOFA score ↑ MV > 7 days	↑ Days on MV ↑ Hospital-LOS	38
2004 [11]	Prospective	Postoperative and trauma patients	106/393 (27)	APACHE II score ↑ Elderly	↑ Mortality	41
2007 [12]	Prospective	VAP suspected/ICU > 5 days	128/201 (64)	HSV + in pharyngeal swab HSV-like skin or mucosa lesions	↑ Days on MV ↑ ICU LOS	48
2008 [24]	Retrospective	Suspected VAP	99/308 (32)	Elderly	↑ Mortality in patients with high HSV load in BAL fluid	26
2009 [25]	Prospective	MV > 48 hour	65/105 (61)	Corticosteroids IgG HSV 1+ at admission	↑ Days on MV ↑ ICU LOS ↑ Hospital-LOS	35
2011 [26]	Prospective	Suspected VAP in mixed population	19/177 (11)	Elderly ↑ Comorbidity and severity index	↑ ICU LOS	76

ARDS: acute respiratory distress syndrome; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; NA: not available; VAP: ventilator-associated pneumonia; SOFA: sequential organ failure assessment; BAL: bronchoalveolar lavage; ¶: retrospective study on lung biopsy samples

Pathogenesis

Reactivation of the latent virus seems to be the initial mechanism of HSV respiratory infection: All patients with herpetic respiratory infection in the ICU have previous HSV-positive serology and, usually, a pharyngeal swab positive for HSV, or oral-labial lesions preceding the lower tract infection [10, 25]. Manipulation and traumatism of the airways predispose patients to viral reactivation in the oropharyngeal mucosa and upper airway, with subsequent micro-aspiration to more distal airways, thereby causing potential lung parenchyma involvement [10, 14]. Therefore, viral reactivation on the tracheobronchial mucosa could explain, in some cases, how respiratory infection presents without any evidence of viruses in the oropharyngeal mucosa [12, 16]. Although hematogenous spread has been described, this mechanism seems to be limited to patients with a major degree of immunosuppression [16].

Typically, viral reactivation begins between day 3 and 5 of mechanical ventilation. This reactivation is followed by an exponential increase in the viral load in the inferior airways, which reaches a peak on day 12. Viral load at this point can reach up to 10^8 copies/ml as measured by PCR performed on tracheobronchial secretions [25]. This viral load corresponds to the viral concentration found in the vesicular lesions of the oral mucosa. This phase is followed by a slow decline of the viral load. This chronology appears relevant when considering the diagnosis of viral VAP on an individual basis.

It should be noted that a high viral load (assessed by viral culture) appears to correlate well with the diagnosis of bronchopneumonitis based on histologic examination (cytology of the bronchoalveolar lavage [BAL] fluid and/or bronchial biopsies are considered as gold standard). A viral load of 8×10^4 copies/ 10^6 cells has sensitivity and specificity of 81 % and 83 %, respectively, for the diagnosis of herpetic bronchopneumonitis [12].

In animal models, instillation of HSV into the nostrils causes pneumonia and triggers a strong inflammatory response with extensive tissue damage secondary to induction of inducible nitric oxide synthase (iNOS) on the lung parenchyma. Inhibition of this enzyme improves tissue damage, pulmonary compliance and survival. Interestingly, these effects are independent of the viral load, thus suggesting a mechanism of inflammatory response amplification rather than direct viral pathogenicity [27].

It should be noted that although viral reactivation is the main mechanism of pathogenesis of HSV pneumonia during mechanical ventilation, several cases of HSV clusters due to nosocomial transmission have been reported in the ICU [28].

Clinical Outcomes

The detection of HSV in the lower respiratory tract does not necessarily mean lung infection and, on an individual basis, it is unclear whether it represents viral contamination of the lower respiratory tract from the mouth and/or throat, local tracheobronchial viral excretion or HSV broncho-pneumonitis [14]. For these reasons, the exact role of HSV remains to be clarified: Is it just a marker of disease severity or a real pathogen with its own morbidity and mortality?

The analysis is even more complicated when the association of virus and bacteria in viral VAP (52 % of cases) is taken into consideration [10, 12]. Several studies have reported more days on mechanical ventilation and longer stays in

the ICU and/or hospital in patients infected with HSV [10, 13, 15, 25, 26]. Interestingly, these were prospective studies that evaluated a large number of patients and failed to show an increase in mortality. The only prospective study that is often cited as an example of increased mortality in the group of HSV+ patients did not reach statistical significance when adjusted for severity, assessed by APACHE II [23]. The studies that reported increased mortality in HSV infected patients were retrospective [10, 29] or prospective with a very small sample size and limited to populations with ARDS [15]. As a result, the question of the effects of infection on mortality remains to be clarified.

Treatment

Despite the high incidence and association with adverse clinical outcomes, there are no randomized controlled trials (RCTs) that make it possible to provide definitive recommendations regarding intervention in these patients. In all the studies, treatment was prescribed by clinicians and analysis of clinical outcomes under controlled conditions was not available. The only interventional study was a small randomized trial that evaluated the efficacy and safety of acyclovir for preventing reactivation of HSV in patients with ARDS [29]. Although acyclovir was effective in preventing viral reactivation in the respiratory tract (absolute risk reduction of 65 %), there was no difference in severity of respiratory failure, duration of mechanical ventilation or mortality between the control and intervention arms.

Given the particular characteristics of this phenomenon (high incidence, association with unfavorable clinical outcomes and potential therapeutic interventions), the need for RCTs that could clarify this issue is imperative.

Cytomegalovirus

Most healthy immunocompetent adults have been infected with CMV, a fact that is evidenced by the presence of specific immunoglobulin (Ig) G for this virus [30]. In most cases, the infection remains latent without causing disease. Reactivation and CMV disease has traditionally been described in populations with marked alterations in cellular immunity [31]. However, in the past two decades there has been increasing evidence that reactivation of CMV is a common finding in the immunocompetent critically ill patient [32]. The frequency of CMV varies depending on the diagnostic methods used, from 12 % when cultures are used to 33 % when PCR is used [30].

Viral reactivation begins between days 14 and 21 of the ICU stay. Risk factors for reactivation are prolonged ICU stays, higher severity scores on admission, and severe sepsis. In this group, the incidence may reach up to 36 %. Although a clear cause and effect has not been found, reactivation is associated with increased mortality and longer hospital stay [30, 32]. Viral reactivation in humans can begin in the lung parenchyma [23, 28, 33]. In animal models with latent CMV, sepsis may produce pulmonary reactivation of the viral infection; this reactivation is associated with a persistent increase in cytokine-mediated inflammatory response in the lung and both findings (reactivation and persistent inflammation) do not occur in the presence of prior ganciclovir treatment [34]. Thus, to the epidemiological evidence of the association of CMV-unfavorable clinical outcomes is added the biological evidence of potential pathogenicity in the lungs.

In 1996, Papazian et al published the first study that showed a high incidence of CMV reactivated pneumonia during mechanical ventilation [33]. The authors studied 85 patients with ARDS, prolonged mechanical ventilation and suspected VAP with negative cultures for bacteria in respiratory specimens (25 open lung biopsies and 60 post mortem biopsies). Conclusive histopathological findings of CMV pneumonia were found in 25 patients (only 3 cases also showed evidence of bacterial pneumonia). The same authors studied the diagnostic value of open lung biopsies on patients with acute lung injury (ALI), suspected VAP and negative cultures of respiratory specimens. Among 100 patients, evidence of CMV infection was found in 30 subjects (3 patients had HSV findings), 4 cases also showed evidence of ARDS in a fibroproliferative phase. With the diagnosis of pulmonary fibrosis, CMV pneumonia was the most frequent finding that conditioned changes in medical treatment [35].

The value of the different diagnostic techniques is not clear; thus, in the first study mentioned, the BAL culture had sensitivity and specificity of 53 % and 92 %, respectively [33]. In another study by the same authors, diagnosis was based on histologic findings after negative cultures and negative pp65 antigenemia [35]. The only study that evaluated PCR assay in BAL in an unselected sample of patients with suspected VAP found 13 % of positive samples without cytoplasmic inclusions and no histological evaluation was performed; it was therefore not possible to reach a definitive diagnosis [12].

The diagnosis of VAP due to CMV may, therefore, be more common than thought, but there are issues that still need to be clarified regarding the appropriate diagnostic tests. Previous studies suggest a low sensitivity of standard diagnostic tests. However, in the populations studied, CMV appears to have a clear pathogenic role, as evidenced by the extensive presence of pneumonitis and of cytoplasmic inclusions in biopsy specimens [33, 35].

Individual management of patients, is further complicated when considering the risk and benefits of treatment with ganciclovir, which has potentially serious adverse effects. For these reasons, RCTs are needed to clarify the role of antiviral treatment in patients with CMV reactivation. Similarly, it is difficult to make a final recommendation regarding the overall approach to individual patients with suspected CMV VAP. It may be suggested that this entity be suspected in patients with risk factors (persistent pulmonary infiltrates with clinical deterioration and no evidence of bacterial infection). If the patient also shows evidence of viral reactivation (preferably assessed by PCR), initiation of antiviral therapy should be considered. Lung biopsy appears to play an important role in this group of patients because it can demonstrate CMV pneumonia even when respiratory specimens are negative.

Mimivirus

Acanthamoeba polyphaga (mimivirus) is a double-stranded DNA virus with the largest viral genome yet described [36]. Although it was thought to be a potential causative agent of pneumonia, the role has not been clearly defined. This microorganism was first described in 1992 as part of a suspected outbreak of *Legionella* pneumonia. Initially categorized as a bacterium, it was finally reclassified as a virus in 2003. Subsequently, serological evidence of mimivirus has been reported in between 7 % and 9 % of patients with community-acquired and nosocomial pneumonia [37, 38].

The potential role of this virus was questioned in a study that evaluated one cohort with pneumonia using different serologies; results were negative in all cases. The nosocomial pneumonia cohort included 71 samples of elderly patients from health care centers; it is not known if any of them received invasive mechanical ventilation [39].

One study systematically evaluated ventilated patients with suspected VAP [40]. Of 300 patients with suspected VAP, 59 had positive serology for mimivirus (19.6 %); 64 % of these had, additionally, positive BAL for bacteria. A comparison of mimivirus-seropositive patients with a seronegative group matched for age, diagnostic category, and severity showed that the positive group experienced increased duration of mechanical ventilation and ICU stay; no differences in mortality were found. It should be noted that the overall effectiveness of matching was 95 % and other relevant variables, such as adequate antibacterial therapy and the bacteremia rate, were similar in the two groups.

Thus, although no definitive recommendations can be made regarding screening for this microbiological agent, there is cumulating evidence of the potential role of this new virus in VAP.

VII

Conclusion

Respiratory viruses are not a common cause of VAP. Herpesviridae (HSV and CMV) are detected frequently in the lower respiratory tract of ventilated patients. HSV is detected between days 7 and 14 of invasive mechanical ventilation; presence of the virus does not necessarily imply pathogenicity, but the association with adverse clinical outcomes supports the hypothesis of a pathogenic role in a variable percentage of patients. Bronchopneumonitis associated with HSV should be considered in patients with prolonged invasive mechanical ventilation, reactivation with herpetic mucocutaneous lesions, and those belonging to a risk population with burn injuries or ALI.

Reactivation of CMV is common in critically ill patients and usually occurs between days 14 and 21 in patients with defined risk factors. The potential pathogenic role of CMV seems clear in patients with ALI and persistent respiratory failure in whom there is no isolation of a bacterial agent as a cause of VAP. The best diagnostic test is not defined although lung biopsies should be considered in addition to the usual methods before starting specific treatment.

Because of the lack of randomized clinical trials, it is not possible to make a definitive recommendation regarding the antiviral treatment for suspected HSV or CMV reactivation pneumonia during mechanical ventilation. The decision to start antiviral treatment should be made on an individual basis, taking into consideration the risk factors mentioned above, a correct interpretation of diagnostic methods and the whole clinical picture of the patient. There is an urgent need for RCTs to address this aspect.

The role of mimivirus is uncertain and yet to be defined, but serologic evidence of this new virus in the context of VAP appears to be associated with adverse clinical outcomes.

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