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Herpes simplex virus type 1 and respiratory disease in critically-ill patients: real pathogen or innocent bystander?

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ABSTRACT

Herpes simplex virus type 1 (HSV-1) has been associated with pulmonary disease, mostly in severely immunocompromised patients. After reactivation and shedding in the oropharynx, the virus may reach the lower respiratory tract by aspiration or by contiguous spread. HSV-1 can be detected in clinical specimens by virus culture or quantitatively by nucleic acid amplification techniques. With these techniques, HSV-1 is often detected in the respiratory secretions of critically-ill patients. However, a clear diagnosis of HSV-1 pneumonia is difficult to establish because clinical criteria, radiological features and laboratory findings all lack specificity. Lower respiratory tract HSV-1 infections have not been associated with specific risk-factors. There is also an absence of consistent data concerning the effect of antiviral treatment on the outcome of critically-ill patients. Further studies are needed to better define the pathogenic role of HSV-1 in the lower respiratory tract of these patients, to improve the diagnosis, and, especially, to assess the need for antiviral treatment in the individual patient.

Keywords Critically-ill patients, diagnosis, herpes simplex virus, pathogenesis, respiratory tract infection, review

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INTRODUCTION

Herpes simplex virus type 1 (HSV-1) causes a variety of infections that involve mucocutaneous surfaces, the central nervous system and, occasionally, visceral organs such as the lung [1,2]. The virus has been reported to be associated with pulmonary disease since 1949 [3], but until two decades ago, HSV pneumonia was considered to be rare. This diagnosis was usually based on autopsy findings [4–11]. The more frequent use of fibreoptic bronchoscopy and bronchoalveolar lavage (BAL) in recent years has resulted in the virus being isolated with increasing frequency from respiratory secretions. This has been paralleled by an increase in the frequency of the diagnosis of HSV tracheobronchitis or pneumonia, mostly in immunocompromised hosts [12–19]. However, the significance of the presence of HSV-1 in respiratory secretions from these patients, and especially from mechanically-ventilated patients, is still a topic for debate. This review focuses on the potential clinical importance of HSV-1 respiratory infections in critically-ill patients, with special reference to the controversies in the literature concerning pathogenesis, clinical spectrum, risk-factors and response to antiviral therapy.

THE CAUSATIVE AGENT

HSV-1 can infect nearly every mucocutaneous and visceral site in the human body. Infections with HSV in humans have been described since ancient Greek times [20,21]. The word *herpes*, which means to creep or to crawl, is found in the original Greek description of the appearance of spreading skin lesions [22]. Clinical descriptions

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of herpes labialis go back to the time of Hippocrates [21]. Early in the 20th century, the virus was transmitted successfully from humans to various animals. The virus was cultured in rabbit testicular tissue as early as 1925, isolated in chick embryos in 1940, and grown successfully in conventional tissue culture systems about 15 years later [21]. The histological association of herpes virus infection with the formation of multinucleated giant cells with intra-nuclear inclusions was first described in 1934 [23].

HSV-1 is classified in the α-herpes virus group of the Herpesviridae, together with HSV type 2 (HSV-2) and varicella-zoster virus. All herpes viruses possess an internal core with a single large, linear, double-stranded DNA molecule, an icosahedral capsid with 162 capsomeres, and a lipid envelope. HSV-1 encodes at least 80 different structural and non-structural polypeptides, including ten different glycosylated proteins. The predominant antibody response to HSV infection is raised against these surface glycoproteins. There is extensive cross-reactivity among the different glycoproteins of HSV-1 and HSV-2. Therefore, differentiation between HSV-1 and HSV-2 infections in commercial antibody assays is not possible. Type-specific antibody assays based on glycoprotein G1 (gG1) for HSV-1 and glycoprotein G2 (gG2) for HSV-2 exist, but are used rarely in routine diagnostic laboratories. The virus structure, function and biological properties have been extensively described previously [2,24–26].

PATHOGENESIS

HSV infections are very common in the human population. Primary HSV infections are usually asymptomatic, but can manifest as gingivostomatitis or pharyngitis [1,2]. Following initial acquisition, HSV-1 establishes latency and remains in a non-replicating form in sensory ganglia for life, commonly in the trigeminal ganglia, but the virus has also been isolated from the superior cervical and vagus ganglia [27,28].

Depending on age (> 5 years) and socio-economic status, 40–98% of the human population in different countries has antibodies to HSV-1 [29–32]. Despite the presence of these antibodies, the virus reactivates intermittently, following local stimuli (e.g., tissue lesion or UV light) or systemic stimuli (e.g., fever, hormonal imbalance or impairment of the immune system during emotional stress or surgery). Reactivation of HSV-1 has been associated with asymptomatic virus excretion in saliva [33–36], ulceration of the mouth mucosa or herpes labialis [37–40], or more serious disease such as herpetic oesophagitis [10,41,42], tracheobronchitis or pneumonia in immunocompromised hosts [4,11,12,14,16,17,19,36,43–48]. Because the primary infection is often asymptomatic, reactivation can be the first clinical manifestation of infection.

Classically, HSV-1 infects squamous epithelium [4,36]. Factors promoting squamous metaplasia, such as trauma, smoking, burns, radiation therapy or chemotherapy, are mentioned in several studies as predisposing the patient to lower respiratory tract infection by HSV [36,46,49]. However, metaplasia may also occur as a secondary response to the infection itself, as the virus is known to cause cytotoxic changes in the respiratory mucosa, with disruption of the protective mucociliary surface [12]. It has also been suggested that intubation, instrumentation and mechanical trauma of the airways predispose to herpetic pulmonary infections [5,6,9,45]. Airway trauma is likely to make the trachea more susceptible to infection with HSV by permitting the virus to migrate from the oral cavity to the trachea by contiguous spread [11]. However, not all patients from whom HSV-1 is isolated from the lower respiratory tract are intubated [12,36,43].

HSV-1 may reach the lower respiratory tract by three different routes. Contiguous spread to the lung parenchyma, or aspiration of the virus in patients shedding the virus from mucocutaneous or oropharyngeal lesions, may play a role in many cases [6]. Focal necrotising pneumonitis has been suggested to result from this local spread [11,50]. Dislodgement of infected particles from the mucous adhesive layer inside the endotracheal tube, followed by their migration to the lower airways, may also contribute to this mechanism [51]. The concept of haematogenous seeding is supported by Ramsey *et al*. [11], and is thought to lead to diffuse interstitial pneumonia. Recovery of HSV from circulating lymphocytes or peripheral buffy coat blood cells provides support for this hypothesis [36,52]. A third mechanism, namely reactivation of latent infection within the vagal ganglion, with spread along the vagus nerve to the lung epithelium, has also been postulated [43]. This suggestion is supported by the isolation of

HSV from the jugular portion of the vagus ganglion in cadavers [27]. The precise way in which HSV-1 migrates from ganglia to epithelium is not understood, and the exact contribution of each of the three pathogenic mechanisms, although all three are plausible, remains unknown.

Both humoral and cell-mediated immunity are involved in the response to HSV-1 infection [26]. The initial stage of HSV-1 infection is influenced by natural killer cells and type 1 and 2 cytokines. Once infection of epithelial cells takes place, neutralising antibodies are ineffective and T-cell immune responses prevail [52,53]. The most severe HSV-1 disease occurs in immunocompromised patients, suggesting that T-cell-mediated immunity is very important in the control and resolution of recurrent HSV-1 infection. Thus, viral reactivation might be an index of the depression of the host immune response. The various alterations in cell-mediated immunity in response to the HSV-1 antigen have been assessed by reduced skin reactivity, decreased T-lymphocyte counts and T-cell subsets, impaired lymphocyte transformation, reduced lymphokine production, decreased natural killer cell activity, and/or decreased cytokine production [54–58].

Although rare, nosocomial transmission of HSV-1 from patient to patient, and from patient to healthcare worker, has been reported [33,59–61]. The source of these hospital and occupational infections is usually found to be HSV-1-positive respiratory secretions of patients. Full compliance with infection control measures in the case of contact with secretions of HSV-positive patients is therefore important.

CLINICAL FEATURES AND INCIDENCE

Primary infection with HSV-1 usually occurs in early childhood and in young adulthood. The initial infection can be asymptomatic or give rise to combinations of fever, sore throat, gingivostomatitis, localised lymphadenopathy, anorexia and malaise [1,2,24]. After the primary infection, the virus can reactivate from its latency, leading to asymptomatic excretion in saliva or to intra-oral mucosal ulceration or oro-labial lesions. The frequency of recurrences varies among individuals.

HSV infection of the upper respiratory tract is a common, usually self-limiting, disease. In studies among university students, infections with HSV-1 were associated with 6–12% of acute respiratory illnesses [35,62]. HSV-1 has also been described as the cause of prolonged acute laryngotracheobronchitis [63]. In contrast, HSV infection of the middle and lower respiratory tract in adults is thought to occur rarely, and is diagnosed almost exclusively in immunocompromised patients. In 1949, Morgan and Finland first suggested that HSV could be a respiratory tract pathogen, and reported the post-mortem isolation of 'a strain of herpes virus' from the lung of a patient with an atypical pneumonia [3]. Despite many reports of HSV-1 and lower respiratory tract infections since that time, the true incidence remains unknown. In the 1960s and 1970s, according to Tuxen [64], a total of 66 cases of HSV lower respiratory tract infections appeared in the literature [3–11,65–69]. The diagnosis was made in only three (4%) living patients [7,66,69], with the remaining cases being diagnosed at autopsy.

Following the initial observation of Morgan and Finland, it was 1965 before Cheever *et al*. [65] reported a patient with Hodgkin's disease and HSV inclusions in biopsy specimens from the tongue, oesophagus, upper respiratory tract and lungs. Four large-scale autopsy studies during the period 1966–1982, in which nearly 9000 autopsies were examined for the presence of HSV in the trachea, bronchi or lungs [4,6,10,11], enabled Tuxen [64] to calculate that the incidence of HSV lower respiratory tract infections was as low as 0.5%. Most patients in these studies were intubated, or severely immunocompromised, because of major burns or underlying malignancies. Similarly, the case reports and studies on small series of patients with lower respiratory tract infections reported during the 1970s associated detection of HSV with severe immunosuppression and with high mortality [5,7–9,41,42,66–69]. For example, Nash and Foley [5] identified 15 patients with herpetic involvement of the lower respiratory tract, 14 of whom had burn injuries.

In recent years, studies have focused on critically-ill patients. Tuxen *et al*. [43] described the first large prospective series of patients in whom HSV involvement of the lower respiratory tract had been diagnosed in living patients. HSV-1 was found in the tracheobronchial secretions of 14 (30%) of 46 patients with adult respiratory distress syndrome (ARDS), whereas no case was diagnosed among mechanically-ventilated

patients without ARDS. Isolation of HSV-1 was associated with prolonged ventilator support and increased mortality. An even higher incidence of 62% was found by the same author in 1987 in a study of the prophylactic use of acyclovir in lower respiratory tract infections in critically-ill patients with ARDS [56]. Nearly all patients for whom the isolation of HSV from the lower respiratory tract has been reported since that time have been immunocompromised or critically-ill patients undergoing immunosuppressive therapy [70], organ transplantation [71,72], or major surgery [16,44,47,73–75]; patients with malignancies [76,77], severe trauma [17,78], or burns [48,58]; or patients who have stayed in an intensive care unit (ICU) [14,19,45,46,79]. Table 1 summarises a number of these studies. The incidence of HSV-1 in respiratory specimens varies between 2% and 50%, but these studies are difficult to compare because of large differences in study design, study populations and/or diagnostic methods. Only a few cases document HSV pneumonia in immunocompetent patients [36,81–84], patients with no previous history of chronic lung disease [12], or patients following general surgery [74]. In a retrospective study of the clinical features and disease course of 22 critically-ill patients with HSV-1 isolated from BAL fluid [85], there were no signs of more frequent or more severe lung injury or ARDS in non-surviving than in surviving patients. The absence of a more complicated disease course, in combination with the absence of interstitial radiographical abnormalities and bronchoscopic airway disease at bronchoscopy, in these critically-ill patients argues against the pulmonary pathogenicity of HSV-1.

Unfortunately, there are few prospective studies of HSV infection. A recent prospective study by Bruynseels *et al*. [19] of 764 ICU patients showed that the prevalence of HSV-1 in the upper respiratory tract is as high as 22% in critically-ill patients, compared with 2–3% in healthy volunteers and patients not admitted to the ICU. HSV-1 was detected in lower respiratory tract specimens from 39% of patients with HSV-1 in their throat, and in 5% of patients with an HSV-negative throat. Of the patients with ARDS, >40% had HSV-1 in the throat, and HSV-1 was isolated from the lower respiratory tract in 20% of cases. It was concluded that HSV-1 in the throat is an independent risk-factor for the development of lower respiratory tract infection with HSV. Whether HSV-1 reactivation or infection could trigger the subsequent development of ARDS, or whether ARDS was present before the isolation of HSV-1, remains unclear. In the context of a possible association of HSV-1 with ARDS, it is remarkable that a study examining the diagnostic value of open lung biopsies in patients with ARDS found only one case of HSV-1 pneumonia among 36 patients [86].

DIAGNOSIS

The diagnosis of HSV pneumonia in immunocompromised hosts, as well as in immunocompetent patients, is difficult because clinical criteria, laboratory findings and radiological features all lack specificity. Therefore, HSV infection can be

Table 1. Summary of clinical studies of herpes simplex virus (HSV) respiratory infections in critically-ill patients (adapted from [80])

Year	Ref.	HSV-positive patients	Incidence % (95% CI)	Method(s)	Setting	Design	Manifestation	Risk-factors	Mortality
1982	[43]	14/46	30 (19–45)	Cy, I, C, S, H	ARDS	Prosp	Tracheobronchitis	Not studied	57%
1988	[12]	9/9	–	H, C, IHC, B	Bronchospasm	Retrosp	Tracheobronchitis	Not studied	0%
1992	[14]	37/308	12 (9–16)	BAL, C, Cy, S	Pulmonary infection	Prosp	Pulmonary infiltrate	Intubation	24%
1993	[45]	42/42	–	C	Various	Retrosp	Tracheobronchitis	Intubation	57%
1995	[16]	3/6	50 (19–81)	C, BAL, Cy	Post-thoracotomy	Retrosp	Pneumonia	Immunosuppression	0%
1995	[15]	53/1199[a]	–	C, BAL	Immunosuppression	Retrosp	Pneumonia	Intubation	21%
1996	[72]	6/245	2 (1–5)	C, IF, BAL	Liver transplantation	Retrosp	Pneumonia	Immunosuppression	17%
1998	[73]	8/142	6 (3–11)	C, BAL	Surgical ICU	Retrosp	Fever, lymphopenia	Thrombocytopenia	63%
2000	[17]	4/74	5 (2–13)	C, B	Trauma	Retrosp	Pulmonary infiltrate	–	27%
2003	[74]	11/104	10 (6–18)	C, S	ICU > 5 days	Prosp	Occult	None	7%
2003	[19]	58/361[b]	16 (13–20)	C, BAL	ICU > 3 days	Prosp	–	HSV in throat	38%
2004	[79]	106/393	27 (23–32)	PCR	ICU	Prosp	–	APACHE II, age	41%

[a]Data refer to the number of BAL specimens investigated.
[b]Data refer to the incidence of HSV isolation from the lower respiratory tract.
H, histology; C, culture; Cy, cytology; IHC, immunohistochemistry; I, direct immunofluorescence; S, serology; B, bronchoscopy; BAL, bronchoalveolar lavage; APACHE, Acute Physiology, Age and Chronic Health Evaluation score; ARDS, adult respiratory distress syndrome; ICU, Intensive Care Unit. Prosp, prospective study; Retrosp, retrospective study.

missed easily, both clinically and at autopsy [5,11,36].

Clinical manifestations

Fever, productive cough, dyspnoea, bronchospasm and/or chest pain are mentioned as the most frequent clinical manifestations of HSV lower respiratory tract infection, although none of these symptoms is specific. Symptoms might also be overshadowed by the underlying disease of the patient. Herpes labialis or oropharyngeal lesions do occur in critically-ill patients and can be quite extensive [11,36]. These symptoms can precede or coincide with the onset of HSV-1 pneumonia in such patients, but a direct relationship with these manifestations is not yet clear [12,43].

Bronchoscopy and lung biopsy

Bronchoscopy allows direct inspection of the respiratory epithelium. Local or diffuse tracheal or tracheobronchial oedema, erythema, mucopurulent secretions, ulcers or a thick, fibrinous exudative membrane have all been observed in association with HSV-1 [12,14,45,47,49,56], but bronchoscopic examination can also be normal [36,54].

Lung biopsy is unreliable, and may be hazardous in critically-ill patients. Ramsey *et al*. [11] did not find herpes virus, either by histological examination or by culture, in open lung biopsy specimens of six critically-ill patients, although HSV was isolated from lung tissue at autopsy. Similar results have been described for a patient in whom an open lung biopsy specimen showed no evidence of HSV by histology or culture, despite diffuse bilateral infiltrates, an increase in serum antibody titres, and bronchoscopic cultures that were positive for HSV-1 [70]. Papazian *et al*. [86] performed open lung biopsies for patients with ARDS [86]. An unexpectedly high number of cases of cytomegalovirus pneumonia were diagnosed, but only one case of HSV-1 pneumonia was found. A transbronchial biopsy might offer an alternative approach, but has limited utility, considering the small size of the tissue specimens that are obtained.

Radiological findings

Aquino *et al*. [87] described the characteristics of chest radiographs of 24 patients with HSV-1 pneumonia. Most patients had a combination of segmental and sub-segmental mixed ground-glass opacities and scattered areas of consolidation on the chest radiograph, compatible with a diffuse and multifocal distribution of parenchymal disease. Pleural effusions were also quite common. In a retrospective study [88] of 17 patients with HSV-1 pneumonia, bilateral lobar or diffuse lung opacities were the main findings on the chest radiograph. Unilateral consolidation, large zones of atelectasis and significant amounts of pleural fluid were observed less frequently. Thus, a characteristic radiographical pattern for HSV-1 pneumonia was not found.

Laboratory diagnosis

Laboratory methods used to detect HSV include virus isolation, microscopy, detection of HSV DNA by PCR, and serology. Virus isolation remains the reference method [89]. Virus isolation in cell culture is specific, relatively inexpensive, and provides a virus strain that can be typed. A discernible cytopathic effect in tissue culture usually develops within 24–48 h of inoculation. However, the simple isolation of HSV-1 from respiratory secretions does not differentiate between true infection and a carrier state, since asymptomatic shedding does occur, especially in (critically) ill patients [19,36,50,90,91]. To solve this diagnostic problem, quantitative viral culture has been suggested [47], but no studies have evaluated this possibility to date.

Cytological examination is less sensitive than virus culture, but can be used to demonstrate actual tissue involvement. The characteristic features of HSV infection are the presence of multinucleated cells with ground-glass intra-nuclear changes and Cowdry type A intra-nuclear inclusion bodies in the affected tissues [36,43]. Detection of these histological hallmarks of HSV tissue infection is quite specific for true lower respiratory tract infections [5,6,69,92,93]. The specificity of both cytological examination and virus culture is increased further if samples are taken by BAL. However, the nuclear changes typical of HSV infection were detected in only one-third of patients with severe respiratory disease and positive HSV-1 BAL specimens [14]. In contrast, cytology with typical HSV changes was observed in all patients with herpetic tracheobronchitis by Sherry *et al*. [12].

Several methods for the rapid detection of HSV antigen directly in infected tissue have been developed. These include the use of polyclonal and/or monoclonal antibodies, and their detection by microscopical observation of immunofluorescence, immunoperoxidase staining and/or by ELISA. In combination with tissue culture, these antigen detection methods increase the speed of diagnosis by allowing the detection of HSV before an overt cytopathic effect is seen [50].

HSV DNA can be detected with a high degree of sensitivity and specificity with nucleic acid amplification by PCR. Primers and probes can be directed at sequences that are conserved among both HSV-1 and HSV-2, or type-specific primers can be used in a multiplex PCR or in separate PCR amplifications [94]. In recent years, nested PCR and real-time PCR techniques have been developed with analytical sensitivities of 1–100 copies [95–98]. Real-time PCR offers the opportunity to determine the HSV viral load. However, studies evaluating these methods for diagnosing HSV pneumonia have not yet been published. Gerardts *et al*. [83] diagnosed HSV pneumonia *post mortem* by PCR and electron-microscopy in a patient for whom virus culture of the lung tissue remained negative. A major drawback of using PCR to detect HSV is that this test detects the presence of HSV DNA, but does not determine whether there is active infection, i.e., active viral replication. True infection might be detected by relating the quantity of HSV RNA to the number of parenchymal cells in standardised BAL specimens, or by determining the ratio of HSV DNA to HSV RNA as a measure of replication of the virus. Studies to evaluate the validity of such approaches are needed.

Serology is not helpful for diagnosing acute HSV respiratory infections. Among healthy adults, >90% have neutralising antibodies to HSV, and serological tests available routinely cannot differentiate reliably among primary, recurrent and past HSV-1 infections [89]. During herpetic tracheobronchitis, no predictable rise in titres was observed by Sherry *et al*. [12], although a significant rise in titre (≥ 4-fold) was found in 58% of patients with HSV-1 lower respiratory tract infection [14].

Pulmonary leakage

In order to evaluate tissue injury caused by HSV-1, the pulmonary leak index was measured in four mechanically-ventilated patients from whom HSV-1 was isolated from tracheal aspirate or BAL fluid [99]. All patients had pulmonary infiltrates, but a normal pulmonary permeability, as measured by the pulmonary leak index. This finding does not support the concept of a role for HSV-1 as a causative agent of pneumonia in critically-ill patients from whom the virus is isolated from respiratory secretions, but suggests harmless shedding of the virus.

RISK-FACTORS AND OUTCOME

Whether HSV causes or contributes to increased morbidity or mortality in patients with lower respiratory tract infections, or whether it is merely an epiphenomenon in a more severely-ill host, is uncertain. Most patients described in the literature had serious underlying disease. The predisposing conditions in adults with lower respiratory tract HSV infections include ARDS [14,43], burns [5,6,48,58,67], organ transplantation [7,11,66,71], neoplasms [4,6,9,36,69], alcoholism [68], renal failure [6] and aplastic anaemia [11]. Pregnancy has also been mentioned as a predisposing factor [5].

A recent study demonstrated a significant reduction in hospital survival among patients receiving assisted ventilation who were shedding HSV-1 compared with non-shedders (40.6% vs. 24.4%, respectively) [79]. Old age and high APACHE II scores were risk-factors for HSV shedding. Schuller *et al*. [45,46] compared immunocompetent with immunocompromised critically-ill patients from whom HSV-1 was recovered from the respiratory tract. Surprisingly, the clinical manifestations of HSV-1 infection were found to be more severe in the immunocompetent patients than in the immunosuppressed patients. Mortality was also higher in the non-immunocompromised group. A history of smoking tobacco, an older age, endotracheal intubation, unresolving acute bronchospasm and leukocytosis were all significantly more frequent in the non-immunocompromised group. These data imply that the pathogenicity of HSV in the respiratory tract might vary with the underlying immune status and the local immune response of the host [45,46]. Whether this difference can be attributed to HSV-1 *per se* is not clear.

Mortality rates of up to 63% are found in clinical studies of HSV respiratory infections in

critically-ill patients (Table 1). Tuxen *et al*. [43] found a mortality rate of 60% in patients with ARDS from whom HSV-1 was isolated from the respiratory tract, compared with 45% in patients with ARDS but without HSV-1. Cook *et al*. [73] reported a higher mortality rate in surgical ICU patients who had HSV-1 (or cytomegalovirus) respiratory infections, and speculated that herpes viruses lead to immunosuppression and predispose to subsequent bacterial and fungal infections. This predisposition to secondary bacterial or yeast infections as a consequence of HSV infection has also been suggested previously [5,10], but Tuxen *et al*. [43] did not observe such a relationship.

Bruynseels *et al*. [19] reported that patients carrying HSV in the throat have a significantly longer duration of stay in the ICU and a higher mortality rate when compared with patients without the virus, although the difference in mortality appeared to be associated with disease severity. In contrast, Porteous *et al*. [100] reported that oral shedding was not related to outcome in critically-ill surgical patients. However, according to this study, mortality associated with HSV-1 shedding was particularly high in patients who failed to develop a rise in antibody titre.

A retrospective cohort study in the ICU found a mortality risk of *c.* 40% in patients from whom HSV-1 was isolated in BAL fluid, mainly because of underlying disease and co-morbidity. These same factors may predispose to endogenous reactivation of the virus [85]. Therefore, HSV seems to be a marker, rather than a mediator, of severe illness. Hence, the isolation of herpes viruses from the respiratory tract secretions may be a consequence of harmless reactivation [91,100], as has been reported for human herpes virus type 6 in critically-ill patients [101,102].

THERAPY

Acyclovir is the treatment of choice for HSV-1 infection; this compound is effective and has low toxicity. However, no randomised, placebo-controlled studies are available concerning the effect of acyclovir on the outcome of critically-ill patients with signs and symptoms of lower respiratory tract infection and with HSV-1-positive respiratory secretions. Although some studies have reported a successful response to acyclovir [12,16,44,49,72,75], others have not demonstrated a clinical benefit [13,45,56,73,103], or did not evaluate the clinical response to treatment [14,47]. Sherry *et al*. [12] treated nine burn patients with herpetic tracheobronchitis and refractory bronchospasm, and all showed clinical and bronchoscopic improvement. Schuller *et al*. [45] found no difference in mortality, duration of mechanical ventilation, or length of stay, between patients who received acyclovir and patients who were not treated. Prellner *et al*. [14] reported 37 immunocompromised hosts with severe airway infection and proof of HSV in BAL fluid, nine of whom died, including seven who were treated with acyclovir. Tuxen *et al*. [56] showed that prophylactic administration of acyclovir lowered the incidence of HSV, but failed to alter patient outcome. HSV-1 was isolated from the respiratory tract of one of 17 ARDS patients, and from 15 of 21 placebo-treated ARDS patients. It was concluded that HSV is not a significant pathogen in the lower respiratory tract and should be treated only if: (1) it occurs in immunocompromised patients (e.g., patients with malignancies, burns, or who have received cytotoxic therapy); (2) there is evidence of pulmonary parenchymal invasion; or (3) there is unexplained clinical deterioration.

At present there are no guidelines for the treatment of HSV infection in critically-ill patients who are not immunocompromised. Despite this, it will be difficult to withhold antiviral treatment from a critically-ill patient with general signs of infection, extensive mucosal herpes infection, focal or diffuse infiltrates on the chest radiograph, a positive test for HSV-1, and no other causative microorganism.

CONCLUSIONS

Although the isolation of HSV-1 from the respiratory tract of critically-ill patients is reported with increasing frequency, the significance of this finding remains unclear. This is partly because of the large differences in study populations, study designs, diagnostic tools and case definitions among the various studies to date. The major obstacle to understanding the role of HSV-1 in lower respiratory tract infections is the lack of a clinically-useful diagnostic reference standard that is able to differentiate between the presence of reactivated HSV-1 as an innocent bystander and a clinically-significant infection of the lung parenchyma by HSV-1 [47]. Whether HSV-1 in the

lower respiratory tract plays an important role in the outcome of these critically-ill patients is also unclear. HSV-1 is often present in the lower respiratory tract in the absence of inflammation, and the illness caused by HSV has rarely been a reason for hospitalisation [36]. Routine prophylaxis in critically-ill patients is not recommended, and treatment with antiviral agents should be discouraged while the pulmonary pathogenicity of HSV-1 in mechanically-ventilated patients is unclear. However, there are situations in which tentative treatment of the critically-ill patient with acyclovir may be justified.

In conclusion, the respiratory pathogenicity of HSV-1 in the critically-ill patient is at least doubtful. Prospective studies with clearly defined study populations and study methods, including quantitative molecular diagnostic procedures for properly standardised respiratory specimens, are needed to answer the question of whether the virus is able to replicate in the lung tissue and is thereby responsible for tissue damage.

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