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BRIEF REPORT

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Clinical Significance of Herpes Simplex Virus in the Lower Respiratory Tract of Critically Ill Patients

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Herpes simplex viruses (HSV) produce a variety of infections involving mucocutaneous surfaces, the central nervous system and occasionally visceral organs. Herpes simplex virus has been detected in immunohistochemically-stained lung tissue obtained postmortem from burn patients, in patients dying from acute respiratory distress syndrome [1] and in respiratory specimens from a limited number of surgical patients hospitalised in intensive care units (ICUs) [2]. Reactivation of HSV is known to occur in surgical and critically ill patients [3] and has been associated with high mortality [4].

During the last 10 years, HSV was isolated frequently from the respiratory tract of patients in the 30-bed ICU of the University Hospital of Antwerp, a 600-bed third-line hospital. The number of admissions to the ICU is approximately 1,200/year. The ICU is a multipurpose unit hospitalising internal medicine, surgical and trauma patients. We hypothesized that HSV might play a role in respiratory disease in critically ill patients and therefore conducted a retrospective study to evaluate the importance of this infection.

Sampling of deep respiratory specimens, bronchus aspirates (BA) or bronchoalveolar lavage (BAL) is routinely performed in patients with persistent unexplained hypoxemia with a radiographically diffuse interstitial pattern or localised or diffuse infiltrates not responding to antibiotic treatment. The virology laboratory culture records were reviewed from 1992 to 1997 to identify HSV-positive (BA or BAL) specimens.

Herpes simplex virus was isolated on Vero cells and identified by immunofluorescence. The BA or BAL specimens were diluted with three volumes of minimal essential medium (Gibco, UK), vortexed with glass beads and centrifuged. The supernatant was inoculated on Vero cells (obtained in 1999 from Bio Whittaker, Belgium) in two-shell vials and incubated at 37°C. One-shell vial was examined after 48 h for the presence of HSV by immunofluorescence (Antiherpes monoclonal antibodies; Biosoft, France); the second vial was followed for 5–7 days for the appearance of a cytopathic effect.

Between 1992 and 1997, 113 of 4,141 (2.7%) deep respiratory specimens (83 BA and 30 BAL) obtained from 64 patients were positive for HSV. The mean age of the patients was 62 years (range, 16–82 years). Only 50% of these patients had fever (>38°C) at the time of the investigation. The majority (95%) of the patients were intubated prior to isolation of the virus (mean time, 10.3 days; range, 1–61 days). There were 38.6% patients with a smoking history. The period of hospitalisation in the ICU ranged from 4 to 14 days, with a mean of 21 days. Only 20% of these patients had received corticosteroids or other immunosuppressive agents for more than 2 weeks prior to their hospitalisation in the ICU; 73% of them had undergone a surgical procedure, 28.1% of which were coronary bypass grafts and 12.5% other thoracic operations. Thoracic surgery was as prevalent among HSV-negative patients as among the HSV-positive population. The most frequent diagnoses are presented in Table 1.

There was no characteristic HSV radiological pattern. Lung injury as expressed by PaO_2/FiO_2 was severe: almost 60% of patients had a PaO_2/FiO_2 value less than 200 mmHg. Several other pathogens were isolated simultaneously with HSV, except in one patient in whom HSV was the sole pathogen isolated.

The pathogenesis of HSV pulmonary involvement is incompletely understood. Most authors suggest viral reactivation, possibly from the sensory ganglia [5]. Alternatively, the virus may be asymptomatically shed in the mouth and be aspirated in the lower respiratory tract [6]. On the basis of an autopsy series, Nash [7] concluded that the anatomic distribution of HSV involvement in

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Table 1 Diagnoses proposed at the time of herpes simplex virus isolation in 64 patients

Diagnosis	No. (%) of patients[a]
Acute respiratory distress syndrome	14 (21.9)
Lung contusion	3 (4.7)
Aspiration	4 (6.3)
Bronchopneumonia	44 (68.8)
Sepsis/systemic inflammatory response syndrome	26 (40.6)
Multiple blood transfusions	49 (76.6)
Pancreatitis	3 (4.7)
Respiratory insufficiency[b]	26 (40.6)
Chronic bronchitis/emphysema	11 (17.2)
Renal insufficiency	22 (34.4)
Diabetes	9 (14.1)
Peripheral vascular lesions	6 (9.4)
Coronary artery bypass grafting	18 (28.1)
Pneumonectomy/lobectomy	8 (12.5)
Trauma	10 (15.6)

[a] Since several patients had more than one diagnosis, the total number of diagnoses was 253
[b] Other than acute respiratory distress syndrome

the tracheobronchial tree and the lungs suggests that aspiration or continuous spread from the respiratory tract is the most likely pathogenesis.

The importance of local trauma for reactivation of HSV has also been proposed. As HSV typically infects squamous epithelium, factors promoting squamous metaplasia such as trauma, smoking, intubation and burns might predispose to lower respiratory tract infection with HSV [8]. The majority (95%) of our patients were intubated before virus isolation, and 73% had undergone a thoracic operation. Instrumentation and mechanical trauma of the airway could predispose to herpetic pulmonary infections.

The role of immunosuppression was previously recognised as the major risk factor for herpes infection, although only 20% of HSV patients in the population we evaluated had received corticosteroids or other immunosuppressive agents such as cyclosporin or azathioprin. These findings indicate that administration of these drugs, which might theoretically facilitate viral reactivation or infection, was not an important contributing factor in our population of patients with HSV isolation from the lower respiratory tract. Most of our patients had received several blood transfusions, which is also known to have an immunosuppressive effect [9].

In this study, twenty-eight patients received acyclovir therapy (5 mg/kg t.i.d. for 5 days, adjusted for renal function), without effect on the outcome: 31 (48%) of all 64 patients and 12 (43%) of those 28 receiving acyclovir therapy died. The difference is not significant ($P = 0.78$).

There are at present no guidelines for the treatment of HSV infection in critically ill patients who are not immunocompromised. In our study, acyclovir treatment had no effect on the survival of this small number of patients. Tuxen et al. [9] conducted a prospective study on the effect of prophylactic acyclovir in patients with acute respiratory distress syndrome. Acyclovir did prevent infection with HSV, but there was no difference in the duration of mechanical ventilation or mortality, and thus a cause-effect relationship between HSV infection and the aetiology of acute respiratory distress syndrome could not be confirmed.

This retrospective study should be considered a preliminary investigation and has some shortcomings: some clinical information is lacking as well as a priori defined criteria for performing bronchoscopies. Therefore, this study cannot provide a definitive answer as to the clinical significance of HSV in the respiratory tract. Given the significant side effects of acyclovir, a randomised prospective therapeutic trial should be undertaken before treatment of patients can be endorsed.

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