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Research note

Clinical impact of HSV-1 detection in the lower respiratory tract from hospitalized adult patients.

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ABSTRACT

The occurrence and clinical impact of herpes simplex virus (HSV) were evaluated in 342 bronchoalveolar lavage (BAL) specimens from 237 patients. HSV-1 and HSV-2 were detected in 32.1% and <1% patients, respectively. A significant difference of HSV-1 prevalence and load was found in relation to admission to intensive care unit, mechanical ventilation, and mortality within 28 days; in particular, a viral load ≥10^5 copies/ml BAL was significantly associated to critical features. No association was found with immune status or other characteristics. HSV-1 was positive in 9/21 (42.9%) cases of ventilator-associated pneumonia, with poor outcome in six.

Key words: herpes simplex virus; lower respiratory tract; intensive care unit; mechanical ventilation; ventilator-associated pneumonia.

Herpes simplex virus (HSV) is a dsDNA virus encompassing two highly seroprevalent subtypes, HSV-1 and HSV-2 [1]. In critically ill patients, HSV-1 has been reported in 22-54% and 16-32% in the upper and lower respiratory tract, respectively [2-6], and increasingly associated to pulmonary diseases with poor outcome, particularly in the presence of viral load $>10^5$ copies/mL bronchoalveolar lavage (BAL)[5,6,7-12]. Moreover, HSV-1 has been proposed as a severity marker in ventilator-associated pneumonia (VAP)[11]. However, it is unknown whether HSV is a true lung pathogen or its detection represents asymptomatic local reactivation in the presence of other pathogens. Herein, we prospectively evaluated the occurrence and significance of HSV in 342 consecutive BAL specimens from 237 patients (M/F, 149/88; mean age, 56.4 years) over a 12-month period. Specimens from the same patient that were collected <2 weeks apart and those from patients admitted to the hospital <48 hours before BAL sampling were excluded. Indications to BAL included respiratory symptoms, new infiltrates on chest X-ray or routine follow-up in lung transplant recipients (at month 1 post-transplantation and subsequently at three month intervals). The following features were collected: immune and transplant status, comorbidities, coinfections (evaluated by a diagnostic panel including bacterial, fungal, and other viral agents [13]), admittance and length of stay at ICU, total length of hospital stay, mechanical ventilation (MV), VAP (diagnosed according to CDC definitions [14]), mortality within 28 days. The occurrence of HSV-1 and 2 was evaluated by real-time PCR (R-gene^{TM}, Argene, France) targeting the US7 and US2 genes, respectively. According to our center's practice, HSV diagnostics also included rapid shell vial isolation on Vero cell cultures [15]. For statistical analysis, the chi-square test and t-test were used, as appropriate. A p value <0.05 was considered significant.

Overall, HSV-1-DNA was detected in 86/342 (25.1%) specimens from 76/237 (32.1%) patients and HSV-2 in three (0.9%) from as many patients. HSV infection was confirmed by viral isolation in 85% of the specimens, with discordant results occurring mostly in

cases in which acyclovir treatment had been initiated. HSV-1 occurrence and load in relation to main clinical features are reported in Table 1. A significant difference of prevalence and load was found in relation to admission to ICU (p = 0.007 and 0.002, respectively), MV (p = 0.04 and 0.0008), and mortality within 28 days (p = 0.004 and 0.018); as well as in relation to the occurrence of coinfections evaluated in single specimens (p = 0.002 and 0.07), with other herpesviruses and bacterial agents being the most commonly detected. No significant difference was found as regards immune and transplant status, and presence of comorbidities. Also length of stay in ICU and total length of stay in hospital were not significantly different between HSV-1 positive (means: 28 and 43 days, respectively) and negative (19 and 32, respectively) patients. In the subgroup of follow-up specimens from lung transplant recipients, in comparison to those collected for symptomatic indication, HSV-1 occurrence and load were not significantly different. As regards VAP, 9/21 (42.9%) cases were positive to HSV-1 and six (66.7%) died within a period ranging from 3 to 120 days (main agents: *S. aureus*, *P. aeruginosa*, *S. pneumonia*, *E. coli*, gram-negative bacteria). As regards the impact of high level viral replication, the prevalence of admission to ICU (p<0.0001), MV (p = 0.016) and death within 28 days (p = 0.013) was significantly higher in the presence of a HSV-1 load $\geq 10^5$ copies/mL; while no significant difference was found in relation to the immune status (Figure 1). Multiple specimens were available for 46 patients (range, 2-7), 19 of which resulted positive in at least one specimen and 11 in consecutive samples. Among patients with consecutively positive specimens, five were asymptomatic lung transplant recipients with viral loads $<10^3$ copies/ml and usually persisting at the subsequent evaluation at 3 months; six were from ICU and evidenced a typical pattern of HSV-1 kinetics with positivity appearing within one week of MV and an exponential increase in viral load (about 5 logs) in subsequent specimens, as reported in other studies [10]. The treatment was started at the clinician's discretion and no significant difference in outcome or decay in viral load was found

between acyclovir-treated and not treated patients. Interestingly, HSV-1 was positive on BAL specimens (by both molecular methods and viral isolation), in 6/10 ICU patients with influenza AH1N1v. Five of these patients died within two weeks from BAL sampling and three of them (60%) resulted HSV-1-positive also on autopsy lung samples by both molecular methods and rapid viral isolation.

Overall, HSV-1 was detected quite frequently, with rates similar to those previously reported (up to 35%) [5,6,10]. No significant difference of prevalence according to immune and transplant status, as well as comorbidities, was found; whereas HSV-1 prevalence and load were significantly higher in the presence of critical features such as admission to ICU, MV and mortality within 28 days. The evaluation of the subgroup of surveillance specimens in lung transplant recipients, that may be considered as controls with immunosuppression, but no traumatic or inflammatory stimulus, evidenced no significant difference in comparison to specimens collected from symptomatic patients, although the low number of specimens should be considered. Interestingly, HSV-1 infection was quite frequent in the presence of VAP, with prevalence rate higher than that previously reported [11]. However, given the smaller number of patients in our series, further studies should be performed, particularly in consideration of the poor outcome. As previously suggested [6], a viral load $\geq 10^5$ copies/mL was associated to severity features, in contrast to the lack of association to immunocompromised conditions. The relevance of these findings should be more appropriately evaluated also considering the occurrence of coinfections. It has been suggested that the mucosal damage associated with intubation and MV is a potential trigger for HSV-1 reactivation and that aspiration from the upper respiratory tract represents the main source of lower respiratory tract infections. Nevertheless, no conclusion can be drawn as to the causative role in lung and further studies on tissue specimens and performing randomized medical intervention analyses are needed [16].

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Transparency declaration

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Table 1. Results of HSV-1 DNA detection in bronchoalveolar lavage (BAL) specimens and association to clinical features of study population. For evaluation of mean viral load, peak values in each patient were considered. As regards indication to BAL (see text for details) and presence of coinfections, single episodes and not patients were evaluated. N, number; n.s., not significant; yrs, years; ICU, intensive care unit.

Table 1

	HSV-1 pos. N (%)	P	HSV-1 Mean viral load (copies/mL BAL)	p
Total number				
patients 237	73 (30.8%)		5.7×10^5	
specimens 342	86 (25.1%)	-	5.6×10^5	-
Age				
≤50 yrs 76	23 (30.2%)		4.4×10^5	
>50 yrs 161	50 (31.1%)	0.98	5.8×10^5	0.49
Indication to BAL*				
Symptomatic 331	83 (25.1%)		5.8×10^5	
Surveillance 11	3 (27.3%)	0.85	9×10^2	0.49
Admission to ICU				
Yes 99	37 (37.4%)		1.03×10^6	
No 138	36 (26.1%)	0.007	8.8×10^4	0.002
Immune status				
competent 123	38 (30.9 %)		2.6×10^5	
compromised 114	35 (30.7%)	0.91	1.9×10^5	0.89
Transplant status				
yes 78	24 (30.8%)		4.6×10^5	
no 159	49 (30.8%)	0.88	6.2×10^5	0.62
Comorbidities				
yes 73	23 (31.5%)		8.4×10^5	
no 164	52 (31.7%)	0.90	3.5×10^5	0.13
Mechanical ventilation				
yes 72	30 (41.6%)		1.2×10^6	
no 165	45 (27.3%)	0.04	1.4×10^5	0.0008
Coinfections*				
yes 203	64 (31.5%)		7.3×10^5	
no 139	22 (15.8%)	0.002	8.4×10^4	0.07
Death within 28 days				
yes 39	20 (51.3%)		1.2×10^6	
no 198	53 (26.7%)	0.004	3.3×10^5	0.018

Figure 1. Prevalence of admission to intensive care unit (ICU), mechanical ventilation, immunosuppression, and death within 28 days according to viral load of HSV-1 in bronchoalveolar lavage specimens: ≥10^5 (dark bars) vs <10^5 copies/ml (white bars).