Prevalence and clinical relevance of VZV lung detection in intensive care unit: A retrospective cohort study

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Declaration of competing interests: The authors declare no conflict of interest in relation with this study.

Fundings: The authors declare no specific funding for this study.

ABSTRACT

Objective: To assess the clinical relevance of varicella zoster virus (VZV) lung detection among patients hospitalized in intensive care unit (ICU).

Methods: We present a monocentric retrospective cohort study from 2012 to 2020. VZV genome was detected in bronchoalveolar lavage (BAL) fluid by real-time PCR.

Results: Twelve of 1389 (0.8%) patients exhibited VZV lung detection, corresponding to an incidence of 13.4 (95% confidence interval [CI] 5.8-21.0) per 100 person-years. Immunosuppression and prolonged ICU stay constituted the main risks factors. VZV detection was not associated with pulmonary deterioration but associated with a risk of shingles occurrence during the following days.

Conclusion: VZV lung detection is a rare event among ICU patients, occurring mostly in immunocompromised patients with prolonged ICU stay. Due to its scarcity and the lack of association with pulmonary failure, a targeted approach to the VZV lung detection diagnosis may allow a significant cost saving without affecting the quality of patients care.

Keywords. Varicella zoster virus (VZV); reactivation; lung; intensive care unit; pneumonia

INTRODUCTION

Reactivation of herpesviruses in the lung, particularly herpes simplex virus (HSV) and cytomegalovirus (CMV), is common among mechanically ventilated patients in intensive care unit (ICU). These infections are associated with poor prognosis, including increased length of mechanical ventilation, ICU stay, and all-cause mortality [1]. Risk factors for herpes zoster (varicella zoster virus [VZV] reactivation) are well described: immunosuppression (glucocorticoids, solid organ transplantation, human immunodeficiency virus [HIV] infection, autoimmune disease), chronic kidney disease, older age [2]. A non-negligible proportion of ICU patients harbor at least one of those risk factors [3]. Since varicella, the VZV primary infection, is a well-known cause of pneumonia [4], its detection in bronchoalveolar lavage (BAL) fluid from mechanically-ventilated patients may suggest a VZV lung infection. However, data on VZV lung reactivation in ICU relies on case reports [5–8]. We conducted a retrospective monocentric cohort study to assess prevalence, risk factors, and clinical relevance of VZV detection in BAL fluid from ICU patients.

METHODS

All patients hospitalized in ICU in Pitié-Salpêtrière Hospital (Paris, France) from July 2012 to December 2020 for whom VZV detection in BAL was performed were included. Patients' baseline characteristics were collected retrospectively from medical records and manually checked using a standardized form. Immunosuppression was defined as follows: use of corticosteroids, solid or hematopoietic stem cell transplantation, HIV infection, autoimmune disease. HSV, CMV, VZV genomes and albumin gene were quantified in BAL fluid samples using in-house real-time PCRs, as previously described [9–11]. The limits of detection of PCRs were 1.40 log (copies/mL). Viral loads were expressed in copies per 10^6 cells of BAL. Statistical analyses were performed using R software version 4.2.2. Categorical variables were expressed as numbers (percentages) and continuous variables as medians (interquartile ranges [IQR]). Univariate analyses were performed using Fisher's exact test (categorical variables) and Wilcoxon's test (continuous variables). $p<0.05$ was considered

to be statistically significant. In accordance with French laws, patients and/or relatives were informed about the anonymous data collection and told that they could decline inclusion. The database is registered with the Commission Nationale de l'Informatique et des Libertés (registration no. 1950673).

RESULTS

During the study period, 1,392 patients were included, corresponding to 2,325 BAL fluid samples tested for *Herpesviridae*. Three (0.2%) patients admitted for varicella pneumonia were excluded. VZV lung detection was observed in 12 (0.8%) patients, corresponding to an incidence of 13.4 (95% confidence interval [CI] 5.8-21.0) events per 100 patient-years. During this period, HSV and CMV lung detections were observed in 524 (37.6%) and 253 (18.2%) patients, respectively.

Patients with VZV lung detection were more likely to have immunosuppression (p=0.015), especially solid organ transplantation (p=0.0039), solid malignancy (p=0.0039), and lupus (p=0.0001). Moreover, median lengths of ICU stay, mechanical ventilation, and dialysis were statistically higher among patients with VZV lung reactivation (p<0.00001, p=0.0004, and p<0.00001, respectively) than patients without VZV lung detection. Of note, CMV lung detection was statistically more frequent in patients with VZV lung detection (p=0.014) (Table 1).

Shingles occurred in 7/12 (58%) patients with VZV lung detection. Two of them had vesicles prior to VZV detection in BAL fluid, making shingles a predictor of VZV lung detection with low sensitivity (0.17; 95% CI: 0.05-0.45) but high specificity (0.99, 95% CI: 0.99-1.00). For the 5 other patients, VZV was detected in BAL fluid up to 2 weeks before shingles and was not predictive of its location (table 2): thorax (2), side (2), eye (1), leg (1) and disseminated (1).

In our study, 9/12 (75%) patients received acyclovir treatment which tended to be protective against shingles (OR: 0.41, 95% CI: 0.0051-11.7, p=1.00), although not significant. BAL was performed for deterioration of pulmonary function among 8/12 (66.7%) patients with VZV lung detection. All of them had obvious reason for acute respiratory failure: bacterial ventilator-associated pneumonia (4),

91 septic shock (3), and surgical site infection (1). Therefore, VZV lung detection could not be considered
92 as an etiological cause of pulmonary failure. Moreover, VZV lung detection did not affect overall
93 mortality: 42% *versus* 41% (*p*=1.00).
94
95 **DISCUSSION**
96 We present here the first cohort study addressing the question of the clinical relevance of
97 VZV lung detection in ICU patients. Our results showed that this is a rare event (incidence 0.8%)
98 occurring mostly in immunocompromised patients with a long ICU stay. Moreover, VZV detection in
99 BAL fluid was strongly associated with the subsequent occurrence of shingles, especially in the
100 absence of an anti-herpetic treatment, but not with a deterioration of lung function.
101 VZV infection has been reported to constitute a rare event in ICU patients with a frequency
102 of VZV detection in blood of 0.6% among 329 ICU adult patients [12], roughly similar to ours (0.8%) in
103 BAL fluid. Moreover, although VZV reactivation has already been associated with an acute pulmonary
104 failure [4,8], cutaneous symptoms were constituently concurrent.
105 VZV BAL detection up to 2 weeks before shingles was an unexpected finding. Indeed, even if
106 immunocompetent patients with shingles consistently exhibit detectable VZV DNA in blood [13], we
107 show for the first time that VZV genome can be detected in patients before the occurrence of
108 shingles. This led us to make the hypothesis that VZV lung detection in BAL from immunosuppressed
109 patients could result from VZV reactivation in sensory ganglia and spreading to the lungs, likely
110 through blood.
111 This pathogenic mechanism relies mostly on the fact that, unlike varicella pneumonia, we were
112 unable to attribute formally a pulmonary failure to VZV detection in BAL, while most of untreated
113 patients developed a zoster later.
114 This study has several limitations. A high proportion of patients were on extracorporeal
115 membrane oxygenation (ECMO) support. This cohort included only patients with a VZV PCR testing in
116 BAL, so we may have overestimated the incidence of subclinical detection since only the most severe

patients were tested. We did not assess the VZV serological status of the patients. Finally, our study may have lacked the power to determine whether VZV in BAL could cause pulmonary failure. However, since an obvious etiology of respiratory deterioration could be identified for each patient with VZV lung reactivation, VZV pulmonary failure is likely to represent an unusual consequence of a rare event, making irrelevant the systematic VZV detection in BAL from ICU patients. A targeted approach to the VZV lung detection diagnosis may allow a significant cost saving without affecting the quality of patients care. In the present study, the limitation of BAL VZV detection to either immunocompromised patients with ICU stay ≥5 days or immunocompetent patients with ICU stay ≥18 days would have provided estimated cost savings of about 70% without lowering significantly the quality of care.

In conclusion, VZV lung detection is a rare event among ICU patients (<1%) that does not require the systematic VZV detection in all BAL fluid samples. Moreover, guidelines on therapeutic management of VZV lung detection should be proposed.

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Table 1: Characteristics of patients with and without VZV lung detection.

	VZV lung detection (n= 12)	**No VZV lung detection (n=1377)**	***p* value**
Age, years, median (IQR)	47 (25-57)	55 (43-64)	0.95
Male gender, n (%)	5 (42%)	961 (70%)	0.05
Tobacco smoker, n (%)	3 (33%)	320 (32%)	1.00
BMI, kg/m², median (IQR)	25 (22-29)	26 (23-31)	0.62
SOFA score on admission, median (IQR)	12 (6-16)	12 (8-15)	0.95
Immunosuppression*, n (%)	9 (75%)	532 (38%)	**0.015**
Solid organ transplantation, n (%)	6 (50%)	199 (14%)	**0.004**
Solid malignancy, n (%)	5 (41%)	133 (10%)	**0.004**
Hematological malignancy, n (%)	1 (8%)	91 (7%)	0.56
Corticosteroids, n (%)	6 (50%)	281 (20%)	**0.02**
Lupus, n (%)	4 (33%)	30 (2%)	**0.0001**
Duration of mechanical ventilation, days, median (IQR)	41 (20-60)	11 (5-23)	**0.0004**
ICU length of stay, days, median (IQR)	63 (40-79)	16 (7-31)	**<0.0001**
Dialysis duration, days, median (IQR)	35 (18-42)	2 (0-8)	**<0.0001**
ECMO, n (%)	12 (100%)	962 (70%)	**0.02**
Vasopressor treatment length, days, median (IQR)	27 (19-46)	9 (4-18)	**<0.0001**
HSV lung reactivation, n (%)	4 (33%)	524 (37%)	0.74
CMV lung reactivation, n (%)	4 (33%)	253 (18%)	**0.014**
Mortality, n (%)	5 (42%)	560 (41%)	1.00

Results are expressed as numbers (n) and percentages for categorical variables or medians and interquartile ranges (IQR) for continuous variables.

*Immunosuppression: use of corticosteroids, solid or hematopoietic stem cell transplantation, HIV infection or autoimmune disease.

BMI: body mass index; CMV: cytomegalovirus; ECMO: extra corporeal membranous oxygenation; HSV: herpes simplex virus; ICU: intensive care unit; SOFA: sepsis related organ failure assessment; VZV: varicella zoster virus.

Table 2: Characteristics of the 12 patients experiencing VZV lung detection during ICU stay.

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Day	16/08/2013	26/12/2013	22/11/2013	10/09/2014	16/12/2012	22/12/2014	01/07/2015	29/10/2020	23/05/2013	27/01/2018	23/08/2015	14/04/2013
VZV load (log[copies/10^6 cells of BAL])	5.43	3.27	6.82	1.65	2.86	3.49	5.00	4.05	4.19	4.24	>7 log	3.83
ICU length before VZV detection in BAL (days)	45	6	27	19	37	10	1	32	29	7	57	54
Immunosuppression	Lupus	SOT	SOT	no	no	no	SOT	Corticosteroids	Lupus	SOT	SOT	SOT
Herpes zoster location	NA	Disseminated	Thorax	NA	Side	Left eye	NA	Side	NA	Right leg	Thorax	NA
Vesicle first then positive VZV BAL	no	no	yes	no	no	no	no	no	no	no	yes	NA
*Time from positive BAL to acyclovir treatment**	NA	13	-2	NA	3	7	1	1	7	7	3	NA
*Time from positive BAL to skin vesicles**	NA	13	-2	NA	2	7	NA	2	NA	7	-5	NA
Corticosteroid (mg prednisone equivalent)	60	30	25	no	no	no	no	80	50	no	20	40
Current Vasopressor use	yes	yes	yes	yes	no	yes	yes	no	no	yes	yes	no
Current dialysis	no	no	no	no	yes	no	no	no	no	yes	yes	no
Bacteria in BAL	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Oropharyngeal flora	Negative	*Pseudomonas aeruginosa*	Negative	Negative	*Pseudomonas aeruginosa*	Negative	Negative	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*
Cause of BAL	Septic shock	VAP	Shingle discovery : extension review	Undetermined fever	VAP and septic shock	Surgical site infection	Post heart transplant control	VAP	Septic shock	Cardiac tamponade	Shingle discovery : extension review	VAP
Death	yes	no	yes	no	no	yes	yes	no	no	no	yes	no

*Negative value for time from positive BAL to acyclovir treatment (or skin vesicles) means that acyclovir was initiated (skin vesicles appeared) before BAL VZV detection.

BAL: bronchoalveolar lavage; ICU: intensive care unit; NA: Not applicable (no history of vesicle or no acyclovir given). SOT: solid organ transplantation; VAP: ventilation acquired pneumonia; VZV: varicella-zoster virus