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1 **Prevalence and clinical relevance of VZV lung detection in intensive care unit: a retrospective**  
2 **cohort study**

3

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16 study.

17

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19

20 **ABSTRACT**

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

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

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

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

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

38

39 **INTRODUCTION**

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

52

53 **METHODS**

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

65 to be statistically significant. In accordance with French laws, patients and/or relatives were informed  
66 about the anonymous data collection and told that they could decline inclusion. The database is  
67 registered with the Commission Nationale de l'Informatique et des Libertés (registration no.  
68 1950673).

69

## 70 RESULTS

71 During the study period, 1,392 patients were included, corresponding to 2,325 BAL fluid  
72 samples tested for *Herpesviridae*. Three (0.2%) patients admitted for varicella pneumonia were  
73 excluded. VZV lung detection was observed in 12 (0.8%) patients, corresponding to an incidence of  
74 13.4 (95% confidence interval [CI] 5.8-21.0) events per 100 patient-years. During this period, HSV and  
75 CMV lung detections were observed in 524 (37.6%) and 253 (18.2%) patients, respectively.

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

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

87 In our study, 9/12 (75%) patients received acyclovir treatment which tended to be protective  
88 against shingles (OR: 0.41, 95% CI: 0.0051-11.7,  $p=1.00$ ), although not significant. BAL was performed  
89 for deterioration of pulmonary function among 8/12 (66.7%) patients with VZV lung detection. All of  
90 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 constitutently 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

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

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

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

	<b>VZV lung detection (n= 12)</b>	<b>No VZV lung detection (n=1377)</b>	<b>p value</b>
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/m <sup>2</sup> , 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%)	<b>0.015</b>
Solid organ transplantation, n (%)	6 (50%)	199 (14%)	<b>0.004</b>
Solid malignancy, n (%)	5 (41%)	133 (10%)	<b>0.004</b>
Hematological malignancy, n (%)	1 (8%)	91 (7%)	0.56
Corticosteroids, n (%)	6 (50%)	281 (20%)	<b>0.02</b>
Lupus, n (%)	4 (33%)	30 (2%)	<b>0.0001</b>
Duration of mechanical ventilation, days, median (IQR)	41 (20-60)	11 (5-23)	<b>0.0004</b>
ICU length of stay, days, median (IQR)	63 (40-79)	16 (7-31)	<b>&lt;0.0001</b>
Dialysis duration, days, median (IQR)	35 (18-42)	2 (0-8)	<b>&lt;0.0001</b>
ECMO, n (%)	12 (100%)	962 (70%)	<b>0.02</b>
Vasopressor treatment length, days, median (IQR)	27 (19-46)	9 (4-18)	<b>&lt;0.0001</b>
HSV lung reactivation, n (%)	4 (33%)	524 (37%)	0.74
CMV lung reactivation, n (%)	4 (33%)	253 (18%)	<b>0.014</b>
Mortality, n (%)	5 (42%)	560 (41%)	1.00

182

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

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

187 BMI: body mass index; CMV: cytomegalovirus; ECMO: extra corporeal membranous oxygenation;

188 HSV: herpes simplex virus; ICU: intensive care unit; SOFA: sepsis related organ failure assessment;

189 VZV: varicella zoster virus.

190

191

**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 <sup>6</sup> 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	<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus aureus</i>	Oropharyngeal flora	Negative	<i>Pseudomonas aeruginosa</i>	Negative	Negative	<i>Pseudomonas aeruginosa</i>	Negative	Negative	<i>Klebsiella pneumoniae</i>	<i>Klebsiella pneumoniae</i>
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

- 1 \*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.
- 2 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
- 3