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1 **Influenza-induced acute respiratory distress syndrome during the 2010-2016**
2 **seasons: bacterial co-infections and outcomes by virus type and subtype**

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24 **Objectives**

25 We aimed to describe bacterial co-infections and acute respiratory distress (ARDS) outcomes
26 according to influenza type and subtype.

27 **Methods**

28 A retrospective observational study was conducted from 2012 to 2016 in patients admitted to
29 the respiratory intensive care unit (ICU) of Marseille university hospital for influenza-induced
30 ARDS. Microbiological investigations, including multiplex molecular respiratory panel testing
31 and conventional bacteriological cultures, were performed as part of the routine ICU care on
32 the bronchoalveolar lavage collected at admission. Bacterial co-infections, ICU mortality, and
33 respiratory function were investigated according to virus type and subtype.

34 **Results**

35 Among the 45 ARDS-patients included, A(H1N1)pdm09 was the most frequent influenza virus
36 identified (28/45 A(H1N1)pdm09, 8/45 A(H3N2), and 9/45 influenza B). Bacterial co-
37 infections involving a total of 23 bacteria were diagnosed in 16/45 patients (36%).
38 A(H1N1)pdm09 patients presented fewer bacterial co-infections (17.9% vs. 50.0% for
39 A(H3N2) patients and 77.8% for B patients; $p < 0.01$). Overall, mortality at 90 days post-
40 admission was 33.3% (15/45), and there was no significant difference between influenza type
41 and subtype. The need for extracorporeal membrane oxygenation was more frequent for
42 A(H1N1)pdm2009 (20/28, 71.4%) and B patients (7/9, 77.8%) as compared to the A(H3N2)
43 subtype (1/8, 12.5%; $p < 0.01$). A(H1N1)pdm09-ARDS patients were associated with fewer
44 ventilation-free days at day 28 (median [IQR]: 0[0-8] day) as compared with other influenza-
45 ARDS patients (15 [0-25] days, $p < 0.05$).

46 **Conclusions**

47 In a population of influenza-induced ARDS, A(H1N1)pdm09 was associated with fewer
48 bacterial co-infections but poorer respiratory outcomes. These data underline the major role of
49 A(H1N1)pdm09 subtype on influenza disease severity.

50 **Introduction**

51 According to the World Health Organization (WHO), seasonal influenza may result in 290,000-
52 650,000 deaths annually [1]. Influenza surveillance networks estimated that approximately 15%
53 of hospitalized patients required admission to an intensive care unit (ICU), and the mortality
54 could be up to 45% in case of acute respiratory distress syndrome (ARDS) [2–4]. ARDS is a
55 life-threatening form of acute lung injury characterized by diffuse alveolar damage and lung
56 capillary endothelial injury [5]. The development of bacterial co-infections also contributes to
57 the severity of influenza infections, although their frequency and impact may differ according
58 to the circulating influenza virus [6]. It was reported that ARDS encompassed heterogenic sub-
59 phenotypes associated with different clinical outcomes [7]. However, the outcomes of ARDS
60 according to influenza type and subtype have been poorly studied thus far. In this study we
61 aimed to describe bacterial co-infections and ARDS outcomes by influenza type/subtype.

62 **Methods**

63 **Study population and outcome measures**

64 We conducted a retrospective observational study from the 2012-2013 to the 2015-2016
65 influenza seasons in the respiratory ICU of the Marseille university hospital (extracorporeal
66 membrane oxygenation, ECMO, reference centre). Inclusion criteria were the association of an
67 ARDS with a positive influenza polymerase chain reaction (PCR) test performed on the
68 bronchoalveolar lavage (BAL) collected at admission. Exposure variables were the influenza
69 type/subtype. Primary outcome was mortality at day 90. Secondary outcomes were the need for
70 ECMO, the duration of mechanical ventilation (MV), the number of ventilation-free days

71 (VFD) calculated from day 1 to day 28, and the length of ICU stay. Bacterial co-infections were
72 described according to influenza type/subtype. Clinical characteristics and demographic data
73 were retrospectively collected from electronic medical records.

74 **Microbiological diagnosis**

75 All microbiological investigations were performed on the BAL fluid collected at admission as
76 part of our ICU routine care. The main respiratory bacteria and viruses were tested using a
77 multiplex PCR assay (FTD respiratory pathogens 33; fast-track diagnostics, Luxembourg).
78 Influenza A subtyping, conventional bacteriological culture, specific PCR and pneumococcal
79 urinary antigen test (Alere Inc, MA, USA) were also performed. Respiratory bacterial co-
80 infections were defined as procalcitonin level ≥ 0.25 $\mu\text{g/L}$ associated with molecular and/or
81 culture detection of respiratory pathogen, and/or urinary detection of pneumococcal antigen.
82 See supplementary data for additional information.

83 **Ethics**

84 In accordance with the national regulations, patients or relatives were informed at ICU
85 admission of the possible use of anonymous healthcare data collected retrospectively for
86 clinical research. They were also informed of the possibility to refuse the use of this data. The
87 study received approval from the French data protection authority (*Commission Nationale de*
88 *l'Informatique et des Libertés*) and is registered with the national data protection
89 agency (number 2019-57).

90 **Statistical Analysis**

91 Continuous variables are presented as means \pm standard deviations (SD) or medians with
92 interquartile ranges [IQR] and compared using non-parametric Kruskal-Wallis or Mann-
93 Whitney tests. Proportions were compared using the Chi-squared or Fisher's exact test as
94 appropriate. A p-value of <0.05 was regarded as statistically significant. Statistical tests were

95 performed using SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version
96 19.0. Armonk, NY, USA).

97 **Results**

98 **Study population**

99 A(H1N1)pdm2009 subtype represented the most frequent influenza virus detected (28/45
100 A(H1N1)pdm2009, 8/45 A(H3N2) subtype and 9/45 B type). Mean±SD age differed
101 according to influenza type/subtype (A(H3N2): 69.4±9.8 years; A(H1N1): 55.4±14.1 years; B
102 patients: 49.7±19.1 years, $p<0.05$). Most patients had pre-existing comorbidities (35/45,
103 77.8%), but vaccination rate was only 11.1% (5/45; Table 1). Empirical antibiotic therapy was
104 initiated with or adjusted to a broad spectrum β -lactam and macrolide for all patients. Of note,
105 approximately 90% of patients had received antibiotics prior to ICU admission. Antiviral
106 treatment (oseltamivir) was administered to all patients. None received intravenous
107 neuraminidase inhibitors. No viral co-infection was diagnosed in this cohort.

108 **Bacteriological results at admission according to influenza type and subtype**

109 A bacterial co-infection was detected in 16 patients (35.6%). A(H1N1)pdm09 patients
110 presented fewer bacterial co-infections than patients infected with another type/subtype (17.9%
111 vs. 50.0% for A(H3N2) patients and 77.8% for B patients; $p<0.01$). A total of 23 respiratory
112 bacteria were identified, mainly *Staphylococcus aureus* (9/23, 39%) and *Streptococcus*
113 *pneumoniae* (7/23, 30%, table 1). Six of the 23 (26.1%) bacteria responsible of co-infections
114 were detected using conventional cultures.

115 **Table 1. Patient characteristics by influenza type and subtype**

	Total n=45	A(H1N1) n=28	A(H3N2) n=8	B n=9	p-value
Clinical features					
Age, mean value, years ± SD	56.7±15.6	55.4±14.1	69.4±9.8	49.7±19.1	<0.05
Male sex, n (%)	27 (60.0)	17 (60.7)	5 (62.5)	5 (55.6)	ns
Influenza vaccination, n (%)	5 (11.1)	4 (14.3)	1 (12.5)	0 (0.0)	ns
No comorbidity, n (%)	10 (22.2)	6 (21.4)	2 (25.0)	2 (22.2)	ns
Smoking, n (%)	23 (51.1)	16 (57.1)	5 (62.5)	2 (22.2)	ns
Heart disease, n (%)	16 (35.6)	11 (39.2)	3 (37.5)	2 (22.2)	ns
Diabetes, n (%)	13 (28.9)	10 (35.7)	2 (25.0)	1 (11.1)	ns
Obesity, n (%)	12 (26.7)	9 (32.1)	1 (12.5)	2 (22.2)	ns
COPD, n (%)	11 (24.4)	6 (21.4)	3 (37.5)	2 (22.2)	ns
Immunosuppression, n (%)	8 (17.8)	4 (14.3)	3 (37.5)	1 (11.1)	ns
Alcoholism, n (%)	6 (13.3)	2 (7.1)	2 (25.0)	2 (22.2)	ns
Pregnancy, n (%)	1 (2.2)	0 (0.0)	0 (0.0)	1 (11.1)	ns
Patient pathway, n (%)					
Admission from other ICU	24 (53.3)	18 (64.3)	2 (25.0)	4 (44.4)	ns
Admission from emergency department	11 (24.4)	4 (14.3)	5 (62.5)	2 (22.2)	ns
Admission from other unit	7 (15.6)	5 (17.9)	1 (12.5)	1 (11.1)	ns
Other	3 (6.7)	1 (3.6)	0 (0.0)	2 (22.2)	ns
Bacteriological results					
Bacterial co-infection, n (%)	16 (35.6)	5 (17.9)	4 (50.0)	7 (77.8)	<0.01
<i>S. aureus</i>	9 (20.0)	5 (17.9)	0 (0.0)	4 (44.4)	ns
<i>S. pneumoniae</i>	7 (15.6)	1 (3.6)	3 (37.5)	3 (33.3)	<0.05
<i>S. pyogenes</i>	2 (4.4)	0 (0.0)	0 (0.0)	2 (22.2)	<0.05
<i>H. influenzae</i>	5 (11.1)	0 (0.0)	1 (12.5)	4 (44.4)	<0.01

116 SD: standard deviation; ns: non-significant; COPD: chronic obstructive pulmonary disease

117 **Patient outcomes according to influenza type and subtype**

118 Overall, mortality at 90 days post-admission was 33.3% (15/45), and there was no significant
 119 difference between influenza type and subtype. Twenty-six patients (58%) presented with
 120 severe ARDS. The need for ECMO was more frequent for A(H1N1)pdm2009 (20/28, 71.4 %)
 121 and B patients (7/9,77.8%) as compared with A(H3N2) subtype (1/8, 12.5%; p<0.01). The
 122 median [IQR] VFD at day 28 was significantly different between influenza type and subtype
 123 (A(H1N1)pdm09 patients: 0[0-8] days; B patients: 9[0-18] days; A(H3N2) patients: 27[0.0-28]

124 days, $p < 0.05$; Table 2). A(H1N1)pdm09-ARDS patients were associated with fewer
 125 ventilation-free days at day 28 (median [IQR]: 0[0-8] day) as compared with other influenza-
 126 ARDS patients (15[0-25] days, $p < 0.05$).

127 **Table 2. Patient severity and outcome according to influenza type and subtype**

	Total n=45	A(H1N1) n=28	A(H3N2) n=8	B n=9	p-value
Severity at ICU admission					
Mild ARDS, n (%)	4 (8.9)	1 (3.6)	2 (25.0)	1 (11.1)	ns
Moderate ARDS, n (%)	15 (33.3)	10 (35.7)	3 (37.5)	2 (22.2)	ns
Severe ARDS, n (%)	26 (57.8)	17 (60.7)	3 (37.5)	6 (66.7)	ns
SOFA, mean \pm SD	9.0 \pm 4.2	8.9 \pm 4.4	7.5 \pm 3.2	11.0 \pm 3.9	ns
SAPS II, mean \pm SD	48.2 \pm 14.7	46.3 \pm 13.4	49.3 \pm 13.2	53.3 \pm 19.6	ns
PaO ₂ /FiO ₂ (mmHg) mean \pm SD	98.9 \pm 41.7	99.6 \pm 40.7	109.0 \pm 49.2	87.9 \pm 38.3	ns
Patient outcomes					
90-day mortality, n (%)	15 (33.3)	10 (35.7)	3 (37.5)	2 (22.2)	ns
ECMO, n (%)	28 (62.2)	20 (71.4)	1 (12.5)	7 (77.8)	<0.01
MV duration, days, median [IQR]	21.6 [6.0-33.0]	22.5 [13.8-41.8]	1.5 [0.0-12.8]	10.0 [6.0-17.0]	<0.01
VFD at day 28, median [IQR]	0 [0-18]	0 [0-8]	27 [0-28]	9 [0-18]	<0.05
Length of ICU stay, days, median [IQR]	23.3 [8.0-32.0]	25.0 [13.8-42.3]	9.0 [5.0-18.5]	15.0 [6.0-17.0]	<0.05

128 ARDS was categorized as mild, moderate, or severe according to the Berlin conference definition [5]. ICU:
 129 intensive care unit, ns: non-significant; ARDS: acute respiratory distress syndrome, SOFA: sequential organ
 130 failure assessment, SD: standard deviation, SAPS: simplified acute physiology score, ECMO: extracorporeal
 131 membrane oxygenation, IQR: interquartile range, VFD: ventilation free-days.

132 **Discussion**

133 In the present study of influenza-induced ARDS, A(H1N1)pdm09 was found to be predominant
134 and was associated with fewer bacterial co-infections and poorer respiratory outcomes than
135 A(H3N2) or B-induced ARDS.

136 Since 2009, A(H1N1)pdm09 has also been reported to be the most frequently detected in ICU
137 patients underscoring the particular virulence of this influenza subtype [4,8,9]. Töpfer et al.
138 found that A(H1N1)pdm09-ARDS led to a more important impairment of gas exchange as
139 compared to non-A(H1N1)pdm09-ARDS; interestingly, the rate of bacterial co-infection
140 between the two groups was not different [10]. These results are consistent with initial reports
141 from the 2009 pandemic during which A(H1N1)pdm09 subtype was responsible for extremely
142 severe infections mostly without the development of bacterial co-infections [2,11]. Several
143 studies have, however, found greater morbidity and mortality rates in case of bacterial co-
144 infections associated with A(H1N1)pdm09 indicating that viral pneumonia alone is not
145 exclusively responsible for the severity of influenza infections [4,12,13].

146 It has been reported that A(H3N2) particularly affected elderly people, as was found herein,
147 leading to a high mortality and ICU admission rates in this population [9]. Although considered
148 as less severe and mainly responsible for mild presentation in children, B infections can also
149 cause severe and fatal cases [14], notably due to the development of bacterial co-infections [15].

150 In the present study, most of influenza B-induced ARDS patients presented severe forms of
151 ARDS and were more frequently associated with bacterial co-infections at ICU admission.

152 The main limitation of this retrospective study is the number of patients included which did not
153 allow the investigation of the role of co-infections on respiratory function for each influenza
154 type and subtype. However, a high number of influenza-induced ARDS patients might be

155 difficult to achieve and comprehensive descriptive data regarding the microbial epidemiology
156 and ARDS outcomes related to the three circulating influenza viruses are lacking.

157 To conclude, the present study underlines the major role of A(H1N1)pdm09 on influenza
158 disease severity. The detection of this subtype at admission should alert clinicians to the
159 potential evolution towards an extremely severe case requiring long ICU stay.

160 **Conflicts of interest**

161 The authors declare that the study was conducted in the absence of any commercial or financial
162 relationships that could be construed as a potential conflict of interest.

163 **Acknowledgments**

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165 **Author contributions**

166 AB, J-SC, BL, XD, LP, AN, SH conceived the study. AN, MV, LN, FM, SE performed
167 microbiological investigations. CM, FD, LP, SH are the guarantors for clinical data and sample
168 collection. AB and JS-C were the main writers of the manuscript. All authors reviewed and
169 approved the final version of the manuscript.

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