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LETTER

Early bacterial co-infection in ARDS related to COVID-19

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Dear Editor,

Originating in China in late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic reached Europe in March 2020. In its most severe expression, coronavirus disease 2019 (COVID-19) pneumonia presents as the acute respiratory distress syndrome (ARDS), mandating intensive care unit (ICU) admission and invasive mechanical ventilation (IMV) [1]. Bacterial coinfections, well documented in other respiratory viral infections, notably influenza [2], have not yet been investigated at the onset of COVID-19 pneumonia.

To address this, we conducted a prospective cohort study in three ICUs of Lyon University-Affiliated Hospital. This study was approved by the institutional ethics committee (Comité d'Ethique du CHU de Lyon, N°20-42). Consecutive patients with PCR-confirmed SARS-CoV-2 infection requiring IMV for ARDS (Berlin definition) were recruited from March 16th to April 6th 2020, and were followed-up for 28 days. Endotracheal aspirates (ETA) or bronchoalveolar lavages (BAL) were sampled in the 24 h following tracheal intubation, and microbiology analyses were performed, including conventional culture and a multiplex PCR assay (BioFire® FilmArray® Pneumonia Panel; bioMérieux, Marcy-l'Etoile, France) [3]. Early bacterial coinfection was defined as the identification of at least 1 bacterial species by conventional culture and/or PCR, with a threshold of $\geq 10^5$ colony forming units or genome copies per milliliter in ETA, and $\geq 10^4$ in BAL, respectively.

From 56 eligible patients, the 47 consecutive patients with respiratory secretions sampled in the 24 h following tracheal intubation were predominantly male (sex ratio: 3.3), most were younger than 70 years of age ($n=32$, 68.1%), with a high prevalence of obesity (body mass index ≥ 30 kg.m^{-2}, $n=23$, 48.9%). Using ETA ($n=45$) and BAL ($n=2$), early bacterial coinfection was documented in 13 patients [27.7%, by PCR ($n=12$) and conventional culture ($n=1$)]; the median interval between intubation and tracheal sampling was 3 h [IQR (1–9)]. Among the 39 patients with both standard culture and PCR, 29 (74.4%) had both negative culture and negative PCR and 10 (25.6%) both positive culture and positive PCR. There was no significant difference in either characteristics and outcomes according to the presence of coinfection (Table 1). Three bacterial species accounted for $\geq 90\%$ of all identified bacteria: *Staphylococcus aureus* (all methicillin-sensitive), *Haemophilus influenzae*, and *Streptococcus pneumoniae*. Coinfection with multiple bacterial species was documented in 5 patients (10.6%). All coinfected patients were treated appropriately with first-line beta-lactam antibiotics.

COVID-19 patients have been shown to display a complex immune dysfunction that could render them susceptible to secondary infections [4]. The present study is the first to investigate early bacterial coinfections (involving common bacterial species) in patients with COVID-19 ARDS. To our knowledge, such a high prevalence of coinfections have never been documented in other viral infections such as influenza. Of note, this prevalence might be underestimated in view of the high proportion of patients receiving initial empiric antibiotherapy. Also, due to the limited sample size, the high concordance we observed between conventional culture and PCR must be interpreted with caution. As another limitation of the present study, it can be challenging to differentiate infection from colonization in these patients. However, we attempted to account for this by considering the upper

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Table 1 Characteristics of 47 critically ill patients with ARDS related to COVID-19

	No bacterial co-infection ($n=34$)	Bacterial co-infection ($n=13$)	*p* value
Demographics			
Age (years)	68 (56–74)	61 (58–67)	0.323
Gender (male)	25 (73.5)	11 (84.6)	0.702
Body mass index (kg m^{-2})	30 (27–32)	28 (27–36)	0.659
Comorbidities			
Hypertension	18 (52.9)	7 (53.8)	1
Diabetes	8 (23.5)	4 (30.8)	0.713
Immune deficiency	2 (5.9)	0 (0)	1
COPD	2 (5.9)	1 (7.7)	1
Charlson Comorbidity Index	3 (2–4)	2 (1–4)	0.952
Clinical course before IMV			
Time from symptoms to admission (days)	7 (3–8)	6 (4–7)	0.825
Time from hospital admission to IMV (hours)	39 (11–82)	48 (11–116)	0.677
Antibiotics prior to IMV	22 (64.7)	5 (38.5)	0.186
Third generation cephalosporin	21 (61.8)	4 (30.8)	0.101
Macrolide	14 (41.2)	2 (15.4)	0.168
Other	5 (14.7)	3 (23.1)	0.666
Duration before bacterial sampling (days)	2 (1–2)	1 (1–1)	0.119
Fever	28 (82.4)	12 (92.3)	0.655
Purulent tracheal secretions	22 (64.7)	8 (61.5)	1
Septic shock	11 (33.3)	5 (38.5)	0.744
Organ failures at admission			
Number of organ failures	2 (0–2)	2 (0–2)	0.916
SOFA score	6 (3–8)	6 (3–8)	0.962
SAPS II	37 (34–46)	36 (31–41)	0.552
Laboratory measurements at admission			
White blood cell count (G/L)	11.4 (6.11–16.01)	9.51 (7.97–11.06)	0.348
Absolute lymphocyte count (G/L)	0.8 (0.5–1.1)	1 (0.9–1.1)	0.127
C-reactive protein (mg/L)	159 (75–260)	182 (121–235)	0.895
Procalcitonin (µg/L)	0.72 (0.49–1.55)	0.4 (0.22–0.8)	0.345
ARDS			
Mild	2 (5.9)	1 (7.7)	1
Moderate	21 (61.8)	8 (61.5)	
Severe	11 (32.4)	4 (30.8)	
Lowest PaO_2/FiO_2	124 (90–160)	125 (99–150)	0.934
CT-scan (n = 43)			
Ground-glass opacities	32 (100)	11 (100)	NA
< 50%	10 (31.2)	5 (45.5)	0.554
> 50%	22 (68.8)	6 (54.5)	
Consolidation	15 (46.9)	5 (45.5)	1
Bacterial copathogens	NA		NA
Staphylococcus aureus	–	9 (69.2)	
Haemophilus influenzae	–	5 (38.5)	
Streptococcus pneumoniae	–	3 (23.1)	
Moraxella catarrhalis	–	1 (7.7)	
Streptococcus agalactiae	–	1 (7.7)	

Table 1 (continued)

	No bacterial co-infection ($n=34$)	Bacterial co-infection ($n=13$)	*p* value
Duration of initial antibiotherapy in ICU (days)	2 (1–5)	7 (6–7)	< 0.001
Outcomes			
Day-28 mortality	12 (35.3)	5 (35.8)	1
Day-28 ventilator free days	0 (0–5)	0 (0–14)	0.480

Data are expressed as median (interquartile range) or number (percentage), and were compared by the Wilcoxon rank-sum test and by the Fisher exact test, as appropriate

Organ failures were defined according to the SOFA score, as a score of 3 or 4 points for the affected organs. ARDS definition and severity classification were according to the Berlin criteria. Ground-glass opacities were independently quantified by an intensivist and a radiologist

ARDS acute respiratory distress syndrome, *COVID-19* coronavirus disease 2019, *COPD* chronic obstructive pulmonary disease, *IMV* invasive mechanical ventilation, *SOFA* sequential organ failure assessment, *SAPS II* simplified acute physiology score II, PaO_2/FiO_2 ratio of arterial oxygen partial pressure to fractional inspired oxygen, *CT* computed tomography

range of commonly accepted thresholds of bacterial quantification in respiratory secretions.

These data are also in line with the Surviving Sepsis Campaign guidelines [5], arguing for initial empirical antibiotic coverage in COVID-19 patients until microbiology results become available. Further research is needed to extend these findings in larger cohorts, and to determine the impact of early microbiological analyses, on antibiotic stewardship in patients with ARDS related to COVID-19.

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Concept and design: LK, MS, LA. Acquisition, analysis and interpretation of data: LK, CM, OD, MS, LA. Statistical analysis: LK. Drafting of the manuscript: LK, LA. Critical revision of the manuscript: LK, CM, OD, MS, LA.

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Compliance with ethical standards

Conflicts of interest
CM has received lecture fees from bioMérieux. The other authors declare that they have no conflict of interest pertaining to this study.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of our institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. This study was approved by our institutional ethics committee (Comité d'Ethique du CHU de Lyon, N°20-42) with a waiver for informed consent.

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