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Prognostic evaluation of *Acinetobacter baumannii* ventilator-associated pneumonia in COVID-19

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SUMMARY

Background: Since the emergence of the pandemic of SARS-CoV-2, a high reported incidence of VAP in COVID-19 sustained by carbapenem resistant *Acinetobacter baumannii* (CRAB) has been observed, but data are scarce to date.
Materials and methods: We retrospectively collected COVID-19 patients who developed CRAB-VAP - defined according to Center for Diseases Control (CDC) 2020 criteria and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) or Infectious Diseases Society of America (IDSA) guidelines - to describe characteristics and outcome.
Results: Among 21 patients with CRAB-VAP in COVID-19, median age was 66 years (IQR 41-80). Median time of VAP-onset was 7 days (IQR 0-28 days) from ICU - admission and 76.2% had septic shock. Treatment regimens were all colistin-based, in 28% (n=6) including ampicillin/sulbactam and rifampicin. In three cases, cefiderocol was started as rescue. Survival rate at 28-days was 35% (n=7).
Conclusion: Non-fermenting Gram-negative bacteria are an emerging aetiology of VAP in COVID-19 patients. This underscores the urgent need for proper microbiological identification to address therapies and infection control protocols.

Keywords: VAP, *Acinetobacter baumannii*, COVID-19, SARS-CoV-2, ICU.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most frequent ventilator-associated complication (VAC). VAP is also the most common infection acquired in intensive care units (ICUs), with a reported incidence of 5%-40%, depending on the setting and the diagnostic criteria used [1-5]. In European countries in 2017, the EU-VAP/CAP study reported an incidence density of 18.3 VAP episodes per 1,000 ventilator days [3]. Notoriously, VAP is associated with prolonged hospitalizations, increased MV durations and an estimated attributable mortality rate of approximately 10% with a crude mortality rate of 40% [1-5].
It has been two years since the emergence of the pandemic of respiratory infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with respiratory failure requiring mechanical ventilation (MV) reported in 2.3%-33% of the infected patients [6]. According to this evidence, VAP with coronavirus disease 2019 (COVID-19) has recently surfaced as an essential research topic in several works. Data are summarized in Table 1 [7-13]. Multiple VAP episodes with COVID-19

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have been significantly associated with prolonged ICU stays with a steady incidence of carbapenemases producing Enterobacterales but a 7.5-fold and 5.5-fold increased risk of colonization and infection, respectively, by carbapenems resistant *Acinetobacter baumannii* [13-15]. Despite this data little is known about *A. baumannii* infections in COVID-19 and in particular about VAP [16-18]. In this retrospective single center study, we decided to investigate VAP in COVID-19 patients with particular interest on *A. baumannii* aetiology in order to provide information on characteristics and outcome of this increasingly important clinical entity.

Table 1 - Characteristics of included studies on ventilator-associated pneumonia in COVID-19.

	Population	*Time to VAP diagnosis Median (Range) in days*	*Demographic characteristics/Risk factors*	*Sample methods*	*Microbiology*	*Outcomes*	*Early appropriate treatment*
Giacobbe et al. [7]	- *171 patients* (29% of the general population) - Median age 64 (57-71) years - 80% (Male)	9 (5-15) 18 per 1000 ventilator days	- Hypertension (64%) - DM (23%) - Previous antibiotics (95%) - Previous steroids (63%) - Previous anti-IL-6 (64%)	BAL 77 (45%)	- *P. aeruginosa* (35%) - MSSA (23%) - *K. pneumoniae* (19%) - MRSA (10%) - CRE (32%)	30-day case-fatality 46% *Risk factors for mortality:* septic shock at VAP onset (OR 3.30) ARDS at VAP onset (OR 13.21)	45/77 cases (58%) Not protective in mortality
Llitjos at al. [8]	- *92 patients* (52%) - Median age 63 (55–73) years - 76% (Male)	9 (6-14)	- DM (26%) - COPD (10%) - Immunosuppression (15%) - Septic shock at VAP onset (16%) - ARDS (96%, SHR=1.84) - Duration of MV (SHR=1.027)	ETA or BAL, not specified	- Enterobacteriaceae (50%) - Non-fermenting GNB (20%) - Gram-positive cocci (28%) - Polymicrobial (24%)	ICU length of stay, days 20 (12-30) ICU mortality 31%	NA
Luyt et al. [9]	- *43 patients* (86%) in ECMO - Median age 48 (42-56) years - 72% (Male)	10 (8-16)	- VAP recurrence rate 79%	Quantitative growth (≥10^4 CFU/mL) BAL	- Enterobacteriaceae (70%) - Inducible AmpC-cephalosporinase producers (40%) - Non-fermenting GNB (42%) inc. *P. aeruginosa* (37%) - Polymicrobial (38%)	ECMO support, days 21 (10-34) Days on MV 45 (27-62) ICU length of stay, days 48 (34-68) ICU mortality rate, days 17 (34)	81%
Razazi et al. [10]	- *58 patients* (64%)	8 (5-12)	- Recurrent VAP 22 (25%) vs 10 (12%) in NC-ARDS p=ns	Blind protected telescope catheter 89% BAL 11%	- MDR-VAP in C-ARDS vs NC-ARDS: 21 (23%) vs. 9 (11%), p=0.03. - ESBL VAP in NC-ARDS vs C-ARDS: 9 (11%) vs 18 (20%) - MRSA VAP in NC-ARDS vs C-ARDS: 0 vs 1 (1%)	--	Carbapenem was more used in C-ARDS than in NC-ARDS: 48 (53%), vs 21 (26%), p<0.01

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	Population	*Time to VAP diagnosis Median (Range) in days*	*Demographic characteristics/Risk factors*	*Sample methods*	*Microbiology*	*Outcomes*	*Early appropriate treatment*
Rouzé et al. [11]	- *205 patients* (36.1%)	NA	- CPIS 6 (5-7) - PaO2/FiO2 135 (92-180) - SOFA score 8 (5-11)	ETA 125/205 (61.6%) BAL 78/205 (38.4%)	- GNB (83.6%) inc. *P. aeruginosa* 64 (22.3%), *Enterobacter* 54 (18.8%) - MDR isolates 67 (23.3%) - Gram-pos cocci 56 (19.5%) - Polymicrobial 28 (9.8%)	ICU length of stay, days 18 (12–27) ICU mortality 164/568 (28.9%) 28-day mortality 166/568 (29.2%)	145/200 (72.5%)
Maes et al. [12]	- *64 patients* (79%) - Median age 62 (50-70) years	28/1000 ventilator days versus vs 13/1000 for pts not COVID (p=0.009)	- Hypertension (33%) - DM (22%) - Obesity (37%) - Chronic lung disease (20%) - Immunocompromised (15%) - APACHE II (IQR) 15 (11–19) - ARDS on ICU admission (78%)	ETA or BAL 39 (48%) BAL 30 (47%)	- *E. coli* - *P. aeruginosa* - *S. maltophilia* - *E. cloacae* - *K. aerogenes* - *K. pneumoniae* - *S. aureus*	ICU mortality 31 (38%) Median length of stay for patients dying in ICU (IQR) 13 (10-17)	NA
Blonz et al. [13]	- *92 patients* (48.9%) - Mean age 65.3 (±9.5)	- 39.0 per 1000 days MV (until the first VAP episode) - 33 VAP per 1000 days MV (including all 141 episodes of VAP).	- BSI (10.6%) - Thoracic empyema (3.5%) - Pulmonary abscess (1.4%) - Male gender (SHR 2.24) - ECMO (15.2%) (SHR 3.09) - Recurrent VAP 37 (19.7%)	ETA 60 (42.6%), (BAL) 50 (35.4%) plugged telescopic catheter 30 (21.3%)	- Polimicrobial 39.0% - Enterobacteria 49.8% - *P. aeruginosa* 15.1% - GPB in early VAP 47.0% vs 22.8% in late VAP - GNB in late VAP 77.2%	Still in ICU 3 (5.8) VAP single episode vs 10 (25.0) VAP multiple episodes (p=0.009)	69 (89.9%)

Abbreviations: BAL: bronchoalveolar lavage; MSSA: methicillin susceptible Staphylococcus aureus; CRE: carbapenems resistant Enterobacterales; MRSA: methicillin resistant Staphylococcus aureus; ARDS: acute respiratory distress syndrome; VAP: ventilator associated pneumonia; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; MV: mechanical ventilation; ETA: endotracheal aspiration; GNB: Gram negative bacteria; ECMO: extracorporeal continuous membrane oxygenation; NC: not-COVID-19; C: COVID-19; MDR: multi-drug resistant; NA: not applicable.

PATIENTS AND METHODS

We retrospectively collected patients admitted to ICU with COVID-19 who developed *A. baumannii* VAP from 15 September 2020 to 21 March 2021 in a single center Cardinal Massaia Hospital, Asti, Italy. The objective was to describe the characteristics and outcome of patients with *A. baumannii* VAP in COVID-19. The diagnosis of COVID-19 was made in the presence of at least one positive real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 on nasopharyngeal swab or sputum. Ventilator Associated-Pneumonia was defined according to Center of Disease Control (CDC) 2020 VAP criteria for adults with the presence of new or modifying chest X-ray infiltrates occurring more than 48 h after initiation of invasive mechanical ventilation with at least one of the following: a) body temperature ≥38°C or b) total peripheral white blood cell count ≥12,000 cells/μL or ≤4000 cells/μL and at least two of the following:

1) new onset of purulent sputum or change in the character of sputum or increased respiratory secretions or increased suctioning requirements;
2) new-onset or worsening cough or dyspnea or tachypnea;
3) rales or bronchial breath sounds;
4) worsening gas exchange, increased oxygen requirements or increased ventilator demand [19].

In addition, microbiological confirmation was defined by a positive bronchoalveolar aspirate culture ≥10^4 UFC/mL (European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT Guidelines), according to quantitative invasive cultural sampling or a positive endotracheal aspirate culture ≥10^6 UFC/mL, according to quantitative non-invasive cultural sampling (Infectious Diseases Society of America - IDSA [20, 21]). Ethical committee approval was not necessary because of the retrospective collection of data. Demographic and clinical characteristics were summarized through absolute frequencies and percentages for the qualitative variables and through the percentiles (median, first quartile-third quartile) for the quantitative variables. The primary objective of the study analysis was the description of 7-days survival, 21-days survival and 28-days survival by median of numbers and percentages. Differences between survivors and non-survivors were analyzed through Student's *t*-test or Mann Whitney U-test and Chi-square Test or Fisher test, as appropriate.

RESULTS

There were 21 patients with ventilator-associated pneumonia sustained by *A. baumannii* in COVID-19 patients in ICU. The median age was 66 years (IQR 54-73) and 95.3% (n=20) of patients were male. In 95.2% of cases a deep respiratory sample was collected through bronchoalveolar aspiration. All isolates were *Acinetobacter baumannii* carbapenem-resistant (CRAB). The median time of VAP-onset was 7 days (IQR 4-10 days) from ICU admission and 8 days (5-13 days) from endotracheal intubation (ETI). 76.2% of patients had concomitant septic shock. Antibiotic treatment regimens were in all cases colistin-based

Table 2 - Characteristics of patients with carbapenem resistant *Acinetobacter baumannii* ventilator-associated pneumonia in COVID-19.

	Overall (n= 21)	*Survivors (n=7)*	*Non-survivors (n= 14)*	*p value*
Median age (years, IQR)	66 (54-73)	66 (54-73)	66 (53-72)	0.989
Male sex (%)	20 (95.29)	6 (85.71)	14 (100)	0.384
Deep bronchial aspirate culture (%)	20 (95.23)	7 (100)	13 (92.86)	0.543
Median onset VAP from ICU admission (days, IQR)	7 (4-10)	9 (7-11)	7 (4-10)	0.133
Median onset VAP from ETI (days, IQR)	8 (5-13)	11 (7-15)	7 (3-11)	0.147
Septic shock (%)	16 (76.2)	5 (58)	11 (76.2)	0.155
Empirical treatment active against CRAB (%)	6 (28)	3(42.8)	3 (21.43)	0.139
Definitive treatment regimen (%):				
COL + RIF + SUL	6 (28)	3 (42.8)	3 (21.43)	0.139
COL + MER HD + TIG HD	2 (9.5)	0	2 (14.29)	
COL + MER HD + SUL	2 (9.5)	2 (28.57)	0	
COL + FOS HD + SUL	2 (9.5)	2 (28.57)	0	
CFDC rescue	2 (9.5)	1 (14.29)	1 (7.14)	0.744
7-days survival rate (%)	15 (71.4)	--	--	
21-days survival rate (%)	7 (35)	--	--	
28-days survival rate (%)	7 (35)	--	--	

Abbreviations: ICU: intensive care unit; ETI: endotracheal intubation; CRAB: carbapenem resistant Acinetobacter baumannii; COL: colistin; RIF: rifampicin; SUL: ampicillin/sulbactam; MER HD: meropenem high dose; TIG HD: tigecycline high dose; FOS HD: fosfomycin high dose; CFDC: cefiderocol.

combination therapy in 28% (n=6) including ampicillin/sulbactam and rifampicin, in 9% (n=2) including meropenem high dose and tigecycline high dose, in the 9% (n =2) meropenem high dose and ampicillin/sulbactam and in 9% (n=2) with ampicillin/sulbactam and fosfomycin high dose. In two cases, a rescue treatment with cefiderocol in compassionate use was started because of poor clinical response with the first-line antibiotic regimen. Survival rate at 7-days was 71.4% (n=15), at 21-days 35% (n=7), at 28-days 35% (n=7). Among survivors, the median age was 66 years old versus 66 years old in non-survivors. The median time of VAP onset was nine days versus seven days from ICU admission and 11 days versus seven days from ETI in non-survivors. The septic shock occurred concomitantly with VAP in 58% of survivors versus 76.2% in non-survivor patients. On the base of the knowledge of the rectal colonization data, overall 28% (n=6) patients received an empiric treatment active against CRAB [survivors 42.8% (n=3), non-survivors 21.43% (n=3) (p=0.477)]. Moreover, in all cases the empirical regimen was colistin, ampicillin/sulbactam and rifampicin. Among definitive treatment, the used regimen was colistin, ampicillin/sulbactam and rifampicin in 42.8% of survivors versus 21.43% of non-survivors. Only 2 patients out of 5 considered for compassionate use received cefiderocol monotherapy as second line rescue regimen, whereas 3 died before receiving the drug. Among patients treated with cefiderocol as rescue, only one patient survived at 28-days evaluation. Overall, no statistically significant differences among survivors and non-survivors were observed at 28-days (p=0.774) (Table 2).

DISCUSSION

The literature describes a higher incidence and recurrence rate of VAP during COVID-19 than in the pre-COVID-19 period [3, 7, 12-13]. Even though the studies are heterogeneous, and the sample sizes are limited, the median time of VAP onset in COVID-19 patients does not seem to differ to that reported in VAP in non-COVID-19 patients. Similarly, to non-COVID-19 patients, acute respiratory distress syndrome (ARDS) and septic shock at the onset of VAP emerged as independent predictors of mortality [7]. In COVID-19, patients with VAP are confirmed to have a high crude mortality rate and prolonged ICU median stay as non-COVID-19 patients. Our data on *A. baumannii* VAP in COVID-19, appeared similar to those reported in literature on other aetiologies regarding the median time of VAP onset and the finding of lower survival rate in patients with concomitant septic shock which were the vast majority with a frequency of two thirds in our study [7-13]. Data are heterogenous regarding mortality of *A. baumannii* VAP in COVID-19 and since patients' baseline conditions are different and no single pathogen study is available to date to our knowledge, mixed aetiologies of VAP do not allow to do inferences about outcomes. Nonetheless a lower 28-days mortality rate was observed in our study comparing with a study including one third of *A. baumannii* VAP in second wave of COVID-19 pandemic (*i.e.*, 65% versus 100%), whereas another study with a 40% of *Acinetobacter baumannii* VAP and median SOFA score between 10 and 20 showed a lower mortality rate (*i.e.*, 65% versus 45%) [14, 22].

Even in not-COVID-19 patients, the diagnosis of suspected VAP cases is notoriously difficult. Pulmonary infections are typically confirmed in only 20%-60% of cases. Treatment delays are possible, and antibiotic overuse and a low rate of de-escalation are common [1-5, 23-25]. Suspected VAP in COVID-19 is microbiologically confirmed with a deep bronchoalveolar sampling in 35%-45% and with an endotracheal aspirate in around 40%-60% of cases [7, 11-13]. In our population, microbiological confirmation of suspected *A. baumannii* VAP in COVID-19 was obtained in 20/21 of our patients through broncho-aspiration as suggested by the International ERS/ESICM/ESCMID/ALAT Guidelines approach prioritizing high quantitative specificity deep cultural sampling over other methods. Only one case has been identified through a quantitative high sensitivity cultural sampling through the endotracheal aspirate cultural exam as suggested by the IDSA approach. The association between increased antibiotic use and the emergence of antimicrobial resistance in ICUs has been well established. In VAP with COVID-19, although most studies have introduced the term *early antibiotic therapy*, treatments are already ongoing before deterioration and the need for endotracheal intubation and MV [9, 11, 13]. Data regarding molecules and classes according to the epidemiological setting and re-

sistance rates are currently lacking, and it is impossible to establish antibiotic appropriateness. This metric has been evaluated by only one study, resulting in no protective effect on mortality [7]. In VAP with COVID-19, isolates, when available, show a large preponderance of Gram-negative bacteria, including Enterobacterales (50%-0%) [8, 9, 11, 13]. Moreover, non-fermenting Gram-negative bacteria reached up to 40% of all isolates, especially *Pseudomonas aeruginosa* and *A. baumannii* and multi-drug resistance appeared significantly more frequently in patients with COVID-19 than in non-COVID-19 patients with carbapenem-resistant Enterobacterales comprising one-third of all isolates [7, 9, 10, 14]. A reported higher use of carbapenems in patients with VAP and COVID-19 compared with VAP in non-COVID-19 patients could be explained not only by the need for the empirical use of antibiotics, justified by the low rate of microbiological confirmation of VAP, but also by the increased rate of extended-spectrum beta-lactams-producing isolates in deep respiratory samples [10]. In our study, most diagnoses were obtained by the high specificity European approach. Nonetheless, based on clinical suspicion, we observed a relatively more frequent start of an appropriate empiric treatment based on the colonization data among those who survived than non-survivors, even though the sample size was limited and did not reach statistical significance. Among all isolates, non-fermenting Gram-negative bacteria, including *A. baumannii*, and multi-drug resistant bacteria, including carbapenem-resistant enterobacteria emerged among major aetiologies of VAP in COVID-19 patients. This underscores the urgent need for proper microbiological identification to address targeted and combination therapies. It also provides the opportunity to reflect on infection prevention and control protocols to avert colonization in first place, especially intra-individual protections, mitigation strategies and management of respiratory devices in ICU settings during pandemics (i.e., overcrowded ICUs) [26-28].

CONCLUSIONS

During this pandemic, the difficulties of managing patients with COVID-19 have been exacerbated. It has also worsened the already well-known difficulties of diagnosing and managing of patients with suspected VAP. Despite these factors, since 1972, when clinical criteria were introduced by Johanson et al., VAP has been producing new points of discussion for both the new and old generations of doctors [29].

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Conflict of interest
None to declare.

Authors' contribution
IDB and TL collected the data, wrote and revised the manuscript; SC and FDR supervised the work and revised the manuscript; NS revised the manuscript; EC was responsible of sample identification and management; AB and MP supervised the work.

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