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Carbapenem-resistant *Klebsiella pneumoniae* in ICU-admitted COVID-19 patients: Keep an eye on the ball

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ABSTRACT

Here we report on seven intensive care unit (ICU) patients with coronavirus disease 2019 (COVID-19)-related acute respiratory distress syndrome (ARDS) who developed positive rectal swabs and invasive infections due to carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp). Notwithstanding the infection prevention measures introduced during the COVID-19 pandemic and changes in the hospitalised population, attention to CP-Kp infections must remain high, especially in the critically ill setting.

1. Introduction

Bacterial and fungal infections are common complications of viral pneumonia, especially in critically-ill patients, as evidenced during the 2003 severe acute respiratory syndrome coronavirus (SARS-CoV) epidemic, when Gram-negative bacteria (GNB) and *Candida* caused the largest number of secondary infections [1]. It follows that assessing the risk of difficult-to-treat bacterial superinfections such as those caused by GNB is crucial in all suspected cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; 2019 novel coronavirus) infection [2].

Patients with coronavirus disease 2019 (COVID-19) are, in fact, particularly at risk of developing superinfections, especially those caused by multidrug-resistant (MDR) pathogens, despite the improvements in infection control procedures worldwide adopted during the COVID-19 outbreak, the changes in overall hospital admissions for other conditions [3], the considerably younger age and the absence of multiple co-morbidities [4].

Due to the fact that, prior to the COVID-19 outbreak, Italy had an endemic situation regarding the spread of MDR infections, mainly due to carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp) [5], we evaluated the incidence and time course of CP-Kp infections during their intensive care unit (ICU) stay in a cohort of ICU patients affected by COVID-19-related acute respiratory distress syndrome (ARDS).

2. Materials and methods

From 1 March to 20 May 2020, all COVID-19 patients with ARDS admitted to the ICU at 'Città della Salute e della Scienza' Hospital in Turin (Italy) were studied. Bloodstream infection (BSI) and ventilator-associated pneumonia (VAP) were defined according to the European Centre for Disease Prevention and Control (ECDC). Matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF), Microscan WalkAway plus System (Beckman Coulter, Brea, CA, USA) and MASTDISCS® *Combi Carba plus* disk system (Mast Group Ltd., Bootle, UK) were used for bacterial identification, antimicrobial susceptibility testing and to characterise carbapenemase-producing isolates, respectively. Detection of carbapenem resistance genes was carried out using an Xpert Carba-R assay (Cepheid, Sunnyvale, CA, USA). Antimicrobial susceptibility was

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Table 1
Characteristics of ICU-admitted patients with COVID-19-related acute respiratory distress syndrome (n = 7).

Patient	Age (years)	Sex	BMI	Co-morbidities	SOFA score	PCT (μg/L)	Days from symptoms to HA	Days from HA to ICU	Days of MV	Days of VV-ECMO	Days of ICU	COVID-19 therapy	Days from ICU to CP-Kp+	CP-Kp infection/ colonisation	Septic shock	Target antibiotic therapy	28-day mortality
1	50	M	26	None	13	3.84	5	3	24	14	24	DRV/r + HCQ + steroids	7	BSI/VAP	Yes	CAZ/AVI + FOS + TMP/SMX	Death
2	41	M	40	Obesity	16	6.47	7	0	46	23	55	LPV/r + HCQ + steroids + remdesivir	12	VAP/BSI	Yes	CAZ/AVI + TMP/SMX	Alive
3	54	F	45	Obesity, hypertension, COPD	8	2.74	3	0	34	27	34	DRV/COBI + HCQ + steroids + tocilizumab	22	BSI/VAP	Yes	CAZ/AVI + COL	Alive
4	62	F	38	Obesity, hypertension, hypothyroidism	13	0.91	7	13	37	35	37	HCQ + steroids + tocilizumab + remdesivir	6	BSI/VAP	Yes	CAZ/AVI	Alive
5	71	M	30	Ex-smoker	12	0.13	7	1	20	No ECMO	24	HCQ	17	Rectal swab	No	None	Alive
6	52	M	27	Ex-smoker	12	0.4	3	0	42	37	42	HCQ + steroids + tocilizumab	13	VAP	No	MEM + ETP + TGC	Alive
7	67	F	32	Obesity, asthma	10	0.2	7	4	21	No ECMO	21	HCQ + steroids + tocilizumab + remdesivir	7	VAP/BSI	Yes	CAZ/AVI + FOS	Death
Median	54	–	31.3	–	12		7	1	34	27	34	–	12			–	–

ICU, intensive care unit; COVID-19, coronavirus disease 2019; BMI, body mass index; SOFA, Sequential Organ Failure Assessment; PCT, procalcitonin (normal range, <0.5 μg/L); HA, hospital admission; MV, mechanical ventilation; VV-ECMO, venovenous extracorporeal membrane oxygenation; CP-Kp, carbapenemase-producing *Klebsiella pneumoniae*; DRV/r, darunavir/ritonavir; HCQ, hydroxychloroquine; BSI, bloodstream infection; VAP, ventilator associated pneumoniae; CAZ/AVI, ceftazidime/avibactam; FOS, fosfomycin; TMP/SMX, trimethoprim/sulfamethoxazole; LPV/r, lopinavir/ritonavir; COPD, chronic obstructive pulmonary disease; DRV/COBI, darunavir/cobicistat; COL, colistin; MEM, meropenem; ETP, ertapenem; TGC, tigecycline.

interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2019.

3. Results

Among 35 patients, 7 had a positive rectal swab for CP-Kp and bilateral pulmonary infiltrates (Table 1). Six patients developed invasive infections and one patient was colonised by CP-Kp during their ICU stay (two patients were positive for CP-Kp at ICU admission). Six of the seven patients were transferred from other hospitals. The median [interquartile range (IQR)] Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score (SAPS) and Acute Physiology and Chronic Health Evaluation (APACHE) II score at ICU admission were, respectively, 12 (11–13), 54 (51–60) and 25 (24–26), whilst the median (IQR) MuLBSTA score [6] was 9 (9–10). The median (IQR) duration of COVID-19 symptoms before hospital admission was 7 (4–7) days, whilst the median (IQR) duration of ICU stay and mechanical ventilation was 34 (24–40) days and 34 (23–40) days, respectively.

The median (IQR) time between CP-Kp infection and hospital and ICU admission was 13 (12–19) days and 12 (7–15) days, respectively. Six patients developed VAP and five had contextual BSI, in all of five of whom the infection resulted in septic shock with high vasopressor requirement.

All of the patients received hydroxychloroquine, five of them received antiviral treatment and four were treated with tocilizumab. Corticosteroids were given in all but one patient (dexamethasone 8 mg every 8 h, with variability according to different hospitals in transferred patients). At ICU admission, 71.4% of patients had lymphocytopenia. All patients had been previously treated with broad-spectrum antibiotics (all of them with β-lactams, five with azithromycin, two with doxycycline and three with vancomycin), in five cases with a documented prior bacterial co-infection before CP-Kp, including three VAP and two BSI caused by *Pseudomonas aeruginosa* (n = 2), extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* (n = 1), coagulase-negative staphylococcus (n = 1) and *Enterococcus faecium* (n = 1), respectively. We observed two deaths within 28 days and five deaths in the ICU in seven patients. Mortality related to CP-Kp septic shock was 28.6%.

4. Discussion

Few articles are reporting about secondary infections in COVID-19, but some data confirm that superinfections were identified in 13.5–44% of ICU patients owing to various pathogens, including MDR-GNB [2].

Known risk factors for the development of CP-Kp infections do not appear fully applicable in this cohort of patients [4]. In fact, our population was relatively young and free of significant co-morbidities, except obesity (57.1%). The reduction in hospital access for all causes [3], apart from those due to COVID-19, should, at least theoretically, have contributed to a reduction in the dissemination of MDR pathogens. Furthermore, infection control procedures are highly implemented in the context of the COVID-19 pandemic to ensure safety for healthcare workers, maximising contact precautions.

Conversely, factors potentially implicated in the risk of MDR infections are increased patient transfer caused by the pandemic affecting the whole of Northern Italy, previous broad-spectrum antibiotic treatment before hospital admission, the presence of other previous invasive bacterial co-infection, and the severity of the patient cohort requiring venovenous extracorporeal membrane oxygenation (VV-ECMO) support in 71.4% of cases and continuous renal replacement therapy in 28.6%. In particular, in patients undergoing ECMO, colonisation by MDR-GNB is frequent

and is associated with a more than ten-fold odds for subsequent infections that are associated with an increased risk of death [7].

Our results appear to suggest the need to keep a major focus on CP-Kp infections even, and especially, among COVID-19 patients owing to their extreme fragility, probably linked to immunological mechanisms still not fully clarified, and their need for prolonged ICU stay.

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Conflict of interest

None declared.

Ethical approval

This study was approved by the Local Ethical Committee [Prot. no. 0039964; 22/04/2020].

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References

[1] Zheng Z, Chen R, Li Y, et al. The clinical characteristics of secondary infection of lower respiratory in severe acute respiratory syndrome. Chin J Respir Crit Care Med 2003;2:270–4.
[2] Clancy CJ, Nguyen MH. COVID-19, superinfections and antimicrobial development: what can we expect? Clin Infect Dis 2020, doi:http://dx.doi.org/10.1093/cid/ciaa524 [Epub ahead of print] PMID: 32361747; PMCID: PMC7197597.
[3] De Filippo O, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in Northern Italy. N Engl J Med 2020;383:88–9, doi:http://dx.doi.org/10.1056/NEJMc2009166.
[4] Zhou F, Yu T, Du R, Fan G, Liu Y, Xiang J, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62, doi:http://dx.doi.org/10.1016/S0140-6736(20)30566-3.
[5] European Centre for Disease Prevention and Control (ECDC). Surveillance of Antimicrobial Resistance in Europe 2018. ECDC; 2019. https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2018.
[6] Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, et al. Clinical features predicting mortality risk in patients with viral pneumoniae: the MuLBSTA score. Front Microbiol 2019;10:2752, doi:http://dx.doi.org/10.3389/fmicb.2019.02752.
[7] Grasselli G, Scaravilli V, Alagna L, Bombino M, De Falco S, Bandera A, et al. Gastrointestinal colonization with multidrug-resistant Gram-negative bacteria during extracorporeal membrane oxygenation: effect on the risk of subsequent infections and impact on patient outcome. Ann Intensive Care 2019;9:141, doi:http://dx.doi.org/10.1186/s13613-019-0615-7.