Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection 82 (2021) e20–e21

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

Low incidence of co-infection, but high incidence of ICU-acquired infections in critically ill patients with COVID-19

Dear Editor,

Lansbury et al. recently reported in this journal that 7% of hospitalized COVID-19 patients had a bacterial co-infection. This proportion increased to 14% in studies that only included patients who required admission to the intensive care unit (ICU).[1] ICU admission is a risk factor for hospital-acquired infections and nosocomial infections by multidrug-resistant (MDR) bacteria. [2,3] Here, we report our findings of a retrospective cohort study to asses the incidence of co-infections, ICU-acquired infections and their relation to mortality in patients with COVID-19.

We retrospectively include all consecutive patients who were admitted to the Intensive Care Department at Hospital Universitario Ramón y Cajal in Madrid (Spain), with the primary diagnosis of SARS-COV-2 between March 10th and June 19th, 2020. Madrid was one of the pandemic epicenter cities in Europe. All patients had a diagnosis of COVID-19 confirmed by SARS-COV-2 viral RNA polymerase-chain-reaction (PCR) test from nasopharyngeal swabs or lower respiratory tract aspirates as well. We excluded patients in whom no positive PCR was detected despite the clinical diagnosis of COVID-19 and patients with less than 48 h of admission at the ICU. Clinical data were collected from institutional healthcare clinical database record and managed using REDCap® (Research Electronic Data Capture) tool hosted at IRyCIS (Instituto Ramón y Cajal de Investigación Sanitaria). Frequency measurements have been calculated using the incidence rates of each ICU-acquired infections expressed in relation to the number of patients at risk or the number of days at risk. Data were expressed as mean ± standard deviation (S.D) or percentages as appropriate. Since most variables did not always fulfill the normality hypothesis, we compared continuous data by the Mann-Whitney U test and categorical data by Chi-square or Fisher's exact test as appropriate. Study protocol was approved by the institutional Ethics and Clinical Research Committee.

A total of 83 patients were enrolled. Clinical characteristics of critically ill patients are shown in Table 1. Overall mortality in the ICU was 24.1%. Community-based bacteria and viruses were screened at hospital admission in 91.5% (76/83) of patients. In our series, the incidence of bacterial coinfection at admission was only 8.4% and no patient was diagnosed at admission with any other virus than SARS-CoV-2. Isolated bacteria were: *S. pneumoniae* $n=1$, *Legionella pneumophila* $n=2$, *Pseudomonas aeruginosa* $n=1$, *Klebsiella oxytoca* $n=1$ and Methicilin-sensitive *S. aureus* $n=2$. A low prevalence of bacterial co-infection might be underestimated having regard to the high proportion of patients who received empiric antibiotic therapy, such as azithromycin because its antiviral properties. These data are in agree Lansbury et al. and with others reports.[1,4] These findings support stopping empirical antibiotics in the vast majority of patients when COVID-19 infection is confirmed. However, it is important to remark that mortality in the subgroup of patients with co-infection was very high, with a mortality rate of 57.1% versus 21.1% in patient without co-infection ($p=0.033$). Therefore, it is essential to suspect and look for the presence of bacterial co-infection to establish appropriate antibiotic therapy as soon as possible.

Table 1
Clinical characteristics of critically ill patients with COVID-19.

CHARACTERISTIC	PATIENTS $n=83$
Gender (male)	66 (79.5%)
Age (mean ± SD)	61.2 ± 10.4
APACHE II score (mean ± SD)	18.8 ± 7.2
SAPS II (mean ± SD)	44.0 ± 14.8
SOFA score at admission (mean ± SD)	7.7 ± 2.8
Mechanical ventilation	78 (93.9%)
Vassopressors	59 (71.0%)
Acute Renal Failure*	4 (4.8%)
Central nervous system failure*	3 (3.6%)
Liver failure*	2 (2.4%)
ICU LOS (mean ± SD)	19.7 ± 16.4
Treatment	
Hydroxychoroquine sulfate	76(91.5%)
Lopinavir,Ritonavir	71(85.5%)
Remdesivir	14(16.8%)
No antiviral treatment	5(6.0%)
Tocilizumab	50(60.2%)
Corticosteroids	67(80.7%)

Abbreviations: APACHE: Acute Physiology And Chronic Health Evaluation; SAPS: Sepsis-related Simplified Acute Physiology Score; SOFA: Organ Failure Assessment LOS = Length Of Stay.
* Failure = 3 or 4 points in SOFA Score.

Conversely, the incidence of ICU-acquired infection was as high as 51.2% (43/84). In patients undergoing mechanical ventilation for more than 5 days (93.3%), microbiological surveillance samples were obtained during their ICU stay. Table 2 shows incidence rates of ICU-acquired infection. The respiratory tract was the most common site of infection, accounting for 38.5%, followed by bloodstream (30.7%), urinary tract infection (28.0%), soft-tissue (1.7%) and abdominal focus 0.8%.

ICU mortality was significantly different for patients with or without ICU-acquired infection (15/20, 75.0% versus 28/63, 44.4%; $p=0.017$), respectively. There's controversy regarding to nosocomial infection and its relationship with mortality due to several confounding factors that converge in patients admitted to ICU. In large European epidemiological studies of critically ill patients such as the EPIC II study, among 13,796 patients, 51% were considered infected, the ICU mortality rate of infected patients was more than twice than in non-infected patients[2]. There is a lack of evidence

https://doi.org/10.1016/j.jinf.2020.09.010

Table 2
Incidence rates of ICU-acquired Infections.

INCIDENCE RATE	PATIENTS $n = 83$
N° infections/total of patients	131.32%
N° infections (excluding secondary bacteremia)/total of patients	121.68%
N° infections/total days of stay (1000 days of stay):	59.61‰
N° VAP/total of patients:	42.16%.
N° VAP/total days of stay	18.19‰
Rate PBSI/100 patients	33.73%
Rate PBSI /1000 days of stay	15.10‰.
Rate CRBSI/100 patients	8.43%
Rate CRBS I/1000 days of stay	3.71‰.
Rate CAUTI /100 patients	38.55%.
Rate CAUTI/total days of stay (1000 days of stay)	17.18‰.

Abbreviations: N°: number; VAP: Ventilator-associated Pneumonia; PBSI: Primary Bloodstream Infection; CRBSI: Catheter-related Bloodstream Infection; CAUTI: Catheter-related Urinary Tract Infection.

related to superinfections acquired during COVID-19 in patients who require hospitalization. A study conducted in Wuhan, China shows a series of 150 hospitalized COVID-19 patients in whom the presence of secondary infection during hospital admission was one of the risk factors for increased mortality[5]. A recent study found that frequency of hospital-acquired superinfections remained low and this finding was mainly related with ICU admission.[6] To the best of our knowledge, there are no previous data on the influence of nosocomial infection in the ICU and its relationship with mortality.

In conclusion, our results reveal that co-infections in patients diagnosed with COVID-19 admitted to the ICU is uncommon; however, the incidence of ICU-acquired infections very high. When one of both types of infections comes out, this is associated with worse outcomes including higher mortality. Assessment of necessary diagnostic work-up could assist clinicians in decision-making to optimize antibiotic therapy in critically ill patients with COVID-19.

Authors contribution

All authors contributed to study design, data analysis and manuscript preparation. All authors read and approved final version before submission.

Funding information

This study did not have any specific funding.

Declaration of Competing Interest

No conflicts exist.

Acknowledgment

The authors thank the ICU residents and staff, for their efforts in recruiting patients and acquisition of data.

References

1. Louise Lansbury, Benjamin Lim, Vadsala Baskaran, Shen Lim Wei. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect* 2020;**81**(2):266–75. doi:10.1016/j.jinf.2020.05.046.
2. Jean-Louis Vincent, Jordi Rello, John Marshall, Eliezer Silva, Antonio Anzueto, Martin Claude D. et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009;**302**(21):2323–9. doi:10.1001/jama.2009.1754.
3. Hui Ang, Xuan Sun. Risk factors for multidrug-resistant Gram-negative bacteria infection in intensive care units: a meta-analysis. *Int J Nurs Pract* 2018;**24**(4):e12644. doi:10.1111/ijn.12644.
4. Nanshan Chen, Min Zhou, Xuan Dong, Jieming Qu, Fengyun Gong, Yang Han, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;**395**(10223):507–13. doi:10.1016/S0140-6736(20)30211-7.
5. Qiurong Ruan, Kun Yang, Wenxia Wang, Lingyu Jiang, Jianxin Song. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;**46**(5):846–8. doi:10.1007/s00134-020-05991-x.
6. Carolina Garcia-Vidal, Gemma Sanjuan, Estela Moreno-García, Pedro Puerta-Alcalde, Nicole Garcia-Pouton, Mariana Chumbita, et al. Incidence of co-infections and superinfections in hospitalised patients with COVID-19: a retrospective cohort study. *Clin Microbiol Infect* 2020 S1198743X2030450X. doi:10.1016/j.cmi.2020.07.041.

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