



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Incidence of bacterial and fungal bloodstream infections in COVID-19 patients in intensive care: An alarming “collateral effect”

Maria Adriana Cataldo*, Nardi Tetaj, Marina Selleri, Luisa Marchioni, Alessandro Capone, Emanuela Caraffa, Antonino Di Caro, Nicola Petrosillo, the INMICOVID-19 Co-infection Group¹

National Institute for Infectious Diseases Lazzaro Spallanzani-IRCCS, Rome, Italy

ARTICLE INFO

Article history:

Received 26 June 2020

Received in revised form 14 September 2020

Accepted 14 October 2020

Available online 29 October 2020

Several issues related to the coronavirus disease 2019 (COVID-19) epidemic are starting to cause concern, including the occurrence of bacterial and fungal infections, the plausible crisis of antimicrobial stewardship programs and an increase in antimicrobial resistance [1–3]. The real extent of these issues is poorly known due to the lack of ad hoc studies.

In order to assess the incidence of bacterial and fungal bloodstream infections (BSIs) in COVID-19 patients in intensive care, we performed a retrospective cohort study including adult patients with COVID-19 hospitalised in intensive care unit (ICU) from 1 March to 15 April 2020 at the National Institute for Infectious Diseases, Rome, Italy.

In the ICU, infection prevention and control measures during health care of COVID-19 patients were applied according to the WHO recommendations [4]; moreover, measures for preventing the transmission of multidrug resistant (MDR) bacteria were applied according to local protocols issued on the basis of international guidelines [5,6].

The incidence of BSIs/10 000 ICU days was calculated including only the first episode of BSI. Subsequent BSIs acquired after the first episode of BSIs were also collected. Aetiology of BSI and susceptibility patterns of the isolates were recorded. Rate of BSIs in patients admitted to our ICU in the first 6 months of the previous year were obtained. Results of surveillance samples of the rectum

to detect colonisation by MDR organisms were also collected. Finally, the mortality during ICU hospitalisation was recorded.

During the study period, 57 patients were admitted to our ICU. Forty-one were males (72%), the mean age (\pm standard deviation, SD) was 62 ± 13 years. The mean length of hospitalisation (\pm SD) before ICU admission was 8 ± 8 days. Fifty-two patients (91%) had a central indwelling venous catheter and 48 (84%) were on mechanical invasive ventilation. Fifty-six patients (98%) were exposed to antibiotics in the 30 days before study inclusion; administered antibiotics were mainly an association of beta-lactam and macrolide. Regarding the treatment of severe COVID-19, 42 patients (74%) were exposed to corticosteroids and 26 (46%) to interleukin-6 blockers; all included patients received antivirals in the 30 days before the study inclusion, mainly lopinavir/ritonavir associated with hydroxychloroquine.

BSIs occurred in 49% (28/57), with an incidence rate of 373 per 10 000 patient-days. The mean time from the ICU admission to the occurrence of BSI was 13 ± 7 days (range 3–34 days).

The commonest isolated agents included *Enterococcus* spp. (11 cases) and *Pseudomonas* spp. (8 cases); *Candida* spp. were isolated in 5 cases; in 3 patients more than one agent was isolated from blood cultures. Table 1 shows the aetiological agents isolated from blood cultures of 28 patients with BSI.

Seven out of 28 patients (25%) acquired a subsequent BSI during the ICU stay, due to the following aetiological agents: *P. aeruginosa* (2 cases), *C. inconspicua* (1), *C. parapsilosis* (1), *E. faecalis* (1), *Stenotrophomonas maltophilia* (1) and *Hafnia alvei* (1).

Regarding the antimicrobial resistance pattern of the blood isolates, among enterococci (except for *E. gallinarum* that is intrinsically vancomycin-resistant), two *E. faecium* isolates (2/10, 20%) were resistant to vancomycin (VRE). Among *Pseudomonas*

* Corresponding author at: National Institute for Infectious Diseases Lazzaro Spallanzani-IRCCS, Via Portuense, 292- 00149 Rome, Italy.

E-mail address: adriana.cataldo@inmi.it (M.A. Cataldo).

¹ The members of the group are acknowledged at the end of the article.

Table 1

Aetiological agents isolated from blood cultures of 28 patients with bloodstream infection.

Aetiological agent	Number of patients
<i>Pseudomonas aeruginosa</i>	6
<i>Pseudomonas aeruginosa</i> + <i>Enterococcus faecium</i>	1
<i>Pseudomonas putida</i>	1
<i>Enterococcus faecalis</i>	3
<i>Enterococcus faecium</i>	4
<i>Klebsiella aerogenes</i> + <i>Enterococcus faecium</i>	1
<i>Klebsiella aerogenes</i>	1
<i>Klebsiella pneumoniae</i>	1
<i>Escherichia coli</i>	1
<i>Enterobacter cloacae</i>	1
<i>Stenotrophomonas maltophilia</i>	1
<i>Enterococcus casseliflavus/gallinarum</i>	2
<i>Candida albicans</i>	2
<i>Candida parapsilosis</i>	2
<i>Candida glabrata</i> + <i>Candida parapsilosis</i>	1

spp. strains, four (4/10, 40%) were resistant to piperacillin/tazobactam and one to carbapenems (1/10, 10%).

Regarding Enterobacterales, two isolates were extended-spectrum- β -lactamase producing (2/6, 33%); no resistance to carbapenems was observed among these isolates.

All *Candida* spp. isolates were susceptible to echinocandins, only 1 (*C. parapsilosis*) was resistant to fluconazole.

Overall, 17 patients (30%) were colonised by VRE (all *E. faecium*), 12 patients acquired VRE during ICU hospitalisation whereas 5 were already colonised at ICU admission. No patient acquired colonisation by other MDR organisms.

Three VRE-colonised patients acquired BSI due to *E. faecium*; comparing the susceptibility pattern of these bacterial strains, in two patients the strains isolated from blood cultures were phenotypically similar to those isolated from rectal swabs.

No difference in mortality rate was observed among patients with and without BSI; the overall ICU mortality rate was 32% (18/57).

Regarding historical data, in the first 6 months of the previous year 75 patients were admitted at our ICU. Blood cultures performed during ICU admission yielded a recognised bacterial or fungal pathogen in 10 patients, with a prevalence of BSIs of 13% (10/75). The prevalence of intestinal colonisation by VRE was 15% (11/75); no blood cultures yielded VRE.

Our findings evidenced an exaggerated risk of acquiring bacterial and fungal BSIs among critically ill patients with COVID-19 in the ICU, namely an incidence almost 20 times higher than the incidence reported in European ICUs [7].

In the pre-COVID-19 period, the prevalence of BSI in patients staying in our ICU was 3.8 times lower than the prevalence observed in our ICU COVID-19 patients.

Key drivers of the high incidence of bacterial and fungal infections in COVID-19 patients are likely: (1) the immune dysregulation in severe COVID-19; (2) an extensive use of antimicrobials; (3) less adherence to the infection control and prevention measures.

We do believe that further studies collecting data on the role of the “cytokine storm” on the risk of acquiring bacterial and fungal

infections are needed. Moreover, the impact of virus-induced intestinal inflammation on BSI, seen in the BSI aetiology in the our population, deserves further attention.

Funding

INMI authors are supported by the Italian Ministry of Health (Ricerca Corrente).

Competing interests

NP declares honorary fees as speaker from MSD, Pfizer, Shionogi, Becton Dickinson, Cepheid, Johnson & Johnson. All other authors declare no conflicts of interest.

Ethical approval

The Ethics Committee at INMI has authorised the use for research purpose of data collected during routine clinical care of patients with emerging infections.

Acknowledgements

We gratefully acknowledge the Collaborators and Members of the INMI COVID-19 Co-infection Group: Al Moghazi Samir, Busso Donatella, Caravella Ilaria, Chinello Pierangelo, Ciotti Veronica, Dantimi Cristina, D'Arezzo Silvia, De Angelis Giada, Di Lorenzo Rachele, Donno Davide, Fusetti Matteo, Galati Vincenzo, Garotto Gabriele, Giansante Filippo, Girardi Enrico, Granata Guido, Greci Maria Cristina, Ippolito Giuseppe, Macchione Manuela, Marini Maria Cristina, Maritti Micaela, Nisii Carla, Noto Pasquale, Petrecchia Antonella, Ruggeri Alberto, Sampaolesi Alessandro, Santagata Carmen, Scarcia Silvana, Stazi Giulia, Taglietti Fabrizio, Topino Simone, Vaia Francesco, Venditti Carolina, Vulcano Antonella, Zanetti Antonella.

References

- [1] Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis* 2020;ciaa530.
- [2] Stevens MP, Patel PK, Nori P. Involving antimicrobial stewardship programs in COVID-19 response efforts: all hands on deck. *Infect Control Hosp Epidemiol* 2020;41(6):744–5.
- [3] Zhou P, Liu Z, Chen Y, Xiao Y, Huang X, Fang XG. Bacterial and fungal infections in COVID-19 patients: a matter of concern. *Infect Control Hosp Epidemiol* 2020;22:1–2.
- [4] Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed: interim guidance. World Health Organization. Available at <https://www.who.int/publications/i/item/10665-331495>
- [5] Siegel JD, Rhinehart E, Jackson M, Chiarello L. Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in health care settings, 2006. *Am J Infect Control* 2007;35:S165–93.
- [6] Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin Microbiol Infect* 2014;20(Suppl. (1)) 1–55.
- [7] European Centre for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units. ECDC. Annual epidemiological report for 2017. Stockholm: ECDC; 2019.