HEALTHCARE-ASSOCIATED INFECTIONS IN COVID-19 ICU PATIENTS – TWO-CENTRE STUDY

Bartosz Kozłowski[1], Joanna Kubiak-Pulkowska[2], Julianna Pałka[1], Dominika Bożiłow[1], Magdalena Zając[3], Aleksander Deptuła[4]

[1]Anaesthesiology and Intensive Care Unit, 10th Military Research Hospital and Polyclinic, Bydgoszcz, Poland
[2]Jan Biziel University Hospital No. 2, Bydgoszcz, Poland
[3]Faculty of Pedagogy, Kazimierz Wielki University, Bydgoszcz, Poland
[4]Department of Propaedeutics of Medicine and Infection Prevention, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

SUMMARY

Objective: The aim of this retrospective study was to estimate the prevalence of healthcare-associated infections (HAI), microbiological data including resistance patterns and impact of HAI on patients' survival.

Methods: Two-centre study on 172 patients was performed. Medical records of patients hospitalized in the two COVID-19 intensive care units (ICU) localized in Bydgoszcz between 1 October 2020 and 30 March 2021 were analysed retrospectively. Data collection included demographics, microbiological, clinical variables, and patient outcome. All infections were defined according to the HAI-Net ICU protocol of the European Centre for Disease Prevention and Control (ECDC). Detailed data concerning bloodstream infection (BSI), pneumonia (PN) and urinary tract infection (UTI) were collected.

Results: In 97 patients (56.4%), 138 HAI cases were identified. Patients with HAI statistically more often had been administered antimicrobial therapy prior to the admission to ICU (59.8% vs. 34.7%, $p < 0.05$), and needed catecholamines during hospitalization (93.8% vs. 70.7%, $p < 0.001$). The risk of HAI increased by 50% if antimicrobial therapy had been applied before the admission to ICU, and was three times higher if during the hospitalization in ICU catecholamines infusion was needed. Mortality was higher in patients diagnosed with HAI (72.2% vs. 65.3%) but the difference was not statistically significant ($p = 0.34$).

Conclusions: Further investigation of co-infections in critically ill patients with COVID-19 is required in order to identify HAI risk factors, define the role of empiric antimicrobial therapy and proper prevention strategies.

Key words: healthcare-associated infections, intensive care unit, COVID-19, infection control

Address for correspondence: B. Kozłowski, Anaesthesiology and Intensive Care Unit, 10th Military Research Hospital and Polyclinic, IPHC in Bydgoszcz, Powstancow Warszawy 5, 85061 Bydgoszcz, Poland. E-mail: bbkozlowski@gmail.com

https://doi.org/10.21101/cejph.a7135

INTRODUCTION

COVID-19 is caused by a strain of coronavirus named SARS-CoV-2. The term "coronavirus" refers to a vast group of common enveloped, positive-strand RNA viruses known to infect birds and mammals. Coronaviruses own their name to the crown-like glycoprotein spikes on the surface. There are hundreds of types of coronaviruses, but only seven of them are known to affect humans. Four of them cause mild upper respiratory tract infections. The other three may cause major infection and are responsible for the severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV) and COVID-19 epidemics. The most recent coronavirus epidemic emerged in 2019. Coronavirus disease emerged in 2019. The first case was identified in Wuhan, China. It has spread over the world, killing thousands of people. COVID-19 is associated with high rate of hospitalization, admission to intensive care units (ICU) and mortality. According to the World Health Organization (WHO) data we have 180,000,000 confirmed cases of coronavirus infection, including 3,900,000 deaths all over the world (1). Critically ill patients with COVID-19 experience acute respiratory distress syndrome (ARDS) and need invasive mechanical ventilation. This group of patients presents the highest mortality. Co-infection acquired in ICU is suspected to be one of the reasons of high number of deaths. Patients with COVID-19 often have other comorbidities, impaired immune system associated with coronavirus disease per se and by the steroid treatment. Moreover, in most cases invasive mechanical ventilation is required. All the above-mentioned predispose COVID-19 ICU patients to hospital-acquired infections (HAIs). HAIs are still of great concern to every ICU to cope with, not only when dealing with COVID-19 patients. To date, few studies have been reported and related to HAI during COVID-19 (2–9). This retrospective study aimed to estimate the prevalence of HAI, microbial growth, resistance patterns and impact of HAI to patients' survival.

MATERIALS AND METHODS

Medical records of patients hospitalized in the COVID-19 ICU in the 10th Military Research Hospital and Polyclinic in Bydgoszcz, Poland, and in the Biziel University Hospital No. 2 in Bydgoszcz, Poland, between 1 October 2020 and 30 March 2021 were analysed retrospectively. Eligible patients included those hospitalized > 48 h and with positive SARS-CoV-2 polymerase chain reaction test prior to ICU admission. Patients were admitted to the ICU due to the need of invasive mechanical ventilation. At the same time they mostly required either circulatory support or/and continuous renal replacement therapy.

All infections were defined according to the HAI-Net ICU Protocol of the European Centre for Disease Prevention and Control (ECDC) (10), and infections that occurred > 48 h after admission to the ICU were defined as ICU-acquired (HAI). Detailed data concerning bloodstream infection (BSI), pneumonia (PN) and urinary tract infection (UTI) were collected.

Particular HAI pathogens were analysed for resistance mechanisms and markers:

- *Staphylococcus aureus*: susceptibility to methicillin and glycopeptides;
- *Enterococcus* spp.: susceptibility to glycopeptides;
- *Enterobacterales*: susceptibility to cephalosporines III generation and carbapenems;
- *Pseudomonas aeruginosa*: susceptibility to carbapenems;
- *Acinetobacter* spp: susceptibility to carbapenems.

The choice of investigated resistance markers was made based on the EDCD protocol (10). In statistical analysis frequency distribution and descriptive statistics (mean, median, confidence interval) were used. The differences were analysed with non-parametric (χ^2 for nominal variables and the Wilcoxon Mann-Whitney test for ordinal variables) and parametric tests (analysis of variance with Fisher's test for quantitative variables). The results with $p < 0.05$ were considered statistically significant. All statistical analyses were performed with SPSS Statistics program.

RESULTS

Out of 203 patients hospitalized in the COVID-19 ICU during analysed period (2,120 person/days), 172 were included in the study – all were hospitalized > 48 h and were discharged from the ICU before 30 March 2021. Demographic data are presented in Table 1. In 97 patients (56.4%), 138 HAI cases were identified. In some patients more than one HAI occurred (28 patients developed two different HAIs, 8 patients were diagnosed with three different HAIs, and one patient had four various HAIs). Patients with HAI statistically more often had been administered antimicrobial therapy (for any reason) prior to the admission to the ICU (59.8% vs. 34.7%, $p < 0.05$) and required catecholamine infusion during hospitalization (not necessarily at the time of admission to the ICU) (93.8% vs. 70.7%, $p < 0.001$).

The risk of HAI increased by 50% if antimicrobial therapy had been applied before the admission to the ICU and was three times higher if during the hospitalization in the ICU catecholamine infusion was needed (Table 2).

Mortality was higher in patients diagnosed with HAI (72.2% vs. 65.3%) but the difference was not statistically significant ($p = 0.34$) (Table 1).

The risk of death was over two times higher in patients with sudden cardiac arrest prior to the ICU admission and in patients that required catecholamine infusion during hospitalization. Almost two times higher risk of death was observed in patients that developed acute kidney injury (AKI) during ICU hospitalization. Overall 152 various strains of microorganisms were isolated. Detailed data are presented in Table 3.

Bloodstream infection was the most common HAI (81/138) with primary BSI as the largest subgroup (46/81). Out of 81 BSI cases, 17 were catheter-related. Other HAI included pneumonia (52/138) and urinary tract infections (5/138). None of isolated strains of *S. aureus* (n = 5) was methicillin resistant. All *E. coli* strains (n = 2) were susceptible to III generation cephalosporins. Resistance to carbapenems was detected in 36.7% of isolated *Klebsiella pneumoniae* strains (n = 30), 14.3% of *Pseudomonas aeruginosa* (n = 7), and 97.2% *Acinetobacter baumannii* (n = 36). Moreover, 11.4% of *A. baumannii* strains were also polymyxin resistant.

DISCUSSION

The aim of this study was to examine the HAI incidence in critically ill patients with COVID-19. The data collected during our study has shown that HAI occurrence was common and impeded the treatment. In our study HAI incidence was estimated

Table 1. *Patients' characteristics (N = 172)*

	With HAI	Without HAI	p-value
Patients (patient-days)	97 (2,089)	75 (621)	n/a
Age	68.23 ± 10.56	69.45 ± 11.93	0.53
Males/females	66/31	46/29	0.36
Outcome – death	70 (72.2%)	49 (65.3%)	0.34
APACHE II score	25.20 ± 8.63	23.15 ± 9.89	0.13
Catecholamine usage	91 (93.8%)	53 (70.7%)	**< 0.001**
Acute kidney injury	59 (60.8%)	50 (66.7%)	0.43
Cardiac arrest prior to ICU admission	43 (44.3%)	36 (48.0%)	0.63
Antimicrobial therapy prior to ICU admission	58 (59.8%)	26 (34.7%)	**< 0.05**

ICU – intensive care unit. Numbers in bold indicate statistically significant values.

Table 2. Risk of HAI and risk of death

	Relative risk (95% CI)	p-value
Risk of HAI in ICU patients		
Antimicrobial therapy prior admission to ICU	**1.558 (1.184–2.050)**	**<0.001**
Male sex	1.109 (0.885–1.390)	0.184
ICU outcome – death	1.155 (0.852–1.565)	0.177
Using of catecholamines during ICU stay	**2.949 (1.435–6.059)**	**0.002**
AKI during ICU stay	1.114 (0.855–1.452)	0.211
Cardiac arrest prior to ICU admission	1.067 (0.818–1.391)	0.317
Risk of death in ICU patients		
Antimicrobial therapy prior admission to ICU	1.065 (0.873–1.300)	0.267
Male sex	1.099 (0.882–1.369)	0.842
Using of catecholamines during ICU stay	**2.119 (1.278–3.514)**	**0.002**
Acute kidney injury during ICU stay	**1.969 (1.464–2.649)**	**<0.001**
Cardiac arrest prior to ICU admission	**2.158 (1.720–2.708)**	**<0.001**

HAI – healthcare-acquired infection; ICU – intensive care unit; catecholamines: adrenaline or noradrenaline or dobutamine. Numbers in bold indicate statistically significant values.

Table 3. Isolated strains responsible for selected HAIs

	Bloodstream infection				Urinary tract infection	Pneumonia
	S-PUL	S-UTI	CRI3	U0		
HAI (incidence)	n = 15 (8.72)	n = 3 (1.74)	n = 17 (9.88)	n = 46 (26.74)	n = 5 (2.91)	n = 52 (30.23)
Isolated strains of pathogens in HAIs (strains with selected resistance markers)						
S. aureus (OXA-R)				2 (0)		3 (0)
CoNS			7	12		
E. faecalis (GLY-R)	1 (1)		3 (0)	10 (0)	1 (0)	
E. faecium (GLY-R)		1 (0)	3 (1)	15 (4)	1	
E. coli (C3G-R)						2 (0)
K. pneumonia (CAR-R)	4 (3)		1 (1)	2 (1)	2 (1)	21 (5)
K. oxytoca						1
S. marcescens (CAR-R)						2 (0)
A. baumannii (CAR-R)	12 (12)	2 (2)	1 (1)	2 (2)		19 (18)
P. aeruginosa (CAR-R)			1 (0)	2 (0)	1 (1)	3 (0)
S. maltophilia	1		1	1		3
C. albicans			2	3		1
C. parapsilosis				1		
C. krusei				1		
Aspergillus spp.						1

HAI – hospital acquired infection; BSI – bloodstream infection; incidence – number of HAI/100 hospitalization; S-PUL – BSI secondary to pneumonia, S-UTI – BSI secondary to urinary tract infection; CRI3 – catheter related infection; U0 – primary BSI; CoNS – *coagulase negative staphylococci*; OXA-R – metacycline resistance; CAR-R – carbapenems resistance; C3G-R – III generation cephalosporin resistance; GLY-R – glycopeptides resistance

for 56.40/100 ICU patients. Most studies present lower numbers (10–45%) (11–16), but similar outcome has also been reported (17). The frequency of HAI reported before the COVID-19 pandemic varied between 17% and 28%, therefore was much lower (18, 19). It has been observed that critically ill patients requiring mechanical ventilation due to COVID-19 ARDS had a higher incidence of HAI than other patients (2). Our study did not prove this relationship. Designation of an ICU ward for COVID-19 patients separated from other hospital wards was a very significant challenge. Repurposing of wards or establishing new structures for critically ill patients with SARS-CoV-2 infection was made rapidly. Organizational and functional issues occurred, combined with the lack of professional healthcare workforce. All of the above-mentioned may be considered as reasons for lower treatment quality. This also affected effective HAI prevention and probably had a key impact on incidence of healthcare-associated infections. The most common HAI was BSI (47.1%). The frequency of BSI observed in our study was significantly higher than in ICU patients without COVID-19 (13, 20, 21). Reports on the occurrence of BSI in the ICU COVID-19 patients show a much lower frequency of BSI (4, 14). On the other hand, there are reports presenting a similar prevalence of BSI (17). According to Buetti et al., BSI is more frequent in patients with COVID-19 than in ICU patients without this infection, and usually the source of the bloodstream infection remains unidentified (22). We noticed similar results in our study. The source of 56.8% cases of BSI could not be identified. The remaining BSIs were catheter-related or secondary to pneumonia and urinary tract infections. The second most common HAI was ventilator-associated pneumonia (VAP). The incidence of VAP is similar to the one indicated by other researchers (6, 7, 23–25), and is higher than observed in non COVID-19 ICU patients. This is probably due to very high intubation rate in patients treated in ICUs for COVID-19 pneumonia. Grasselli et al. showed that about 80% of ICU COVID-19 patients required mechanical ventilation (7). In our study all patients needed this support. According to the literature pneumonia co-infection caused by *Aspergillus* spp. were also noticed (26). We have also observed one case of pulmonary aspergillosis. Patients treated with high doses of steroids are at risk of these opportunistic infections (29). As steroids are the primary treatment for COVID-19, *Aspergillus* spp. infections should not be unexpected.

Frequency of urinary tract infections was similar to the numbers reported in other papers (7, 27). Unfortunately, there are still only few studies on this subject. Antibiotic resistant microorganisms that cause HAI in patients treated in ICU due to COVID-19 are challenging therapeutic problem. The majority of hospitalized patients received antibiotic treatment prior to ICU admission. The authors of this paper cannot find grounds for the implementation of antimicrobial therapy before the ICU admission. Likely, antibiotics were given due to the fear of bacterial superinfection. It was often difficult to determine the reason for patients' deterioration. Clinical worsening combined with an elevation of C-reactive protein (CRP) and procalcitonin (PCT) levels are regarded as hallmarks of bacterial infection, and resulted in the empirical antibiotic therapy implementation. In our opinion, there were often no indications for this therapy. This overuse of antibiotics increased the risk of developing HAI by more than 1.5 times.

Ventilator-associated pneumonia was caused mostly by *K. pneumoniae* and *A. baumannii*. More than 90% of isolated strains presented resistance to carbapenems. Moreover, 10% of *A. baumannii* strains were also resistant to polymyxins. Multi-drug resistant microorganisms are also reported to be an important concern in all parts of the world. *S. aureus*, *P. aeruginosa* and *S. maltophilia* are presented to be the most common causes of VAP in the Garcia-Vidal et al. research (6). Similar to Grasselli et al. findings the most common cause of VAP were *S. aureus*, *P. aeruginosa* and *Klebsiella* spp. (7). Drug resistant strains were also isolated from blood cultures. In our study the most common pathogen responsible for BSI were Gram (+) bacteria, mostly *Enterococcus* spp., 18.2% of *Enterococcus* spp. strains presented resistance to glycopeptides. Among Gram (−) bacteria isolated from blood cultures *A. baumannii* strains resistant to carbapenems dominated. In few cases fungemia caused by Candida species was observed. Similar findings were presented by Kokkoris et al. (28). According to Grasselli et al. the most common Gram (+) bacteria isolated from blood cultures were *Enterococcus* spp. and the most common Gram (−) bacteria was *P. aeruginosa* (7). Critically ill patients treated due to COVID-19 pneumonia are fighting a double battle. On the one hand, they deal with a very severe virus and all the complications associated with hospitalization in the ICU. On the other hand, they are more predisposed to HAI and often have to struggle with multi-drug resistant strains. Therefore, the high mortality rate among ICU patients requiring mechanical ventilation due to severe COVID-19 come as no surprise. Our work and the research by Grasselli et al. do not show a statistically significant difference in the mortality of patients with and without HAI (7). Three studies from China suggested that subsequent development of superinfections was a factor for mortality rise (2, 11, 12). Similar phenomenon was observed in our study. The vast majority of patients who additionally developed HAI and consequently severe septic shock died but the difference in the mortality of patients with and without HAI was not statistically significant.

CONCLUSIONS

Prompt and accurate antimicrobial therapy of HAI in patients with COVID-19 hospitalized in ICU should result in lower risk of the development of severe septic shock and, in a long run, it could benefit in lowering the mortality.

Antimicrobial overprescription promotes bacterial resistance. It is also necessary to reduce the mislead use of antibiotics. Antimicrobial stewardship should focus more on superinfections in COVID-19 and play a crucial role in optimal antibiotic therapy implementation. Patients with COVID-19 are more prone to bacterial superinfection, so more attention should be directed towards the prevention of not only COVID 19 transmission but also bacterial infections.

Conflict of Interests

None declared

Adherence to Ethical Standards

This research study was conducted retrospectively from data obtained for clinical purposes. No ethical approval was required.

REFERENCES

1. World Health Organization. Coronavirus Disease (COVID- 19) pandemic [Internet]. Geneva: WHO [cited 2021 Jul 4]. Available from: https://covid19.who.int/.
2. He Y, Li W, Wang Z, Chen T, Tian L, Liu D. Nosocomial infection among patients with COVID-19: a retrospective data analysis of 918 cases from a single center in Wuhan, China. Infect Control Hosp Epidemiol. 2020;41(8):982-3.
3. Giacobbe DR, Battaglini D, Ball L, Brunetti I, Bruzzone B, Codda G, et al. Bloodstream infections in critically ill patients with COVID-19. Eur J Clin Invest. 2020;50(10):e13319. doi: 10.1111/eci.13319.
4. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial coinfection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020;26(12):1622-9.

5. Yu Y, Xu D, Fu S, Zhang J, Jang X, Xu L, et al. Patients with COVID-19 in 19 ICUs in Wuhan, China: a cross-sectional study. Crit Care. 2020;24(1):219. doi: 10.1186/s13054-020-02939-x.
6. Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of coinfections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2021;27(1):83-8.
7. Grasselli G, Scaravilli V, Mangioni D, Scudeller L, Alagna L, Bartoletti M, et al. Hospital-acquired infections in critically ill patients with COVID-19. Chest. 2021;160(2):454-65.
8. Dudoignon E, Caméléna F, Deniau B. Bacterial pneumonia in COVID-19 critically ill patients: a case series. Clin Infect Dis. 2020;72(5):905-6.
9. Bhatt PJ, Shiau S, Brunetti L, Xie Y, Solanki K, Khalid S, et al. Risk factors and outcomes of hospitalized patients with severe coronavirus disease 2019 (COVID-19) and secondary bloodstream infections: a multicenter case-control study. Clin Infect Dis. 2021;72(12):e995-1003. doi: 10.1093/cid/ciaa1748.
10. European Centre for Disease Prevention and Control. Surveillance of healthcare-associated infections and prevention indicators in European intensive care units. Stockholm: ECDC; 2017.
11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
12. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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(10229):1054-62.
13. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, 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.
14. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372-4.
15. Baccolini V, Migliara G, Isonne C, Dorelli B, Barone LC, Giannini D, et al. The impact of the COVID-19 pandemic on healthcare-associated infections in intensive care unit patients: a retrospective cohort study. Antimicrob Resist Infect Control. 2021;10(1):87. doi: 10.1186/s13756-021-00959-y.
16. Marin-Corral J, Pascual-Guardia S, Muñoz-Bermúdez R, Salazar-Degracia A, Climent C, Vilà-Vilardell C, et al. Health care-associated infections in patients with COVID-19 pneumonia in COVID critical care areas. Med Intensiva (Engl Ed). 2022;46(4):221-3.
17. Soriano MC, Vaquero C, Ortiz-Fernández A, Caballero A, Blandino-Ortiz A, de Pablo R. Low incidence of co-infection, but high incidence of ICU-acquired infections in critically ill patients with COVID-19. J Infect. 2021;82(2):e20-1. doi:10.1016/j.jinf.2020.09.010.
18. Rafa E, Walaszek MZ, Walaszek M, Domanski A, Rozanska A. The incidence of healthcare-associated infections, their clinical forms, and microbiological agents in intensive care units in Southern Poland in a multicentre study from 2016 to 2019. Int J Environ Res Public Health. 2021;18(5):2238. doi: 10.3390/ijerph18052238.
19. Kolpa M, Walaszek M, Gniadek A, Wolak Z, Dobros W. Incidence, microbiological profile and risk factors of healthcare associated infections in intensive care units: a 10 year observation in a provincial hospital in Southern Poland. Int J Environ Res Public Health. 2018;15(1):112. doi: 10.3390/ijerph15010112.
20. Walaszek M, Rozanska A, Bulanda M, Wojkowska-Mach J; Team PSOHI. Epidemiology of healthcare-associated infections in Polish intensive care. A multicenter study based on active surveillance. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2018;162(3):190-7.
21. Dubiel G, Kozlowski B, Deptula A, Hryniewicz W. Raport NPOA z Programu Czynnego Monitorowania Zakażeń w Oddziałach Anestezjologii i Intensywnej Terapii w 2018 Roku w Polsce [Internet]. Warsaw: Narodowy Program Ochrony Antybiotyków; 2020 [cited 2021 Jul 9]. Available from: http://antybiotyki.edu.pl/wp-content/uploads/2020/07/Raport-ICU-2018.pdf. (In Polish.)
22. Buetti N, Ruckly S, de Montmollin E, Reignier J, Terzi N, Cohen Y, et al. COVID-19 increased the risk of ICU-acquired bloodstream infections: a case-cohort study from the multicentric OUTCOMEREA network. Intensive Care Med. 2021;47(2):180-7.
23. Ippolito M, Misseri G, Catalisano G, Marino C, Ingoglia G, Alessi M, et al. Ventilator-associated pneumonia in patients with COVID-19: a systematic review and meta-analysis. Antibiotics (Basel). 2021;10(5):545. doi: 10.3390/antibiotics10050545.
24. Giacobbe DR, Battaglini D, Enrile EM, Dentone C, Vena A, Robba C, et al. Incidence and prognosis of ventilator-associated pneumonia in critically ill patients with COVID-19: a multicenter study. J Clin Med. 2021;10(4):555. doi: 10.3390/jcm10040555.
25. Maes M, Higginson E, Pereira-Dias J, Curran MD, Parmar S, Khokhar F, et al. Ventilator-associated pneumonia in critically ill patients with COVID-19. Crit Care. 2021 Jan 11;25(1):25. doi: 10.1186/s13054-021-03460-5.
26. Machado M, Valerio M, Álvarez-Uría A, Olmedo M, Veintimilla C, Padilla B, et al. Invasive pulmonary aspergillosis in the COVID-19 era: an expected new entity. Mycoses. 2021;64(2):132-43.
27. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
28. Kokkoris S, Papachatzakis I, Gavrielatou E, Ntaidou T, Ischaki E, Malachias S, et al. ICU-acquired bloodstream infections in critically ill patients with COVID-19. J Hosp Infect. 2021;107:95-7.
29. Lewis RE, Kontoyiannis DP. Invasive aspergillosis in glucocorticoid-treated patients. Med Mycol. 2009;47(Suppl 1):S271-81.

Received September 29, 2021
Accepted in revised form September 21, 2022