Journal of Intensive Medicine 4 (2024) 269–280

Contents lists available at ScienceDirect

Journal of Intensive Medicine

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

Review

Bloodstream infections in the era of the COVID-19 pandemic: Changing epidemiology of antimicrobial resistance in the intensive care unit

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ARTICLE INFO

Handling Editor: Jingling Bao / Zhiyu Wang

Keywords:
COVID-19
Bloodstream infection
ICU
Antimicrobial resistance
Stewardship

ABSTRACT

The Coronavirus disease 2019 (COVID-19) pandemic increased the burden of critically ill patients who required hospitalization in the intensive care unit (ICU). Bacterial and fungal co-infections, including bloodstream infections (BSIs), increased significantly in ICU patients with COVID-19; this had a significant negative impact on patient outcomes. Reported data pertaining to BSI episodes from the ICU setting during the COVID-19 pandemic were collected and analyzed for this narrative review. We searched the PubMed database for articles published between March 2020 and October 2023; the terms "COVID-19" AND "bloodstream infections" AND "ICU" were used for the search. A total of 778 articles were retrieved; however, only 27 were exclusively related to BSIs in ICU patients with COVID-19. Data pertaining to the epidemiological characteristics, risk factors, characteristics of bacterial and fungal BSIs, patterns of antimicrobial resistance, and comparisons between ICU and non-ICU patients during and before the COVID-19 pandemic were obtained. Data on antimicrobial stewardship and infection-control policies were also included. The rates of BSI were found to have increased among ICU patients with COVID-19 than in non-COVID-19 patients and those admitted during the pre-pandemic period. Male gender, 60–70 years of age, increased body mass index, high Sequential Organ Failure Assessment scores at admission, prolonged hospital and ICU stay, use of central lines, invasive ventilation, and receipt of extracorporeal membrane oxygenation were all defined as risk factors for BSI. The use of immune modulators for COVID-19 appeared to increase the risk of BSI; however, the available data are conflicting. Overall, *Enterococci, Acinetobacter baumannii*, and *Candida* spp. emerged as prominent infecting organisms during the pandemic; along with *Enterobacterales* and *Pseudomonas aeruginosa* they had a significant impact on mortality. Multidrug-resistant organisms prevailed in the ICU, especially if antimicrobial resistance was established before the COVID-19 pandemic and were significantly associated with increased mortality rates. The unnecessary and widespread use of antibiotics further increased the prevalence of multidrug-resistant organisms during COVID-19. Notably, the data indicated a significant increase in contaminants in blood cultures; this highlighted the decline in compliance with infection-control measures, especially during the initial waves of the pandemic. The implementation of infection-control policies along with antibiotic stewardship succeeded in significantly reducing the rates of blood contamination and BSI pathogens. BSIs considerably worsened outcomes in patients with COVID-19 who were admitted to ICUs. Further studies are needed to evaluate adequate preventive and control measures that may increase preparedness for the future.

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic, which was the first such outbreak of the 21st century, was officially recognized by the World Health Organization on March 11, 2020.[1] It had major consequences on public health, health systems, and socioeconomic stability.[1,2] The development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and severe pneumonia (with subsequent acute respiratory distress syndrome [ARDS]) led to a substantial increase in hospitalization rates worldwide, especially during the first wave.[3,4] The development of co-infections among hospitalized patients emerged as a significant issue during the COVID-19 pandemic. Although the frequency of co-infections among these patients was not considerably high on admission (<5%),[5,6] the rates progres-

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https://doi.org/10.1016/j.jointm.2023.12.004
Received 7 November 2023; Received in revised form 20 December 2023; Accepted 22 December 2023
Available online 27 March 2024

sively rose to 9%–15% in medical wards and increased exponentially in the intensive care unit (ICU) setting.[7–9] Bloodstream infections (BSIs) and pneumonia, including ventilator-associated pneumonia, were the most frequently reported hospital-acquired infections during the COVID-19 pandemic; the prevalence of community-acquired infections was significantly lower.[5,10,11] Co-infection with either a bacterial or fungal pathogen was found to be a major risk factor for ICU admission, mechanical ventilation, and increased mortality among hospitalized patients with COVID-19.[10–12] Data from a recent meta-analysis that included 171,262 patients confirmed that a higher proportion of those in the ICU presented with co-infections (odds ratio [OR]= 18.8, 95% confidence interval [CI]: 6.5 to 54.8).[10] This meta-analysis demonstrated substantial heterogeneity of more than 95%.[10] Although large volumes of data have already been published regarding COVID-19 co-infections, global data pertaining to the epidemiology of BSIs among ICU patients have not been fully assessed; this may be attributed to the fact that many published studies included mixed populations comprising ICU and non-ICU patients.[5,8,10,11,13] In this context, the epidemiology, risk factors, and clinical outcomes may differ considerably between critically ill patients and those with moderate or less severe presentations of COVID-19. This review therefore aimed to highlight emerging global trends of BSIs in the ICU setting during the pandemic; findings pertaining to predominant pathogens, antimicrobial resistance (AMR), and the role of effective infection-control policies have been discussed.

BSIs in Critically Ill Patients with COVID-19

A total of 778 articles published between March 2020 and October 2023 were retrieved, and 96 of these were evaluated; only 27 focused solely on BSIs in the ICU setting (Supplementary Figure S1). Data pertaining to risk factors for BSIs in the ICU setting (among patients hospitalized with COVID-19), responsible pathogens and AMR patterns (in cases of bacteremia and fungemia), epidemiological characteristics (COVID-19 *vs*. non-COVID-19 patients), and antimicrobial stewardship and infection-control policies, were obtained. The data pertaining exclusively to BSIs among ICU and critically ill patients are shown in Table 1. The evaluated variables included the study setting (multicenter or single center), rates of BSI, administration of extracorporeal membrane oxygenation (ECMO), central line-associated BSI (CLABSI), infections with Gram-positive (GPB) or Gram-negative (GNB) bacteria, infections with multidrug-resistant organisms (MDROs), candidemia, and mortality rates in patients with COVID-19; these were compared with corresponding variables from the non-COVID-19 population. The mortality rate in critically ill patients with COVID-19 and BSIs ranged between 31% and 100%; this was significantly higher than the rates observed in the non-COVID-19 population (with or without BSIs). Notably, infections with MDRO further increased the mortality rate. The included studies demonstrated heterogeneity in terms of design, patient selection, and outcomes; this could be attributed to differences between hospital settings and COVID-19 virulence during each wave of the pandemic (Table 1).

Risk factors for BSI

In patients with COVID-19 who were admitted to the ICU, BSIs were related to the host, virus, hospital environment, length of hospital stay, and the extended and unnecessary use of antimicrobials. Age and gender played an important role; male patients with COVID-19, who were in the seventh decade of their life and were admitted to the ICU with bacteremia, demonstrated significantly higher mortality rates compared with those in all other groups.[14] The presence of bacteremia *per se* was a significant risk factor. Notably, the patterns of BSI differed between the early and later phases of the pandemic. In their study, which included 248 COVID-19 patients admitted to the ICU during the first wave of the pandemic (between February and May 2020), De Santis et al.[15] found that these patients were at higher risk of developing bacteremia; they also demonstrated an increased probability of dying (45.9% *vs*. 31.6%, OR= 1.8, 95% CI: 0.9 to 3.7, P=0.069 and 56.8% *vs*. 40.3%, OR= 1.9, 95% CI: 1.1 to 3.9, P=0.04, respectively). An increased Sequential Organ Failure Assessment score upon ICU admission (median=9.5, interquartile range [IQR]: 8–12 *vs*. median=8, IQR: 5–10; P=0.042) and the need for intermittent mechanical ventilation (IMV) (P=0.013) were associated with significantly higher mortality (54% *vs*. 42.3%, P <0.001).[14] The data suggested that a higher body mass index and longer length of hospital stay were significantly associated with a higher incidence of super infections including BSI; in this context, a 1-unit increment in the body mass index raised the risk of bacterial and/or fungal super infections acquisition by 3% and a 1-day increment in ICU stay increased the risk of developing bacterial and/or fungal super infections by 11%.[16]

The data pertaining to the impact of immune modulator therapy on BSI incidence among COVID-19 patients who were admitted to the ICU are conflicting. The BACTCOVID study from Spain demonstrated that the use of immunomodulators such as tocilizumab did not lead to an increase in hospital-acquired BSI in patients with severe SARS-CoV-2 pneumonia.[17] Bonazzetit et al.[14] also reported similar findings in their study. Conversely, a study from an institutional center in the United States (which employed propensity-score-matching in 6520 of 13,007 patients) found the combination of corticosteroids and tocilizumab to be significantly associated with all BSIs (OR: 1.97, 95% CI: 1.04 to 3.73, P=0.038) and bacterial BSIs (OR: 2.13, 95% CI: 1.12 to 4.05, P=0.021).[18] In another study, multivariable analysis showed treatment with an anti-inflammatory agent to be independently associated with the development of BSI (cause-specific hazard ratio [csHR] for tocilizumab: 1.07; 95% CI: 0.38 to 3.04, csHR for methylprednisone alone: 3.95; 95% CI: 1.20–13.03, and csHR for methylprednisolone plus tocilizumab: 10.69; 95% CI: 2.71 to 42.17, with the non anti-inflammatory treatment group as the reference) (P=0.003).[19] Kurt et al.[20] also reported similar results. In addition to the type of immunomodulator, the dose and length of administration influenced the prevalence of BSI.[21,22]

A high prevalence of AMR in the hospital environment was particularly associated with overwhelming mortality rates (of up to 80%) among patients with COVID-19 who were admitted to the ICU.[20] Among patients who were admitted to the ICU, a significant correlation was observed between blood culture positivity and the presence of an indwelling device.[6] No-

Table 1
Data from 27 studies that exclusively focused on BSIs among COVID-19 patients in the ICU setting.

Study	BSI	Multi center	ECMO	CLABSI	GPB	GNB	*Candida* spp.	MDRO	BSI COVID *vs.* non-COVID-19	Mortality
Abelenda-Alonso et al.[17]	100 (4.9%)	Yes	NA	47.1%	CoNs:27.2% *E. faecalis:* 18.9%	*P. aeruginosa*: 8.8% *K. pneumoniae*: 5.9%	*n*=5	10.65%	No	In-hospital: 49% 30-day: 31%
Aslan et al.[38]	142 COVID-19 (26%)	Yes	NA	33.3%	CoNs :24.8% *Enterococcus* spp.:42.6%	CRAB:33.6% *K. pneumoniae*: 28.1%	*n*=67 (11.2%)	GNB: 24.7% GPB: 8.6%	Yes. Total BSI (*n*=547). COVID 19 is a factor of mortality	28-day: 49%
Bonazzetti et al.[14]	265 (49.3%)	Yes	NA	32.9%	*Enterococci:* 31.8% *S. aureus:* 9.8%	*Enterobacterales:* 14.4% *P. aeruginosa:* 6.2%	*n*=9 (3%)	1–6%	No	30-day: 54%
Buetti et al.[65]	252 (30.4%) COVID-19	Yes	NA	29.4%	39.7%	59.9%	*n*=19 (7.5%)	GNB: 19.4% GPB: 12.7%	Yes. COVID-19: more *A. baumannii* & *Enterococcus*, high mortality	28-day: 58.7%
Carelli et al.[27]	30 (44%)	No	Yes, 32/100 days of ECMO	7%	*n*=20 (*Enterococcus* spp., *n*=13)	*n*=10 (*Acinetobacter*, *n*=3, *P. aeruginosa*, *n*=3)	*n*=2	NA	No	In-hospital: 63.3%
Cogliati Dezza et al.[42]	57 (44%)	No	*n*=3	91%	NA	*A. baumannii:* 100%	NA	CRAB: 100%	NA	28-day: 47%
Cogliati Dezza et al.[67]	18 COVID-19 (39.1%)	No	NA	NA	NA	*A. baumannii*: 78.9% *K. pneumoniae*: 21%	NA	11.2/100 patients	Yes. COVID-19: more MDRO, higher mortality	30-day: 77.8%
De Santis et al.[15]	37 (14.9%)	Yes	NA	NA	CoNs (*n*=14) *Enterococcus* spp. (*n*=13)	*A. baumannii* (*n*=13) *K. pneumoniae* (*n*=8) *P. aeruginosa* (*n*=7)	*n*=11	NA	No	In ICU: 46.7% n-hospital: 56.8%
Dobrović et al.[46]	176 (25/1000 patients-days)	No	NA	NA	*Enterococcus* spp.: 15.8% *S. aureus:* 8%	Overall 57.3% *A. baumannii*: 40% *K. pneumoniae*: 8.6%	1%	CRAB: 100% CRKP: 87% VRE: 20% MRSA: 83%	No	In-hospital: 85.8%
Frattari et al.[40]	191 (44.3%)	No	NA	NA	*E. faecium* (*n*=37) *E. faecalis* (*n*=23)	*A. baumannii:* (*n*=54).	NA	KPC (*n*=16)	No	NA
Giacobbe et al.[19]	31/78 (47/1000 patients-days)	No	NA	9%	CoNs:24% *E. faecium:*9% *E. faecalis:* 18% *S. aureus:* 13%	*E. aerogenes:* 9% *P. aeruginosa:* 4% *E. coli:* 2% *P. mirabilis:* 2%	7%	*Enterobacterales*: 33%	No	25% (days 12–24 after 1st positive blood culture)
Bonazzetti et al.[51]	60 (87/1000 patients-days)	No	NA	NA	*Enterococcus* spp.: 55.8% CoNs:20.5% *S. aureus:* 7.6%	24.8% Enterobacaterales, *n*=19	2.6%	27.3%	Yes, higher BSI incidence *vs.* Pre-COVID-19 (*P* <0.001) esp by *Enterococci*	In-hospital: 49.4%
Hlinkova et al.[25]	CLABSI, 37/464 (7.9%)	No	NA	10.2/1000 catheter-days	*Enterococcus* spp.:16.2% CoNs:10.8%	*A. baumannii*: 21.6% *K. pneumoniae*: 21.6% *P. aeruginosa*: 13.5%	NA	NA	Yes. COVID-19 more CLABSI (*P* <0.001, OR=5.5)	CLABSI & COVID-19: 51.8%
Khatri et al.[18]	256/6520 (3.9%)	No	NA	NA	*S. aureus:* 20.8% *E. faecalis:* 11.3% *E. faecium:* 3.7%	*E. coli:* 8.3% *P. aeruginosa:* 5.8% *K. pneumoniae* 7.5%	*n*=17	VRE:3.7% MRSA: 20.8%	No. Assessment of risk factors for BSI in ICU	NA
Kayaaslan et al.[59]	Candidemia 139/1305 (10.6%)	No	NA	presence of CVC (OR=19.07)	NA	NA	10.6%	NA	No. Only ICU predictive score for candidemia in COVID-19	NA

(*continued on next page*)

Table 1 (*continued*)

Study	BSI	Multi center	ECMO	CLABSI	GPB	GNB	*Candida* spp.	MDRO	BSI COVID *vs.* non-COVID-19	Mortality
Kurt et al.[20]	179 (50.2%)	No	NA	42.5% 20.8/1000 catheter-days	*Enterococcus* spp.: 11.9% *S. aureus:* 7.1%	*A. baumannii*: 39.7% *K. pneumoniae*: 26.6%	5.6%	CRKP: 20.6%	No	In ICU: 59.6%
Kokkoris et al.[45]	27/50 (54%)	No	NA	NA	*Enterococcus* spp. (*n*=6)	*A. baumannii* (*n*=7) *K. pneumoniae* (*n*=4)	*n*=7, 14%	*A. baumannii* & CRKP: 100%	No	In ICU: 33%
Lepape et al.[13]	388/4,465 (8.7%) BSI only	Yes	*n*=3	35.7%	*S. aureus:* 44.4% *E. faecalis:* 11.8%	*Enterobacterales:* 26.9% *P. aeruginosa:* 15.8%	8.2%	(With VAP) ESBL:16.5%, VRE: 7.4%, MRSA:11.3%	Yes. Higher BSI rates and resistance in COVID-19	In ICU: 22.8% (mixed)
Macauley and Epelbaum[58]	12 (5.1%) 51/1000 admissions	No	*n*=2	NA	NA	NA	*n*=12, non-*albicans* 75%	NA	Yes. COVID-19 patients longer ICU stay, more CVC	75%
Pallotta et al.[57]	Candidemia (*n*=53), with COVID-19 (*n*=18)	Yes	*n*=10	NA	NA	NA	*C. albicans* 50% *C. parapsilosis* 28%	NA	Yes Candidemia COVID *vs.* non-COVID, all patients had CVC, mortality NS	30-day: 36%
Pozza et al.[66]	284 (61%) (87/1000 patients-days)	No	NA	NA	*Enterococcus* spp.: 43.1% *S. aureus:* 8.2%	*Enterobacterales:* 21% *P. aeruginosa:* 10.4%	2%	ESBL: 4.7% CRE :2.9% PA :2.9%, VRE: 4.9%, MRSA: 2.1%	No. Waning of *Enterococcus* across COVID-19 waves	43.1%
Palanisamy et al.[49]	64 (8.5%)	No	NA	NA	*Enterococcus* spp.: 17.2%	*A. baumannii:* 32.8% *K. pneumoniae:* 21.9% *E. coli:*10.9%	NA	57.8% CRE: 47.2%	No	100%
Roda et al.[29]	2.2/100 patients-days 40.9% during ECMO	No	*n*=29	NA	*Enterococcus* spp.:27% CoNs:13%	*P. aeruginosa:* 13% *K. pneumoniae:* 7% *A. baumannii:* 7%	*n*=5 (33%)	ESBL, CRE	Yes. Compared to COVID-19 patients, none death in flu patients	In-hospital: 50% ECMO: 40.9%
Russo et al.[39]	18 (56%)	No	*n*=4	NA	NA	*A. baumannii*: 100%	NA	100%	Yes. COVID-19: more colonized by *A. baumannii*	30-day: 81%
Shih et al.[28]	19/44 (43.2%)	No	98%	NA	*E. faecalis* (1st) *S. aureus* (4th) *S. epidermidis* (3rd)	*Klebsiella* spp. *P. aeruginosa* *Serratia* spp.	*Candida* spp. (2nd)	NA	No	37% (all co-infections)
Strelkova et al.[22]	236 (50.2%)	No	NA	NA	40% *Enterococcus* spp.:32%, CoNs:26% *S. aureus:* 15%	Overall:58% *A. baumannii:* 31% *K. pneumoniae:* 20%	1%	CRAB: 100% CRKP: 80%	No. A case control study with a predictive model of BSI	85.6%
Torrecillas et al.[37]	57 (26%)	No	*n*=22 (10%)	NA	CoNs: 11.8% *Enterococcus/S. aureus:* 3.6–5.5%	*Enterobacterales:* 30% Non-fermentive GNB: 20.9%	5%	ESBL/CRE: 1.8%; MRSA/*E. faecium:*2.3%, PA:5.5%	Yes. COVID-19: higher incidence & AMR in BSI	In ICU: 31%

A. baumannii: Acinetobacter baumannii; AMR: Antimicrobial resistance; BSIs: Bloodstream infections; CLABSI: Central-line-associated BSI; CoNS: Coagulase-negative Staphylococci; COVID-19: Coronavirus disease 2019; CRAB: Carbapenem-resistant *Acinetobacter baumannii*; CRE: Carbapenem resistant Enterobacterales; CRKP: Carbapenem resistant *Klebsiella pneumoniae;* CVCs: Central venous catheters; *E. aerogenes: Enterococcus aerogenes; E. coli: Enterococcus coli; E. faecalis: Enterococcus faecalis; E. faecium: Enterococcus faecium;* ECMO: Extracorporeal membrane oxygenation; ESBL: Extended spectrum beta-lactamases; GNB: Gram-negative; GPB: Gram-positive; HR: Hazard ration; ICU: Intensive care unit; *K. pneumoniae: Klebsiella pneumoniae;* KPC: *Klebsiella pneumoniae* carbapenemase; MDR: Multidrug resistant; MDRO: Multidrug resistant organism; MRSA: Methicillin resistant *Staphylococcus aureus*; NA: NS: Non significant; OR: Odds ratio; OXA: Oxacillinase; *P. aeruginosa: Pseudomonas aeruginosa; P. mirabilis: Pseudomonas mirabilis; S. aureus: Staphylococcus aureus;* PA: *Pseudomonas aeruginosa; S. epidermidis: Staphylococcus epidermidis*; VAP: Ventilator associated pneumonia; VRE: Vancomycin resistant Enterococci; WHONET: A free Windows-based database software developed by the World Health Organization.

tably, data from a multicenter study in the hospital setting (that included 795,022 central-line days) suggested that CLABSI rates increased by 51.0% during the period of the pandemic (as compared to the pre-pandemic era); analysis suggested that the rate had risen from 0.56 to 0.85 per 1000 line day (P <0.001).[23] In another cohort of 470 Turkish patients with COVID-19, who were admitted to the ICU, the rate of BSI was found to be 50.2 (95% CI: 44.3 to 56.7) per 1000 patient-days. Central venous catheters (CVCs) and the lower respiratory tract were determined to be the sources of BSIs in 42.5% and 38.9% of episodes, respectively.[20] During the early phases of the pandemic, ICUs recorded a 3-fold increase in CLABSI (especially by coagulase-negative Staphylococci [CoNS]) after 7 days of insertion of a central line. However, these rates subsequently declined and the prevalence had normalized by the end of 2021.[24] In this context, CLABSIs were not exclusively caused by GPB, especially in the ICU setting. A recent study, which reported a significant increase in the rate of CLABSIs during the COVID-19 pandemic (as compared to pre-pandemic levels), found GNB to be the most common causative organism (60.2%).[25] An increased length of ICU stay[25] and a high prevalence of contamination of *in situ* CVCs were identified as predisposing factors.[21,26] The need for ECMO treatment was found to be an independent risk factor for the development of BSIs; a longer duration of ECMO and the administration of pre-ECMO respiratory support (P=0.04, OR: 1.06, 95% CI: 1.02 to 1.11) demonstrated a particular association. However, the overall mortality rate (50%) did not differ between the BSI and non-BSI groups.[27] Findings from other studies further suggested a longer duration of ECMO and longer ICU and hospital stay to be independently associated with bacterial co-infections (BSIs and/or respiratory tract infections); however, these factors also demonstrated no impact on overall mortality (P=0.46).[28] A small study compared data from a series of patients who were receiving ECMO for influenza or COVID-19; the mean time from ECMO initiation to BSI detection in the COVID-19 group was 5.5 (IQR: 4.2–8.0) days. Although the duration was comparable with that observed in the group with influenza, the COVID-19 group had a mortality rate of 40%; in contrast, none of the patients died in the influenza group.[29]

The duration of ICU stay for COVID-19 was found to be another important risk factor for BSI, as most episodes were recorded in cases with prolonged (more than 10 days) stay.[14,19,30,31] The estimated cumulative risk of developing at least one episode of BSI was almost 25% after 15 days and possibly exceeded 50% after 30 days.[19] In this context, prolongation of ICU stay had been found to increase the risk of colonization and subsequent infection by GNB in an English cohort.[30]

Emerging data published during the course of progression of the pandemic suggested COVID-19 infection to be an independent risk factor for the development of bacterial and/or fungal co-infections. In this context, a study found that viral reactivation led to an increased risk of BSIs among COVID-19 patients; however, studies did not identify any predisposing factors for SARS-CoV-2 reactivation.[32] In one of the larger studies, which was performed at the University of Alabama in Birmingham and the Ochsner Louisiana State University Health Shreveport, a total of 13,781 patients were hospitalized with COVID-19 between 2020 and 2022; none had community-acquired bacterial co-infections. Compared to the historical control group (n=99,170), patients with COVID-19 demonstrated a significantly higher likelihood of bacterial co-infections and an elevated (≥15) neutrophil-to-lymphocyte ratio.[12] In this context, a retrospective analysis of 88,201 blood cultures (from a cohort of 28,011 patients who were admitted to a multicenter network of hospitals within New York City at the early phase of the pandemic) revealed a significantly higher rate of bacteremia among those who were admitted to the ICU for COVID-19 (than among those with COVID-19 and BSI on admission and without COVID-19) (P <0.001).[33] In a cohort of patients who required ventilation for SARS-CoV-2-related ARDS, the incidence of co-infections reached up to 60% and that for BSIs was found to be 20%.[34] Primary (31%) and catheter-related (25%) BSIs were the most frequent types of co-infection, followed by pneumonia (23%).[35] In a large single-center study that included over 14,000 patients, the hospital-related predictors of BSIs included COVID-19 infection (OR=1.43, 95% CI: 1.21 to 1.69; P <0.001), hospitalization length (OR=1.04, 95% CI: 1.03 to 1.04; P <0.001), ICU admission (OR: 1.38, 95% CI: 1.19 to 1.60; P <0.001), malignancies (OR=1.48, 95% CI: 1.34 to 1.65; P <0.001), and kidney failure (OR=1.81, 95% CI: 1.61 to 2.04; P <0.001).[31] The issue of extended and unnecessary use of antimicrobials has been discussed later.

Pathogens and AMR

Secondary infections were a frequent complication in patients with COVID-19 who required ICU admission (up to 50% depending on study parameters) and had significant impact on mortality.[8,9,36] During the early phases of the pandemic, the GPB responsible for BSIs included *Staphylococcus aureus* (mostly methicillin-susceptible [MSSA]), CoNS, and *Enterococci*; the GNB mostly included *Enterobacterales*.[36] The predominance of different pathogens depended on the source of infection and varied among centers, countries, and continents. In a single-ICU study performed during the pandemic, BSIs were mostly found to be caused by *Enterococcus faecalis* and *Candida* spp., whereas ventilator-associated pneumonia was primarily caused by *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. BSIs could either be community or hospital acquired. Less than 9% of co-infections in patients with COVID-19 were community acquired; in contrast, hospital-acquired BSIs were common and accounted for more than 30% of cases.[5,8]

Bacterial BSIs

During the early phases of the COVID-19 pandemic, BSIs were observed in patients with prolonged ICU stay (median 21 days) and were associated with high mortality (47%).[37] Data from the Eurobact II study, which included more than 547 patients, showed that GNB, GPB, and fungi accounted for 67.1%, 21.5%, and 11.2% of BSI isolates, respectively.[38] At the time of admission to the ICU, corticosteroid use, central line placement, and ECMO treatment were associated with the development of BSIs and with a subsequent increase in 30-day mortality.[27,39] The available data regarding previous colonization, particularly by *Acinetobacter baumannii*, are conflicting. In their study, Frattari et al.[40] found no correlation between the development of BSIs and prior colonization. However, in their multicenter ICU cohort study, Montrucchio et al.[41] found that colonization during prolonged ICU stay led to the development of infec-

tions. In critically ill patients who demonstrated colonization by carbapenem-resistant *A. baumannii* (CRAB) during the COVID-19 pandemic, serious infections, multisite colonization, and the need for mechanical ventilation were identified as risk factors for the development of BSI.[42]

High heterogeneity was observed in the resistance patterns described among different studies; this could be attributed to the pre-existing endemicity of MDRO in many countries.[43] The highest increase was observed for AmpC-producing bacteria (relative risk=11.1, 95% CI: 2.6 to 47.9) and non-fermenting rods (relative risk=7.0, 95% CI: 1.5 to 31.4).[37] In particular, the rates of *Acinetobacter* spp. and *Enterococcus* spp. infections were significantly higher compared to those in the pre-endemic era. In this context, the European Antimicrobial Resistance Surveillance Network showed a considerable increase in *Acinetobacter* spp. infections (by 57%). BSIs were more common in the European Union and the European Economic Area in the first year of the COVID-19 pandemic (2020–2021) than in the pre-COVID-19 era (2018–2019).[43] *A. baumannii* infections emerged as a major concern in the ICU; this was not only related to the high incidence but also to the extensive drug-resistance patterns observed in most countries.[20,39,43,44] In an Italian study, the prevalence of hospital-acquired BSIs for *Acinetobacter* spp. (0.16 × 100 patient-days) and *S. aureus* (0.24 × 100 patient-days) had peaked between the first and the second waves of the pandemic.[31] Similarly, a Turkish study found *A. baumannii* (40%) and carbapenem-resistant *Klebsiella pneumoniae* (21%) to be the most common pathogens followed by *Enterococcus* spp. (12%) and *S. aureus* (7.1%).[20] In a cohort of Greek patients with COVID-19, extensively drug-resistant *A. baumannii* and carbapenem-resistant *K. pneumoniae* comprised the majority of GNB responsible for BSIs; this was in agreement with previously reported data.[45]

A report from the European network suggested that the prevalence of carbapenem-resistant GNB rose from 59% in 2017 to 75% in 2021 (during the COVID-19 pandemic); this was mostly observed in the ICU setting (increase by 144%, P <0.001).[42] In this context, CRAB infections are a major concern in the ICU, as the available treatment options are considerably limited. A study from Croatia that included 176 ICU patients found *A. baumannii* to be the most common etiological organism (40.3%) for BSIs, accounting for 25/1000 patient-days at risk; notably, 100% cases were carbapenem resistant. Pulsed-field gel electrophoresis revealed a homogeneous genetic background of clinical isolates, with a clonal spread of OXA-23-positive MDRO among blood isolates in the ICU.[46] In a study from Greece that included a mixed cohort of non-ICU and ICU patients with COVID-19, MDROs were detected in the majority of cases of BSIs (with an attributable mortality of 88%). Overall, 100% of the *Acinetobacter* spp. strains were carbapenem-resistant and 43/45 of the *Klebsiella* spp. strains and half of the *P. aeruginosa* strains produced carbapenemases, reflecting the pre-existing endemicity of MDRO in this setting.[47] Another Greek study that included a cohort of only non-ICU patients during the same period found 100% of the *A. baumannii* strains to be resistant to carbapenems, in both COVID-19 and non-COVID-19 patients.[48] In a study from Turkey, carbapenem resistance was detected in 90.4% of *Acinetobacter* spp., 53.1% of *Klebsiella* spp., and 48.8% of *Pseudomonas* spp.[38] Carbapenem resistance was independently and significantly associated with mortality (adjusted HR=2.46, 95% CI: 1.58 to 3.84).[38] In a study from Western India that included 750 patients with COVID-19, 8.5% of the cases of BSI were caused by *A. baumannii* (which was the commonest isolate and was found in 32.8% of cases); this was followed by *K. pneumoniae*, which was found in 21.9% cases. The overall incidence of MDRO infections in this cohort was 57.8%%.[49]

Analysis of data from a large number of blood isolates from the WHONET-Greece network demonstrated significant differences between the slope for non-susceptibility trends of *A. baumannii* blood and respiratory isolates to amikacin, tigecycline, and colistin; *K. pneumoniae* blood and respiratory isolates to meropenem and tigecycline; *P. aeruginosa* respiratory isolates to imipenem, meropenem, and levofloxacin.[47] Increasing rates of resistance were detected early in the pandemic in other countries that did not have a previous history of high carbapenem resistance; as demonstrated by a study from the United States (New York), this was particularly relevant for *A. baumannii*.[50] Studies that reported resistance patterns among ICU infections caused by CRAB or CR *Enterobacterales* all demonstrated remarkably high mortality, especially at the COVID-19 era.[51] The issue of CRAB endemicity further hampered adequate antimicrobial selection and represented a major challenge for infection control teams worldwide.

Among the GPB associated with BSIs, *Enterococcus* spp. was identified as the predominant causative pathogen in COVID-19 patients, in both ICU and non-ICU settings. Data obtained from an Italian ICU between February 21 and March 30, 2020, suggested that the prevalence of *Enterococcus* spp. had increased in blood cultures during the initial phases of the pandemic.[51] The cumulative incidence of ICU-acquired enterococcal BSI was found to be 229 (172–298) episodes per 1000 ICU admissions.[19] Resistance patterns were also found in GPB-related BSIs. *Enterococci* demonstrated up to 80% resistance to ampicillin, and the prevalence of vancomycin-resistant *Enterococci* had also increased.[19,48,49] These cohorts demonstrated no resistance to either tigecycline or linezolid. In this context, the gut maybe the source of BSIs caused by MDR *Enterococci*; the resistance patterns probably reflect alterations in the microbiota that result from an unnecessary consumption of antibiotics.

S. aureus bacteremia was less frequent than expected in most series. A study that exclusively evaluated *S. aureus*-related BSI episodes in patients who were hospitalized with COVID-19 demonstrated hospital-onset bacteremia (≥4 days from the date of admission) and age to be significant predictors of high (up to 66%) 14-day hospital mortality.[52] Hospital-acquired BSIs were more likely to be caused by methicillin-resistant *S. aureus*; however, MSSA predominated in cases of community-acquired BSI.[36] In this context, a study found that the slopes for non-susceptibility trends of *S. aureus* isolates to oxacillin and *E. faecium* isolates to glycopeptides differed significantly from those of the pre-pandemic era.[50] CoNS isolates were detected more frequently in blood cultures, especially in the early phases of the COVID-19 pandemic, and were often associated with CLABSI. Notably, the incidence of CoNS-related CLABSIs increased by 130% (P <0.001) and accounted for 0.07–0.17 events per 1000 line days.[23] The CoNS isolates were considered as contaminants in the absence of clinical relevance. A high prevalence of blood culture contamination was reported during the COVID-19 pandemic; this mainly reflected the lack of hand hygiene and

non-adherence to infection control precautions.[23,53] Miscellaneous pathogens such as *Burkholderia cepacia, Elizabethkingia meningoseptica*, and *Achromobacter xylosoxidans* were also found in patients with BSIs who were hospitalized for COVID-19. These were probably derived from the water supply and bottles of normal saline, which represented a common environmental source in the health care setting.[1] Notably, all studies highlighted the urgent need for implementation of effective infection-control policies and antimicrobial stewardship programs.[54]

Fungal BSIs

Fungemia has always been a major issue in critically ill patients. As seen from population-based surveillance data (collected between April and August 2020 by the Emerging Infections Program of the Centers for Disease Control and Prevention), the predisposing factors differed between patients with and without COVID-19. Liver disease, solid-organ malignancies, and a history of prior surgical intervention were thrice as more common in non-COVID-19 patients with fungal infections; conversely, patients with COVID-19 were 1.3-fold more likely to have a history of ICU care, need for mechanical ventilation, presence of a CVC, and receipt of corticosteroids and immunosuppressants.[55–56] All-cause in-hospital mortality was found to be twice as higher among patients with COVID-19 (62.5%) than in those without (32.1%).[56] Another study that included patients from four ICUs in Italy between 2019 and 2021 showed that among the 53 critically ill patients with candidemia,18 (34%) also had COVID-19; cardiovascular disease was the most prevalent (42%) and was followed by neurological disease (17%), chronic pulmonary disease, chronic kidney failure, and solid tumors (13% each).[57] Patients with COVID-19 who received corticosteroid therapy during hospitalization were at an increased risk of fungal infections. In cases with at least one comorbidity and prolonged length of ICU stay, both factors were associated with higher rates of mortality.[47,57,58] In this context, a large cohort study from Turkey that included 1305 ICU patients with COVID-19 found the presence of a CVC (OR=19.07, 95% CI: 8.12 to 44.8, P <0.0001), multifocal colonization (OR=2.28, 95% CI: 1.39 to 3.72, P=0.001), length of ICU stay ≥14 days (OR=3.62, 95% CI: 2.42 to 5.44, P <0.0001), and corticosteroid administration (OR=0.51, 95% CI: 0.34 to 0.76, P=0.001) to be the only statistically significant independent risk factors for fungal BSIs.[59]

In patients who had fungemia in the ICU setting, those with and without COVID-19 demonstrated different sites of primary infection. In patients who had candidemia, a significantly higher proportion of those with COVID-19 had pneumonia, ARDS, septic shock, and had required ECMO. *Candida parapsilosis* was the most frequent isolated species and was often found after a previous BSI episode.[45] Notably, the incidence of fungal BSIs increased significantly during the COVID-19 pandemic (P=0.02). The prevalence of *Candida* spp. infections rose by 56.9% (P=0.01) compared to that in the pre-pandemic era and accounted for 0.14–0.21 cases per 1000 line days.[23] ICU admission, mechanical ventilation, parenteral nutrition, and corticosteroid administration were all more common in patients with candidemia who were hospitalized for COVID-19.[60] The FiCoV study, which was a large multicenter study from Italy, demonstrated that *Candida* BSIs were more prevalent among critically ill patients with COVID-19 and were associated with a high fatality rate. The mortality rate was further increased by the spread of azole-resistant *C. parapsilosis*, which was the most frequent isolate (72%) and was followed by *C. albicans* (35.2%).[57,61]

Epidemiology (COVID-19 *vs.* non-COVID-19 Patients)

Several studies were designed to identify potential factors that could predict differences in outcomes between ICU patients with and without COVID-19. The main findings of recently published case–control studies have been summarized here. All studies identified COVID-19 as an independent predisposing factor for secondary BSIs. Lepape et al.[13] analyzed the data from 30,105 patients who were divided into three groups, namely, the 2020 non-COVID-19 (n=23,798), 2020 COVID-19 (n=4465), and 2019 control (n=39,635) groups. The 2020 COVID-19 group demonstrated the highest BSI/1000 days (6.4% [6.4%–6.4%] *vs*. 3.9% [3.8%–3.9%] in the 2020 non-COVID-19 group); both groups had similar microbial epidemiology. However, COVID-19 group had fewer *S. aureus* and more resistant *Enterobacterales* infections compared to controls. The data revealed no differences in terms of age, receipt of immunosuppressive treatment, or neutropenia; however, transfer from nursing homes, need for IMV, prolonged hospitalization, high Simplified Acute Physiology Score values, and use of CVCs were more frequent in the ICU COVID-19 group.[13] Pasquini et al.[62] reported similar findings from their cohort of 26,012 patients, 1182 of whom had COVID-19. In patients with COVID-19, BSIs were diagnosed in 107 cases; the incidence rate of 8.19 episodes per 1000 patient-days was significantly higher compared to that of non-COVID-19 patients (2.72/1000 patient-days) and patients admitted to the ICU during 2019 (2.76/1000 patient-days). BSI onset was found to be delayed during COVID-19 (16 days *vs*. 5 days). Notably, the 30-day mortality had nearly doubled (40.2%) among patients with COVID-19 compared to their non-COVID-19 counterparts (23.7%).[62]

In patients with COVID-19, BSIs were frequently caused by MDRO and were often center-dependent.[62] A retrospective evaluation of data from patients who were consecutively hospitalized across 271 United States health care facilities between June 1, 2019, and September 4, 2021, revealed that among 5,239,692 admissions, 20,113 and 39,740 were related to community-onset BSIs that occurred before and during the pandemic, respectively (P ≤0.006).[63] Patients with both COVID-19 and community-acquired BSI demonstrated a high probability of ICU hospitalization and prolonged length of hospital stay. Hospital-acquired BSIs occurred more frequently during rather than before the COVID-19 pandemic (P <0.001); the rates were as high as 7.3/1000 admissions and were associated with a significant mortality burden.[63]

In COVID-19 patients who were admitted to the ICU, the initial co-infection rate did not surpass 10%; however, at the end of ICU hospitalization, almost 50% of patients were diagnosed with secondary bacterial or fungal infections. In this context, a large multicenter cohort study compared three groups of patients, namely, patients with COVID-19, a previous cohort of influenza patients, and patients without viral pneumonia who were admitted to the ICU for other medical or surgical reasons; the findings showed the prevalence of BSI to be the

highest among patients with COVID-19 (15.1%). The rate was higher compared to that of the non-viral pneumonia group (7%) and influenza group and was not related to the distribution of pathogens. In this context, *S. aureus*, and mostly MSSA, were predominant during the first 48 h; *Enterobacterales* represented the primary organisms after this period and demonstrated low resistance rates.[64] More robust data were retrieved by the Eurobact II study, a prospective observational multicontinental cohort study, which evaluated health-care associated BSIs (HA-BSIs) treated in the ICU; it included data from 53 centers from 19 countries across 5 continents.[65] In this study, the epidemiology of pathogens differed based on the source of bacteremia. Overall, 829 patients (median age: 65 years [IQR: 55, 74]), of whom 538 (64.9%) were male, were treated for HA-BSIs. Respiratory sources of infection and primary HA-BSIs were more frequently reported in COVID-19 patients than in controls (40.1% *vs*. 26.0%, P <0.001 and 25.4% *vs*. 17.2%, P=0.006, respectively). HA-BSIs were more common in patients with COVID-19 than in those without (18.8% *vs*. 13.6%) and were caused by *Enterococcus* spp. (20.5% *vs*. 9%) and *Acinetobacter* spp. The former demonstrated an increased HR for mortality (1.91, 95% CI: 1.49 to 2.45).[65]

A single center study from Italy included 404 critically ill COVID-19 patients who were admitted to the ICU. A total of 284 (61%) patients from this cohort developed at least one episode of BSI, with an overall crude incidence of 87 events every 1000 patient-days (95% CI: 77 to 98).[66] The BSI rate did not change significantly between the four consecutive phases of the epidemic (P=0.357); however, a trend for fewer episodes of enterococcal bacteremia was observed during the latter waves of the pandemic (P=0.004). Nevertheless, it remained responsible for a third of all BSI episodes.[66] Another single center study compared the incidence of BSIs between the pre-COVID-19 and COVID-19 period in Italy.[67] It found that among the 63 BSI episodes recorded, patients without COVID-19 had a higher incidence of infections with MDR GNB (mostly *K. pneumoniae*); conversely, those with COVID-19 demonstrated a higher incidence of *A. baumannii* infections. These findings were in agreement with those from another study.[48] Patients with COVID-19 were more likely to be in a critical condition at BSI onset, have a shorter duration of hospitalization from BSI onset to death, and have higher 30-day mortality.[67]

A large single center observational study from Italy included more than 14,000 patients from the pre-COVID-19 and COVID-19 periods; the cohort was divided into COVID-19 positive and negative groups and included patients admitted to the hospital and ICU. The findings demonstrated that patients who tested positive for COVID-19 had a significantly higher incidence of HA-BSI (P <0.001) and higher rates of ICU admission and death (P <0.001).[31] In this context, a Brazilian study showed a significant increase in the incidence of CLABSI during the initial phase of the pandemic compared to the pre-pandemic era (median 1.60 [IQR: 0.44–4.20] *vs*. 2.81 [IQR: 1.35–6.89], P=0.002); in particular, these infections were caused by *Candida* spp. and *Enterococcus* spp.[68] A study had compared data pertaining to BSI in patients with COVID-19 with those of historical controls with either influenza A or B. After correcting for the high rate of contamination, the incidence of clinically relevant bacteremia in the COVID-19 group was found to be 1.0% (95% CI: 0.3 to 1.8); this was significantly lower (P=0.04) than the rate observed in the influenza group.[69] The findings suggest that critically ill patients with influenza may also develop BSIs.[69]

Notably, a study demonstrated a 5-fold increase in the incidence of candidemia during the pandemic, compared to the 2014–2019 period; this was mostly related to indwelling central lines and prolonged ICU stay.[58] The emergence of BSI in the ICU may be partly explained by transcriptional evidence of persistent immune dysfunction, which was associated with 28-day mortality owing to SARS-CoV-2.[32] However, relevant data are lacking.

Antimicrobial Stewardship and Infection-Control Policies

Studies performed in different settings worldwide indicate that antibiotic overuse and abuse during the COVID-19 pandemic had led to the spread of resistant microbial strains. Data from the European Union and European Economic Area network showed an increase in the prevalence of *E. faecalis, A. baumannii*, and *C. albicans*; in particular, the resistant strains that were difficult to treat were found in countries with high pre-pandemic rates of AMR.[43] Health-care-associated infections, and especially CLABSI and candidemia, had significantly increased in Europe and the USA during the COVID-19 pandemic.[10,60,70,71] The Centers for Disease Control and Prevention reported an increase in hospital infections including CRAB (78%), carbapenem-resistant *Enterobacterales* (35%), extended-spectrum beta-lactamase-producing *Enterobacterales* (32%), vancomycin-resistant *Enterococci* (14%), and methicillin-resistant *S. aureus* (13%).[70] CLABSIs were more frequent in hospitals with >10% hospitalizations for COVID-19 than in those with a low incidence of COVID-19.[23] The increase in AMR paralleled the increase in antibiotic prescriptions during the pandemic, both in the hospital and community.[72] Data analysis showed that antimicrobial consumption increased by 3.5% per week (P=0.016) for 6 weeks after the first lockdown; this was followed by a sustained weekly reduction of 6.4% (P=0.001). Approximately 33% of patients with COVID-19 had received unnecessary empirical antimicrobial treatment.[73] Resistance was associated with geographical area (P=0.002) and the early use of systemic steroids (P=0.018).[74] The duration of antibiotic administration was significantly longer during rather than before the COVID-19 period (mean [range]: 222 [145–309] min *vs*. 139 [102–179] min, P=0.002); this may have further compromised outcomes of critically ill patients with severe pneumonia who required IMV and ICU care.[75] Antimicrobial stewardship programs, wherever available, showed remarkable results in terms of reduction of AMR. This was particularly relevant in the ICU setting, where BSIs (especially those caused by MDRO) had led to a significant increase in mortality. Findings from a Spanish ICU showed that a 96% reduction in antimicrobial consumption was achieved in an attempt to reduce AMR; this included a reduction in unjustified combination therapies by 60% (with a shift toward monotherapy) and had no adverse impact on patient outcomes.[76,77] This suggests that in addition to a quantitative approach, qualitative approaches need to be adopted for antimicrobial prescription; it is also essential to restrict unnecessary antimicrobial consumption.[54]

The lessons learned from the first wave of the COVID-19 pandemic may be summarized in the following key points: (1) avoid starting antimicrobials empirically, unless the patient has a sus-

pected co-infection (that is confirmed by biomarkers such as procalcitonin), (2) select monotherapy instead of combinations (as atypical pathogens did not cause infections in the ICUs, and the use of azithromycin did not show any benefit on COVID-19 outcomes); in cases where the use of combinations is necessary, the duration should not exceed 5 days and de-escalation should be encouraged, when possible,[78] and (3) perform blood and urine sampling for cultures before administration of any antimicrobial therapy; in this context, the use of biomarkers such as procalcitonin may safely shorten the length of antimicrobial treatment in cases of bacterial co-infection.[79] The implementation of antimicrobial stewardship programs was found to be safe and did not negatively influence the rates of co-infections or mortality.[76] The only factor that was proven to be associated with increased mortality was a high Sequential Organ Failure Assessment score at the time of admission to the ICU.[14,76]

Adherence to infection-control policies appears to have weakened during the COVID-19 pandemic; this led to the spread of nosocomial infections and a higher incidence of MDRO infections. Studies from Europe and Asia highlighted a lack of strict compliance with hand hygiene during the early phase of the pandemic.[21,80] Colonization by MDRO had become more common among ICU patients during the COVID-19 pandemic; phylogenetic analysis of clinical isolates showed clustering within the same center, clearly indicating the presence of horizontal transmission.[81] Exhaustion among health care personnel while working in the extraordinary conditions of the pandemic is a factor that needs to be considered in this context. This may have affected adherence to guidelines for the prevention of hospital infections. Notably, a study on HA-BSIs demonstrated an increase in the non-adherence from 10% to 15% in the pre-pandemic era to 22.8% during the first wave of the pandemic.[44] A significant increase in nosocomial infections was observed in low- and middle-income countries during the first 5 months of the pandemic due to the rapid increase in patient numbers in the setting of restricted resources. Infection-control programs should, therefore, prioritize countries at higher risk.[82] The European Society of Clinical Microbiology and Infectious Diseases has published relevant guidelines in this regard.[83] The incidence of nosocomial infections in the ICU decreased significantly in settings where consistent control measures were applied. For instance, a large study from China that included data from more than 2,000,000 hospitalized patients demonstrated a decline in the rate of CLABSIs from 9.4 to 2.2/1000 catheter days (P <0.001); the numbers were even lower than those in the pre-pandemic era.[84] The implementation of stringent policies and the continuous evaluation for improvement of compliance among health care workers (HCWs) (in regard to hand hygiene and routine medical and nursing procedures) are recommended to prevent the horizontal spread of nosocomial-acquired infections.[54] In this context, a recent meta-analysis showed that CRAB and *C. auris*, both long known to colonize surfaces in the hospital environment, were most frequently responsible for MDRO outbreaks in the ICU during the COVID-19 pandemic.[85] Non-adherence to personal protective equipment use, scarcity of equipment, lack of compliance with hand hygiene, and high antibiotic consumption were identified as the main factors associated with MDRO outbreaks in the ICU during the COVID-19 pandemic.[85] Environmental contamination, a prolonged state of critical illness, invasive procedures, lack of HCW education, overcrowding, and staff burnout contributed to an increased risk of outbreaks by MDRO.[85] Disruptions to AMR surveillance programs and low HCW/patient ratios in many countries further promoted the expansion of MDRO outbreaks.[85] Special practices for the care of ICU patients with COVID-19 (e.g., the need for 4–5 HCWs to periodically place a patient in the prone position) are believed to be associated with the increase in colonization by MDROs and thus, the related outbreaks.[86] The lessons learnt from the MDRO outbreaks during the COVID-19 pandemic suggest that a strong set of measures, adapted to the conditions of the pandemic, may maximize the effect of infection control.

Conclusions

The impact of bacterial and fungal BSIs in ICU patients with COVID-19 needs to be highlighted and warrants investigation. In this review, high heterogeneity was observed among the published studies. Evidence was obtained from case series and comparative analyses that included different sample sizes, target populations, cohorts (single *vs*. multiple centers), and study periods (before, during the first wave of the pandemic, and throughout the four waves); they also included mixed populations (ICU and non-ICU patients). Data pertaining to vaccination (as a variable in multilogistic models of mortality risk factors) are conspicuously lacking from most studies on co-infections. In ICU patients with COVID-19, BSIs are mostly hospital acquired and are caused by GNB, especially, *A. baumannii, K. pneumoniae*, and *P. aeruginosa*. However, GPB (mainly *Enterococci*) and fungi (mainly *C. parapsilosis*) are also responsible in many cases. In particular, MDRO prevalence in countries with high pre-existing AMR rates is an emerging issue. It is strongly associated with the failure to adhere to infection-control measures, understaffing, HCW burnout, and lack of HCW education; it is also associated with the unnecessary administration of broad-spectrum antibiotics. The length of hospital/ICU stay, presence of comorbidities, the seventh decade of life, male gender, administration of IMV, prolonged use of central lines, and bacterial colonization are associated with a surge in BSIs in the ICU setting, and they lead to increased mortality among patients with COVID-19. The implementation of infection-control bundles aimed at preventing the horizontal transmission of MDROs and antimicrobial stewardship programs are necessary and have already been proven to be efficacious in reducing the burden of BSIs and subsequent mortality rates in critically ill patients with COVID-19. In this context, real-world data and feedback (based on transforming attitudes in relevant personnel) suggest that the implementation of antimicrobial stewardship and simple and cost-effective measures have had considerable impact on antibiotic consumption (in terms of quantitative and qualitative improvements). However, the benefits obtained in terms of the decline in AMR rates, especially in countries and settings with high MDRO endemicity, warrant further investigation. In addition, policies need to be implemented to ensure the long-standing and persistent prevention and control of infection.

Author Contributions

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oti: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Acknowledgments

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2023.12.004.

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