



# Antimicrobial use and aetiology of bloodstream infections in critically ill patients during early stages of SARS-CoV-2 pandemic

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## SUMMARY

**Background:** During early stages of COVID-19 pandemic, antimicrobials were commonly prescribed.

**Aim:** To describe clinical, microbiological and antimicrobial use changes in bloodstream infections (BSI) of ICU patients during the first wave of COVID-19 pandemic compared to pre-COVID-19 era.

**Methods:** Observational cohort study of patients admitted to ICU of Bellvitge University Hospital was conducted during the COVID-19 pandemic (March-June 2020) and before COVID-19 pandemic (March-June 2019). Differences in clinical characteristics, antimicrobial consumption and incidence and aetiology of BSI were measured.

**Findings:** COVID-19 patients had significantly less comorbidities with obesity the only risk factor that increased in frequency. COVID-19 patients more frequently required invasive supportive care measures, had longer median ICU stay and higher mortality rates. The incidence of BSIs was higher in COVID-19 period (RR 3.2 [95%CI 2.2–4.7]), occurred in patients who showed prolonged median ICU stay (21days) and was associated with high mortality rate (47%). The highest increases in the aetiological agents were observed for AmpC-producing bacteria (RR 11.1 [95%CI 2.6–47.9]) and non-fermenting rods (RR 7.0 [95%CI 1.5–31.4]). The emergence of bacteraemia caused by Gram-negative rods resistant to amoxicillin-clavulanate, which was used as empirical therapy during early stages of the pandemic, led to an escalation towards broader-spectrum antimicrobials such as meropenem and colistin which was also associated with the emergence of resistant isolates.

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**Conclusions:** The epidemiological shift towards resistant phenotypes in critically ill COVID-19 patients was associated with the selective use of antimicrobials. Our study provides evidence of the impact of empirical therapy on the selection of bacteria and their consequences on BSI over the subsequent months.

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## Introduction

COVID-19 pandemic remains a serious health threat worldwide. In Spain, SARS-CoV-2 virus was detected for the first time at the end of January 2020. From that time onwards there was an exponential increase in the number of cases to 248,960 cases and 28,346 deaths at the end of June 2020 [1,2]. Despite most infected patients being asymptomatic or having a mild clinical course, some may develop critical illness characterised by severe lung dysfunction, septic shock and/or extrapulmonary organ failure with high mortality rates (30–70%) [3,4].

While admission to the ICU is necessary for patients requiring life support, this also poses them at risk of acquiring nosocomial infections such as bloodstream infections (BSIs). Thus, management of nosocomial complications associated with COVID-19 in ICU patients may require the use of broad-spectrum antimicrobials. Furthermore, during the initial stages of COVID-19 pandemic, antimicrobials were commonly prescribed as empirical treatment in moderate or severe COVID-19 infections [5]. Empirical therapy was based on the management of other viral respiratory tract infections such as Influenza virus, where bacterial co-infections caused by *Staphylococcus aureus* or *Streptococcus pneumoniae* are frequently reported [6–8]. However, the incidence of concomitant bacterial infections in patients with COVID-19 appear to be lower than those reported for Influenza virus [9–12]. In this regard, the WHO guide for Clinical Management of COVID-19 recommends empirical antimicrobial therapy in severe disease with clinical suspicion of bacterial infection, where treatment should be based on clinical judgment, patient's host factors and local epidemiology [13].

The objectives of this study were to compare the patterns of antimicrobial use and the clinical and microbiological characteristics of BSI in ICU patients admitted to a Spanish tertiary referral hospital during pre-COVID-19 and COVID-19 periods.

## Material and methods

### Study design and clinical data

Bellvitge University Hospital (HUB) is a tertiary care centre with 700 beds and three mixed (medical-surgical) ICUs that account for 34 beds. As of March 2020, these units were converted to exclusively treat COVID-19 patients. Also, due to the high number of patients admitted (three times higher than the usual activity of the ICUs), other hospital units were converted to provide intensive care to COVID-19 and non-COVID-19 patients. We conducted an observational cohort study of all patients admitted to the three original ICUs during the first stages of COVID-19 pandemic (COVID-19 group, March to June 2020) and before COVID-19 pandemic (pre-COVID-19 group, March to June 2019). All COVID-19 patients had the SARS-CoV-2

diagnosis confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR). Clinical data were collected retrospectively. Data included age, gender, SOFA (Sequential Organ Failure Assessment) score at ICU admission, comorbidities and length and outcome of ICU stay. Only patients who stayed in ICU for more than 48 hours were considered for the analysis.

### Microbiological methods

To assess the impact of antimicrobial therapy on invasive infections, episodes of BSI during ICU stay were analysed. Data on respiratory bacterial isolation was also collected as a representative of the samples that could indicate patient's colonization. Microbiological data were collected from the laboratory information system. Respiratory tract samples (RTS) included good quality sputum or tracheal aspirate, bronchial aspirate and bronchoalveolar lavage. Bloodstream infections (BSI) were defined as growth of bacteria or fungus from one or more blood cultures (BCs). True bacteraemia caused by common skin colonisers were considered in patients with clinical signs of infection and two or more positive BCs drawn from different venepuncture sites. Only one episode per microorganism, sample type and patient were included. Incidence data are reported as episodes per 100 patients.

RTS and BCs were processed using conventional procedures. All isolates were routinely identified by MALDI-TOF® MS (Bruker Daltonik) and tested for antimicrobial susceptibility by microdilution (Microscan®, Beckman Coulter) following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations and criteria [14].

For analysis purposes, BSI-related microorganisms were classified as follows: 1) Enterobacterales Group 1–2 2) Enterobacterales Group 3; 3) Non-fermenting Gram-negative rods 4) *Staphylococcus aureus*/*Enterococcus* spp. 5) Coagulase-negative staphylococci (CoNS) and 6) *Candida* spp. Enterobacterales classification was made according to their wild-type phenotypic pattern of drug susceptibility (Group 1: *Escherichia coli*, *Proteus mirabilis*; Group 2: *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Citrobacter koseri* and *Citrobacter amalonaticus*; Group 3: *Enterobacter* spp., *Klebsiella aerogenes*, *Citrobacter freundii*, *Serratia marcescens*, *Morganella morganii*, *Providencia* spp., *Proteus vulgaris* and *Proteus penneri* [AmpC-producing bacteria]). Due to their common susceptibility to amoxicillin-clavulanate, groups 1 and 2 were analysed together.

Microorganisms isolated from RTS were divided in five categories: 1) Potentially pathogenic respiratory tract bacteria (RTB) including *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* 2) Enterobacterales Group 1–2; 3) Enterobacterales Group 3 4) Non-fermenting rods and 5) *Staphylococcus aureus*/*Enterococcus* spp.

## Antimicrobial consumption

Monthly antimicrobial consumption was calculated using defined daily dose (DDD) per 100 patient-days of bed occupancy as defined elsewhere [15]. Data were obtained from the hospital electronic dispensing system. Antimicrobials were grouped according to their spectrum of activity: Broad-spectrum antimicrobials (piperacillin-tazobactam, cefepime, imipenem, meropenem and ertapenem), antimicrobials against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecium* (teicoplanin, daptomycin, linezolid), and systemic antifungals (azoles, echinocandins).

## Statistical analysis

Differences between pre-COVID-19 and COVID-19 periods were assessed through SPSS® software package (SPSS, version 23) using T-test or Mann-Whitney U test for continuous variables and Chi-square or Fisher's exact test for categorical variables, when appropriate. Differences in the incidence between periods were assessed by risk ratio (RR) and 95% confidence intervals were calculated. Statistical significance was set at  $P < 0.05$  (two-sided).

## Results

### Clinical characteristics

During the study period, 424 (pre-COVID-19) and 263 patients (COVID-19) were admitted to ICU. Among them, 306 (72%) and 220 (84%) stayed in ICU for more than 48 hours and were selected for the analysis. Demographics and clinical data by group are shown in Table I. Both groups were similar regarding age and SOFA score at ICU admission. COVID-19 patients were more frequently males, had less comorbidities and had a significantly higher prevalence of obesity (13% vs 25%). A higher proportion of COVID-19 patients required mechanical ventilation (MV) (77% vs 87%), extracorporeal membrane oxygenation (ECMO) (2% vs 10%) and renal replacement therapy (12% vs 18%). Patients in COVID-19 group also showed longer median ICU stay (7 vs 10 days) and longer duration of mechanical ventilation (3 vs 12 days). ICU-mortality rate was also significantly higher for the COVID-19 group (21% vs 31%). When comparing patients who developed BSI during ICU stay, baseline characteristics were similar (Supplementary Table S1). Obesity and MV requirement remained in a significantly higher proportion in the COVID-19 group (13% vs 30% and 77% vs 98%, respectively).

### Microbiological analysis

The monthly distribution of pathogens and their incidence by period are shown in Figure 1 and Table II, respectively. An overall increase in the incidence of BSI was detected in COVID-19 period (RR 3.2 [95% CI 2.2–4.7]). This was mostly related to an increase of pathogens belonging to Enterobacterales Group 3 (RR 11.1 [95%CI 2.6–47.9]), non-fermenting rods (RR 7.0 [95% CI 1.5–31.4]) and CoNS (RR 4.5 [95%CI 2.1–9.8]). There were not statistically significant differences in the number of RTS isolates between periods, but the incidence of pathogens of the RTB (RR 0.5 [95% CI 0.2–1.1]) and the *S. aureus*/

**Table I**

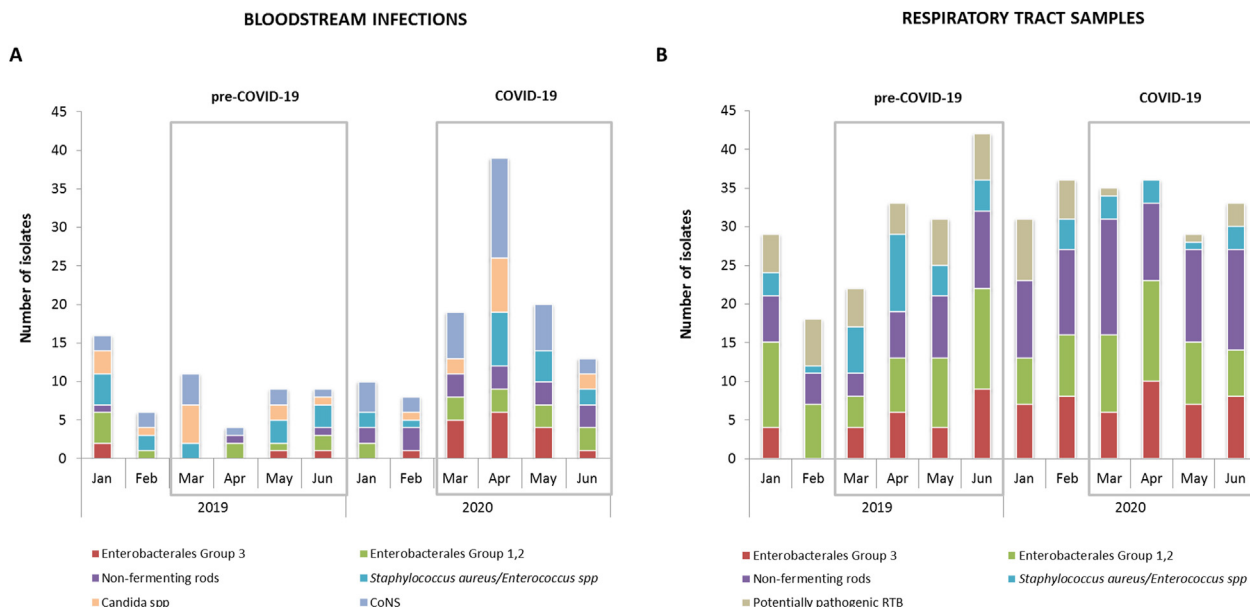
Clinical characteristics of patients admitted to ICU by period. Significant differences between periods are highlighted in bold

	Pre-COVID-19 group (n = 306)	COVID-19 group (n = 220)	<i>P</i> -value
Characteristics			
Age	66 (56–74)	64 (55–72)	0.208
Male sex	205 (67%)	169 (77%)	<b>0.014</b>
SOFA	7 (5–9)	6 (5–9)	0.177
Comorbidities			
None	19 (6%)	35 (16%)	<b>&lt;0.001</b>
Two or more	205 (67%)	112 (51%)	<b>&lt;0.001</b>
Hypertension	178 (58%)	124 (56%)	0.679
Diabetes mellitus	85 (28%)	60 (27%)	0.898
Obesity <sup>a</sup>	39 (13%)	55 (25%)	<b>&lt;0.001</b>
Active Smoker	81 (26%)	28 (13%)	<b>&lt;0.001</b>
Cardiovascular disease	150 (49%)	87 (40%)	<b>0.031</b>
COPD	41 (13%)	12 (5%)	<b>0.001</b>
Chronic kidney disease	62 (20%)	30 (14%)	<b>0.049</b>
Transplant	10 (3%)	11 (5%)	0.317
Malignancies	65 (21%)	28 (13%)	<b>0.012</b>
During ICU stay			
Vasopressor therapy	222 (73%)	163 (74%)	0.694
Renal replacement therapy	37 (12%)	40 (18%)	0.051
Bloodstream Infection	31 (10%)	57 (26%)	<b>&lt;0.001</b>
ECMO	5 (2%)	22 (10%)	<b>&lt;0.001</b>
Mechanical ventilation (MV)	236 (77%)	191 (87%)	<b>0.005</b>
Duration of MV (days)	3 (1–11)	12 (6–29)	<b>&lt;0.001</b>
Length of ICU stay (days)	7 (4–14)	10 (5–20)	<b>&lt;0.001</b>
UCI discharge			
Death	63 (21%)	68 (31%)	<b>0.007</b>

Data are median (Interquartile range) or n (%).

<sup>a</sup> Obesity was defined according to the body mass index (BMI) categories which based on WHO classification. Obesity is considered by a BMI of  $>30$  kg/m<sup>2</sup>. (WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Geneva: World Health Organization, 1995)

*Enterococcus* spp. (RR 0.3 [95% CI 0.1–0.9]) groups were lower in COVID-19 patients. On the other hand, the incidence of Enterobacterales Group 3 (RR 1.8 [95% CI 1.1–3.0]) and non-fermentative rods increased (RR 2.4 [95% CI 1.5–3.7]). Interestingly, the occurrence of some epidemiological important multidrug resistant (MDR) isolates such as extended spectrum  $\beta$ -Lactamase (ESBL) or carbapenemase-producing Enterobacterales (CPE), MRSA and *E. faecium* was lower in the COVID-19 period. In contrast, the incidence of MDR *Pseudomonas aeruginosa* increased (RR 4.2 [95%CI 1.4–12.8]). This was unrelated to an increase of carbapenemase-producing isolates (only one strain producing VIM-type carbapenemase, detected in the pre-COVID-19 period). The genetic relatedness



**Figure 1. Overview of the pathogens' distribution showing the epidemiological change among microorganisms isolated from ICU patients at early stages of SARS-CoV-2 pandemic. A) Number of pathogens isolated from blood cultures by period (January-June 2019 and January-June 2020). B) Number of pathogens isolated from Respiratory Tract Samples by period (January-June 2019 and January-June 2020).**

of MDR *P. aeruginosa* isolates was also studied through PFGE (pulsed-field gel electrophoresis), ruling out the existence of clonal dissemination (data not shown).

### Antimicrobial consumption and emergence of resistant isolates

An increase in the consumption of most antimicrobials and antifungals was observed throughout the COVID-19 period (Supplementary Table S2). Data showed high amoxicillin-clavulanate usage during the first month of SARS-CoV-2 pandemic according to hospital recommendations regarding empirical antimicrobial treatment in patients with COVID-19. Amoxicillin-clavulanate usage increased from 6.4 DDD per 100 patients-day to 27.9 DDD per 100 patients-day in March 2020 compared to March 2019. As the pandemic progressed, we observed notable shifts in the use of antimicrobials. Amoxicillin-clavulanate consumption dropped in April 2020 (3.6 DDD per 100 patients-day) and the consumption of broad-spectrum antimicrobials such as meropenem increased (from 12.7 DDD per 100 patient-days to 34.1 DDD per 100 patient-days, from March to April). It is also remarkable the increased consumption of antimicrobials used for the treatment of infections caused by Gram-positive bacteria such as teicoplanin, linezolid or daptomycin (from 21.9 DDD per 100 patient-days in February 2020 to 61.9 DDD per 100 patient-days in April 2020). From May on a reduction in the use of most antimicrobials was observed except for colistin and ceftolozane-tazobactam that increased from 7.0 and 0.0 DDD per 100 patient-days in February 2020 to 20.9 and 12.2 DDD per 100 patient-days in May 2020, respectively.

We aimed to study whether these patterns of antimicrobial consumption were associated with the emergence of resistant isolates. Because the majority of BSI during the COVID-19 period were caused by Gram-negative bacilli, the analysis

focused on these bacteria. As shown in Figure 2, the high rates of amoxicillin-clavulanate use in March 2020 were accompanied by the emergence of strains resistant to this antimicrobial. In contrast, the number of susceptible isolates remained stable. Likewise, the incidence of isolates susceptible to meropenem or colistin showed a decreasing trend from March, while that of resistant isolates reached its peak in April, coinciding with the increase in the use of these antimicrobials. The appearance of resistant isolates was mostly associated with bacterial species naturally resistant to these antimicrobials (AmpC-producing bacteria for amoxicillin-clavulanate and *S. marcescens* for colistin) or bacterial species that frequently develop antimicrobial resistance (*P. aeruginosa* for meropenem) (Supplementary Table S3).

### Discussion

The early stages of SARS-Cov-2 pandemic were characterised by a lack of available evidence about the effective treatment of COVID-19 and consequently the management of critically ill patients was based on the accumulated experience in other pathogens. Recent studies have reported the frequency of co-infections and superinfections in moderate to severe COVID-19 patients [10,16] but data describing changes in local epidemiology during initial stages of COVID-19 pandemic are scarce. In this study, we found that the use of empirical therapy during early stages of SARS-CoV-2 pandemic was associated with the emergence of microorganisms with a characteristic resistance phenotype, which required a high use of broad-spectrum antimicrobials over the following months.

Compared to the pre-COVID period, patients with SARS-CoV-2 infection admitted to ICU required longer stay, more days on MV, more use of ECMO and had higher mortality rates. This is in concordance with reported data on critically ill patients with COVID-19 [17,18]. Our data also show that obesity may have a



Table II

Pathogens isolated from blood cultures and respiratory tract samples by period. Incidence is shown as number of episodes per 100 patients. Statistically significant differences between periods are highlighted in bold.

	Pre-COVID-19		COVID-19		RR (95% CI)
	n	Incidence	n	Incidence	
Bloodstream infections					
All episodes	31	10.1	72	32.7	3.2 (2.2–4.7)
Polymicrobial episodes	1	0.3	14	6.4	<b>14.5 (2.6–147.0)</b>
Enterobacterales Group 1-2	5	1.6	12	5.5	<b>3.3 (1.2–9.3)</b>
Enterobacterales Group 3	2	0.7	16	7.3	<b>11.1 (2.6–47.9)</b>
Non-fermentative rods	2	0.7	10	4.5	<b>7.0 (1.5–31.4)</b>
<i>Staphylococcus aureus/Enterococcus spp.</i>	7	2.3	12	5.5	2.4 (1.0–6.0)
CoNS	8	2.6	26	11.8	<b>4.5 (2.1–9.8)</b>
<i>Candida spp.</i>	8	2.6	11	5.0	1.9 (0.8–4.7)
Significative RTS isolation					
Enterobacterales Group 1-2	32	10.5	36	16.4	1.6 (1.0–2.4)
Enterobacterales Group 3	23	7.5	30	13.6	<b>1.8 (1.1–3.0)</b>
Non-fermentative rods	27	8.8	46	20.9	<b>2.4 (1.5–3.7)</b>
<i>Staphylococcus aureus/Enterococcus spp.</i>	23	7.5	8	3.6	<b>0.3 (0.1–0.9)</b>
Potentially pathogenic RTB	18	5.9	4	1.8	0.5 (0.2–1.1)
MDR bacteria <sup>a</sup>					
ESBL/CP-producing Enterobacterales	10	3.3	4	1.8	0.6 (0.2–1.8)
MRSA/ <i>Enterococcus faecium</i>	10	3.3	5	2.3	0.5 (0.2–1.4)
MDR <i>Pseudomonas aeruginosa</i> <sup>b</sup>	4	1.3	12	5.5	<b>4.2 (1.4–12.8)</b>

<sup>a</sup> Includes all isolates collected from BSI and RTS.

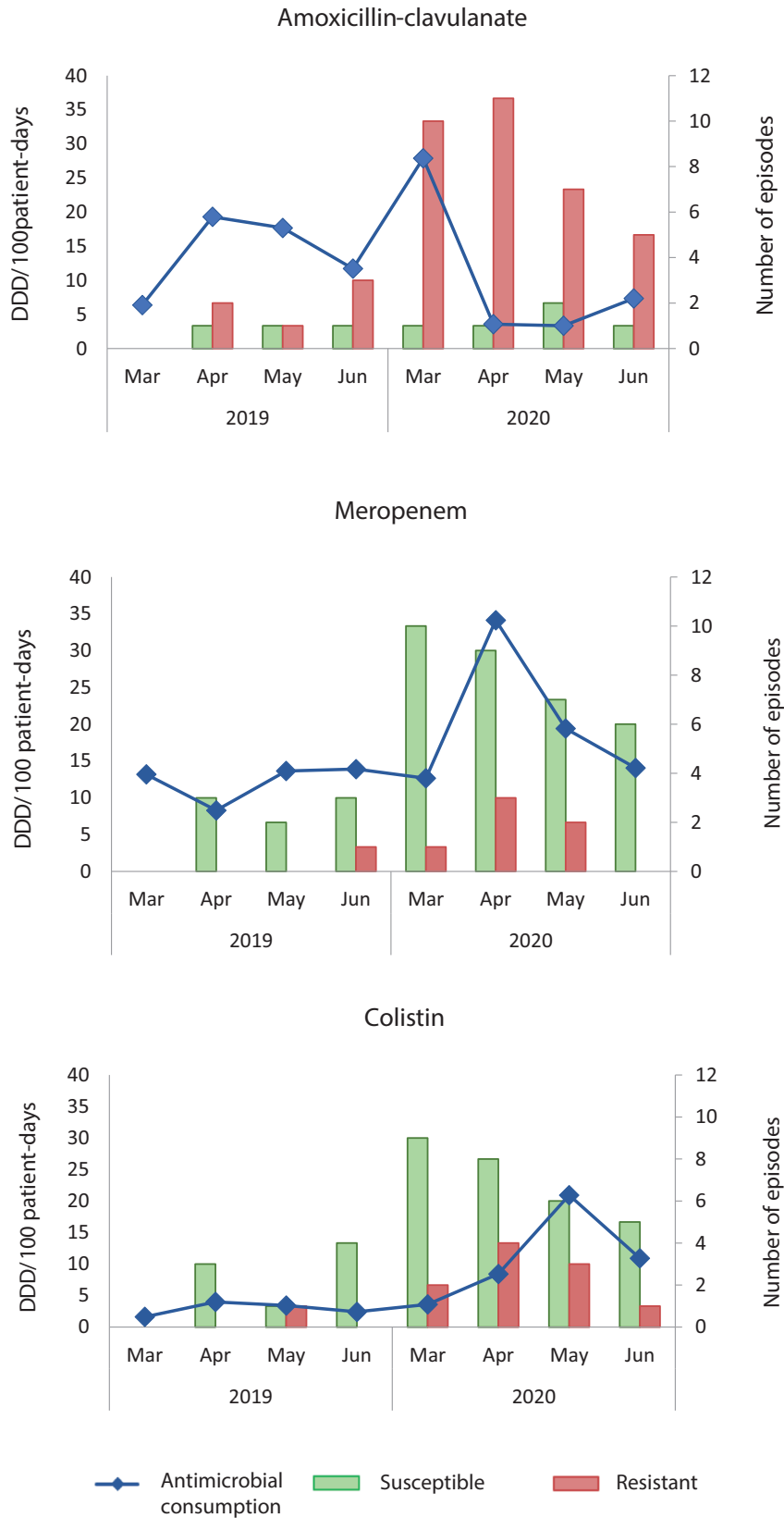
<sup>b</sup> MDR *P. aeruginosa* was defined according to Magiorakos et al. criteria [38].

role on the development of severe SARS-CoV-2 infection, as observed by other authors [19,20]. In fact, critically ill COVID-19 patients showed lower frequencies of comorbidities related to disease severity such as malignancies, cardiovascular diseases, COPD or chronic renal failure. These data indicate that COVID-19 patients differed significantly from the usual population of critically ill patients. Longer stay and greater use of some invasive support such as MV or ECMO means greater exposure to nosocomial infections [21,22]. The uncontrolled systemic inflammation induced by SARS-CoV-2 may also facilitate the invasion of the bloodstream by bacterial pathogens [23]. Additionally, other factors such as the prone positioning, a high work overload and a reduced hand hygiene or skin-decolonisation could have contributed to the increased rate of BSIs [24,25].

In our setting, empirical antimicrobial therapy for hospitalised patients was recommended by local guidelines during early stages of COVID-19. The use of antimicrobials showed increased rates and a biphasic pattern, with amoxicillin-clavulanate and broad-spectrum antimicrobials being the most frequently prescribed drugs [26]. Increased antimicrobial consumption has already been reported in Spain and other countries [8,27]. The emergence and expansion of MDR bacteria has also been described which could be related to the high antimicrobial consumption [28,29]. Nevertheless, our data differ from a typical clonal MDR expansion. In the context of increased BSI frequency, the incidence of infections caused by particular groups of pathogens was significantly higher. For instance, the increase in Gram-negative bacteria resistant to amoxicillin-clavulanate was particularly high. This was related to an increase in several AmpC-producing species and non-fermenting rods suggesting that it was probably not part of

an outbreak but rather caused by selection secondary to antimicrobial pressure. In fact, the frequency of BSI caused by some multidrug resistant isolates typically associated with nosocomial outbreaks such as ESBL/CPE-producing bacteria or MRSA/*E. faecium* was low. This could be associated with the fact that 1) these patients had less comorbidities and may have had less contact with the healthcare setting and 2) COVID-19 infection prevention measures could have helped reduce horizontal transmission and prevent nosocomial outbreaks. The use of amoxicillin-clavulanate could also justify the low frequency of isolation of pathogens associated with community-acquired pneumonia among respiratory samples that are frequently the cause of early ventilator-associated pneumonia. Data in this line have been recently reported in England indicating a reduction in the incidence of pneumococcal invasive disease because of the implementation of anti-COVID-19 transmission measures and also to the overuse of certain antimicrobials [30].

The initial selection of pathogens resistant to amoxicillin-clavulanate led to an antimicrobial escalation during the following months towards broader spectrum antimicrobials that in turn also led to an increase in the incidence of bacteria resistant to these antimicrobials. At this point the need to use empirical antimicrobials in patients with severe COVID-19 to prevent bacterial co-infection was not clear. The frequency of bacterial co-infection on admission appears to be infrequent in COVID-19 patients [10,31,32], but not the acquisition of secondary infections during hospitalisation, which has been frequently described [16,33]. It seems that the use of empirical antimicrobial therapy should be restricted to patients with a high clinical suspicion of bacterial infection, as recommended [13]. Additionally, our data highlights the extreme importance



**Figure 2.** Evolution of the monthly number of BSI episodes caused by Gram-negative bacteria resistant to amoxicillin-clavulanate, meropenem and colistin and their consumption. Antimicrobial consumption is expressed as defined daily doses (DDD) per 100 patient-days.

of antimicrobial stewardship programs that, in addition to reducing the inappropriate use of empirical antimicrobials, could also help shorten the duration of antimicrobial treatment. In fact, during the early phases of the pandemic, the antimicrobial stewardship program in the ICU had to be discontinued and this may have contributed to antimicrobial over-administration.

Our study adds potentially useful data on the impact of antimicrobial therapy on bacterial infection dynamics among COVID-19 patients. The study has some limitations of note. This is a single-centre experience, and our data may not be translated into other settings. Also, our study does not include patients less than 48 hours of ICU stay that could have led us to miss events which occurred in this population. However, the study design allowed us to homogenise the study population to reduce unknown confounding factors. Moreover, the systematic collection of clinical data performed by the same team minimises the existence of potential biases.

## Conclusions

Our study shows a high frequency of BSI in severe COVID-19 patients which could contribute to the increased mortality seen in these patients. The use of empirical antimicrobial therapy during early stages of SARS-CoV-2 pandemic changed the epidemiology of BSIs towards microorganisms with a characteristic resistance phenotype, which in turn led to the use of broad-spectrum antimicrobials. This highlights the epidemiological and clinical impact of empirical antimicrobial therapy which should be thoroughly evaluated to avoid adverse effects.

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Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization.

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## Conflict of interest statement

The authors declare no conflicts of interest.

## Ethics approval and consent to participate

The Clinical Research Ethics Committee of Bellvitge University Hospital approved this research (PR076/21) and waived the requirement of written informed consent as this was a retrospective and non-interventional study with isolates obtained as part of the clinical routine. All confidential information was anonymized and protected according to national normative. All methods were performed in accordance with the relevant national guidelines and international regulations.

## Consent for publication

Not applicable.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.infpip.2022.100241>.

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