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Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: a prospective observational study

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Background: Bacterial and fungal superinfections may complicate the course of hospitalized patients with COVID-19.

Objectives: To identify predictors of superinfections in COVID-19.

Methods: Prospective, observational study including patients with COVID-19 consecutively admitted to the University Hospital of Pisa, Italy, between 4 March and 30 April 2020. Clinical data and outcomes were registered. Superinfection was defined as a bacterial or fungal infection that occurred ≥48 h after hospital admission. A multivariate analysis was performed to identify factors independently associated with superinfections.

Results: Overall, 315 patients with COVID-19 were hospitalized and 109 episodes of superinfections were documented in 69 (21.9%) patients. The median time from admission to superinfection was 19 days (range 11–29.75). Superinfections were caused by Enterobacterales (44.9%), non-fermenting Gram-negative bacilli (15.6%), Gram-positive bacteria (15.6%) and fungi (5.5%). Polymicrobial infections accounted for 18.3%. Predictors of superinfections were: intestinal colonization by carbapenem-resistant Enterobacterales (OR 16.03, 95% CI 6.5–39.5, $P < 0.001$); invasive mechanical ventilation (OR 5.6, 95% CI 2.4–13.1, $P < 0.001$); immunomodulatory agents (tocilizumab/baricitinib) (OR 5.09, 95% CI 2.2–11.8, $P < 0.001$); C-reactive protein on admission >7 mg/dl (OR 3.59, 95% CI 1.7–7.7, $P = 0.001$); and previous treatment with piperacillin/tazobactam (OR 2.85, 95% CI 1.1–7.2, $P = 0.028$). Length of hospital stay was longer in patients who developed superinfections ompared with those who did not (30 versus 11 days, $P < 0.001$), while mortality rates were similar (18.8% versus 23.2%, $P = 0.445$).

Conclusions: The risk of bacterial and fungal superinfections in COVID-19 is consistent. Patients who need empiric broad-spectrum antibiotics and immunomodulant drugs should be carefully selected. Infection control rules must be reinforced.

Introduction

Bacterial and fungal infections represent an important complication of viral diseases and may be associated with worse outcomes, especially during seasonal influenza epidemics.[1] Coinfections, diagnosed within the first 24 h from hospital admission, are usually caused by community-acquired bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae* or *Staphylococcus aureus*.[2,3] Superinfections, occurring at least 48 h after hospital admission, are frequently caused by hospital-acquired, MDR organisms (MDROs) or fungi.[2] Data about superinfections complicating COVID-19 are scanty. Patients with severe COVID-19 may require prolonged hospitalization either in general wards or in ICUs and a significant proportion of these are treated with empiric, broad-spectrum antibiotic therapy that increases the risk of MDRO selection.[4] Breaks in the infection control procedures due to patient

isolation may further contribute to the spread of MDROs, making them responsible for local clusters. The use of drugs targeting cytokines, such as IL-1 and IL-6, might also increase the risk of superinfections in patients with COVID-19.[3]

The aim of our study was to identify the predictors of superinfections complicating hospitalized patients with SARS-CoV-2 pneumonia.

Methods

Ethics

The research was conducted in accordance the Declaration of Helsinki and national and institutional standards. The Internal Review Board (IRB) of the Comitato Etico Area Nord-Ovest (CEAVNO) approved the study (approval number 17681) and written informed consent was obtained from study participants.

Study design and definitions

This was a single-centre, prospective, observational study including patients with COVID-19 consecutively admitted to the tertiary care University Hospital of Pisa, Italy, between 4 March and 30 April 2020. Patients with pneumonia and laboratory-confirmed SARS-CoV-2 infection with an RT–PCR test on a nasopharyngeal swab were included.

Since during the study period there was limited evidence for any anti-COVID-19 treatment, the patients were treated according to an internal guide for the management of COVID-19 patients elaborated by a panel of experts (infectious disease physicians, pneumologists, microbiologists, emergency medicine experts and intensivists). It was regularly updated according to any new release from the scientific literature (Table S1, available as Supplementary data at *JAC* Online).[5] Immunomodulant agents used in our hospital were tocilizumab and baricitinib. The decision to prescribe one of the two immunosuppressants was made by the attending physician. Tocilizumab was used at the dosage of 400 mg IV, followed by a second administration of 400 mg IV after 24 h. In two patients, tocilizumab was used in the setting of the randomized clinical trial (RCT) NCT04346355;[6] in the remaining cases, tocilizumab was prescribed off-label after approval by hospital pharmacy and acquisition of written consent by the patient. Baricitinib was administered at a dose of 4 mg/day for 14 days with the same procedures used for the off-label use of tocilizumab.[7]

All patients were prospectively followed up: a dedicated staff of research fellows identified patients with SARS-CoV-2 pneumonia as soon as they arrived at the Emergency Department, followed the patients during the hospital stay and collected all data prospectively without interfering with the therapeutic decisions. Epidemiological and demographic information, medical history, comorbidities, information on clinical symptoms at admission and treatments received during the hospital course were collected. To assess comorbidity burden, the age-adjusted Charlson Comorbidity Index was calculated. The severity of disease at hospital admission was estimated by the SOFA score.[8]

Infections in patients with COVID-19 were categorized as coinfections, diagnosed within the first 24 h of COVID-19 hospital admission, or superinfections, if diagnosis occurred $\geq$48 h after admission for COVID-19.[2] Only superinfection episodes were included in the study. Specific types of infection were classified in the following categories: ventilator-associated pneumonia (VAP), hospital-acquired pneumonia (HAP), urinary tract infection (UTI), acute bacterial skin and soft structure infection (ABSSSI), intra-abdominal infection (IAI) and bloodstream infection (BSI).[9] According to internal hospital protocols, all patients underwent rectal swab for molecular detection of *bla* genes involved in carbapenem resistance at admission and cultural screening for the identification of carbapenem-resistant Enterobacterales (CRE) periodically during the hospital stay. MDROs were defined as microorganisms non-susceptible to at least one agent in three or more antimicrobial categories.[10]

Gram staining and a rapid identification protocol were performed on positive blood cultures and other biological samples, as previously reported.[11] MALDI-TOF MS (Bruker Daltonics) was used for species identification. The presence of a *bla* gene was determined by PCR using the GeneXpert® System (Cepheid), as previously reported.[12] Antimicrobial susceptibility tests were performed with the Tecan automated system (Tecan Trading AG, Switzerland) according to the manufacturer's instructions. MICs were classified according to breakpoints established by EUCAST (v10.0).

Study outcome

The primary objective of our study was to identify predictors independently associated with the development of superinfections in hospitalized patients with COVID-19.

The secondary objective was to evaluate the outcome of patients with COVID-19 who developed superinfections during their hospital stay.

Statistical analysis

Continuous and categorical variables are presented as median (IQR) and absolute number (percentage), respectively. The Mann–Whitney *U*-test, χ^2

Table 1. Microbial aetiology of 109 episodes of superinfections in hospitalized patients with COVID-19

Organism	*n* or *n*/*N*
GNB	66 (60.6%)
Enterobacterales	49/109 (44.9%)
K. pneumoniae	34
Escherichia coli	9
Enterobacter spp.	4
Citrobacter freundii	2
Non-fermenting GNB	17/109 (15.6%)
P. aeruginosa	12
A. baumannii	3
S. maltophilia	2
Gram-positive bacteria	17 (15.6%)
Enterococcus spp.	6
S. aureus	5
CoNS	4
C. striatum	2
Fungi	6 (5.5%)
Candida spp.	5
Aspergillus fumigatus	1
Polymicrobial infections	20 (18.3%)
CoNS + *E. faecalis*	1
CoNS + *Enterobacter* spp.	1
S. aureus + *K. pneumoniae*	2
Enterococcus spp. + *Corynebacterium* spp.	1
P. aeruginosa + *Enterobacter* spp.	1
P. aeruginosa + *S. aureus*	1
P. aeruginosa + *K. pneumoniae*	8
E. coli + *Proteus* spp.	1
A. baumannii + *K. pneumoniae*	1
Candida spp. + *K. pneumoniae*	1
Candida spp. + *Enterococcus* spp.	2

test and Fisher's exact test were used to compare differences between groups.

According to the study outcome, we performed a comparison between patients who developed superinfection during their hospital stay and those who did not. Treatment variables were considered as potential predictors of superinfections if they occurred before the occurrence of superinfection. The variables of C-reactive protein (CRP) and procalcitonin (PCT) values were dichotomized according to the median value in the overall population. To identify factors independently associated with the development of superinfections, a multivariate regression analysis was performed. The multivariate analysis using logistic regression prediction models was constructed using a forward stepwise procedure, entering all variables with univariate $P < 0.05$. The final multivariate model was chosen according to the Akaike information criterion and to parsimony and clinical interpretability of data. Statistical significance was established at $P < 0.05$. All reported P values are two-tailed. The results obtained were analysed using a commercially available statistical software package (SPSS 20.0; IBM, Armonk, NY, USA and R 3.5.1, Vienna, Austria).

Results

Overall, during the study period, we documented 109 episodes of superinfections in 69 of 315 (21.9%) patients hospitalized for COVID-19. Of these episodes, 78 occurred in patients cared for in ICUs (71.6%) and 68 of these were diagnosed in those undergoing invasive mechanical ventilation (62.4%). The median time from hospital admission to the diagnosis of superinfection was 19 days (range 11–29.75).

Table 1 summarizes the microbial aetiology of the 109 episodes. The most frequently isolated microorganisms were Enterobacterales (44.9%) followed by non-fermenting Gram-negative bacilli (GNB) (15.6%), Gram-positive bacteria (15.6%) and fungi (5.5%). Polymicrobial infection was diagnosed in 18.3% of cases.

MDROs caused 71 episodes of superinfections (65.1%). Overall, the rate of MDR infections increased during the hospital stay (Figure 1). Fifty-two episodes of MDR infections were caused by CRE (25 NDM-producing and 3 KPC-producing *Klebsiella pneumoniae*), 11 by ESBL-producing Enterobacterales, 6 by non-fermenters (3 *Acinetobacter baumannii*, 2 *Stenotrophomonas maltophilia*, 1 *Pseudomonas aeruginosa*) and 7 by mixed strains (1 ESBL-producing *K. pneumoniae* + *P. aeruginosa*, 5 NDM-producing *K. pneumoniae* + *P. aeruginosa* and 1 NDM-*K. pneumoniae* + *A. baumannii*).

Documented MDR Gram-positive infections included 6 methicillin-resistant CoNS, 4 MRSA, 3 MDR *Corynebacterium striatum* and 4 *Enterococcus faecium*. Two superinfections were caused by mixed MDR Gram-positive and GNB (1 ESBL-producing *K. pneumoniae* + MRSA, 1 NDM-producing *K. pneumoniae* + MRSA). Site of infections according to the aetiology are reported on Table 2; there were 44 BSIs (40.3%), 31 UTIs (28.4%), 26 VAPs (23.8%), 3 HAPs (2.7%), 3 ABSSSIs (2.7%) and 2 IAIs (1.8%). Among the 44 BSIs, 21 (47.7%) episodes were related to central venous catheters (CVCs).

A comparison between patients who developed superinfection and those who did not is shown in Table 3. Compared with controls, patients who developed superinfections had a higher median SOFA score, higher prevalence of lymphopenia and increased CRP and PCT values on admission. Intestinal colonization by CRE was more common in patients with superinfections than in controls. Patients with CRE intestinal colonization were hospitalized in ICU in the majority of cases (73.5%) and had a duration of hospital stay

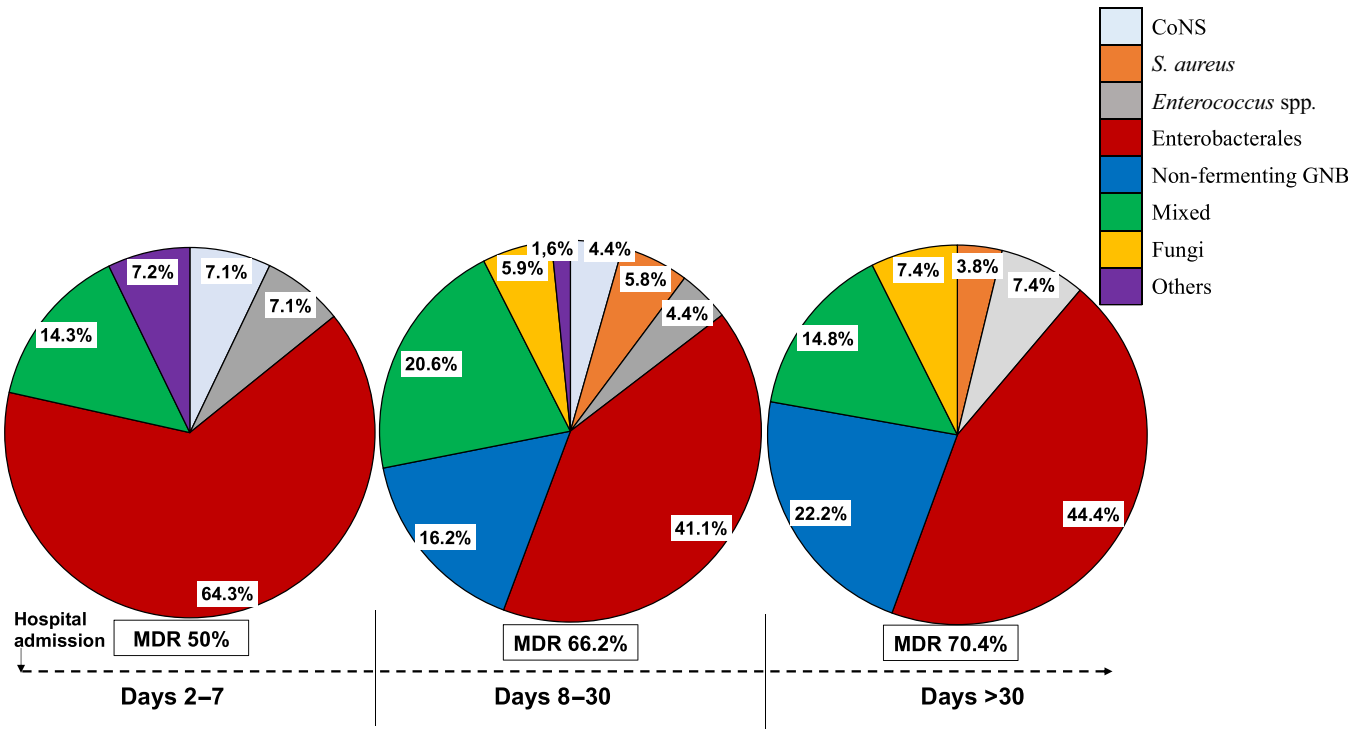

Figure 1. Aetiology of superinfections according to time from hospital admission. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 2. Aetiology by site of 109 superinfections in hospitalized patients with COVID-19

Infection type and organism	*n*
Bacteraemia/fungaemia	44 (40.3%)
CoNS	4
S. aureus	4
Enterococcus spp.	2
K. pneumoniae	11
E. coli	2
Enterobacter aerogenes	2
P. aeruginosa	4
S. maltophilia	1
A. baumannii	1
C. striatum	2
Candida parapsilosis/orthopsilosis	5
Mixed	6
VAP	26 (23.8%)
S. aureus	1
K. pneumoniae	8
E. coli	2
C. freundii	2
P. aeruginosa	1
A. baumannii	2
A. fumigatus	1
Mixed	9
UTI	31 (28.4%)
K. pneumoniae	12
E. coli	5
Enterobacter spp.	2
P. aeruginosa	7
Enterococcus spp.	4
Mixed	1
HAP	3 (2.7%)
K. pneumoniae	1
S. maltophilia	1
Mixed	1
ABSSSI	3 (2.7%)
K. pneumoniae	1
Mixed	2
IAI	2 (1.8%)
K. pneumoniae	1
Mixed	1

significantly longer than non-colonized ones [28 (IQR 19.5–37.5) versus 13 (IQR 7–20.5) days, $P < 0.001$]. Among 49 CRE intestinal carriers, 24 (49%) developed superinfections caused by the CRE colonizing strain (22 NDM-producing and 2 KPC-producing *K. pneumoniae*), while 14 (28.6%) infection episodes were due to other bacterial strains (4 *P. aeruginosa*, 2 *S. aureus*, 6 Enterobacterales and 2 CoNS). Piperacillin/tazobactam and remdesivir were more frequently used in the group developing superinfection while doxycycline and low-molecular-weight heparin were more frequently used in the control group. Steroids and immunomodulators (tocilizumab or baricitinib) were more frequently administered to patients who developed superinfections.

The multivariate analysis identified intestinal colonization by CRE (OR 16.03, 95% CI 6.5–39.5, $P < 0.001$), invasive mechanical ventilation (OR 5.6, 95% CI 2.4–13.1, $P < 0.001$), use of immunomodulators (tocilizumab or baricitinib) (OR 5.09, 95% CI 2.2–11.8, $P < 0.001$), CRP values on admission >7 mg/dl (OR 3.59, 95% CI 1.7–7.7, $P = 0.001$) and the receipt of piperacillin/tazobactam (OR 2.85, 95% CI 1.1–7.2, $P = 0.028$) as predictors independently associated with the development of hospital-acquired superinfections (Table 4).

Discussion

Our study confirms that bacterial and fungal superinfections may complicate the hospital course of patients with COVID-19 in a significant proportion of cases. We identified some predictors of superinfections in COVID-19 patients; previous rectal colonization by CRE, the need for invasive mechanical ventilation, the use of immunomodulators, high CRP values on admission and treatment with piperacillin/tazobactam are factors independently associated with superinfections.

These findings raise some important considerations. First, as outlined by a recent survey, broad-spectrum antibiotic use in patients with COVID-19 is extremely frequent, with piperacillin/tazobactam as the most frequently prescribed antibiotic.[13] Interestingly, the use of piperacillin/tazobactam was associated with increased risk of subsequent superinfections in our series. The use of antibiotics in patients with severe SARS-CoV-2 pneumonia, except for documented bacterial coinfection or superinfection, has no demonstrated efficacy and increases the risk of MDRO selection. Our results confirm that the implementation of antimicrobial stewardship programmes is a pivotal strategy to be urgently adopted in SARS-CoV-2 pandemic settings.[14]

Second, intestinal colonization by CRE is an independent predictor of superinfection in COVID-19. This is not surprising, considering that the association between rectal carriage by CRE and risk of subsequent infection is well described.[15] There is preclinical evidence that the gut microbiota might be perturbed by SARS-CoV-2; the gut microbiota of patients with SARS-CoV-2 infection is characterized by enrichment of opportunistic pathogens and alterations in gut cells have also been observed in the absence of gastrointestinal manifestations and after recovery.[16] However, the administration of broad-spectrum antibiotics (piperacillin/tazobactam in our series) is the major risk factor for intestinal colonization by CRE. Remarkably, we found that 77.5% of CRE rectal carriers developed a subsequent superinfection, not only by the same CRE colonizing strain (two-thirds of cases) but also by other microorganisms. Probably, intestinal colonization by CRE is not only a risk factor for subsequent CRE infection but also a marker of susceptibility to other nosocomial infections since the vast majority of CRE carriers resided in ICU and had a prolonged hospitalization.

Finally, the use of anti-IL-6 (tocilizumab) or Janus kinase (JAK) inhibitors (baricitinib) increased the risk of developing superinfections. This finding is remarkable. These agents have been widely used in patients with COVID-19, but there is evidence that they are associated with an increased risk of subsequent bacterial superinfections.[17] Considering the evolving evidence on these immunomodulant agents and the potential risk of superinfections, the use of anti-IL-6 or JAK inhibitors should be used in the context of RCTs;

Table 3. Comparison of hospitalized COVID-19 patients with and without superinfections

Variable	Superinfections (*N* = 69)	No superinfections (*N* = 246)	*P* value
Demographics			
Age, years, median (IQR)	71 (60–78.5)	69 (56–81)	0.278
Age ≥65 years, *n* (%)	48 (69.6%)	140 (56.9%)	0.058
Male sex, *n* (%)	51 (73.9%)	159 (64.6%)	0.148
Coexisting comorbidities, *n* (%)			
COPD	9 (13)	40 (16.3)	0.515
Arterial hypertension	30 (43.5)	107 (43.5)	0.998
Cardiovascular disease	22 (31.9)	81 (32.9)	0.870
Diabetes mellitus	14 (20.3)	50 (20.3)	0.995
Haemodialysis	1 (1.4)	5 (2)	0.754
Solid cancer	14 (20.3)	30 (12.2)	0.087
Chronic kidney disease	5 (7.2)	22 (8.9)	0.656
Charlson Comorbidity Index, median (IQR)	3 (1–5)	3 (1–5)	0.715
SOFA score on admission, median (IQR)	3 (2–4)	2 (1–3)	**0.007**
Inflammatory markers on admission, *n* (%)			
Lymphopenia (<800 cells/μL)	44 (63.8)	99 (40.2)	**0.001**
WBC >10 $\times 10^3$/μl	34 (34.8)	52 (21.1)	**0.019**
PCT >0.5 ng/mL	17 (24.6)	37 (15)	0.062
CRP > 7 mg/dl	45 (65.2)	100 (40.7)	<**0.001**
Inflammatory markers before infection			
CRP, mg/dl, median (IQR)	12.3 (6.2–17.3)	—	—
CRP > 7 mg/dl, *n* (%)	52 (75.4)	—	—
PCT, ng/mL, median (IQR)	1.2 (0.2–2.4)	—	—
PCT > 0.5 ng/mL, *n* (%)	44 (63.8)	—	—
Intestinal colonization by CRE, *n* (%)	38 (55.1)	11 (4.5)	<**0.001**
Antibiotics at onset, *n* (%)			
Doxycycline	20 (29)	130 (52.8)	<**0.001**
Azithromycin	9 (13)	33 (13.4)	0.936
Ceftriaxone	27 (39.1)	120 (48.8)	0.156
Piperacillin/tazobactam	23 (33.3)	22 (8.9)	<**0.001**
Fluoroquinolones	2 (2.9)	6 (2.4)	0.830
Anti-COVID-19 treatment, *n* (%)			
PIs (LPV/r or DRV/r)	46 (66.7)	154 (62.6)	0.535
Remdesivir	13 (18.8)	0	<**0.001**
Hydroxychloroquine	54 (78.3)	184 (74.8)	0.554
Low-molecular-weight heparin	60 (87)	184 (74.8)	**0.033**
Immunomodulatory treatment, *n* (%)			
Steroids	51 (73.9)	90 (36.6)	<**0.001**
IL-6 or JAK inhibitors	20 (29)	31 (12.6)	**0.001**
Interventions, *n* (%)			
Non-invasive mechanical ventilation	29 (42.6)	39 (15.9)	<**0.001**
Invasive mechanical ventilation	35 (50.7)	20 (8.1)	<**0.001**
ICU admission, *n* (%)	44 (63.8)	41 (16.7)	<**0.001**
Length of hospital stay, days, median (IQR)	30 (18.5–38)	11 (7–19)	<**0.001**
Length of hospital stay before infection, days, median (IQR)	15 (10–21)	—	—
Length of hospital stay after infection, days, median (IQR)	14 (8.5–21)	—	—
Mortality, *n* (%)	13 (18.8)	57 (23.2)	0.445

DRV/r, darunavir/ritonavir; LPV/r, lopinavir/ritonavir. *P* values in bold are statistically significant ($P < 0.05$).

it should be based on a reasoned comprehensive evaluation and surveillance of superinfections should be promoted in patients who received these drugs.

Superinfections occurring in our hospital are mainly caused by Gram-negative bacilli and a high proportion of infections were caused by MDROs. This reflects local epidemiology characterized

Table 4. Multivariate analysis of predictors independently associated with superinfection episodes in hospitalized patients with COVID-19

Predictor	OR (95% CI)	*P* value
Intestinal colonization by CRE	16.03 (6.5–39.3)	**<0.001**
Invasive mechanical ventilation	5.58 (2.4–13.1)	**<0.001**
IL-6 or JAK inhibitors	5.09 (2.2–11.8)	**<0.001**
CRP on admission >7 mg/dl	3.59 (1.7–7.7)	**0.001**
Piperacillin/tazobactam	2.85 (1.1–7.2)	**0.028**

P values in bold are statistically significant ($P < 0.05$).

by a high prevalence of MDR GNB.[12,18,19] Moreover, our findings suggest that COVID-19 was associated with a less effective implementation of infection control procedures in our hospital. This is not surprising, because of several reasons: difficulties for healthcare workers to adhere to standard precautions (long shifts wearing the same equipment and possible shortages of certain equipment); focus on self-protection rather than on cross-transmission of bacteria across patients; overcrowded wards; shortages of professionals with appropriate training in infection control procedures; and possible decreased laboratory ability to detect MDR carriage.[20] Since there is great concern about potential exacerbation of MDRO spread after the COVID-19 outbreak, it will be crucial to continue monitoring rates of antibiotic-resistant bacterial infections and implementing infection control measures, especially in this phase.

Our study has some limitations. First, it is a single-centre study conducted in a setting with a high prevalence of MDROs. Moreover, piperacillin/tazobactam has been widely empirically prescribed during the first wave for COVID-19 patients who had clinical (e.g. fever) and laboratory (e.g. increased CRP values) signs of infections. The rationale was to prevent coinfections by other bacteria (e.g. *S. pneumoniae*, Enterobacterales, *P. aeruginosa* etc.). These factors led to unnecessary use of piperacillin/tazobactam in our hospital (also because piperacillin/tazobactam use is not restricted by our internal formulary). We acknowledged that this factor may reduce the generalizability of the study, and highlights the importance of antimicrobial stewardship programmes during the COVID-19 pandemic. According to the results of this study, we modified the therapeutic approach to COVID-19 patients during the ongoing second wave; we are now discouraging the use of antibiotics unless evidence of bacterial infection or signs of haemodynamic instability are present. Currently, the use of antibiotics has dropped by 50% compared with the first wave (internal unpublished data from the University Hospital of Pisa). Second, the sample size is relatively small and the CIs of the significant predictors are quite broad. However, unlike other studies, which described coinfections and superinfections in COVID-19, this study was specifically focused on superinfections occurring during hospital stay and evaluated predictors of hospital-acquired infections in patients with COVID-19. Third, we did not perform systematic surveillance for pulmonary aspergillosis (by detection of galactomannan on bronchoalveolar lavage) in our patients and this may have underestimated the incidence of this fungal infection in COVID-19 patients.[21,22] Finally, the association between the use of immunomodulators and the risk of superinfections should be confirmed by RCTs.

In conclusion, we observed a great number of superinfections complicating the course of hospitalized patients with COVID-19. The widespread use of antibiotics in the COVID-19 pandemic may exacerbate antimicrobial resistance and may ultimately lead to increased morbidity as an unintended consequence of this already tragic pandemic. Immunomodulant drugs may increase the risk of superinfections and should be used with caution, preferably in the context of RCTs.

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Members of the PISA COVID-19 Study Group

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Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

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