Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study

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ABSTRACT

Objectives: To describe the burden, epidemiology and outcomes of co-infections and superinfections occurring in hospitalized patients with coronavirus disease 2019 (COVID-19).
Methods: We performed an observational cohort study of all consecutive patients admitted for ≥48 hours to the Hospital Clinic of Barcelona for COVID-19 (28 February to 22 April 2020) who were discharged or dead. We describe demographic, epidemiologic, laboratory and microbiologic results, as well as outcome data retrieved from electronic health records.
Results: Of a total of 989 consecutive patients with COVID-19, 72 (7.2%) had 88 other microbiologically confirmed infections: 74 were bacterial, seven fungal and seven viral. Community-acquired co-infection at COVID-19 diagnosis was uncommon (31/989, 3.1%) and mainly caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*. A total of 51 hospital-acquired bacterial superinfections, mostly caused by *Pseudomonas aeruginosa* and *Escherichia coli*, were diagnosed in 43 patients (4.7%), with a mean (SD) time from hospital admission to superinfection diagnosis of 10.6 (6.6) days. Overall mortality was 9.8% (97/989). Patients with community-acquired co-infections and hospital-acquired superinfections had worse outcomes.
Conclusions: Co-infection at COVID-19 diagnosis is uncommon. Few patients developed superinfections during hospitalization. These findings are different compared to those of other viral pandemics. As it relates to hospitalized patients with COVID-19, such findings could prove essential in defining the role of empiric antimicrobial therapy or stewardship strategies. **Carolina Garcia-Vidal, Clin Microbiol Infect 2021;27:83**

Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has presented a formidable medical challenge to health systems and clinicians [1–4]. With >250 000 cases diagnosed by 9 July 2020, Spain has particularly suffered from this pandemic [5]. Many decisions have been made with limited clinical experience and scientific evidence, especially concerning

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treatments for patients hospitalized with coronavirus disease 2019 (COVID-19). One such clinical decision regards the delivery of antibiotic therapy to patients with COVID-19. Bacterial, especially *Streptococcus pneumoniae* and *Staphylococcus aureus*, and viral or fungal co-infections are common complications described as arising in other pandemics caused by *influenza* viruses [6–9]. However, information concerning incidence of such co-infections in patients with COVID-19 has been scarce. Similarly, information related to COVID-19 superinfections is lacking, although it is essential to ensure rational antimicrobial stewardship.

We aimed to describe the burden and epidemiology of community-acquired co-infections and hospital-acquired superinfections in a large cohort of all consecutive hospitalized patients admitted with COVID-19 for ≥48 hours in Barcelona who were either currently discharged or dead. The impact of co-infections and superinfections on patient outcomes was also assessed.

Methods

Study design and patients

This observational cohort study was performed at the Hospital Clinic of Barcelona (Spain), a 700-bed university centre that provides broad and specialized medical, surgical and intensive care for an urban population of 500 000 adults (>18 years old). All patients admitted with COVID-19 for ≥48 hours between 28 February and 22 April 2020 and who were currently discharged alive or had died during hospitalization were included. All patients had a diagnosis of COVID-19 confirmed by real-time reverse transcription PCR (RT-PCR) testing performed on nasopharyngeal throat swab specimens, and/or by fulfilling clinical diagnostic criteria provided during the pandemic peak for SARS-CoV-2. These criteria comprised the presence of any of the following respiratory symptoms: sore throat, congestion, cough, dyspnoea, new loss of taste and/or smell as well as uni- or bilateral interstitial infiltrates on chest X-ray.

The institutional ethics committee of the Hospital Clinic of Barcelona approved the study; as a result of its nature as a retrospective data review, the committee waived the need for receipt of informed consent from individual patients (HCB/2020/0273).

Data collection and outcomes

For all patients hospitalized with COVID-19, data concerning demographics (age, gender), epidemiology, comorbidities, laboratory tests, microbiologic results (blood and urine cultures, respiratory samples, urinary antigen tests and antimicrobial susceptibility), treatment and outcomes (intensive care unit (ICU) admission, length of hospital stay and mortality) were collected directly from electronic health records as previously described [10]. The records of all patients with positive microbiologic results were reviewed by one of our researchers (CGV, EMG or CC) to assess clinical significance.

Procedures

Investigation of bacterial, viral and fungal pathogens in blood, normally sterile fluids, sputum and other samples was performed with standard microbiologic procedures at hospital admission, as requested by the attending physician. Bacterial respiratory infection was diagnosed in patients with one or more positive cultures of respiratory pathogens obtained from blood, pleural fluids, good-quality sputum (>25 polymorphonuclear leukocytes and <25 epithelial cells) and bronchoalveolar lavage, and/or a positive urinary antigen test. *S. pneumoniae* antigen in urine was detected with a rapid Standard F *S. pneumoniae* Ag fluorescent immunoassay assay (SD Biosensor, Gyeonggi-do, South Korea). Specific rapid RT-PCR testing was used for*influenza* A and B viruses, as well as respiratory syncytial virus diagnosis (cobas Liat System; Roche, Basel, Switzerland). Multiplex PCR testing (Flow System; Roche) was also used for *influenza* viruses A, B and C;*parainfluenza* 1, 2, 3 and 4; and metapneumovirus diagnosis.

Definitions

Bloodstream infection was defined as the growth of a non-skin flora commensal on one or more blood culture. To define a bloodstream infection as that caused by a common skin colonizer such as coagulase-negative staphylococci or *Corynebacterium*, we required two or more blood cultures drawn from different sites and a clinical evaluation from one of our researchers (CGV or EMG). We then considered the clinical significance of such bloodstream infection. Urinary infection was defined as the growth of a bacterium or fungus in a cultured urine sample from a patient with clinical symptoms and/or the consideration of such urinary infection as clinically significant by one of our researchers (CGV or EMG). *Aspergillus* tracheobronchitis was defined as the isolation of *Aspergillus* species from endobronchial specimens of intubated patients with purulent secretions, as well as clinical validation from one of our researchers (CGV or CC).

All of these clinically indicated infections were categorized as co-infections or superinfections. If diagnosis was at the time of or within the first 24 hours of COVID-19 hospital admission, these infections were defined as community-acquired co-infections. If diagnosis occurred ≥48 hours after admission for COVID-19, these infections were defined as hospital-acquired superinfections.

Statistical analysis

For the purpose of the present study, a descriptive analysis of clinical and laboratory tests was performed. Continuous and categorical variables were presented as median (interquartile range (IQR)) and absolute number (percentage) respectively. We used the Mann-Whitney *U* test, chi-square test and Fisher exact test to compare differences between patients who had other infections and those who did not. Significance was set at $p < 0.05$. Statistical analyses were performed by SPSSPC+ 22.0 (IBM, Armonk, NY, USA).

Results

We assessed 989 consecutive adults with COVID-19 at our hospital who had either been discharged or had died during the study period. Of these, 552 (55.8%) were male; the median (IQR) age was 62 (48–74) years. Main patient characteristics by group are shown in Table 1. Table 2 details the number of microbiology tests requested by attending physicians and the positive results with clinical significance. A total of 88 non–COVID-19 infections were documented in 72 patients (7.3%). Seventy-four were bacterial, seven fungal and seven viral. A total of 74 bacterial infections were diagnosed in 61 of 88 patients (three infections in one patient, two in 12 individual patients and one in every remaining patient). The most common bacteria isolated were *S. pneumoniae*, with 12 cases; *S. aureus*, 12; *Pseudomonas aeruginosa*, 10; *Escherichia coli*, 7; and *Klebsiella pneumoniae*, 6.

Community-acquired co-infections

Overall, 31 (3.1%) of 989 patients had 37 community-acquired co-infections. Thirty community-acquired bacterial co-infections were documented in 25 patients (2.5%). Specifically, bacterial pneumonia co-infection was documented in 21 patients (2.1%) at

Table 1
Main characteristic of patients hospitalized for COVID-19 for ≥48 hours

Characteristic	No infection ($n = 917$)	Community-acquired co-infection ($n = 31$)		Hospital-acquired superinfection ($n = 43$)	
		Value	p[a]	Value	p[b]
Age (years)	61 (48–74)	63 (54.5–74)	0.671	67 (55.75–74.25)	0.006
Male sex	510 (55.6)	18 (58.1)	0.956	26 (60.5)	0.822
Comorbidities					
Hypertension	167 (18.2)	7 (22.6)	0.537	7 (16.3)	0.748
Diabetes mellitus	89 (9.7)	7 (22.6)	0.019	7 (16.3)	0.160
Chronic heart disease	122 (13.3)	9 (29)	0.013	7 (16.3)	0.576
Chronic lung disease	95 (10.4)	6 (19.4)	0.110	7 (16.3)	0.218
Chronic renal disease	47 (5.1)	8 (25.8)	<0.001	6 (14)	0.013
Cancer	77 (8.4)	1 (3.2)	0.259	8 (18.6)	0.021
Inflammatory markers at onset					
C-reactive protein	7.06 (3.31–13.29)	6.76 (3.20–9.79)	0.714	11.78 (5.55–17.87)	0.012
Ferritin	544 (249.5–1100)	208 (154–431.5)	0.042	797 (296–1743)	0.575
Lymphocyte count	0.9 (0.6–1.2)	0.8 (0.6–1.1)	0.892	0.783 (0.5–1.1)	0.088
Lactate dehydrogenase	287 (233–372)	264 (221–377.5)	0.477	311.5 (247.5–471–8)	0.193
Treatment at onset					
Lopinavir/ritonavir	732 (79.8)	27 (87.1)	0.227	35 (81.4)	0.802
Hydroxychloroquine	799 (87.1)	29 (93.5)	0.225	40 (93)	0.186
Azithromycin	751 (81.9)	26 (83.9)	0.779	36 (83.7)	0.761
Remdesivir	39 (4.3)	0 (0)	0.226	2 (4.7)	0.559
Ceftriaxone	528 (57.6)	24 (77.4)	0.028	32 (74.4)	0.029
Ceftaroline	26 (2.8)	2 (6.5)	0.232	5 (11.6)	0.001
Immunomodulatory treatment					
Tocilizumab	200 (21.8)	5 (16.1)	0.450	16 (37.2)	0.018
Methylprednisolone	238 (26)	9 (29)	0.701	25 (58.1)	<0.001
Dexamethasone	23 (2.5)	4 (12.9)	0.01	8 (18.6)	<0.001
Length of hospital stay	9 (5–15)	8 (4.5–11.5)	0.565	20 (11–27.75)	<0.001
ICU admission	109 (11.9)	8 (25.8)	0.02	29 (67.4)	<0.001
Length of ICU admission	3 (1–10)	3 (0–9)	0.888	5 (0.5–20)	0.095
Death	86 (9.4)	5 (16.1)	0.21	8 (18.6)	0.047

Data are shown as median (interquartile range) or *n* (%). Two patients with community-acquired co-infection developed hospital-acquired superinfections.
COVID-19, coronavirus disease 2019; ICU = intensive care unit.
[a] Comparison of patients without infection versus patients with community-acquired co-infection.
[b] Comparison of patients without infection versus patients with hospital-acquired superinfection.

COVID-19 diagnosis. Two of these co-infections were with different bacteria. *S. pneumoniae* (one patient had a *Moraxella catarrhalis* co-infection) and *S. aureus* (one patient had a *Haemophilus influenzae* co-infection) were the most common bacteria in this scenario. Two patients had infections caused by methicillin-resistant *S. aureus*. Diagnosis of community-acquired bacterial co-infection was performed with one or more of the following tests: urinary antigen test in 12 cases; good-quality sputum, two; and blood cultures, one.

Viral community-acquired co-infection was detected in seven (0.6%) of 989 patients, of whom one presented with bacterial co-infection as well; there were four cases of *Influenza* A virus co-infection one of *Influenza*B virus, one of respiratory syncytial virus and one of herpetic disease. Two (28.6%) of these seven patients, with *Influenza*A and *Influenza*B virus co-infection respectively, died.

Hospital-acquired superinfections

A total of 51 hospital-acquired superinfections were documented in 43 patients. Of these, 44 were bacterial and were diagnosed in 38 patients (3.8%). The mean (SD) time from hospital admission to superinfection diagnosis was 10.6 (6.6) days. Of these 44 superinfections, 25 (56.8%) occurred in patients admitted to the ICU. The most frequently isolated microorganisms were *P. aeruginosa* (n = 8), *E. coli* ($n = 6$), *Klebsiella* spp. ($n = 5$), and *S. aureus* ($n = 5$). The most common hospital-acquired superinfections were those of the respiratory tract and bacteraemia. Multidrug-resistant Gram-negative bacteria were isolated in seven patients: multidrug-resistant *P. aeruginosa* infection (n = 3), extended-spectrum β-lactamase (ESBL) *E. coli* (n = 2) and ESBL *K. pneumoniae* (n = 2).Table 3 details epidemiology of all bacterial co-infections and superinfections.

Seven (0.7%) of 989 patients had fungal hospital-acquired superinfections; three cases were caused by *Aspergillus fumigatus* and four by *Candida albicans*. Two patients were diagnosed with bacterial and fungal superinfections. All three patients with tracheobronchitis caused by *A. fumigatus* had prior lung disease and a median (IQR) age of 75 (70–75) years. These patients were also critically ill and received mechanical ventilation support and high doses of corticosteroid. In this series of patients, only one died. Patients with *C. albicans* superinfection had the following clinical syndromes: two cases of candidaemia in an ICU setting, one case of a nosocomial urinary tract infection related to a urinary catheter and one case of a complicated intra-abdominal infection. Two patients died.

Outcomes

Overall mortality for patients hospitalized with COVID-19 for ≥48 hours was 9.8% (97/989). Table 1 details the most important outcomes in hospitalized patients with COVID-19 who presented without infection, those with community-acquired co-infection and those with hospital-acquired superinfection. Remarkably, patients with community-acquired co-infections were admitted to the ICU more frequently. Compared to those without infection, patients with hospital-acquired superinfections had prolonged length of hospital stay and higher mortality.

Discussion

We present a large series of patients from a Spanish region dramatically affected by the COVID-19 pandemic, focusing on

Table 2
No. of microbiology tests ordered and positive results with clinical significance in patients with COVID-19

Test	No. of patients with positive results/no. total patients	No. of patients with positive results/no. tested patients	No. of tests with positive results/no. total tests
Blood culture	16/989 (1.6%)	16/267 (5.9%)	37/680 (5.5%)
Urine culture	19/989 (1.9%)	19/337 (5.6%)	19/717 (2.6%)
Respiratory sample (non −COVID-19)	25/989 (2.5%)	25/252 (9.9%)	23/845 (2.7%)
Pneumococcal urinary antigen	12/989 (1.2%)	12/230 (5.2%)	12/234 (5.1%)
Influenza A PCR	4/989 (0.4%)	4/248 (1.6%)	5/252 (1.9%)
Influenza B PCR	2/989 (0.2%)	2/250 (0.8%)	2/255 (0.8%)
Respiratory syncytial virus PCR	1/989 (0.1%)	1/251 (0.4%)	1/256 (3.9%)
Other respiratory virus PCR[a]	0/989	0/5	0/16

COVID-19, coronavirus disease 2019.
[a] Five patients underwent PCR testing for *Influenza* C, human *Metapneumovirus*, and *Parainfluenza* 1, 2, 3 and 4. All results were negative.

Table 3
Detailed epidemiology of microbiologic documented bacterial infections in 74 patients hospitalized with COVID-19

Bacterial co-infection	*n*/*N* (%)
Infection at COVID-19 diagnosis	30/74 (40.5)
Community-acquired pneumonia co-infection	21/30 (70)
Streptococcus pneumoniae	12/21 (57.1)
Staphylococcus aureus	6/21 (28.6)
Haemophilus influenzae	2/21 (9.5)
Moraxella catarrhalis	1/21 (4.8)
Lower respiratory co-infection in patients with bronchiectasis	2/30 (6.6)
Pseudomonas aeruginosa	2/2 (100)
Concurrent urinary tract infection	7/30 (23.3)
Escherichia coli	1/7 (14.2)
Klebsiella pneumoniae	1/7 (14.2)
Enterococcus faecium	1/7 (14.2)
Proteus mirabilis	1/7 (14.2)
Citrobacter koseri	1/7 (14.2)
S. aureus	1/7 (14.2)
Hospital-acquired superinfections complicating patients admitted for COVID-19	44/74 (59.5)
Ventilator-associated pneumonia	11/44 (25)
S. aureus	4/11 (36.4)
P. aeruginosa	3/11 (27.3)
Stenotrophomonas maltophilia	2/11 (18.2)
K. pneumoniae	1/11 (9)
Serratia marcescens	1/11 (9)
Hospital-acquired pneumonia	4/44 (9)
S. aureus	1/4 (25)
P. aeruginosa	1/4 (25)
S. maltophilia	1/4 (25)
K. pneumoniae	1/4 (25)
Bacteraemia	16/44 (36.3)
Coagulase-negative staphylococci	7/16 (43.7)
P. aeruginosa	3/16 (18.7)
E. faecium	3/16 (18.7)
E. coli	2/16 (12.5)
Streptococcus anginosus	1/16 (6.2)
Urinary tract infection	12/44 (27.3)
E. coli	4/12 (33.5)
K. pneumoniae	3/12 (25)
Enterococcus faecalis	2/12 (16.7)
E. faecium	1/12 (8.3)
P. aeruginosa	1/12 (8.3)
S. marcescens	1/12 (8.3)
Polymicrobial intra-abdominal infection (*E. coli, E. faecium, E. faecalis*)	1/44 (2.3)

Some patients had more than one bacterial infection.
COVID-19, coronavirus disease 2019.

describing community-acquired co-infections and hospital-acquired superinfections in these patients. Remarkably, bacterial pneumonia co-infection in patients hospitalized for COVID-19 was lower compared to co-infections occurring in patients with other respiratory virus infections, such as *influenza* H1N1 or *influenza* H3N2 [6,8,11,12]. A minority of patients had bacterial or fungal superinfections and co-infections caused by other viruses.

Our results are concordant with a recent review that summarized nine studies reporting data concerning co-infections in patients with COVID-19. An 8% rate for bacterial and fungal co-infections was described [13]. In a recent letter, Kim et al. [14] reported relatively low rates (ranging from 0 for most pathogens to 12% in rhinovirus/enterovirus) of co-infections between SARS-CoV-2 and other respiratory pathogens. Bacterial community-acquired

pneumonia co-infections documented in our cohort have been especially low. Considering the high number and severity of bacterial co-infections previously reported in patients with *influenza* H1N1 and H3N2 [6–9], at the arrival of the COVID-19 pandemic, our hospital protocol recommended the initiation of antibiotic therapy for all hospitalized patients with COVID-19. Experience acquired within the first few weeks led us to reconsider this approach so as to administer empiric antibiotic therapy solely to patients who were admitted for COVID-19 and who presented with a chest X-ray suggestive of bacterial infection, need for direct ICU admission or severe immunocompromised condition. Our results support the avoidance of antibiotic therapy in most patients hospitalized for COVID-19. The reason why bacterial co-infections are so low in patients with COVID-19 is unknown; it is tempting to speculate that some immunologic factors like macrophage hyperactivation play a role. Nonetheless, when bacterial co-infection is suspected, we recommend an antibiotic approach with optimal *S. aureus* coverage, such as ceftaroline or ceftriaxone/cefazolin plus levofloxacin, in areas with low methicillin-resistant *S. aureus* prevalence.

Frequency of hospital-acquired superinfections remained low even though many patients were undergoing treatment resulting in severe immunosuppression. Some factors may provide an explanation for this observation, including empiric antibiotic use, isolation measures or host macrophage activation. Further, the lack of additional microbiologic tests after SARS-CoV-2 was detected may have also contributed. Further studies will be needed to elucidate the role of each measure in decreasing superinfections. Superinfections have been mainly related to ICU admission, especially with the use of mechanical ventilation and catheters; expected epidemiology linked closely to the predominant hospital flora. In our study, the rate of multidrug-resistant infections was relatively low, possibly as a result of the impact of COVID-19 isolation measures precluding horizontal transmission among patients.

Aspergillosis complicating COVID-19 was clinically quite different and not as frequent as that observed in patients with *influenza* [12,13]. In patients with COVID-19, aspergillosis usually manifested as tracheobronchitis, especially in association with patients with prior lung disease, prolonged mechanical ventilation and high immunosuppressor dose. We think that this fact may also be partly related to the different immunologic dysfunctions in *influenza* and COVID-19 infections [11,13,15]. Macrophages are the key host cell in fighting *Aspergillus* spp. as a result of their involvement in *Aspergillus* spore recognition [16]. Patients admitted with COVID-19 also had *Candida* spp. superinfections, mainly related to parenteral nutrition and urinary catheters.

Anecdotal cases of co-infections during SARS-CoV-2 and other viral infections have been previously reported [16–19]. Our results support the notion that respiratory virus community-acquired co-infection is relatively uncommon in hospitalized patients with COVID-19. However, viral co-infections could lead to severe diseases, and this study was conducted in a mostly non-*influenza* season (incidence could vary in fall/winter).

Overall mortality in the cohort of patients hospitalized ≥48 hours was 9.8%. We found that patients with other infections had worse outcomes, prolonged length of hospital stay, higher rates of ICU admission and increased mortality. These finding are in agreement with previous studies, which documented an association between co-infection in respiratory virus pandemics and poor prognosis [6–8]. However, this is unadjusted to baseline patients' characteristics and cannot be completely attributed to co-infection and/or superinfections.

The strengths of this study comprise the large number of patients included, as well as the clear, complete collection of clinical and microbiologic data. However, our study does have some major limitations that should be acknowledged. Firstly, this is a retrospective study reporting clinically significant, microbiologically documented infections. However, no systematic testing for co-infections was performed, and it is possible that either some attending physicians did not order microbiologic tests for their patients or some patients may have had co-infections or superinfections that were not documented by the microbiologic tests performed. One concern our team had is whether initial challenges arising during the management of patients with COVID-19 potentially decreased the number of requests for microbiologic tests to rule out other infections. Despite this, infection rates reported in our study remained low, even in patients in whom urinary antigen testing or other types of test had been performed. Secondly, we described a cohort of patients currently discharged or dead. Some patients with severe COVID-19 infection that required ICU admission, mechanical ventilation and prolonged length of hospital stay remain hospitalized. It is conceptually easy to believe that superinfection is higher in this population. Thirdly, respiratory RT-PCR techniques used were limited to the virus. PCR testing for the detection of atypical pathogens was not performed in our patients. Additionally, and as we mention above, we initially treated all hospitalized patients with antibiotics within the first few weeks; the impact of such a practice in preventing superinfections remains unknown. That stated, these four limitations might underestimate the frequency of co-infections or superinfections in patients with COVID-19. Lastly, this study was conducted at a single centre, which may have influenced our descriptions of nosocomial infections. Frequency and microbiologic epidemiology may also vary significantly according to different geographical contexts.

In conclusion, bacterial, fungal and viral co-infections and superinfections in hospitalized patients with COVID-19 are low; however, when present, they may cause severe diseases with worse outcomes. *S. pneumoniae* and *S. aureus* are the most common pathogens to cause community-acquired pneumonia co-infections. In our area, *P. aeruginosa* and *E. coli* were frequent bacteria that caused hospital-acquired superinfections. Our findings are important when defining the role of empiric antimicrobial therapy or stewardship strategies in hospitalized patients with COVID-19.

Transparency declaration

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