Bacterial and Fungal Co-infection in a Cohort of 333 Patients Hospitalized for COVID-19 (COINFECOVID Study)

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1 BACTERIAL AND FUNGAL CO-INFECTION IN A COHORT OF 333 PATIENTS
2 HOSPITALIZED FOR COVID-19 (COINFECOVID STUDY)

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13 **BACTERIAL AND FUNGAL CO-INFECTION IN A COHORT OF 333 PATIENTS**
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22

23 **ABSTRACT**

24 **Background:** Coinfections in COVID19 appear to worsen hospitalized patients
 25 prognosis.

26 **Objective:** To describe the characteristics of bacterial and fungal coinfections in
 27 patients admitted for COVID19 and to identify the risk factors associated with its
 28 occurrence.

29 **Patients and Methods:** Single-center retrospective study reviewing medical records of
 30 patients with COVID19 diagnosed with bacterial or fungal infection during hospital
 31 admission.

32 **Results:** 333 patients were analyzed during March 15-May 15, 2020. 16.82% had some
 33 coinfection during admission. Coinfections were more frequent in patients with
 34 comorbidities (80.36% vs 19.64% p<0.025) and in those ICU admitted (52.46% vs
 35 8.86%, p<0.001). Coinfections were significantly more frequent in patients with
 36 neutrophilia>7500 and increased procalcitonin on admission as well as
 37 lymphopenia<1500 on day 5. Mortality in patients with coinfection was 26.79% vs
 38 23.47% in non-coinfected (p 0.596). Length of stay was longer in coinfecting patients
 39 (mean 30.59 vs 13.47, p<0.01). Most frequent microorganisms were *Enterococci*,
 40 *Candida spp*, *Enterobacteriaceae* and *Pseudomonas spp*. 74% of patients received
 41 ceftriaxone: 17.34% of those treated had a coinfection compared to 15.48% not
 42 treated (p 0.694).

43 **Conclusions:** Occurrence of coinfections is frequent and prolongs hospital stay without
 44 influencing mortality. The presence of comorbidities and ICU stay were identified as
 45 the main risk factor for coinfection, while increased neutrophils and procalcitonin at
 46 admission and lymphopenia during evolution were the main biological predictors.
 47 *Enterococcus* was the most frequent pathogen. Ceftriaxone use does not protect
 48 against appearance of bacterial infections. *C. albicans* was the most frequently isolated
 49 fungus and was associated with prolonged ICU stay.

50 **KEY WORDS:** Bacterial and fungal Co-infections, Antibiotics, Ceftriaxone, COVID-19,
 51 SARS-COV-2

52 INTRODUCTION

53 The abrupt onset of the SARS-COV-2 pandemic has required the rapid adjustment of
54 Health Systems and their care protocols in the absence, in many cases, of adequate
55 scientific evidence to support decision making

56 Bacterial and fungal coinfections in COVID 19 patients are a matter of concern for
57 clinicians. Very few studies have specifically evaluated COVID-19-associated
58 superinfections and the issue is far from clear (1). However, in clinical practice,
59 hospitalized patients with COVID-19 are frequently treated with antibiotics (2) and, in
60 fact, the use of ceftriaxone is very common on admission in many hospital protocols.

61 As has long been known viral respiratory infections predispose patients to co-
62 infections and these can be responsible for increased disease severity and higher
63 mortality. *In vitro* and animal studies demonstrate viral-bacteria synergy promoted by
64 enhanced bacterial adherence and immune-mediated interactions (3). Most deaths in
65 the 1918 Spanish flu were due to secondary bacterial infection (4) and a worse course
66 has also been associated with secondary bacterial infections in the 2009 H1N1
67 pandemic (5). Severe influenza was also been associated with high mortality invasive
68 pulmonary aspergillosis (6). Given the homology with influenza, it was foreseeable to
69 expect the appearance of co-infections in patients with more severe COVID-19. Based
70 on earlier experience with influenza, the use of broad-spectrum antimicrobials in
71 severely ill hospitalized patients is to either prevent or to manage hospital acquired
72 infections or when a concomitant bacterial pulmonary infection is suspected at
73 admission (7). Therefore, antimicrobial treatment has an important role in the
74 management of patients with COVID-19 with suspected or documented concomitant
75 bacterial or fungal infection. As mentioned above, patients hospitalized with COVID-19,
76 especially the more severe forms, are frequently treated with antibiotics (8,9,10),
77 although bacterial infection is rare on admission (11). Clinical and/or radiological
78 presentation of SARS-CoV2 infection on admission may be similar to that of atypical
79 bacterial pneumonia. In addition, during the course of evolution, the appearance of
80 pulmonary infiltrates in the inflammatory phase of the lung may be difficult to
81 distinguish from hospital-acquired pneumonia. In fact, the diagnosis of mechanical
82 ventilator-associated bacterial pneumonia in a patient with respiratory distress
83 COVID19 related can be extremely difficult (12). Thus, clinicians continue to struggle
84 with ruling out bacterial respiratory infection in patients with COVID19.

85 Consequently, the empirical use of broad-spectrum antibiotics is common and even
86 reasonable in patients at risk of poor progression. Although the limited literature
87 available is not unanimous, bacterial and fungal co-infections appear to worsen the
88 prognosis of patients and are a major cause of concern for clinicians caring for patients
89 with COVID-19. Secondary bacterial infections develop in patients during or after initial
90 infection and can be associated with high morbidity and mortality rates. At least one

in seven COVID-19 patients was found to be additionally infected with a secondary bacterial infection with 50% of the fatalities caused by secondary bacterial infection (pulmonary or other) (13). Nevertheless, the indiscriminate use of antibiotics has been associated with the development of bacterial resistance and the limitation of future treatment options. For that reason, it is essential to be able to adequately identify patients at risk of co-infection in order to institute early treatment while avoiding overuse of antibiotics. Antimicrobial Stewardship programs will play a key role in limiting unnecessary antibiotic use and antimicrobial resistance consequences (1). Serum biomarkers such as procalcitonin (PCT) have been used as a guide to antibiotic therapy in patients with respiratory tract illnesses without an increased frequency of adverse outcomes (14). The absence of data suggesting coinfection would allow suspending or avoiding the initiation of antibiotherapy. On the other hand, the idiosyncrasy of each center with regard to the endemia of certain healthcare-associated infections and in particular of our hospital for carbapenemase-producing enterobacteriaceae and *Candida auris* infections (15) means that the descriptions of the frequency of nosocomial infections associated with COVID-19 cannot be extrapolated and that the therapeutic protocols must necessarily be adapted to the local epidemiological reality.

OBJECTIVE: To describe the characteristics of bacterial and fungal coinfection in patients admitted for COVID19 and to identify the risk factors potentially associated with its occurrence.

PATIENTS AND METHODS: Single-center retrospective study reviewing the electronic medical records of patients with COVID19 diagnosed with bacterial or fungal infection during admission to a general university hospital serving a population of 371,871 inhabitants. Statistical analysis of the variables was performed using the SPSS program for Windows, version 23.0 (IBM Corp., Armonk, NY, USA), using Chi-square tests to compare proportions of qualitative variables, Kolmogorov-Smirnov to test the normality of quantitative variables, Student's t test for comparison of means of normal variables, and nonparametric Mann-Whitney U test for comparison of medians of age and sex. Finally, to identify variables that could be considered risk factors (calculation of odd ratio, OR), univariate and multivariate analyses were performed using multiple logistic regression.

RESULTS: We analyzed 333 patients admitted during the period March 15-May 15, 2020 whose median age was 72 years, 53.75% male and 46.25% female. Cultures obtained from clinically significant samples were studied. Epidemiological surveillance cultures were not considered for analysis in this study. 56 patients (16.82%) had some bacterial or fungal coinfection at any time during admission. The median age of patients without coinfection was 68.88 years while the median age of patients with coinfection was 72.36 (p 0.31). Coinfections were more frequent in patients with previous comorbidities (80.36% vs 19.64% p<0.025) and in those admitted to ICU

131 receiving mechanical ventilation (52.46% vs 8.86%, $p < 0.001$). The most frequent type
132 of infection seen was ventilator-associated pneumonia (VAP) followed by bacteremia
133 and urinary tract infections (UTIs). The most frequent microorganisms isolated in
134 clinical samples are detailed in Figure 1. The median number of days until the
135 appearance of coinfection was 18 (range 10-27.5). Table 1 shows the main factors
136 associated with an increased risk of presenting a coinfection in the univariate analysis.
137 In the multivariate analysis, the following were risk factors for coinfection: length of
138 stay > 15 days, renal failure, PCT day 1 > 5, ICU admission. Mortality in patients with
139 coinfection was 26.79% vs 23.47% in those without coinfection, with no significant
140 differences ($p = 0.596$). Significant differences were observed in the number of days of
141 stay with or without coinfection (mean 30.59 vs 13.47, $p < 0.01$). Patients admitted to
142 the ICU showed a significant higher frequency of coinfections. The microorganisms
143 isolated are detailed in Table 2. The 7 patients with candidemia (2 *C. albicans*, 4 *C.*
144 *auris*, 1 *C. parapsilosis*) had a median ICU length of stay of 36.4 days and only one of
145 them died. 246 of the total number of patients (74%) received ceftriaxone, 64.86% at
146 admission, and up to 87.69% of patients received any antibiotic at some point during
147 hospital stay. In the group of patients with coinfections, 15.48% had not received
148 ceftriaxone compared to 17.34% who had been administered the drug ($p = 0.694$). The
149 use of antibiotic therapy at admission was not a protective factor for the occurrence of
150 coinfection (OR = 0.979, 95% CI 0.879 – 1.090). *Enterococcus spp.* infection appeared
151 in 6.50% of those who received ceftriaxone vs. 4.60% of those not treated ($p = 0.52$) and
152 *Candida spp.* in 7.72% vs. 6.90% ($p = 0.801$). Treatment with carbapenems increased the
153 risk of enterococcal coinfection (OR = 5.776, 95% CI 2.451 – 13.616). The most relevant
154 biological parameters are detailed in Table 3. We found statistically significant
155 differences in the occurrence of coinfections in patients with neutrophilia <7500 and
156 increased procalcitonin on admission as well as lymphopenia < 1500 on day 5 of
157 evolution.

158 **Table 1. Variables associated with risk of coinfection in univariate analysis**

	p value	OR	IC 95%
Length of stay > 15 days	< 0.01	6.388	3.432 – 11.891
Any comorbidity	< 0.025	1,964	1,058 – 3,643
Renal insufficiency	0.049	1,851	1,029 -3,330
Lymphocytes at day 5 < 1500	0.004	3,214	1,330 – 7,770
Day 1 neutrophils > 7500	0.03	2,050	1,282 – 3,280
PCT day 1 $\geq$ 2	0.41	2,378	1,202 – 4, 701
PCT day 1 $\geq$ 5	0,25	2.80	1.433 – 5.748
ICU admission	< 0.01	5.923	3.775 – 9.295
Carbapenem treatment	< 0.01	4.075	2.590 – 6.411

160 **Figure 1. Microorganisms Frequency (%) as a proportion of the total number of**
 161 **isolations (n=56)**

162

163 **Table 2. Frequency of microorganisms according to ICU admission**

Microorganism (%)	NO	YES
<i>S. aureus</i>	0,4	8,2
<i>CN Staphylococcus</i>	1,1	4,9
<i>Enterococcus</i>	3	19,7
Resistant <i>Enterobacteriaceae</i>	1,5	8,2
Resistant <i>Pseudomonas spp</i>	0,4	13,1
<i>Acinetobacter spp</i>	0	13,1
<i>C. albicans</i>	1,5	13,1
<i>C. non albicans non auris</i>	1,1	8,2
<i>C. auris</i>	0,4	8,2
Toxigenic <i>C. difficile</i>	0	1,6

166

167

168 Table 3. **Biological parameters in patients with coinfections**

		%	p value
Neutrophils day 1			
<7500		≥7500	0.003
12.97		26.60	
Neutrophils day 5			
<7500		≥7500	0.8006
17.54		18.84	
Lymphocytes day 1			
<1500		>1500	0.426
17.58		13.3	
Lymphocytes day 5			
<1500		>1500	0.004
22.96		7.14	
C-reactive protein day 1			
<1		1-5	0.118
3.70		15.31	
		>5	
19.12			
C-reactive protein day 5			
<1		1-5	
15.73		15.38	
		>5	
24.24			
Procalcitonin day 1			
<2		2-5	0.010
16.07		33.33	
		>5	
50			
Procalcitonin day 5			
<2		2-5	0.324
16.88		25	
		>5	
40			

DISCUSSION: The appearance of coinfections during admission is frequent in patients with COVID19 and has a negative impact on the prolongation of hospital stay in our series, without influencing mortality. The frequency of coinfections is higher in our series than in others in our immediate geographical area (16).

The presence of comorbidities and ICU stay are identified as the main risk factors for occurrence. The higher incidence of bacterial and fungal infections in patients admitted to the ICU may be explained by the mechanical ventilation itself and by the increased lung damage caused by higher viral replication resulting in cytokine storm and dysregulation of the immune system of the host (17). In contrast, we found no significant differences in mortality in patients with coinfections. Other authors have described a frequency of pulmonary superinfection between 8 and 32%, although these infections are not usually directly related to the cause of death (18).

Enterococcus was the most frequently isolated microorganism in patients with coinfections. The high relative frequency of enterococcal infections could be explained by the high empirical use of ceftriaxone, although the small number of patients who did not receive it does not allow us to observe differences. Also, the higher frequency of enterococcal infections found in patients receiving carbapenems could be related to greater severity of the clinical condition of these patients. In our series, use of ceftriaxone has not been shown to be protective against the subsequent appearance of bacterial infections although it is not associated with a higher frequency of candidiasis. The episodes of invasive candidiasis detected (all catheter-related candidemia) occurred in patients admitted to the intensive care unit with specific risk factors associated with prolonged stay. Other series describe a lower frequency of invasive candidiasis, all of them caused by *C. albicans* and also related to line-infections, with no differences with patients with influenza (19). The endemic nature of *C. auris* infections in our center (15) probably explains the higher frequency found of invasive *Candida* infections. In our experience, mortality of invasive candidiasis is lower compared to that observed in other series. We do not have a clear explanation for this, but it could be related to our experience in the treatment of *C. auris* infections and early initiation of targeted antifungal therapy. A low frequency of other proven invasive fungal infections like aspergillosis and other has been described by authors in our country and has been related to the scarcity of invasive diagnostic techniques and post mortem studies due to the risk of contagion (20). However, these authors warn about the need to be alert to the presence of fungal markers in clinical samples and to initiate early antifungal treatment if necessary.

In our series, C-reactive protein values are of no value in predicting the possible presence of bacterial or fungal coinfection. On the contrary, PCT could be a good predictor of the presence of coinfection at the time on admission although its role seems to be more useful to rule out concomitant bacterial infection than to confirm it. Other authors have also reported that elevated PCT values at admission correlated

210 with a higher risk of concomitant bacterial infection (21). PCT is a useful marker for the
211 diagnosis, prognosis and follow-up of bacterial infections. In routine clinical practice,
212 its use has effectively reduced antibiotic drug use for lower respiratory tract infection
213 without increasing the risk of complications (22). PCT high levels at day 1 may be an
214 indicator of presence of bacterial coinfection in COVID-19 but it would be more useful
215 in helping to save the use of antibiotics in patients with normal values (23).

216 According to our findings, empirical use of antibiotics should be reserved for severely
217 ill COVID-19 patients, with constant reassessment of their necessity and should be
218 stopped as early as possible if the bacterial or fungal coinfection is reasonably ruled
219 out.

220 **DECLARATIONS**

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222 **Conflicts of interest:** The authors declare that they have no conflicts of interest

223 **Ethical approval:** The present study (registration number 95/2020) was authorized by
224 the research ethics committee of the Consorcio Hospital General Universitario de
225 Valencia (Spain).

226 **Consent to participate:** An exemption of written informed consent was approved by
227 the research ethics committee of the Consorcio Hospital General Universitario de
228 Valencia (Spain)

229 **Author contribution:** All authors contributed to the study conception and design. Data
230 collection were performed by Paz Herrero, Javier Pitarch, Fernando Alonso, Mercedes
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234 Emilio Ballester. The work teams were coordinated by Miguel G. Deltoro and
235 Concepción Gimeno. Statistical analysis was performed by Neus Gómez and Hilary
236 Piedrahita. The manuscript was written by Vicente Abril. All authors read and approved
237 the final manuscript.

238 **Consent for publication:** All authors consented to publish this study

239 **Data Availability:** The data supporting the findings of this study are available within
240 the corresponding author.

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