

Bacterial and fungal co-infection in a cohort of 333 patients hospitalized for Covid-19 (Coinfecovid study)

Vicente Abril^{1*}; Neus Gómez¹; Hilary Piedrahita²; Mercedes Chanzá³; Nuria Tormo³; Francisco Sanz⁴; Francesc Puchades⁵; Pilar Ortega⁶; Carolina Ferrer⁷; COINFECOVID collaborative group

¹Infectious Diseases, Consorcio Hospital General Universitario, Valencia, Spain.

²Preventive Medicine, Consorcio Hospital General Universitario, Valencia, Spain.

³Microbiology, Consorcio Hospital General Universitario, Valencia, Spain.

⁴Pneumology, Consorcio Hospital General Universitario, Valencia, Spain.

⁵Internal Medicine, Consorcio Hospital General Universitario, Valencia, Spain.

⁶Hospital Pharmacy, Consorcio Hospital General Universitario, Valencia, Spain.

⁷Anesthesiology and Reanimation, Consorcio Hospital General Universitario, Valencia, Spain.

*Corresponding Author: Vicente Abril

Infectious Diseases, Consorcio Hospital General Universitario, Valencia, Spain.

Email: vicente.abril.lopezdemedrano@gmail.com

Abstract

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

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

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

Results: 333 patients were analyzed during March 15-May 15, 2020. 16.82% had some coinfection during admission. Coinfections were more frequent in patients with comorbidities (80.36% vs 19.64% p7500 and increased procalcitonin on admission as well as lymphopenia <1500 on day 5. Mortality in patients with coinfection was 26.79% vs 23.47% in non-coinfected (p 0.596). Length of stay was longer in coinfecting patients (mean 30.59 vs 13.47, p<0.01). Most frequent microorganisms were Enterococci, Candida spp, Enterobacteriaceae and Pseudomonas spp. 74% of patients received ceftriaxone: 17.34% of those treated had a coinfection compared to 15.48% not treated (p 0.694).

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

Keywords: bacterial and fungal co-infections; antibiotics; ceftriaxone; COVID-19; SARS-COV-2.

Introduction

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

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

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

Consequently, the empirical use of broad-spectrum antibiotics is common and even reasonable in patients at risk of poor progression. Although the limited literature available is not unanimous, bacterial and fungal co-infections appear to worsen

the prognosis of patients and are a major cause of concern for clinicians caring for patients with COVID-19. Secondary bacterial infections develop in patients during or after initial 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 receiving mechanical ventilation (52.46% vs 8.86%, p<0.001). The most frequent type of infection seen was ventilator-associated pneumonia (VAP) followed by bacteremia and urinary tract infections (UTIs). The most frequent microorganisms isolated in clinical samples are detailed in Figure 1. The median number of days until the appearance of coinfection was 18 (range 10-27.5). Table 1 shows the main factors associated with an increased risk of presenting a coinfection in the univariate analysis. In the multivariate analysis, the following were risk factors for coinfection: length of stay > 15 days, renal failure, PCT day 1 > 5, ICU admission. Mortality in patients with coinfection was 26.79% vs 23.47% in those without coinfection, with no significant differences (p 0.596). Significant differences were observed in the number of days of stay with or without coinfection (mean 30.59 vs 13.47, p<0.01). Patients admitted to the ICU showed a significant higher frequency of coinfections. The microorganisms isolated are detailed in Table 2. The 7 patients with candidemia (2 *C. albicans*, 4 *C. auris*, 1 *C. parapsilosis*) had a median ICU length of stay of 36.4 days and only one of them died. 246 of the total number of patients (74%) received ceftriaxone, 64.86% at admission, and up to 87.69% of patients received any antibiotic at some point during hospital stay. In the group of patients with coinfections, 15.48% had not received ceftriaxone compared to 17.34% who had been administered the drug (p 0.694). The use of antibiotic therapy at admission was not a protective factor for the occurrence of coinfection (OR = 0.979, 95% CI 0.879 – 1.090). Enterococcus spp. infection appeared in 6.50% of those who received ceftriaxone vs. 4.60% of those not treated (p 0.52) and Candida spp. In 7.72% vs. 6.90% (p 0.801). Treatment with carbapenems increased the risk of enterococcal coinfection (OR = 5.776, 95% CI 2.451 – 13.616). The most relevant biological parameters are detailed in Table 3. We found statistically significant differences in the occurrence of coinfections in patients with neutrophilia <7500 and increased procalcitonin on admission as well as lymphopenia <1500 on day 5 of evolution.

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 ≥ 2	0.41	2,378	1,202 – 4, 701
PCT day 1 ≥ 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

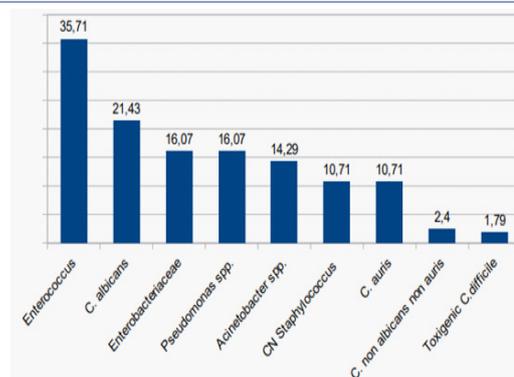


Figure 1: Variables associated with risk of coinfection in univariate analysis.

Table 2: Frequency of microorganisms according to ICU admission.

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

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

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		0.426
22.96		7.14		
C-reactive protein day 1				
<1	1-5	>5		
3.70	15.31	19.12		0.118
C-reactive protein day 5				
<1	1-5	>5		
15.73	15.38	24.24		
Procalcitonin day 1				
<2	2-5	>5		
16.07	33.33	50		0.010
Procalcitonin day 5				
<2	2-5	>5		
16.88	25	40		0.324

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 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 10 with a higher risk of concomitant bacterial infection [21]. PCT is a useful marker for the diagnosis, prognosis and follow-up of bacterial infections. In routine clinical practice, its use has effectively reduced antibiotic drug use for lower respiratory tract infection without increasing the risk of complications [22]. PCT high levels at day 1 may be an indicator of presence of bacterial coinfection in COVID-19 but it would be more useful in helping to save the use of antibiotics in patients with normal values [23].

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

Declarations

Funding: No funds were used for this research

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

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

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

Author contribution: All authors contributed to the study conception and design. Data collection were performed by Paz Herrero, Javier Pitarch, Fernando Alonso, Mercedes Chanzá, Nuria Tormo, Francisco Sanz, Francesc Puchades, Pilar Ortega, Carolina Ferrer María Martínez, Johana Gutiérrez, Magdalena García, Carmen Ricart, Mercedes Melero, Juan Monzó, José Ignacio Mateo, Mónica Descalzo, Santiago Pintos and José Emilio Ballester. The work teams were coordinated by Miguel G. Deltoro and Concepción Gimeno. Statistical analysis was performed by Neus Gómez and Hilary Piedrahita. The manuscript was written by Vicente Abril. All authors read and approved the final manuscript.

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

COINFECVID collaborative group members: Paz Herrero¹; Javier Pitarch¹; Fernando Alonso¹; María Martínez²; Concepción Gimeno³; Miguel G. Deltoro²; Johana Gutiérrez²; Magdalena García²; Carmen Ricart²; Juan Monzó²; José Ignacio Mateo²; Mercedes Melero⁴; Santiago Pintos²; Mónica Descalzo²; José Emilio Ballester²

¹Internal Medicine. ²Infectious Disease. ³Microbiology. ⁴Preventive Medicine

Consorcio Hospital General Universitario. Valencia (Spain).

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