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Bacterial co-infections in COVID-19 pneumonia in a tertiary care hospital: Surfing the first wave

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ABSTRACT

The aim of this study is to review bacterial isolates from respiratory samples of patients with severe COVID-19 disease during the first 2 months of the first wave in our hospital. A single-center retrospective observational study in critically ill adult patients was performed. A total of 1251 respiratory samples from 1195 patients were processed. Samples from 66 patients (5.52%) were determined to be microbiologically significant by a semi-quantitative culture. All patients received broad spectrum antibiotherapy as an empirical treatment. The isolated bacteria were mainly *Enterobacterales* followed by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Bacterial co-infections in ICU stay could seem not dependent on the virus that has produced the viral pneumonia similarly as with other respiratory viruses such as Influenza virus.

1. Introduction

The pandemic yield by SARS-CoV-2 has been ongoing for more than one year. Around 178 million cases and 3.8 million deaths have been reported up to June 2021 by the World Health Organization (WHO) (World Health Organization, 2021). This virus can cause community-acquired pneumonia and hospital-acquired pneumonia with an important rate of Intensive Care Unit (ICU) admissions (Koehler et al., 2020; Zhou et al., 2020). Due to the long-term intubation, bacterial and fungal infections (Koehler et al., 2020; Zhou et al., 2020; Schawvlieghe et al., 2018) are a frequent complication of viral pneumonias as reported in Influenza virus infections (Olli et al., 2011; Abelenda-Alonso et al., 2020) and also in SARS-CoV-2 infections (Olli et al., 2011; Falces-Romero et al., 2020; David et al., 2020). There are no guidelines for managing viral, bacterial or fungal co-infections with SARS-CoV-2, but 200 million viral community-acquired pneumonias occur every year (Olli et al., 2011) and many studies have addressed the issue of viral pneumonia and bacterial co-infections (Koehler et al., 2020; Zhou et al., 2020; Schawvlieghe et al., 2018; Olli et al., 2011; Falces-Romero et al., 2020; David et al., 2020; Wu et al., 2020). The aim of this study is to review bacterial isolates from respiratory samples of patients with severe COVID-19 during the first two months of the first wave of maximum incidence in our hospital. During this period the population attended in our hospital was only COVID patients as described by Borobia et al. (Borobia et al., 2020).

2. Material and methods

Single-center retrospective observational study of patients with positive RT-PCR for SARS-CoV-2 and significative semi-quantitative bacterial culture in respiratory samples during the first wave of the pandemic in our hospital (March-April 2020), a 1268 bed third level hospital in Madrid covering urban and rural areas. Demographic data (gender, age), risk factors and clinical characteristics (malignancies, antibiotherapy and anti-COVID-19 therapy, ICU stay and outcome) and microbiological data (respiratory sample cultures and isolated microorganisms) were recovered from clinical records of the patients.

This study was performed at the Clinical Microbiology and Parasitology Department at the University Hospital La Paz. Two commercial real-time PCR were used indistinctly for the detection of SARS-CoV-2 in respiratory samples (TaqMan® 2019 nCoV assay Kit V1, ThermoFisher Scientific Inc, Franklin, MA, USA and SARS-CoV-2 RT-PCR Kit, Vircell S.L., Granada, Spain). Bronchial aspirates (BAS), bronchoalveolar lavages (BAL) and tracheal aspirates were cultured in standard general media according to the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) (Cacho-Calvo et al., 2007). All included samples met > 100,000 CFU/mL criteria. Bacterial species were identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS – Bruker Daltonics, Bremen, Germany) with Bruker's MBT Compass Explorer 4.1 and susceptibility testing was done using an automated broth microdilution assay system (Microscan Walkaway®, Beckman Coulter, Brea, USA)

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according to the manufacturer specifications. Results were interpreted according to the criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (EUCAST, 2021). Multidrug-resistant isolates were defined when presenting resistance to more than one antibiotic. Gram stains were also reported to give a better interpretation of the samples.

The study was approved by the Clinical Research Ethics Committee of Hospital Universitario La Paz with the code HULP: PI-4193.

3. Results

During the period of the study 1251 respiratory samples from 1195 patients were processed. All patients admitted to our center had diagnostic of COVID-19 by a positive RT-PCR. Respiratory samples in ICU patients were obtained and cultured for bacteria at least 48 hours after admission. Samples from 66 patients (5.52%) were determined to be microbiologically significant. Among them there were 62 BAS (93.9%), 1 BAL (1.5%) and 3 tracheal aspirates (4.5%). Fifty three patients were male (80.3%), 13 were female (19.7%). The age ranges were detailed in Table 1. All of them were subjected to mechanical ventilation during the ICU stay. Eighteen patients (27.3%) had diabetes as an underlying risk factor and hypertension was present in 28 (42.4%). No underlying malignancies were present; however, there were 3 patients with immunosuppressive diseases (HIV, Crohn's disease and HLA B27 ankylosing spondylitis). Following the national guidelines from the Spanish Agency for Medicine and Medical Devices (AEMPS) in use at that time, patients were treated with corticosteroids, tocilizumab and azithromycin (for its immunomodulant properties) (World Health Organization, 2021). All demographic, clinical and microbiological data are detailed in Table 1.

β-lactams were administered as an empirical treatment for infections to all of our patients being ceftriaxone the most prescribed one. Linezolid was the second antibiotic more prescribed in these patients (16, 24.2%). Fifty seven patients had monomicrobial cultures and nine had 2 significant bacterial isolates. Among them, there were thirty one (42%) *Enterobacterales* (*Escherichia coli, Klebsiella* spp., and others, fourteen ESBL-producers), eighteen *S. aureus* (eight of them methicillin-resistant), and seventeen *P. aeruginosa* (two of them carbapenem-resistant, though no carbapenemase was detected). Other multidrug-resistant species isolated were detailed in Table 1. Nineteen patients had bacteremia related to their respiratory infections, with the same isolated microorganism in blood culture and in respiratory sample. The median length of stay in the ICU before the first positive significant respiratory isolate was 15 days and the mortality rate during this period was 54.5%. The first respiratory sample of the patients collected and cultured for bacteria was at least 48 hours after ICU admission.

Table 1
Demographic, clinical and microbiological characteristics of the patients included in the study (N = 66).

Demographic characteristics	
Gender	Male: 53 (80.3%) Female: 13 (19.7%)
Age range (years)	<50: 8 (12.1%) 50–60: 19 (28.8%) 61–70: 23 (34.9%) 71–80: 16 (24.2%)
RISK factors and clinical characteristics	
Arterial hypertension	28 (42.4%)
Diabetes	18 (27.3%)
Mechanical ventilation	66 (100%)
Malignancies/immunosuppressive diseases	3 (4.5%)
Anti-COVID-19 therapy	Tocilizumab: 31 (47%) Corticosteroids: 37 (56.1%) Azithromycin (immunomodulant properties): 48 (72.7%)
Most prescribed antibiotherapy	B-lactams: 66 (100%) Linezolid: 16 (24.2%)
Median of ICU stay until positive respiratory sample (days)	15 (range 3–44)
Related bacteremia (same isolated microorganism in blood culture and in respiratory sample)	19 (28.8%)
Died	36 (54.5%)
Microbiological characteristics (isolates, N = 74)	
Respiratory sample culture	Monomicrobial: 61 (92.5%). Polimicrobial: 5 (7.5%)
Staphylococcus aureus	18 (24.3%): 8 MRSA
Pseudomonas aeruginosa	17 (23%): 2 carbapenem-resistant isolates[a]
Enterobacterales	31 (42%): 14 ESBL producing isolates - *Kebsiella pneumoniae/Klebsiella aerogenes*: 15 (20.3%) - *Escherichia coli*: 9 (12.2%) - Other: 7 (9.5%)
Multidrug-resistant bacteria[b] (*Achromobacter spp., Burkholderia spp., Stenotrophomonas spp., Chryseobacterium spp., Corynebacterium spp.*)	8 (10.8%)

ESBL = extended spectrum beta-lactamase; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*.
[a] No carbapenemase-producing isolate.
[b] Resistance to more than one antibiotic.

4. Discussion

Comparing the number of bacterial co-infections in the study period were much lower than the approximately 40% of bacterial co-infections described by Falsey et al. (Falsey et al., 2013), even though the demographic and clinical features of our patients were similar. This might be due to the fact that during the first COVID-19 wave empirical treatment with broad spectrum antibiotics were prescribed in all patients.

Broad spectrum antibiotic were prescribed as an empirical treatment and when clinically significant microorganisms were isolated in a respiratory sample. ICUs are a hotspot for isolating multidrug-resistant microorganisms as they have a high antimicrobial pressure. Antibiotic therapy should not be started until bacterial co-infection is suspected and it should be based on up-to-date antibiotic guidelines, host risk factors, prior microbiological and epidemiology resistant data and taking into account recommendations from the stewardship team. One of the factors for the selection of multidrug-resistant bacteria in our study (*Chryseobacterium* spp., *Burkholderia* spp., *Stenotrophomonas* spp. . .) could be the use of broad spectrum antibiotics.

Few studies have approached bacterial co-infection based on quantitative culture of respiratory samples. Some have addressed this topic by PCR on throat swab samples (David et al., 2020; Zhu et al., 2020) with the limitation of not being able to distinguish colonization from actual infection and the possibility of not detecting pathogens not included in the PCR design. In our study, the clinically significant bacterial isolates associated to COVID-19 were very similar to those isolates found in other viral pneumonia co-infections such as Influenza virus (*S. aureus* and *P. aeruginosa* followed by pathogens of the *Enterobacterales* order (Parte et al., 2020). *Streptococcus peumoniae* and other pathogens involved in community-acquired pneumonia such as *Haemophilus* spp. and *Moraxella* spp. were not isolated during our study (Abelenda-Alonso et al., 2020). This could have been due to the fact that we did not recover samples at admission, so our isolates were mainly nosocomial microorganisms.

The main limitations of our study are that it is a single-center study with small numbers, short time period of the study, sampling only reflects extended ICU stay, and the samples not obtained during admission reflecting more community acquired pathogens. Also impact of giving azithromycin on bacterial microbiome affecting culture results. Further multicentric studies addressing larger cohorts in

other regions will clarify more the matter of bacterial co-infection in COVID-19 patients.

In conclusion, we have observed that bacterial co-infections in ICU stay could seem not dependent on the virus that has produced the viral pneumonia in the first place such as with Influenza virus. It would seem that SARS-CoV-2 is no exception to this issue.

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Authors' contribution

M.R.B has contributed in conceptualization, data curation, formal analysis, investigation, methodology, project administrations, resources, software, writing, supervision and validation, visualization.

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J.C.R.R and M.D.P has contributed in supervision and visualization.

J.G.R has contributed in supervision, visualization and validation.

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Declaration of competing interest

None.

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