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Research Article

Co-Infections with Prioritary Pathogens in Patients with Severe Covid-19: What is the Factor Leading to the Death of the Patients?

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Abstract

Coronavirus disease 2019 (COVID-19), caused by a virus, the severe acute respiratory syndrome 2 determined to date above 625 million confirmed cases and about 7 million deaths worldwide. In literature several cases of individuals affected by SARS-CoV-2 infection and pathogen and other respiratory viruses' co-infection and/or superinfection are described. At present only few studies indagated the presence of co-infections and the prevalence of multi-drug resistant microorganisms in patients affected by COVID-19. The aim of our study is to evaluate the presence of co-infections with COVID-19 and potentially multi-resistant bacteria in the patients hospitalized in the Intensive Care Unit of the A.O.U. "G. Martino", Messina, Italy, also searching for statistically significant associations with qualitative and quantitative variables as sex, age and number of bacteria. The sample was made up of 281 patients affected by COVID-19 and having positive blood cultures. It consists of 187 men (66.55%) and 94 women (33.45%) (average age 65 ± 14.82 DS). About half of the investigated subjects (n = 141) resulted positive for pathogens with critical priority and ESKAPE, who's about two-thirds (n = 94; 66.67%) were men and about one-third (33.33%) were women, noticing significative gender differences ($p < 0.01$). The average number of co-infections was equal to 1 ± 0.74 DS. We did not find any statistically significant difference between the number of co-infections and the age of the examined patients. The most frequently isolated microorganisms were *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Staphylococcus aureus*. Although COVID-19 has led to changes in behaviors, healthcare-associated infections remain a public health problem. It is necessary to continue to carry out primary prevention interventions through the correct sanitizing operations and the monitoring of the healthcare workers' behaviors. Since most of the examined patients died, the cause of death and the burden of co-infections in this sample are currently under evaluation.

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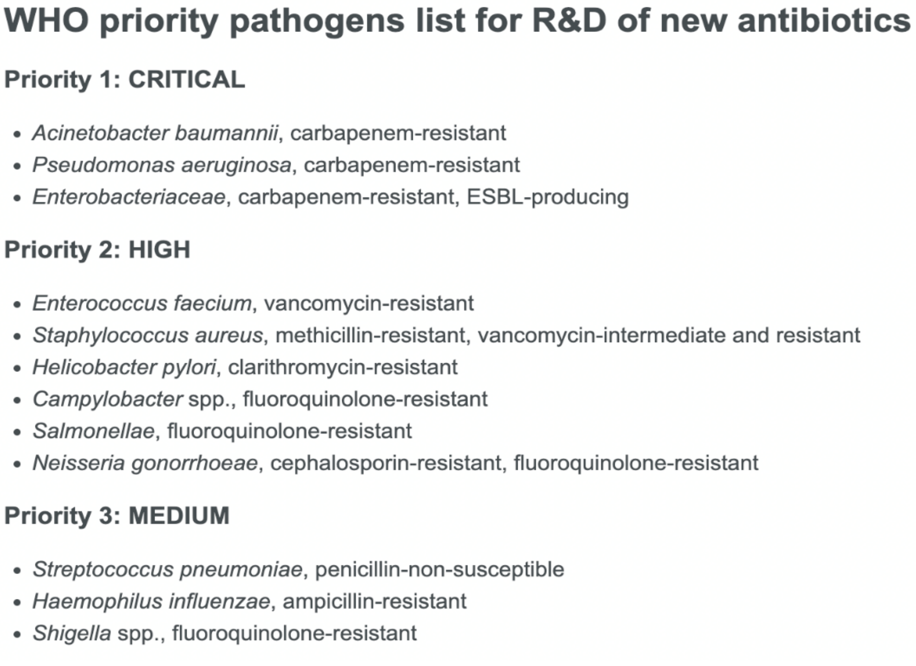
Introduction

Coronavirus disease 2019 (COVID-19), caused by a virus, the severe acute respiratory syndrome 2 (SARS-CoV-2) determined to date above 625 million confirmed cases and about 7 million deaths worldwide [1]. Thanks to the introduction of COVID-19 vaccinations this infection is now less frequent and less severe than in the past. Nevertheless, SARS-CoV-2 infections continue to cause a wide range of clinical manifestations, including asymptomatic, mild symptomatic and severe symptomatic forms, pneumonia, multiorgan involvement and death. In many cases, the patients with comorbidities entry into ICU and require mechanical ventilation. In literature several case of individuals affected by SARS-CoV-2 infection and pathogen and other respiratory viruses co-infection and/or superinfection are described. This relation is already known and investigated for other respiratory pathogens, for instance influenza virus, whose clinical presentation is frequently complicated by a bacterial co-infection leading sometimes to death. The systemic immune mechanisms play a key role in the development of co-infections, according to the complex interaction between the host and the viral and bacterial pathogens. In critical patients affected by influenza the co-infection with *Streptococcus pneumoniae* is the most frequent, followed by *Haemophilus influenzae* and *Staphylococcus aureus* [2,3]. At present only few studies indagated the presence of co-infections and the prevalence of multi-drug resistant microorganisms in patients affected by COVID-19. Magiorakos et al. [4] define multi-drug resistance (MDR) as the acquired non-susceptibility to at least one antimicrobial drug in three or more antimicrobial categories, extensively drug-resistance (XDR) as the non-susceptibility of one bacteria species to all antimicrobial agents except in two or less antimicrobial categories and PDR as the non-susceptibility of bacteria to all antimicrobial agents in all antimicrobial categories. Moreover, on the 27th February 2017, the WHO published a list of multi-drug resistance “priority pathogens”, including 12 families of bacteria that pose the greatest threat to human health: among them, 3 have a critical priority and 6 have a high priority, as reported in the Figure 1. This list was compiled in order to lead and promote the development of new antibiotics [4].



WHO priority pathogens list for R&D of new antibiotics

Priority 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

Figure 1: Priority pathogens according to WHO

The aim of our study is to evaluate the presence of co-infections with COVID-19 and potentially multi-resistant bacteria in the patients hospitalized in the Intensive Care Unit of the A.O.U. “G. Martino”, Messina, Italy, also searching for statistically significant associations with qualitative and quantitative variables as sex, age and number of bacteria.

Materials and Methods

Study design and participants

A retrospective cohort study was carried out by the Operative Unit of Hospital Hygiene, University Hospital "G. Martino" of Messina, Italy, involving patients affected by COVID-19 hospitalized in the Intensive Care Unit from the 30th January 2020 (date of the first two Italian confirmed COVID cases) to the 31st December 2021, and reporting positive blood cultures, stratifying them for age, sex, number of bacteria and outcome. COVID-19 was diagnosed through RT-PCR (real-time reverse transcriptase-polymerase chain reaction) of samples obtained by nasopharyngeal and/or pharyngeal swabs.

Data collection

The data related to the patients were collected through the electronic medical charts recorded in the laboratory of the AOU "G. Martino", Messina. We collected age, sex and microbiological data of the patients. The identification of the microorganisms and the antimicrobial susceptibility test were executed using an automatic system that is Vitek. The antimicrobial susceptibility tests were executed using Minimum inhibitory concentration (MIC) panels for gram-positive and gram-negative bacteria and the results were interpreted in compliance with the CLSI (Clinical & Laboratory Standards Institute) methods [6]. The data collection included only samples taken from the patients only at least 48 hours after the hospitalization in order to exclude potential community-acquired infections. All the hematological data were collected from samples executed when secondary infections were suspected.

Data analysis

As regards the qualitative data we calculated absolute and relative frequency. Quantitative data were summarized as mean and standard deviation. The statistical analysis were performed using Epi info. P-values < 0.05 were considered statistically significant.

Results

The sample was made up of 281 patients affected by COVID-19 and having positive blood cultures. It consists of 187 men (66.55%) and 94 women (33.45%) (average age 65 ± 14.82 DS). About half of the investigated subjects (n = 141) resulted positive for pathogens with critical priority and ESKAPE, whose about two-thirds (n = 94; 66.67%) were men and about one-third (33.33%) were women, noticing significative gender differences ($p < 0.01$).

The isolated germs and the partition by gender are shown in the figure 2 and in the figure 3.

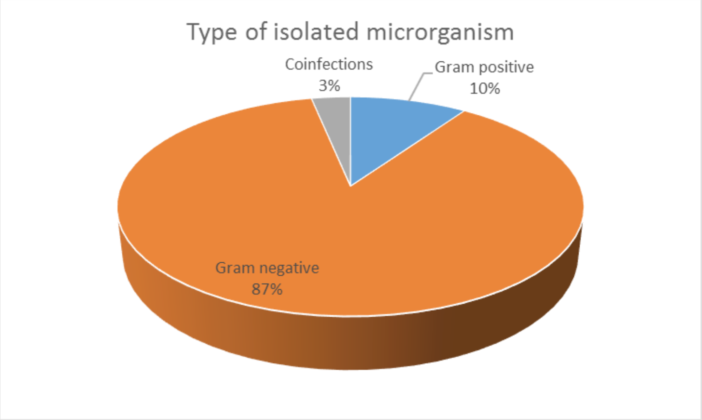


Figure 2: Isolated Microorganism

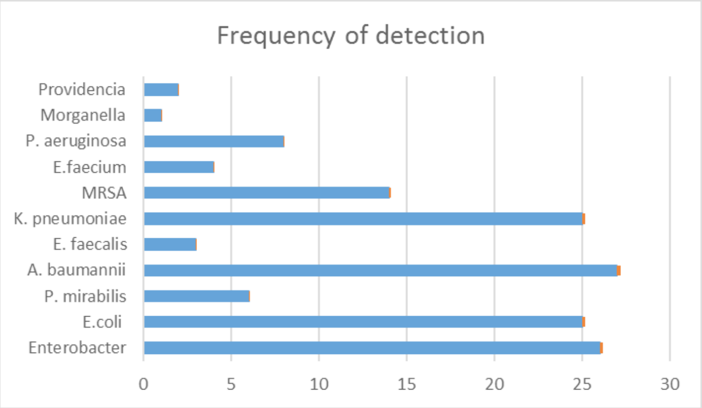


Figure 3: Frequency of detection of the isolated germs

The average number of co-infections was equal to 1 ± 0.74 DS. We did not find any statistically significant difference between the number of co-infections and the age of the examined patients. More than two-thirds of the patients (n = 97; 68.79%) were positive for a single bacterium, whose 65.98% (n = 64) were men and 34.02% (n = 33) were women.

Thirty patients (21.28%) were positive for two bacteria, whose 63.33% (n = 19) were man and 36.67% (n = 11) were women. Only less one out of ten (n = 14; 9.92%) were positive for three bacteria, whose 78.57% (n = 11) and 21.43% were women.

	Isolated microorganisms	**Outcome**
	Acinetobacter baumannii, Klebsiella pneumoniae	ND
	Acinetobacter baumannii, Serratia marcescens	ND
	Acinetobacter baumannii, Klebsiella pneumoniae	ND
	Acinetobacter baumannii, Klebsiella pneumoniae	D
	Acinetobacter baumannii, Enterococcus faecalis	ND
	Klebsiella pneumoniae, Pseudomonas aeruginosa	ND
	Acinetobacter baumannii, Klebsiella pneumoniae	D
	Klebsiella pneumoniae, Staphylococcus aureus, Acinetobacter baumannii	ND
	Klebsiella pneumoniae, Escherichia coli, Morganella morganii	D
	Enterococcus faecium, Acinetobacter baumannii	D
	Acinetobacter baumannii, Enterococcus faecalis	ND
	Acinetobacter baumannii, Enterococcus faecalis	ND
	Escherichia coli, Pseudomonas aeruginosa	ND
	Pseudomonas aeruginosa, Klebsiella pneumoniae	D
	Acinetobacter baumannii, Klebsiella pneumoniae	ND
	Enterobacter aerogenes, Enterococcus faecalis	D
	Klebsiella pneumoniae, Enterobacter cloacae	ND
	Klebsiella pneumoniae, Enterococcus faecium	ND
	Enterococcus faecium, Acinetobacter baumannii	D
	Acinetobacter baumannii, Proteus mirabilis	ND
	Acinetobacter baumannii, Pseudomonas aeruginosa	ND
	Escherichia coli, Staphylococcus aureus, Acinetobacter baumannii	ND
	Acinetobacter baumannii, Enterobacter cloacae	D
	Enterobacter cloacae, Staphylococcus aureus, Acinetobacter baumannii, Enterococcus faecalis	ND
	Acinetobacter baumannii, Enterococcus faecium	ND
	Enterococcus faecalis, Acinetobacter baumannii	ND
	Acinetobacter baumannii, Klebsiella pneumoniae	ND
	Enterobacter aerogenes, Enterococcus faecalis	ND
	Providencia stuartii, Pseudomonas aeruginosa	ND
	Klebsiella pneumoniae, Acinetobacter baumannii, Enterococcus faecium	D
	Acinetobacter baumannii, Klebsiella pneumoniae, Enterococcus faecalis	ND
	Staphylococcus aureus, Acinetobacter baumannii	ND
	Acinetobacter baumannii, Staphylococcus aureus	D
	Acinetobacter baumannii, Pseudomonas aeruginosa	ND

Table 1: Patients with more germs co-infections and outcome (D = dead; ND= not dead)

The most frequently isolated microorganisms were *Acinetobacter baumannii* (n = 66; 46.8%) with statistically significant differences for gender ($p < 0.001$), *Klebsiella pneumoniae* (31.91%) with statistically significant differences for gender ($p < 0.001$) and *Staphylococcus aureus* (17.73%) ($p > 0.05$) (Figure 1). The largest number of deaths were observed after co-infections with gram-negative bacteria (88% on the total sample) (Table 3). Moreover, the percentage of deaths was higher in patients in 2021 (51.16%) than in 2020 (25.45%) (Table 3).

	2020 (n=55) %(n)	**2021 (n=86) %(n)**
Gram negative died	25.45 (14)	38.37 (33)
Gram negative not died	61.82 (34)	39.53 (34)
Gram positive died	0 (0)	11.63 (10)
Gram positive not died	7.27 (4)	5.81 (5)
Coinfection died	0 (0)	1.16 (1)
Coinfection not died	5.45 (3)	3.49 (3)

Table 3: Percentage of died by Gram classification

Staphylococcus aureus always resulted methicillin-resistant, whereas we observed different resistances for *Klebsiella pneumoniae* and *Acinetobacter baumannii*, respectively 81% and 68% of them carbapenem-resistant **(table 2).**

Noticed resistance	*K.pneumoniae*	*A. baumannii*
Colistin	0%	20%
Cephalosporins	0%	28%
Carbapenems	81%	68%
Aminoglycosides	78%	40%

Table 2: Resistance rate noticed for gram-negative bacteria by classes of antibiotics tested

Discussion

About half our sample was positive for pathogens with critical priority and ESKAPE germs. This data is superimposable to a study carried out in Saudi Arabia, in which little more than half of subjects (53%) contracted a healthcare-associated infection [5]. Several studies conducted in many countries reported as bacterial co-infection incidence among hospitalized patients affected by COVID-19, with infection rates ranging from 12.4% to 50% [6-10]. In our study most of the noticed cases was represented by gram-negative germs, in accordance with a previous study [11]. A recent study examined the risk of death due to secondary bacterial infections in patients affected by COVID-19 [6], noticing a higher death rate (with a significant increase from 13% to 61%). In our sample the most frequently isolated microorganisms were *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Staphylococcus aureus*, similarly to other studies in which *K. pneumoniae* was the most frequently isolated microorganism [11]. Most of the deaths were observed after co-infections with gram-negative (88%) **(table 3)**. *Staphylococcus aureus* always resulted methicillin-resistant, whereas we observed different resistances for *Klebsiella pneumoniae* and *Acinetobacter baumannii*, respectively 81% and 68% of them carbapenem-resistant. As regards Klebsiella pneumoniae, the European surveillance effectuated by the ECDC reported that more than one-third of the isolated bacteria (38%) were resistant to at least one antimicrobial drug category (MDR) with a lesser susceptibility rate to carbapenems and a higher to cephalosporins (12), in contrast with whom we observed in our sample. Our data probably derives from the greater vulnerability of the immune system of our patients, already compromised by COVID-19. The same result was observed for *Acinetobacter baumannii*, resulted for about two-thirds of the bacterial strains (65.6%) multi-drug resistant, having a resistance of 38% to carbapenems and of 37% to aminoglycosides. At last, all the *Staphylococcus aureus* strains resulted methicillin-resistant, in contrast to the European data in which only one-fifth of the microorganisms were positive [12]. Our data do not allow to establish if the presence of co-infections determined an increase of the length of hospitalization in the ICU and of the deaths. Another limitation is the lacking evaluation of the presence of co-infection with viruses. Moreover, data regarding the increase of the death rate among the patients with co-infections do not consider the state of health at the moment of admission and the presence of co-morbidities. Moreover, the percentage of deaths was higher in patients in 2021 (51.16%) than in 2020 (25.45%). We noticed that died patients had more frequently infection with Gram negative microorganisms, but we did not performed statistical analysis give due the meager sample size and the presence in our study of more patients with Gram negative infections.

Finally, our study considers only the evaluation of the positive blood cultures, not investigating the presence of positivity's in other districts.

Conclusions

Although COVID-19 has led to changes in behaviors, healthcare-associated infections remain a public health problem. It is necessary to continue to carry out primary prevention interventions through the correct sanitizing operations and the monitoring of the healthcare workers' behaviors. Since most of the examined patients died, the cause of death and the burden of co-infections in this sample are currently under evaluation.

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