

The Changing Pattern of Bacterial and Fungal Respiratory Isolates in Patients with COVID-19 Admitted to Intensive Care Unit

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Abstract

Objectives

Severe acute respiratory syndrome 2 (SARS-CoV-2) pandemic has had a heavy impact on national health system, especially in the first wave. That impact hit principally the Intensive Care Units (ICUs). The large number of patients requiring hospitalization in ICUs lead to a complete upheaval of intensive wards. The increase in bed, the fewer number of nurses per patient, the constant use of personal protective equipment, the new antimicrobial surveillance protocols could have had deeply effects on microbiological flora of these wards. Moreover, the overconsumption of antimicrobial therapy in COVID-19 patients, like several studies report, could have impact of this aspect. Aim of this study is to evaluate the changing pattern of microbiological epidemiology during and before COVID-19 pandemic in a tertiary hospital ICUs.

Methods

A retrospective, observational study was conducted in ICUs of "ASST Papa Giovanni XXIII", a large tertiary referral hospital in Northern Italy. We have retrospectively collected the microbiological data from BAL and TA of patients hospitalized in ICUs from 22nd February 2020 to 31st May 2020 (Period 1) and from 22nd February 2019 to 31st May 2019 (Period 2). We compared the prevalence and the antibiotic profile of bacterial and fungal species in the two time periods.

Results

The prevalence of *Pseudomonas* spp. shows a statistically significant increase from period 2 to period 1, as well as the prevalence of *Enterococcus* spp. On the contrary, the prevalence of Gram negative non fermenting bacteria (GN-NFB), *Haemophilus influenzae* and *Streptococcus pneumoniae* showed a significant reduction between two periods. There was a statistically significant increase in resistance of *Pseudomonas* spp. to carbapenems and piperacillin/tazobactam and *Enterobacterales* spp. for piperacillin/tazobactam, in period 1 compared to period 2, respectively.

Conclusions

A changing pattern in prevalence and resistance profiles of bacterial and fungal species was observed during COVID-19 pandemic.

Introduction

Severe acute respiratory syndrome 2 (SARS-CoV-2) has spread worldwide since 2019. Patients with SARS-CoV-2 infections may develop a severe form of coronavirus disease (COVID-19) requiring hospitalization and admission to intensive care units (ICU) in approximately 30% of them¹. A large proportion of COVID-19 patients received antimicrobial therapy for proven or suspected co-bacterial

infections during their ICU stay² and several studies have highlighted the antibiotic over-exposure in this population, despite the low rate of culture-proven bacterial co-infections³. This may be caused by several factors including the severity of COVID-19, the uncertainties about this new disease and the limitations of invasive diagnostic procedures due to the SARS-Cov-2 transmission precautions. Moreover, COVID-19 pandemic has represented an exceptional stress for the hospital setting, especially for the ICU setting, due to the overwhelming number of patients requiring a prolonged ICU stay.

The above-mentioned factors may have affected the local fungal and bacterial epidemiology. The aim of this study is to describe the prevalence of bacterial and fungal species in a cohort of COVID-19 patients admitted to ICUs compared to the patients observed at the same hospital during the previous year (before the COVID-19 pandemic).

Materials And Methods

“ASST Papa Giovanni XXIII” is a large tertiary referral hospital (990 beds) placed in Bergamo, one of the most affected provinces during the COVID-19 pandemic in Northern Italy in 2020. During the COVID-19 pandemic, following the large number of patients admitted to ICU wards, a surveillance program with collection of respiratory specimens [i.e. bronchoalveolar lavages (BAL) or tracheal aspirates (TA)] was performed every 48-72 hours or weekly in all the patients, according to the different intensive wards, while such procedures, in not COVID-19 patients, had been previously performed only in selected individuals and according to clinical judgment. We have retrospectively collected the microbiological data from BAL and TA of patients hospitalized in ICUs from 22nd February 2020 to 31st May 2020 (Period 1) and from 22nd February 2019 to 31st May 2019 (Period 2). We compared the prevalence of bacterial and fungal species in the two time periods. Then, we have categorized the most prevalent bacterial species potentially pathogenic of the respiratory tract (*Enterobacterales*, *Pseudomonas* spp. and *Staphylococcus aureus*) on the basis of their antibiotic resistant profile as multidrug resistant (MDR) for *Enterobacterales* and *Pseudomonas* spp., (according to definitions by Magiorakos et al⁴) and methicillin resistant (MR) for *Staphylococcus aureus* (according to cefoxitin screening). In addition, we calculated the odds ratio (OR) with 95% confidence interval (CI) to evaluate the difference of the prevalence of bacterial and fungal species and the resistant pathogens in the two study periods.

Results

A total of 194 patients were admitted to ICU with COVID-19 in period 1 (namely 65% of 297 patients admitted in ICU in that time period), compared to 176 patients who were admitted in period 2. A total of 736 samples (3.8 per patient) and 392 (2.2 per patient) were collected during the period 1 and period 2, respectively. The proportion of positive respiratory specimens (for at least 1 pathogen, either bacterial or fungal) was 48% (355/736 samples) and 47.7% (187/392 samples) in period 1 and 2, respectively.

Table 1 shows the prevalence of bacterial and fungal species by group. In both periods, the most frequent bacterial isolates were *Pseudomonas* spp. and *Enterobacterales*; The prevalence of *Pseudomonas* spp.

shows a statistically significant increase from period 2 to period 1, as well as the prevalence of *Enterococcus* spp. On the contrary, the prevalence of Gram negative non fermenting bacteria (GN-NFB), *Haemophilus influenzae* and *Streptococcus pneumoniae* showed a significant reduction in period 2 versus period 1.

Table 1
Prevalence of fungal and bacterial pathogens from respiratory samples.

	Period 1, 2020 (%)	Period 2, 2019 (%)	OR	95% CI
<i>CoNS</i>	10 (2.3)	5 (1,7)	1.38	0.47-4.09
<i>Enterobacterales</i>	101 (22.9)	102 (33.7)	0.59	0.42-0.81
<i>Enterococcus</i> spp.	35 (7.9)	7 (2.3)	3.65	1.6-8.32
GN-NFB	12 (2.7)	19 (6.3)	0.42	0.2-0.88
<i>Haemophilus</i> spp.	1 (0.2)	11 (3.6)	0.06	0.01-0.47
<i>Pseudomonas</i> spp.	114 (25.9)	40 (13.2)	2.29	1.54-3.4
<i>Staphylococcus aureus</i>	50 (11.3)	37 (12.2)	0.92	0.59-1.45
<i>Streptococcus</i> spp.	3 (0.7)	9 (3.0)	0.22	0.06-0.83
Other pathogens	8 (1.8)	8 (2.6)	0.68	0.26-1.89
<i>Aspergillus</i> spp.	48 (10.9)	21 (6.9)	1.64	0.96-2.8
<i>Candida</i> spp.	59 (13.4)	44 (14.5)	0.73	0.6-1.39
Total	441	303	-	-
CoNS: coagulase negative staphylococci; GN-NFB: gram negative non fermenting bacteria.				

Table 2 compares the prevalence of resistant pathogens and the resistance profile for the antibiotic of interest. There were no statistically significant differences between the proportion of resistant pathogens in the two study periods. Nevertheless, there was a statistically significant increase in resistance of *Pseudomonas* spp. to carbapenems and piperacillin/tazobactam and *Enterobacterales* spp. for piperacillin/tazobactam, in period 1 compared to period 2, respectively.

Table 2
prevalence of antibiotic resistant pathogens according to the antibiotic of interest.

	Period 1- 2020 (%)	Period 2 - 2019 (%)	OR	95% CI
<i>Pseudomonas</i> spp. MDR	42 (36.8)	14 (35)	1.08	0.51-2.3
<i>Pseudomonas</i> spp. PIP/TZ-R	75 (65.8)	15 (37.5)	3.21	1.52-6.77
<i>Pseudomonas</i> spp. CARBA-R	60 (52.6)	10 (25)	3.33	1.49-7.45
<i>Pseudomonas</i> spp. CTZ/CEF-R	40 (35.1)	14 (35)	1	0.47-2.14
<i>Enterobacterales</i> MDR	33 (32.7)	34 (33.3)	0.97	0.54-1.74
<i>Enterobacterales</i> PIP/TZ-R	33 (32.7)	18 (17.6)	2.27	1.17-4.37
<i>Enterobacterales</i> CARBA-R	0 (0)	0 (0)	-	-
<i>Enterobacterales</i> 3GC-R	16 (15.8)	18 (17.6)	0.88	0.42-1.84

MDR: multi drug resistant; PIP/TZ-R/S: piperacillin/tazobactam resistant/susceptible; CARBA-R/S: carbapenem resistant/susceptible; CTZ/CEF-R/S: ceftazidime/cefepime resistant/susceptible.

Discussion

We observed a variation of microbiological respiratory isolates before and during COVID-19 pandemic. In period 2, the prevalence of potentially pathogenic bacterial isolates from respiratory samples in ICU patients was aligned with the one of previous studies in the same settings⁵. In period 1, we observed the reduction of several bacterial species, especially *Enterobacterales* and the parallel increase of *Pseudomonas* spp. and *Enterococcus* spp.

In the interpretation of this changing epidemiology, some observations may be useful.

Firstly, the isolation of bacterial and fungal species does not necessary imply an active infection caused by these pathogens and, certainly, the systematic respiratory tract sampling, aimed to early intercept an infectious complication in the context of the SAR-CoV-2 pneumonia, may have led to an overestimation of microbiological events compared to a standard and less aggressive approach.

Secondly, with regard to the changing epidemiology for *Enterococcus* spp. and *Pseudomonas* spp., the longer ICU stay for COVID-19 patients compared to the ones hospitalized for other causes⁶ represents an important risk factor for colonization and/or infection caused by these bacteria^{7,8}.

Thirdly, the tropism for respiratory tract by *Pseudomonas* spp. is well known, especially in patients with underlying lung disease (such as cystic fibrosis and chronic obstructive pulmonary diseases⁹). In a recent surveillance of VAP in COVID-19 patients, *Pseudomonas aeruginosa* was the most common pathogen

responsible for ventilator-associated lower respiratory tract infections¹⁰ and the most common isolate in a population of critically ill patients hospitalized for influenza-associated ARDS¹⁰. We can speculate that the combination of the lung impairment by SARS-CoV-2 and the predisposition of *Pseudomonas* spp. could act synergistically to put these patients at risk for colonization/infection by this pathogen.

Fourthly, most COVID-19 patients during ICU hospitalization received empirical antibiotic therapy². In the ICU departments the antibiotics belonging to beta lactams class are the most widely used¹¹. In our study, we observed a high resistance rate for this antibiotic class by *Pseudomonas* spp. and *Enterobacterales* in period 2, that was dramatically increased compared to period 1. We can speculate that the antibiotic pressure may have favored the emergence of resistant bacteria¹².

Fifthly, the decrease of other bacterial species associated to respiratory tract infections is consistent with the low incidence rate of co-bacterial infections in COVID-19 patient¹³ and the global reduction of prevalence of other respiratory pathogens, secondary to the public health measures against COVID-19¹⁴.

Sixthly, the high degree of immunosuppression induced by steroid therapy, used as salvage therapy in COVID-19 patients during ICU stay in the first wave, may have influenced the rate and the microbiological pattern of respiratory bacterial/fungal complications compared to period 2¹⁵.

Lastly, as mentioned above, the clinical significance of the colonization of the respiratory tract has not been investigated as the aim of the study was to describe the changing microbiological scenario during the COVID-19 pandemic which may help designing the antimicrobial stewardship programs.

Declarations

Ethic approval and consent to participant

All methods were carried out in accordance with Declaration of Helsinki. This study was approved by the ethics committee of The Papa Giovanni XXIII Hospital (Protocol N. 257/2020). To maintain the principle of confidentiality, the data used were anonymized. The need for informed consent was waived by the ethical Committee of the "Papa Giovanni XXIII" Hospital due to retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon request.

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Authors' contributions

G.Z., D.R and A.T. conceived of the presented clinical research. M.C and I.R. collected the clinical and microbiological data. G.Z. and D.R. verified the analytical methods and wrote the manuscript. M.R. and C.F. supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Not applicable.

Ethics declarations

The Ethical Committee of the “*Papa Giovanni XXIII*” Hospital approved the study. All patients were enrolled in accordance with the Helsinki declaration

Conflict of interest

The authors declare that they have no conflict of interests.

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