

Blood stream infections during the first wave of COVID-19. A short microbiological retrospective picture at Papa Giovanni XXIII Hospital, Bergamo, Italy

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SUMMARY

This paper aims to describe the etiology of bloodstream infections in COVID-19, Papa Giovanni XXIII Hospital, Bergamo, Italy. Two periods were evaluated: February 22-May 21, 2019/2020. We considered: the number of patients and blood culture sets, species of isolates (bacteria, specifically those indicated by EARS criteria; CoNS; *Candida albicans*) and their antibiotic sensitivity. In 2020 *Escherichia coli* and Carbapenemase-producing *Klebsiella pneumoniae* disappeared. *Candida albicans* and MDR *Pseudomonas aeruginosa*, *Enterococcus faecium* and *Acinetobacter baumannii* were largely present. The analysis shows:

1. BSIs number was the same;
2. In the first month of the COVID-19 period, BSIs were uncommon;
3. Microbial etiologies were different; 4. MDR isolates were less common.

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INTRODUCTION

On January 30, 2020 the World Health Organization labeled the outbreak of coronavirus disease 2019 (COVID-19) as a Public Health Emergency of International Concern. On February 21, 2020 the first Italian patient affected by COVID-19 was registered in Lombardy, Italy. Since February 23, 2020 the Bergamo area has been officially affected by SARS CoV2 infection and COVID-19 patients have been admitted to Papa Giovanni XXIII hospital.

Since the beginning of the Italian COVID-19 epidemic, microbiology laboratories have played a central role not only in the molecular diagnosis of SARS CoV-2 but also in the evaluation of secondary microbial infections, such as blood stream infections (BSIs), respiratory or urinary infections. This retrospective, single-center study was conducted at Papa Giovanni XXIII Hospital, Bergamo, Italy. The study describes the evolution of microbial (bacterial and fungal) etiologies observed in blood cultures in patients admitted

to hospital at the beginning of the COVID-19 period and compares them with those admitted in the same hospital in the same quarter in a non-COVID-19 period.

MATERIALS AND METHODS

We compared two historically similar periods at the Papa Giovanni XXIII Hospital in Bergamo, Italy: from February 22 to May 21 in 2019 and 2020, respectively. We examined the microbiological data obtained from blood cultures obtained from all the hospitalized population in those periods. We evaluated only the etiologies of the positive blood cultures diagnosed at the internal Microbiology and Virology (MV) laboratory.

For both periods, we considered the following parameters: total number of patients, number of blood culture sets, number of bottles, species of microbial isolates and their antibiotic sensitivity. To better define the timing of the observations and the possible microbiological differences in etiologies and chemosensitivity patterns during the very first periods of the SARS CoV-2 spread in the admitted population, each period was divided into three subperiods:

- 1) February 22 to March 21, 2019 vs 2020;
- 2) March 22 to April 21, 2019 vs 2020;
- 3) April 22 to May 21, 2019 vs 2020.

Key words:

COVID-19, blood stream infections, bacteria, yeasts, MDR.

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We considered all bacterial and fungal etiologies found from blood cultures, both for pathogens and contaminants. However, to evaluate the chemosensitivity pattern differences, we considered only the following etiologies: *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *S. aureus*, *S. pneumoniae*, *E. faecalis*, *E. faecium* as indicated by the European Antimicrobial Resistance Surveillance Network (EARS-Net) criteria with particular attention to Multi Drug Resistant (MDR) bacteria, and *Candida* spp. Coagulase-negative staphylococci (CoNS) were considered significant only if one of these organisms was present in $\geq 50\%$ of all blood culture sets obtained from one patient on the same day; otherwise, CoNS were considered as representative markers of possible contamination in the pre-analytical phase.

The Matrix-Assisted Laser Desorption Ionization Time-Of-Flight mass spectrometry (MALDI-ToF) was applied to identify bacteria and yeasts, using the instrument VITEK[®]MS (bioMérieux sa, Marcy l'Etoile, France). Procedures were performed according to the manufacturer's technical instructions.

Antimicrobial Susceptibility Testing (AST) results were generated using the VITEK2[®] analyzer and E test method (bioMérieux) and, where necessary, by the broth microdilution system Sensititre[™] DKMGN (Thermo Fisher Scientific, UK) and the agar dilution method for fosfomycin susceptibility testing AD Fosfomycin 0.25-256 (Liofilchem srl, Roseto degli Abruzzi, Italy).

AST interpretation was done according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints and methodology (EUCAST, Version 9.0, 2019 and Version 10.0, 2020). In particular, *E. coli* and *K. pneumoniae* were defined as MDR if the phenotypic analysis of the antibiotic profile revealed a reduced or total absence of sensitivity to carbapenems (Imipenem and Meropenem) and sensitivity to colistin; *P. aeruginosa* and *A. baumannii* were considered MDR if resistant to carbapenems; *S. aureus* was considered MRSA if resistant to methicillin and

other anti-staphylococcal beta-lactams; *E. faecium* and *E. faecalis* were considered as VRE if resistant to glycopeptides. The same bacteria were defined as panderug-resistant (PDR) if they were resistant to all antimicrobial agents, as in the international expert proposal for interim standard definitions for acquired resistance (Magiorakos AP *et al.*, 2012). *Candida* spp. and CoNS were not evaluated for resistance phenotypes.

Data registration was done using the SirSCAN 2000 automatic[™] system (i2a Diagnostics, Montpellier, France). All data were extrapolated with the software VirtuosoPlus (Dedalus Italia SpA, Florence, Italy).

To define a nosocomial origin of the BSI, the only criterium was the positivity of blood cultures collected more than 48 hours after the hospital admission. Statistical analysis was performed by applying the two-tailed exact Fisher test over 2x2 contingency table using Python SciPy implementation. Significance level was set at 0.05.

The study was authorized by the Ethical Committee of the Bergamo Province (2020-0075, May 14, 2020).

RESULTS

The hospital population in the considered periods (February 22-May 21) of the two years under examination is completely different. In 2019, "Papa Giovanni XXIII" Hospital hosted 8280 patients representing all chronic and acute pathologies; instead, in 2020, 1911 out of 6403 of the people admitted to the hospital were SARS CoV-2 microbiologically positive, and many of them underwent assisted ventilation treatment using endotracheal tube or CPAP, remaining in intensive and sub-intensive care units for more than 48 hours.

In the two examined periods, 1584 patients admitted at the "Papa Giovanni XXIII" Hospital in 2019 required blood cultures, compared with 1438 in 2020. In the considered 2019 quarter, MV laboratory received 2315 blood culture samples: 1790 (77.3%) were negative and 525 (22.7%) were positive. In the

Table 1 - Total number of blood cultures processed in the examined 2019 and 2020 periods.

	2019			TOTAL
	1 st PERIOD (Feb 22 to Mar 21)	2 nd PERIOD (Mar 22 to Apr 21)	3 rd PERIOD (Apr 22 to 21 May)	
No. patients whose blood cultures were required	503	564	517	1584
No. Blood cultures	729	814	747	2290
No. Blood cultures-NEG	577 (79.1%)	622 (76.4%)	560 (74.9%)	1790 (77.3%)
No. Blood cultures-POS	152 (20.9%)	192 (23.6%)	181 (24.1%)	525 (22.7%)
	2020 (COVID-19)			
No. patients whose blood cultures were required	536	409	493	1438
No. Blood cultures	777	648	776	2201
No. Blood cultures-NEG	667 (85.9%)	440 (67.9%)	572 (77.7%)	1679 (76.3%)
No. Blood cultures-POS	110 (13.1%)	208 (32.1%)	204 (22.3%)	522 (23.7%)

considered 2020 quarter, MV laboratory received 2201 blood culture samples: 1679 (76.3%) were negative and 522 (23.7%) were positive (Table 1).

Figure 1 shows the BSI episodes occurring in the period Feb-May 2019 vs 2020. The global number of BSIs is quite similar (427 in 2019 vs 411 in 2020) even if the distribution of community and nosocomial origin of BSIs is different: in particular, community-acquired BSI were 236 out of 427 (55.3%) in 2019, but 194 out of 411 (47.2%) in 2020. Statistical association is observed (Fisher-test, $p=0.022$).

In addition, the global distribution between EARS (259 in 2019 vs 247 in 2020) and non-EARS

(bacteria and yeasts) pathogens (168 vs 164) is similar (Fisher-test, $p=0.89$). However, it must be noted that in the first subperiod of the COVID-19 time, BSIs were significantly less than in 2019 (71 vs 123, $p<0.001$) even if the EARS pathogen ratio was not different from 2019 (40 out of 106 vs 31 out of 98 cases, Fisher-test, $p=0.38$). The second subperiod is characterized by a very similar BSI distribution between EARS and non-EARS etiologies. On the contrary, in the third subperiod of the COVID-19 time, BSIs were more than in 2019 (145 vs 182, $p<0.01$) even if the EARS pathogen ratio was not different from 2019 (118 out of 182 vs 97 out of 145 cases, Fisher-test, $p=0.73$).

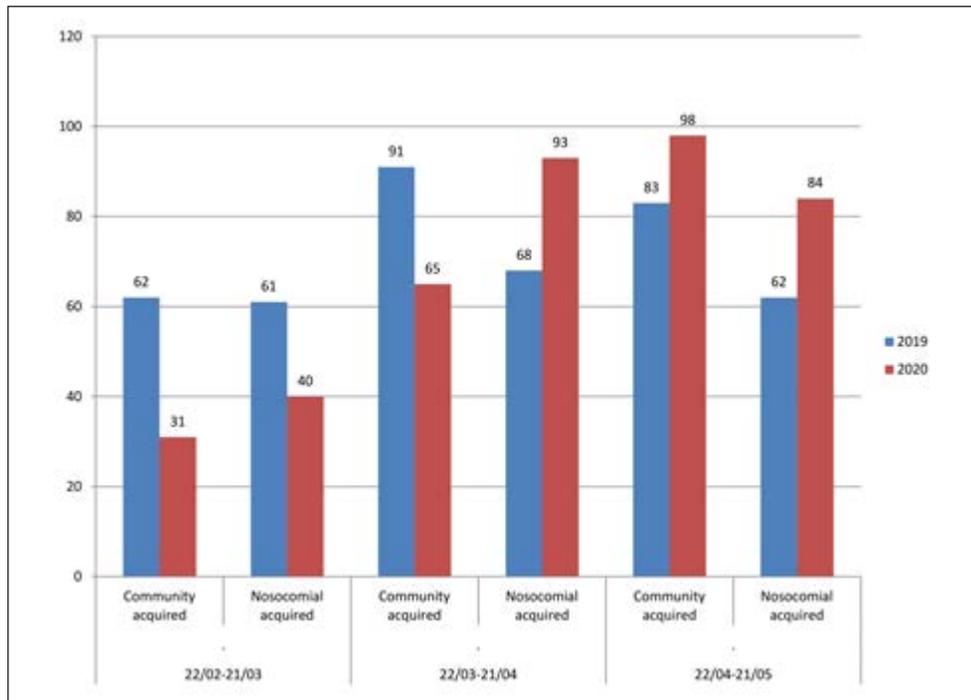


Figure 1 - Number of community and nosocomial BSIs in the period Feb-May 2019 vs 2020.

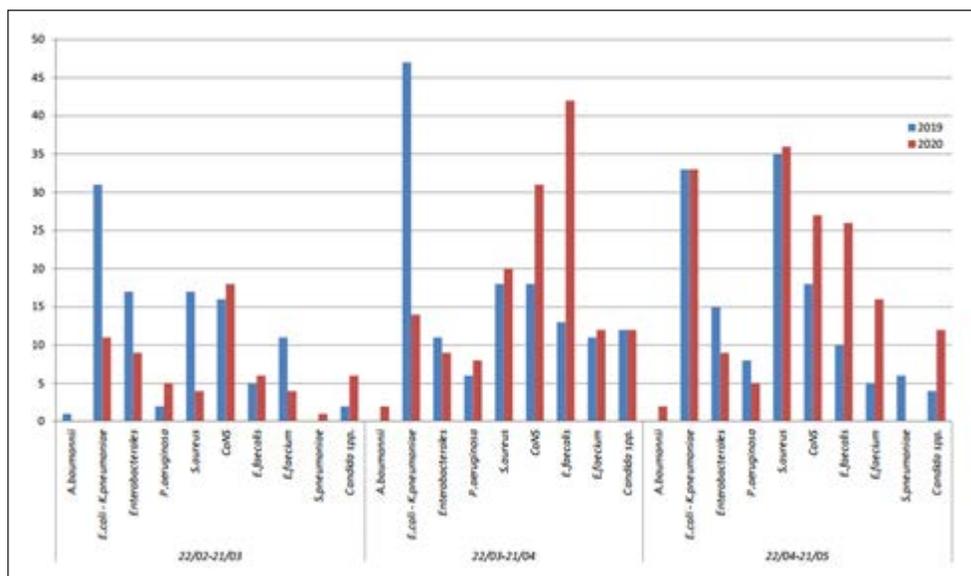


Figure 2 - Number of BSIs plotted according to EARS etiology and examined subperiod.

Figure 2 summarizes the BSI etiologies as represented by the ECDC criteria and their distribution in sub-periods. In particular, Gram Negative and Gram Positive EARS etiologies as identified during the considered quarters in 2019 and 2020 are represented in

Figures 3 and 4, respectively: *E. coli* (86 vs 50, $p=0.001$), *K. pneumoniae* (25 vs 8, $p=0.004$), *P. aeruginosa* (16 vs 18, $p=0.72$), and *A. baumannii* (1 vs 4, $p=0.21$) were the considered Gram Negative strains; *E. faecalis* (28 vs 74, $p<0.001$), *E. faecium* (27 vs 32,

Figure 3 - Number of Gram Negative EARS identified during the considered quarters in 2019 and 2020.

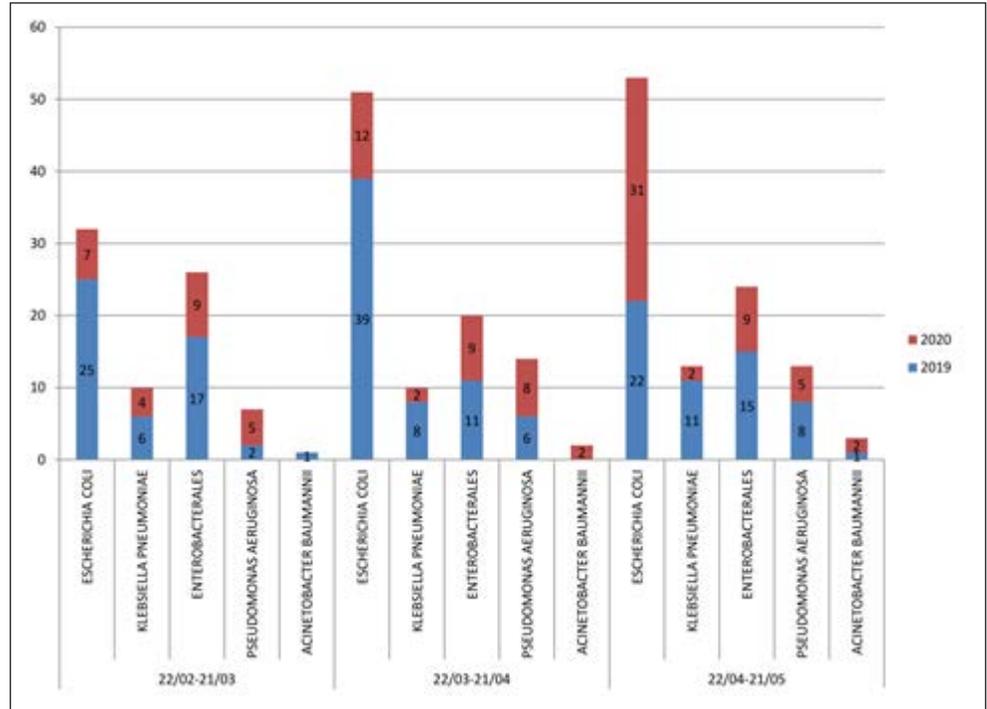
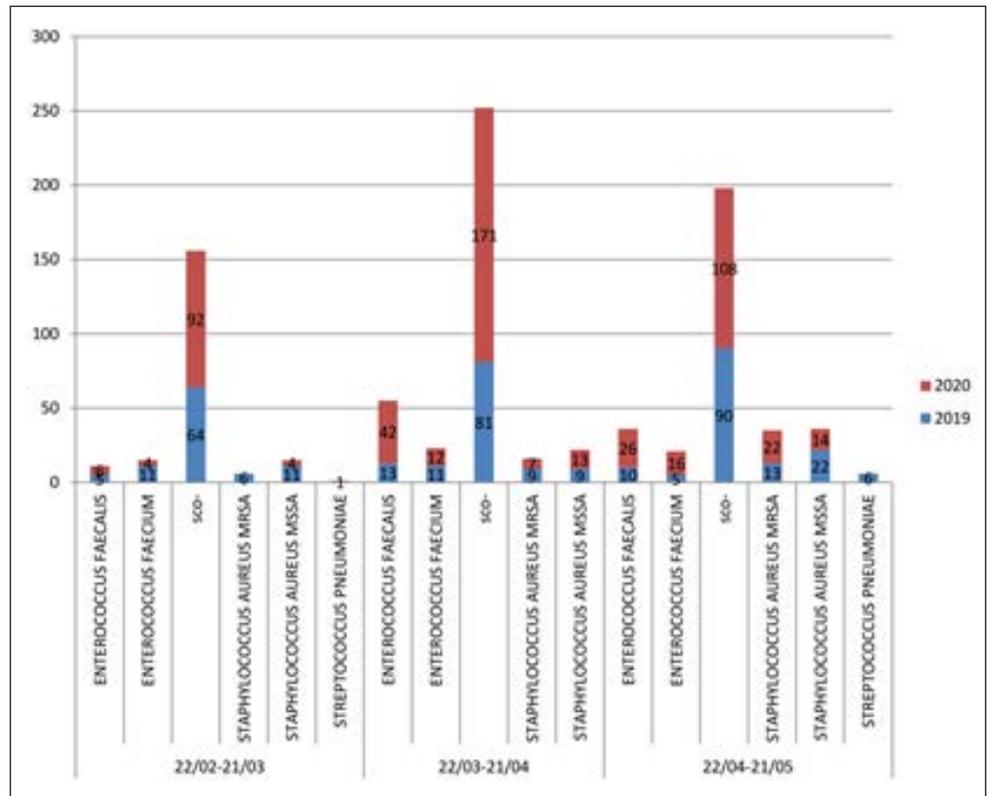


Figure 4 - Number of Gram Positive EARS identified during the considered quarters in 2019 and 2020.



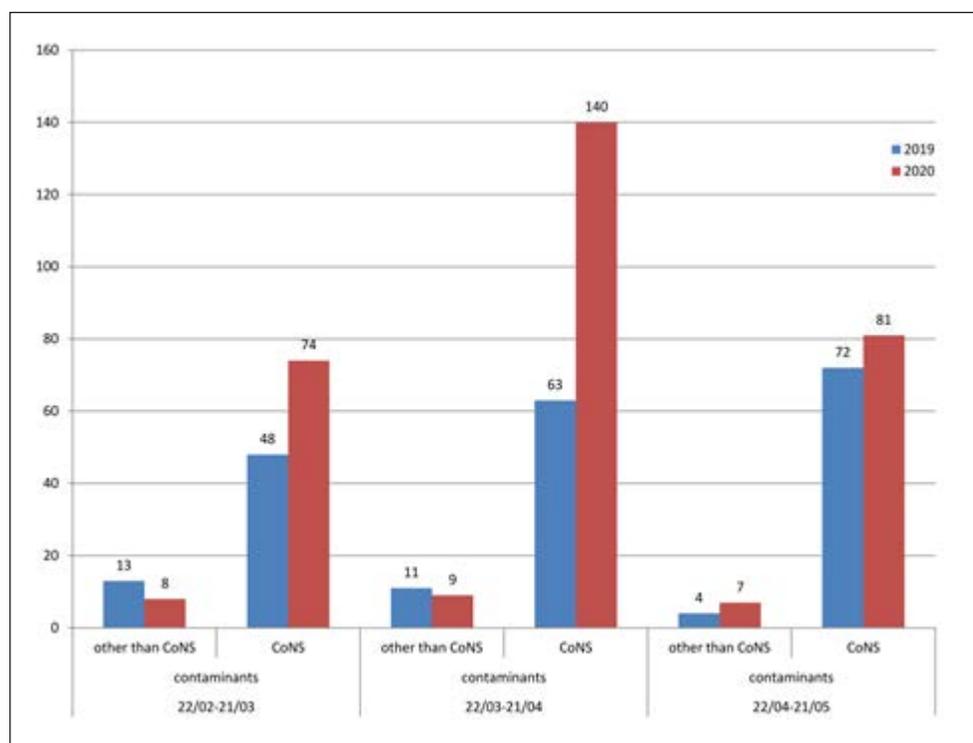


Figure 5 - Number of contaminant bacteria identified from blood cultures during the considered quarters in 2019 and 2020.

$p=0.41$), *S. aureus* (70 vs 60, $p=0.54$), and *S. pneumoniae* (6 vs 1, $p=0.12$) were considered the Gram positive cocci implicated as causative agents of BSI.

In addition, 168 vs 164 non-EARS microorganisms (bacteria and yeasts) were isolated in 2019 and 2020 respectively. In particular, Enterobacterales other than *E. coli* and *K. pneumoniae* (43 vs 26; $p=0.03$); Non-Fermentative Gram-negative bacteria other than *P. aeruginosa* and *A. baumannii* (7 vs 5; $p=0.77$); *Staphylococcus* spp. other than *S. aureus* (55 vs 78, $p=0.007$); *Streptococcus* spp. other than *S. pneumoniae* (35 vs 15, $p=0.003$); Gram Positive bacilli including *Listeria monocytogenes* (4 vs 8, $p=0.25$) and anaerobes including *Bacteroides fragilis* and *Clostridium perfringens* (6 vs 2, $p=0.28$) were isolated. The distribution of yeast etiologies in 2019 and in 2020 is very different in number (18 vs 30, $p=0.06$) and species identification between *C. albicans* (4 vs 22) and *Candida* other than *albicans* (14 vs 8, $p<0.001$). Among these, *C. glabrata* (1 vs 5, $p<0.01$), *C. lusitaniae* (2 vs 0, $p=0.5$), *C. parapsilosis* (3 vs 2, $p=1.0$) and *C. tropicalis* (8 vs 1, $p=0.07$) were the represented species.

Data regarding possible blood culture contaminants show an increase between the two considered quarters (211 vs 319, $p<0.001$), even if the large majority of contaminants were observed in the second subperiod of 2020 (Mar-Apr 149 vs Feb 22-Mar 21 82; and vs Apr-May 88). In particular, CoNS were the large majority of the isolated strains in 2019 and 2020, respectively (183 vs 295, $p=0.04$) in comparison with non-CoNS bacteria (28 vs 24). Data are shown in Figure 5.

Concerning the MDR bacteria, Figure 6 shows the data. Multi-drug resistance was observed in 2019 vs 2020, respectively, in 7/111 vs 0/58 ($p=0.10$) *K. pneumoniae*, 6/27 vs 5/27 ($p=1.00$) *E. faecium*, 1/15 vs 4/18 ($p=0.35$) *P. aeruginosa* and 0/1 vs 4/4 ($p=0.02$) *A. baumannii*.

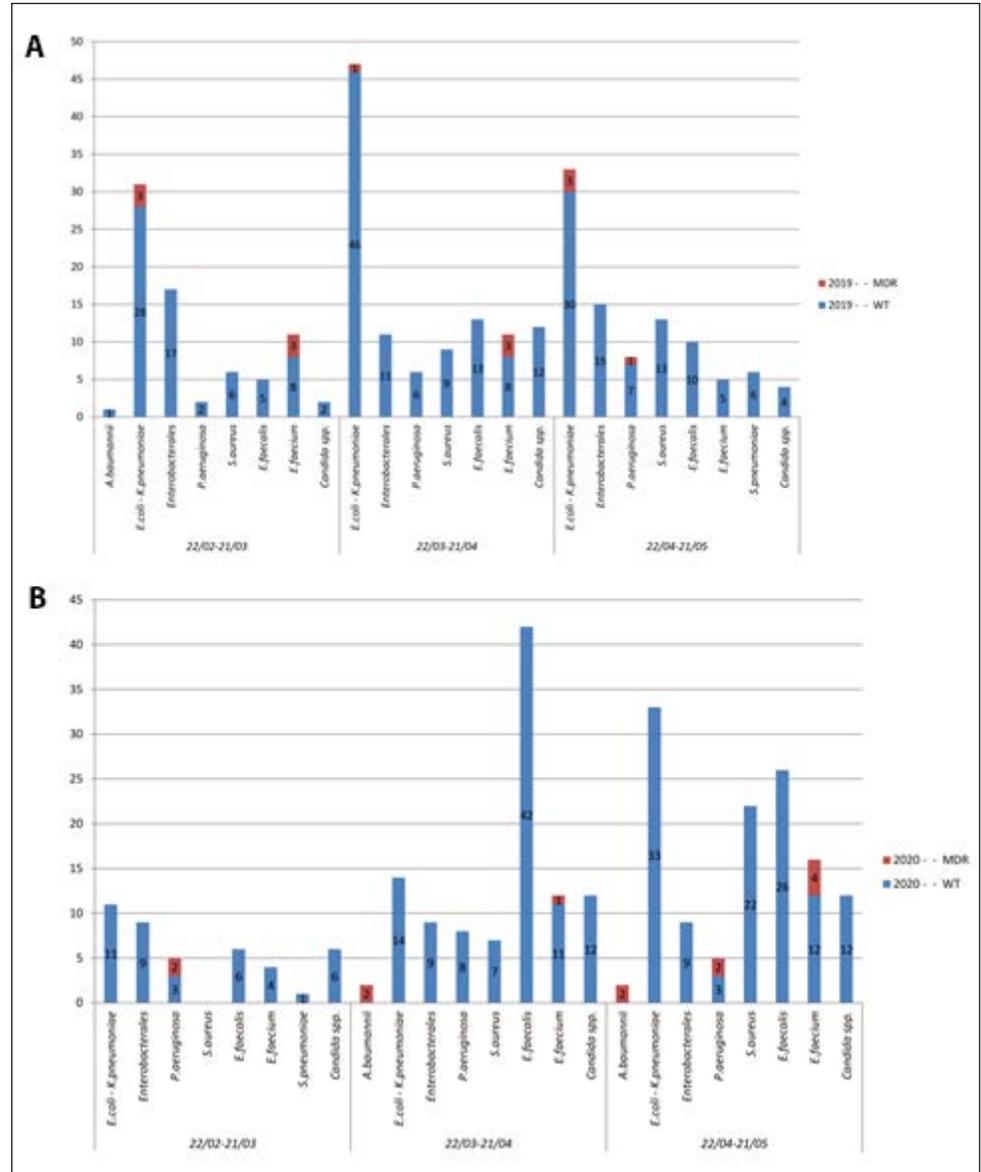
DISCUSSION

The aim of this retrospective study was to give a microbiological picture of the microorganisms isolated, as pathogens and contaminant, from blood cultures collected during the first wave of COVID-19 at the Papa Giovanni XXIII Hospital, Bergamo, Italy.

As the first step of our retrospective analysis, we highlighted a different distribution of bacterial and fungal isolates. In the first subperiod (Feb 22 to Mar 21) a change in microbial BSI etiologies was observed from 2019 to 2020. In fact, in 2019 *E. coli*, *K. pneumoniae*, *S. aureus*, other Enterobacterales and *E. faecium* largely prevailed. In 2020, the same bacteria were less represented: however, *Candida* spp. still appeared. Clinically-significant CoNS occurred with the same frequency in the two years. In this subperiod, Tocilizumab, Ceftriaxone and Azithromycin were largely used for the therapeutical management of COVID-19 patients. Community-acquired BSIs were largely most frequent in both the 2019 and 2020 first subperiods.

In the second subperiod (Mar 22 to Apr 21) of both considered years (2019 vs 2020), we noticed the biggest differences. In 2019, *E. coli* and *K. pneumoniae* still predominated. Other Enterobacterales, *P. aerugi-*

Figure 6 - EARS MDRO identified during the considered quarters in 2019 (A) and 2020 (B).



nosa, *S. aureus*, *E. faecium* and *Candida* spp. were almost the same in the two years. However, in 2020, CoNS and *E. faecium* predominated. Clinically-significant CoNS occurred with the same frequency in the two years. In this subperiod, Tocilizumab was suspended, and steroids were added for the therapeutical management of COVID-19 patients. Antibiotics were also suspended, and added only in selected clinical cases. Nosocomial-acquired BSIs were largely more frequent in the second 2020 subperiod than in 2019. In the third subperiod (Apr 22 to May 21) of both considered years (2019 vs 2020), a clear difference remained: the number of CoNS, *E. faecalis*, *E. faecium* and *Candida* spp. was higher in 2020. Tocilizumab was suspended, and steroids were added. Antibiotics were also suspended, and added only in selected clinical cases. Nosocomial-acquired BSIs were largely more frequent in the third 2020 subperiod than in 2019.

As the second step of our retrospective analysis, contaminant frequency was examined. A significant increase of CoNS was observed, particularly in the second 2020 subperiod, even if other etiologies were similar.

As the third step of our retrospective analysis, we focused on MDR bacteria. Resistant bacteria, both pathogenic and non-pathogenic, occur everywhere. Bacteria that are becoming resistant to antibiotics - and which therefore represent a current or existing threat to public health - were monitored. In 2019, it was clear that the main MDR bacteria isolated in the three subperiods were *K. pneumoniae* Carbapenemase-producing, *E. faecium* VRE and few MDR *P. aeruginosa*, present only in the third period. Instead, in 2020 *K. pneumoniae* Carbapenemase-producing disappeared. MDR *P. aeruginosa* was present in higher numbers (in the first and third period). Vancomy-

cin resistant *E. faecium* was present only in the third period. *Acinetobacter baumannii*, absent in 2019, when isolated, was MDR in 2020.

The BSIs retrospective analysis comparing 2019 vs 2020 shows that:

- 1) The incidence rate of BSIs was higher in 2020, and the cumulative risk of developing BSIs in patients during the COVID-19 period increased with the length of the hospital stay (Giacobbe DR et al. 2020). In fact, the nosocomial origin of BSI was statistically confirmed as prevalent in 2020 vs 2019 when the large majority of cases was directly detected when people were admitted to the Emergency Room.
- 2) In agreement with Hughes and Sepulveda data, in the first month of the COVID-19 period, blood cultures are largely negative (BSIs positive 13.1% vs negative 85.9%). However, when patients long-stayed in Papa Giovanni XXIII Hospital (completely converted into an overburdened Intensive Care hospital), BSIs increased, even if etiologies were quite similar.
- 3) Microbial etiologies were quite different in 2019 vs 2020. Although tocilizumab and/or steroids were administered only for limited periods at Papa Giovanni XXIII Hospital, the effect of these drugs (Lamers MM et al., 2020), together with the perturbation of gut microbiota likely occurring in COVID-19 patients (Donati Zeppa S et al., 2020), may justify the Enterobacterales, *Enterococcus* spp. and *C. albicans* (but not *Candidae non-albicans*) transposition. In particular, concerning *Candida* infections, in addition to the well-known predisposing factors occurring in critically ill patients (Arastehfar A et al., 2020), the use of tocilizumab must be added as a predisposing condition (Antinori S. et al., 2020, Peman J et al., 2020). In our experience, tocilizumab was used during the first COVID-19 month in hospital when candidemias were observed in patients after a long-stay in hospital, in the second and third subperiods. Also, MDR isolates were largely less common in the COVID-19 period vs 2019. Gram positive (*Enterococcus* spp., *S. aureus*), non-fermentative Gram negative (*P. aeruginosa*, *A. baumannii*) bacteria and *Candida* spp. were largely spreading. In particular, *C. albicans* inverted its trend, becoming largely represented vs *C. non-albicans* whose habitat is not strictly digestive.
- 4) The global increase of CoNS is significant, and their isolation as pathogens is also higher. This fact may suggest that the presence of clinically significant CoNS is due to the general intensive management of the patients admitted in the COVID-19 period. However, the critical situation of the phlebotomist team dedicated to the preanalytical phase can also justify, particularly in the most dramatic month (March 2020), the increase of CoNS contamination. Even if several Authors hypothesized a higher risk of blood culture contamination during the COVID-19 pandemic because of multiple factors (for example: working at surge capacity and the scarcer healthcare resources, lower adherence to antiseptics protocols due to the strain on the healthcare system, most of the attention put into prevention of airborne transmission during COVID-19 outbreak, or the bacterial pathogenic behavioral activities by their quorum sensing) (Lansbury L, 2020, Razzaque MS, 2020), the continuous educational courses on BSIs and blood culture collection done in the hospital provided to medical doctors and nurses during the last five years may explain why the contaminant ratio was unchanged after the second subperiod.
- 5) During the COVID-19 period, the classic MDR Enterobacterales were almost completely absent. It is noteworthy that, according to the reports of the EARS-Net, the number of MDR bacteria isolated at Papa Giovanni XXIII Hospital by the VM laboratory has always been low compared to the average national data (in 2019, ESBL *E. coli*: 17.1%; Carbapenemase-producing *K. pneumoniae*: 12.2%; Piperacillin-Tazobactam Resistant *P. aeruginosa*: 13.3%; MDR *A. baumannii*: 20.0%; MRSA: 22.4%; Vancomycin-Resistant *E. faecalis*: 0.0%; Vancomycin-Resistant *E. faecium*: 11.6%). The finding of a low proportion of patients with MDROs is noteworthy and may be a consequence of virtuous antimicrobial use during the COVID-19 pandemic, when Ceftriaxone and Azithromycin were used only during the first subperiod and then suspended (Cheng LS et al., 2020; Getahun H, 2020; Lai C-C, et al., 2020).
- 6) Also, our experience confirms the increase of MDR reported by Perez S et al., 2020 for *A. baumannii*, but not for other bacteria. However, it must be noted that the continuous educational courses on hand hygiene done in hospital provided to medical doctors and nurses since 2002 and continued also during the COVID-19 spread may explain why the diffusion of MDRO is less frequent than elsewhere (Monnet DL et al., 2020; Kampmeier S et al., 2020).
- 7) Assuming that the COVID-19 population was representative of the general population when admitted to hospital, it means that the MDR circulation in outpatients without particular risk factors excluded the SARS CoV-2 infection is really not significant;
- 8) Diagnosis of BSI in the COVID-19 era can be difficult especially for CoNS development. Further studies will clarify whether the increased risk of BSI had an influence on the outcome of the disease. Our results show what the clinical impression has been, and what is now starting to emerge from the international literature (Lansbury L et al., 2020; Garcia-Vidal C et al., 2021).

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