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Microbial Coinfections in Patients with SARS-CoV2

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Abstract
Since December 2019, the COVID-19 pandemic has spread from its epicenter in Wuhan. The objective of this study is to determine the prevalence of microbial co-infections in patients with SARS CoV2 and to analyze the responsible germs and their antibiotic resistance profiles.

Material and methods: this is a descriptive study, which includes all microbiologically documented infections, all infectious sites combined, in patients with SARS CoV2 virus, treated at the Mohammed VI University Hospital in Marrakech.

Results: 985 samples were received, including 40 Distal protected aspirate (DPA) and bronchial aspirations, 22 bronchial sputum, 43 requests for respiratory PCR, 714 requests for cytobacteriological examination of the urine (CBEU), 125 blood cultures, and 41 peripheral catheterizations. 160 infections have been documented, dominated by urinary tract infections and bacteremia. Gram negative bacteria took the top spot. Of all the bacteria isolated from all sites, 16% were multidrug-resistant (MDR) bacteria.

Conclusion: The overall proportion of SARS CoV2 patients who have bacterial coinfection is lower than in previous influenza pandemics

Keywords: SARS coV2, bacterial coinfections, viral coinfections, fungal coinfections, antibiotic resistance.

Introduction

Respiratory viruses other than SARS Cov2, such as seasonal influenza, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS CoV1, exhibit different levels of bacterial and fungal coinfection (1). However, few information is available on the frequency, nature and susceptibility profiles of the pathogens responsible for co-infection with SARS CoV2. In a study in Wuhan, bacterial superinfections in COVID-19 patients and which reached 16% were a factor of poor prognosis (2). Therefore, there is a clinical need for robust investigation of coinfection in patients with SARS Cov2.

The objective of this work is to determine the prevalence of microbial coinfections in patients with SARS CoV2 and to analyze the responsible germs and their antibiotic resistance profiles.

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Material and methods

This is a descriptive study, which includes all microbiologically documented infections, all infectious sites combined, in patients with SARS CoV2 virus, taken care of at the Mohammed VI University Hospital of Marrakech during the period between 1/04/2020 and 15/06/2020. During this period, all services of the Mohammed VI University Hospital of Marrakech were dedicated to the care of patients with SARS CoV2.

Strain identification was done by MALDI TOF. Multiplex PCR on respiratory samples allowed the identification of certain strains and the detection of resistance genes. The antibiogram for bacteria was performed by BD Phoenix.

Results:

During this period, 985 samples were received, including 40 distal protected aspirate (DPA) and bronchial aspirations, 22 bronchial sputum, 43 requests for respiratory PCR, 714 requests for cytobacteriological examination of the urine (CBEU), 125 blood cultures, and 41 catheterizations peripheral devices.

During this period, 160 documented infections were collected (i.e. a positivity rate of 16%). Urinary tract infections accounted for 51% of coinfections, followed by bacteremia (25%), pneumonia (21%), and infections linked to peripheral catheterizations (3%).

Infections in intensive care represented 25% of documented infections. In intensive care, 57% of the infections documented in patients with Covid19 were pneumonia, and 27% were bacteremia. In terms of other excluded intensive care units, urinary tract infections represented 71% of documented infections.

The sex ratio of patients who developed coinfections was 1.15, and the mean age was 40 years.

Regarding the profile of the germs involved, Gram-negative bacteria took first place (76%), they were dominated by Enterobacteriaceae (51%) followed by Acinetobacter baumanii (6%) and Pseudomonas aeruginosa (5%). For Gram-positive bacteria, Staphylococcus aureus predominated (10%). Yeasts occupied 13% of the germs isolated.

Table I summarizes the distribution of the germs isolated and their predominance according to the service and the sampling site.

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Table I: distribution of germs according to the collection site and the department

Germe	%	Predominance according to the site					Predominance by service	
(n=160)		CBEU	Blood culture	DPA	PCR	catheterizations peripheral devices.	intensive care	except intensive care
E. coli (n=44)	27	**98%**	2%	0%	0%	0%	6%	**94%**
K. pneumoniae (n=28)	17	**55%**	10%	10%	25%	0%	14%	**86%**
Candida spp (n=19)	12	**65%**	15%	10%	0%	10%	37%	**63%**
S. aureus (n=16)	10	7%	37%	0%	**56%**	0%	**69%**	31%
Enterococcus spp (n=14)	9	**50%**	**50%**	0%	0%	0%	36%	**64%**
Acinetobacter baumanii (n=11)	6	27%	**45%**	10%	0%	18%	**55%**	45%
P. aeruginosa (n=7)	5	15%	28%	**57%**	0%	0%	**71%**	29%
E. cloacae (n=7)	5	38%	**62%**	0%	0%	0%	0%	**100%**
Legionella (n=2)	1	0%	0%	0%	**100%**	0%	50%	50%

Regarding urinary tract infections, 69% of cases were secondary to Enterobacteriaceae (75% dominated by E. coli), and 12% secondary to Candida spp, 7% to Enterococcus faecalis, and 4% to Acinetobacter baumanii. For uropathogenic Enterobacteriaceae, 74% were resistant to amoxicillin, 35% to the combination amoxicillin and clavulanic acid, 27% to fluoroquinolones, and 22% to trimethoprim sulfametoxazole.

Multidrug-resistant Enterobacteriaceae represented 8% of Enterobacteriaceae and were resistant to 3rd generation cephalosporin C3G by production of ESBL (extended spectrum beta lactamase). All strains isolated of Acinetobacter baumanii were resistant to all antibiotics tested except amikacin and trimethoprim sulfametoxazole in one case each. All strains of Enterococcus faecalis were susceptible to amoxicillin.

Bacteremia, which represented 25% of coinfections, came from intensive care units in 36% of cases. They were dominated by Enterobacteriaceae at 33%, non-fermentative bacteria (Pseudomonas aeruginosa and Acinetobacter baumanii) at 19%, Enterococcus spp at 17%, Methicillin-sensitive Staphylococcus aureus (SASM) at 12%, and Candida spp at 10%. None of these bacteremias were secondary to respiratory infection.

Enterobacteriaceae responsible for bacteremia had 100% resistance to amoxicillin, 71% to the combination amoxicillin and clavulanic acid, and no resistance to fluoroquinolones, aminoglycosides and trimethoprim sulfametoxazole. 38% of these Enterobacteriaceae were multi-resistant, they were resistant to carbapenems at 33% and to aminoglycosides and trimethoprim sulfametoxazole at 50%. All strains of Acinetobacter baumanii were multidrug-resistant. Enterococcus faecium was resistant to amoxicillin in 71% of cases.

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Secondary bacterial pulmonary infections were the prerogative of intensive care units. The bacteria responsible were dominated by Pseudomonas aeruginosa at 33%, Klebsiella pneumoniae, Providencia rettgeri at 25% each, and Candida spp at 17%. Pseudomonas aeruginosa was resistant to Ceftazidime and imipenem, fluoroquinolones and aminoglycosides, respectively, in 25%, 75% and 25% of cases. While Klebsiella pneumoniae was characterized by 100% resistance to C3G, 33% to imipenem, and 100% to fluoroquinolones and Gentamicin with retained sensitivity to Amikacin.

Respiratory infections documented by respiratory multiplex PCR accounted for 15% of all coinfections. PCR identified 4 cases of coinfection with other respiratory viruses: 2 cases of rhinovirus, one case of adenovirus and one case of influenza A virus, and 20 cases of bacterial coinfection dominated by Staphylococcus aureus (9 cases) expressing the Mec A resistance gene in 2 cases, and Klebsiella pneumoniae (7 cases) resistant to carbapenems in 3 cases by expression of the Oxa48 gene. The rest of the lung infections were shared between Haemophilus influenzae (2cas) and Legionella (2cas).

Of all the bacteria isolated from all sites, 16% were multidrug-resistant (MDR) bacteria.

Figure 1 shows the resistance rates of BMRs to C3Gs and carbapenems, and Figure 2 the resistance rate of Staphylococcus aureus to methicillin.

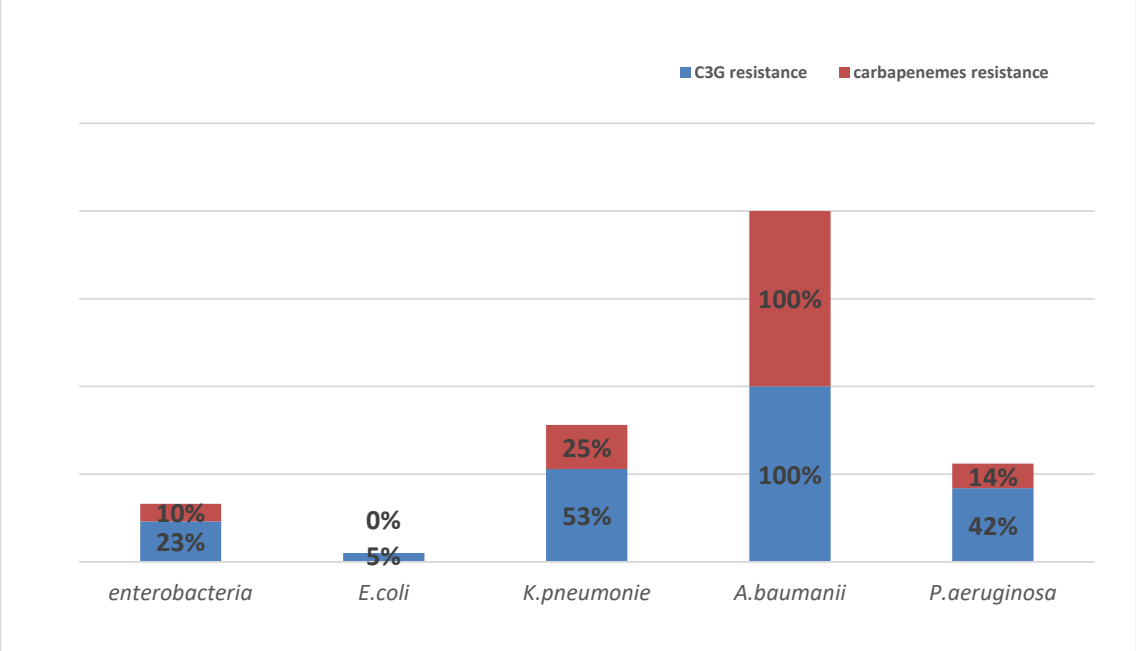

Figure 1: Percentage of resistance to C3Gs and carbapenems in multi-resistant Gram-negative bacilli

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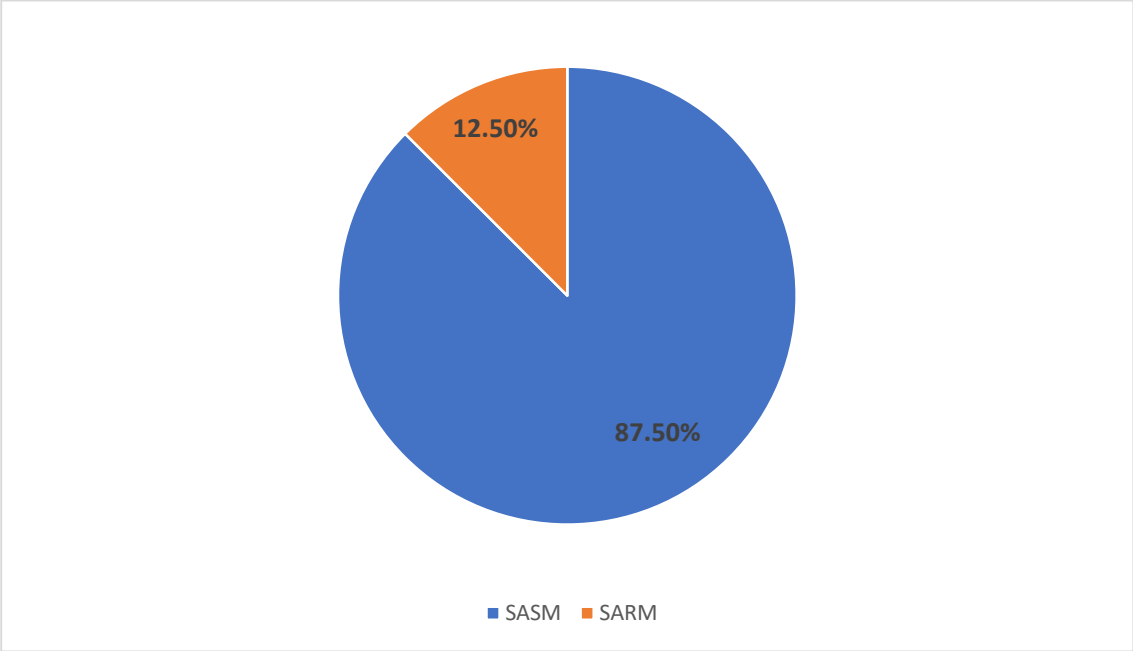

Figure 2: Percentage of methicillin resistance in Staphylococcus aureus isolates

Discussion:

The results of this study indicate a higher coinfection rate than what has been reported in the literature. Indeed, out of 9 studies that report bacterial coinfection in COVID-19 cases, 8% bacterial and fungal coinfection have been reported. (3)

However, the coinfection rate in this study (16%) matches that reported by a Chinese study by Zhou et al. (4), who reported 15% of bacterial coinfections in hospitals in China.

That said, bacterial coinfections remain less common in patients with SARS CoV2 than in patients with seasonal influenza. In fact, during the 2009 influenza pandemic, 25% of severe cases of A H1N1 influenza were associated with a bacterial infection (5).

The bacteria most commonly associated with influenza infection are those that commonly colonize the nasopharynx, such as Streptococcus pneumoniae, Staphylococcus aureus, and Streptococcus pyogenes (5). This contrasts with pathogens identified in the literature in patients with SARS CoV2, where M. pneumoniae dominated, followed by P.aeruginosa, H. influenzae and K. pneumoniae (1). In this study, the atypical bacteria represented by Legionella represented 1.2% and it was E.coli, K. pneumoniae and Candida spp which dominated, this can be explained by the predominance of urine samples compared to other samples.

MDR bacteria represented 16% of the bacteria isolated in this study. The current literature provides little data on the sensitivity of isolated bacteria, co-infected with SARS CoV2, to antibiotics. However, and despite the low rate of bacterial coinfections, the rate of prescription of

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antibiotics, especially broad-spectrum, is high. For example, in a Chinese study (6), antibiotics were used in 99% of patients, while no bacterial or fungal coinfection was reported. In addition, very few atypical bacteria have been identified in co-infection with SARS CoV2 (3). Even documented M. pneumoniae infections have been diagnosed by detection of IgM, which by itself is not a very specific test and can lead to overestimation of M. pneumoniae infections (1). This study reports 1.2% of coinfections with atypical germs (Legionella). Therefore, prolonged use of macrolides must be weighed against the potential likelihood of coinfection with atypical bacteria within COVID-19 cohorts.

Coinfection by other respiratory viruses is estimated at 3% (1, 7), an American study showed that the most common viruses found were rhinovirus/enterovirus (6.9%), respiratory syncytial virus (5.2 %) and not SARS CoV2 Coronaviridae (4.3%) (8). The rate of viral coinfection in this series was 2.4%, specifying that respiratory PCR was requested only in 44 patients. It is therefore evident that the presence of non-SARS Cov2 pathogens does not eliminate the presence of the SARS Cov2 virus and vice versa.

Conclusion:

The overall proportion of SARS CoV2 patients who have bacterial coinfection is lower than in previous influenza pandemics. Overall, these results support discontinuation of empiric broad-spectrum antibiotics in the vast majority of patients when SARS CoV2 infection is diagnosed. As the pandemic evolves around the world and more and more publications emerge, these results will need to be constantly reviewed.

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