

Evaluation of Bacterial infections and its antimicrobial resistance pattern among hospitalized patients with COVID-19

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Abstract:

Background: The coinfection of the SARS-CoV-2 with other microorganisms, such as virus, bacteria, and fungi, is a very important factor in COVID-19. For optimal utilisation of antimicrobials, understanding the proportion of secondary bacterial infections in COVID-19 is crucial.

Methods: This is a single-center study on 128 patients with confirmed COVID-19. Bacterial co-infection was determined by positive bacterial culture and resistant pattern was determined by Kirby Bauer disc diffusion method.

Results: 186 samples collected from 128 patients. Bacterial co-infection was detected in 19% of the samples. The culture positivity showed no significant difference across genders and different age groups. The rate of positive sputum culture was 36%, followed by 18% in Urine and 14% in Blood. The commonest organisms isolated were Enterobacteriaceae (60%) followed by Non-fermenters (20%) and Gram-Positive Cocci (20%). The antibiotic resistant profile showed that resistance was observed in both Gram positive and gram-negative isolates to most of the routinely used drugs.

Conclusions: Bacterial co-infection is relatively common in COVID-19. The antimicrobial resistance rates of the majority of bacteria were generally high, which indicates that more accurate use of antibacterial agents is necessary. De-escalation of antibiotics as a part of antimicrobial stewardship will help in more rational use of antibiotics.

Keywords: COVID -19, bacterial coinfection, antimicrobial resistance, antimicrobial stewardship

Date of Submission: 29-04-2021

Date of Acceptance: 13-05-2021

I. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first appeared in 2019, has spread to most of the countries around the world, and the corona virus disease 2019 (COVID-19) has progressed into a global pandemic. Globally, as on 18 February 2021, there have been 109,594,835 confirmed cases of COVID-19, including 2,424,060 deaths, reported to WHO [1].

Other respiratory viruses, such as seasonal/pandemic influenza, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-1, show differing levels of bacterial/fungal co-infection [2].

The coinfection of the SARS-CoV-2 with other microorganisms, such as virus, bacteria, and fungi, is a very important factor in COVID-19, and it can raise difficulties in diagnosis, treatment, prognosis of COVID-19, and even an increase in disease symptom and mortality [3].

Clinically, it is challenging to differentiate between isolated COVID-9 related viral infection and possible superadded bacterial or fungal infection.

While antibiotics are ineffective for treatment of COVID-19, they are prescribed in patients with suspected or documented COVID-19 for a variety of reasons. This includes difficulty in ruling out bacterial co-infection on presentation, but also the possibility of bacterial secondary infection during the course of illness. However, this assumption raises concerns of antibiotic overuse and subsequent harm associated with bacterial resistance [4].

For optimal utilisation of antimicrobials, understanding the proportion of COVID-19 who actually have secondary bacterial infections is crucial.

Hence, this study was conducted to understand the occurrence of bacterial infection in patients infected with SARS-CoV-2 along with its antibiotic resistance pattern.

II. Materials And Methods

Study design, population and data collection:

This is a single-center study conducted in the Department of Microbiology, Rajarajeswari Medical college and Hospital. It is one of the designated hospitals to treat patients with COVID-19 in Bangalore. Samples were collected from confirmed cases of COVID-19 between August 2020 and January 2021 after obtaining informed consent. This study included clinically suspected sepsis patients from both intensive care unit and non-ICU settings. Demographic details like age and gender were collected.

Pathogen detection and antimicrobial susceptibility

Bacterial infections were determined by positive Blood, Sputum, Urine and Pus cultures. The specimens were collected and cultured. Pathogen identification and antimicrobial susceptibility testing were carried out manually using specific culture media and Identification by biochemical tests. Antibiotic susceptibility test was done using Kirby Bauer disc diffusion method and the results were interpreted according to the criteria of Clinical and Laboratory Standards Institute Standard M100, 30th edition [5].

The same strains from one patient were counted only once. Any fungus isolated from cultures were excluded from the study. The study was approved by the Institutional Ethics Committee.

Statistical analysis

Demographic variables were summarized using means for continuous variables. Continuous variables were compared using *t* test. Categorical variables were compared using *z* score test. A *p* value of < 0.05 was considered statistically significant.

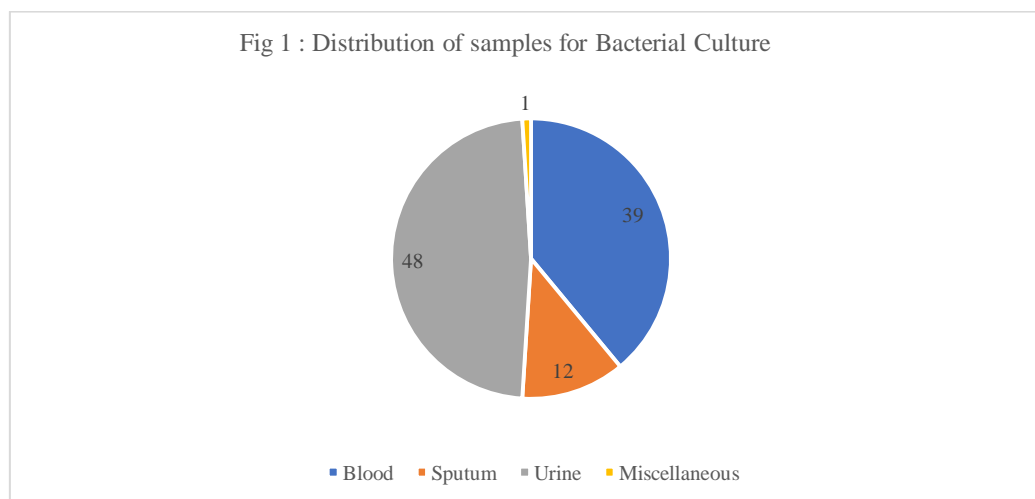
III. Results

A total of 128 patients with clinical features of sepsis were subjected to Microbial cultures. The mean age \pm SD of the study population was 45 ± 21.30 . the majority of the patients were males (63% $n=80$). The rate of bacterial infection among COVID patients was 19% ($n=35$). There was no significant change in the rate of culture positivity between males and females aged ≤ 45 years and ≥ 45 years (Table 1)

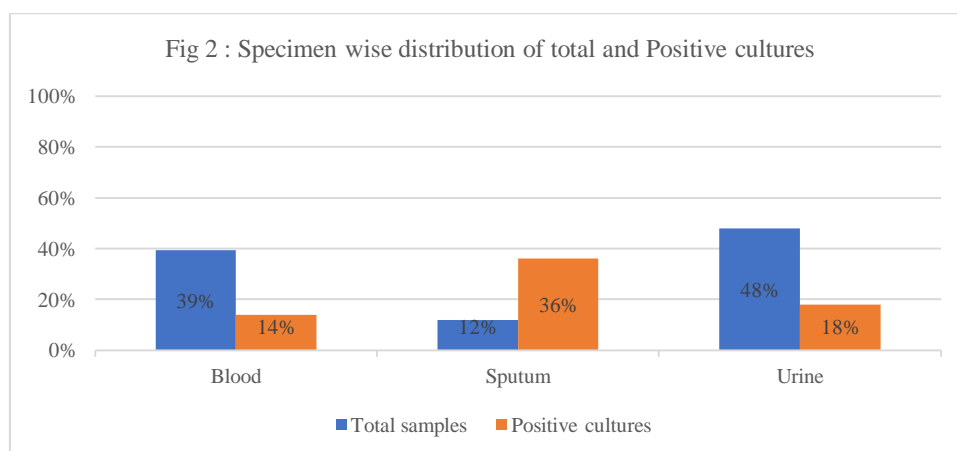
Table no 1 : Differences in culture positivity between age group less and more than 45

Gender	Age	Positive	Negative	Total	Chi-square (1 df)	P-Value
Male	≤ 45	7	23	30	0.386	0.533
Female		6	29	35		
Male	> 45	16	34	50	1.395	0.237
Female		2	11	13		
Total		31	97	128		

A total of 186 samples were collected from 128 patients. Urine samples represented highest (48%), followed by blood (39%), sputum (12%) and miscellaneous samples (1%) included 1 each of pus and pleural fluid sample. [Fig 1]



A total of 64(34%) isolates were obtained from 186 cultures, of which bacterial isolates represented 35 (19%) and 29 (15%) fungal isolates that were excluded from the study. The rate of positive sputum culture was more (36%) after excluding the samples which grew normal upper respiratory flora, followed by Urine sample (18%) and Blood (14%). [Fig 2]



The culture positivity among different samples showed no significant difference across genders and different age groups. (Table 2)

Table no 2: Characteristics of the patients

Characteristics	Total	Age group		Statistical Analysis	P-value	
		≤ 45	>45			
	128	65	63	t-test		
Age	45.328±21.302	27.923±12.680	63.286±10.874	16.914	<0.0001	
				z- score		
Gender	Male	80	30	50	-3.1623	0.00158
	Female	48	35	13	4.49	<0.00001
Bacterial Culture	Positive	31	13	18	-1.27	0.204
	Negative	97	52	45	1.005	0.3125
Sample-wise Positivity	Sputum	8	3	5	-1	0.3173
	Blood	10	3	7	-1.788	0.0734
	Urine	16	8	8	0	1

The commonest organisms isolated were *Enterobacteriaceae* (60%) followed by Non-fermenters (20%) and Gram-Positive Cocci (20%). (Table 3)

Table no 3: Distribution of Bacterial pathogens

Organism	n=35 (%)	
<u>GNB</u>	21	60%
E coli	14	40%
Kleb. pneumoniae	6	17%
Pr. Mirabilis	1	3%
<u>NFGNB</u>	7	20%
P. aeruginosa	3	9%
Acinetobacter sp.,	4	11%
<u>GPC</u>	7	20%
CONS	6	17%
Enterococci	1	3%

3 patients out of 128 had mixed infections. (Table 4)

Table no 4: Mixed infections

Mixed infections (n=3)
1. <i>P.aeruginosa</i> & <i>K.pneumoniae</i> - Sputum sample
2. <i>Acinetobacter</i> spp (Sputum), <i>K.pneumoniae</i> (Blood), <i>E.coli</i> (Urine)
3. <i>K.pneumoniae</i> (Blood), <i>P.aeruginosa</i> (Urine)

The antibiotic resistant profile showed that resistance was observed in both Gram positive and gram-negative isolates to most of the routinely used drugs. Most isolates were sensitive to Carbapenems. Among the *Staphylococcus* spp., isolated 67% of the isolates were Methicillin resistant. Carbapenem resistance was mostly with *Acinetobacter* spp., (50%). 1 isolate of *Enterococcus* spp, from blood culture was found to be vancomycin resistant. The resistance pattern is shown in Table 5

Table no 5: Antibiotic resistance rate

Antibiotic Resistance Rate of Bacterial isolates							
GNB	BL-BLI	Cephems	Aminoglycosides	Co-trimoxazole	Fluroquinolones	Carbapenems	Monobactam
<i>E. coli</i>	31	85	54	69	77	8	15
<i>K.pneumoniae</i>	33	83	17	33	33	17	33
<i>Ps.aeruginosa</i>	33	33	33		33	33	33
<i>Acinetobacter</i>	100	100	100	100	75	50	
<i>Pr mirabilis</i>	Pan Sensitive						
GPC	Methicillin	Co-trimoxazole	Fluroquinolones	Macrolides	Aminoglycosides	Vancomycin	Linezolid
<i>Staphylococcus spp</i>	67%	60	50	100	17	0	0
<i>Enterococcus</i>	VRE						

IV. Discussion

Coinfection with bacteria, other respiratory viruses, and fungi in COVID-19 patients has been reported to occur [3,6], with bacteria being a major causative agent of coinfection [7]. Bacterial coinfection in particular is a worrying problem as it complicates treatment in COVID-19 patients and may worsen the prognosis and increase the likelihood of fatality [3,8].

Bacterial coinfections are common in COVID-19 patients, mostly the infections are related to respiratory, urinary and blood stream infections as also mentioned by Clancy CJ et al [9] as well.

In a study from Wuhan, co-infection rates in 221 SARS-CoV-2 Patients, severely affected patients and less severely affected patients had 25.5% and 0.8% bacterial infections respectively [10]. In another study from New York city, 3.6% of the patients developed Co-infections out of which the mortality rate was 57% [11].

A study by Goncalves Mendes Neto, Alvaro et al. reported 19% of concomitant bacterial infection, which is similar to the bacterial infections in our study population (19%) [12].

Similar rates of 5%–27% was reported in a multicentric retrospective study analysis from several hospitals in Wuhan, China, through mid-February 2020 [9].

Higher rates of coinfections presented in other studies are mainly because the study population included in ICU patients (14%–31%) and non-survivors (50%) [13,14].

Co-infection rates in our study is 14% in blood culture and 36% in Respiratory cultures. similar rates of positivity rate of 9.3% in blood culture & 34.8% in respiratory samples has been reported by S. Hughes et al [15].

According to the sites of SBIs, lung infections were the main type, which may be related to the decrease of airway defence function following SARS-CoV-2 infection [16].

Around 80% of the bacterial strains isolated in this study were mainly Gram-negative bacteria which is consistent with the previous study [17].

The most common organism was *E. coli* (40%) similar to the study by Goncalves Mendes Neto *et al* [12].

Although the bacteria of secondary bloodstream infections were mainly Gram-positive bacteria (6/10), 5 isolates were Coagulase negative staphylococci, out of which 3 (67%) showed methicillin resistance. As it is

difficult to differentiate pathogens from colonizers, it was advised to maintain stringent skin disinfection practices before collecting blood samples for bacterial cultures.

Increasing incidence of possible colonizers can also be explained by unfamiliarity of additional personal protective equipment worn by healthcare workers taking blood samples from patients with COVID-19. Hence escalation of antibiotics should be reserved only for patients who are clinically deteriorating.

Positive cultures from respiratory samples showed a predominance of gram-negative bacilli (7/8). The pathogens detected in the samples were *K. pneumoniae* (n=3), *P. aeruginosa* (n=2) & *Acinetobacter* (n=3). Most isolates recovered from Sputum cultures were resistant to commonly used antibiotics leaving carbapenems as the only choice.

The number of secondary urinary tract infections was relatively small (18%), and *E. coli* was still the main bacterium. As per antimicrobial susceptibility tests, the resistance for Cephems, Fluroquinolones and Co-trimoxazole was more than 65%. As the initial empirical choice, β -lactams combinations with β -lactamase inhibitors could be recommended, rather than ciprofloxacin and ceftriaxone.

As part of emerging pandemic, infection-control and antimicrobial stewardship programs have had to rapidly adapt in real time in the face of an evolving body of evidence [6].

Given the difficulty of differentiating COVID-19 from bacterial pneumonia, the uncertainty regarding bacterial superinfections, the lack of specific antiviral agents with proven efficacy, and the high mortality, antibiotics should be considered as part of the empirical treatment strategy for the most severe suspected or confirmed COVID-19 cases, provided their use is regularly re-evaluated [18].

A large number of studies have shown that during COVID-19 pandemic, antibiotic prescriptions were extensive and excessive during treatment, and 90% of patients were prescribed empirical antibiotics [19].

Antimicrobial treatment might prevent secondary infections and reduce complication rates. However, only pathogen identification and susceptibility testing allows the de-escalation of empirical antimicrobial therapy and increases our knowledge of the bacterial spectrum and antimicrobial resistance, which represents a major pillar of Antimicrobial stewardship [20].

Overuse of broad-spectrum therapy may also confer harm by selecting for antibiotic-resistant bacteria, increasing the risk of adverse events, such as *Clostridium difficile* infections, and raising costs [21].

The paucity of available data makes it difficult to predict the impact that this pandemic may have on antimicrobial stewardship programmes and long-term rates of antimicrobial resistance (AMR) [22].

Limitations

First, this was a single-centre study, the aetiology and antimicrobial resistance in different healthcare settings or different regions may vary.

Second, Respiratory samples were not available for all patients; many of the patients were unable to produce sputum during their admission, and invasive respiratory sampling was restricted in order to minimize aerosol-generating procedures.

Third, our analysis of the treatment effect of SBIs was insufficient due to low rate of bacterial isolates isolation, further studies need to be carried out.

V. Conclusion

Bacterial infections in patients with COVID-19 are relatively common. Gram-negative bacteria, especially *E.coli*, *K. pneumoniae* and *A.baumannii* are the main bacteria. The antimicrobial resistance rates of the majority of bacteria were generally high, which indicates that more accurate use of antibacterial agents is necessary. Therefore, Antibacterial therapy, if indicated, should be prescribed in line with local guidelines and reviewed with clinical response and de-escalate as early as possible based on antimicrobial susceptibility results.

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