Original Article

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Microbiology Section

Alarming Rise in Secondary Infections and Antimicrobial Resistance in COVID-19 Patients Admitted at a Tertiary Care Centre in Dehradun, Northern India

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ABSTRACT

Introduction: Secondary infections (SIs) are emerging as a serious threat among hospitalised patients of Coronavirus Disease-2019 (COVID-19). Overuse of antibiotics and inadequate infection control practices due to COVID-19 patients' workload leads to a sudden upsurge of Multidrug Resistance (MDR) pathogens in healthcare settings attributing to higher mortality rates among the same.

Aim: To detect the secondary infection rate among COVID-19 patients admitted to the hospital ward and Intensive Care Unit (ICU), and report the impact on antimicrobial resistance and patient outcome.

Materials and Methods: A retrospective study was conducted for a period of three months of the second COVID-19 wave from 15th April 2021 to 14th July 2021 in the Department of Microbiology, Himalayan Institute of Medical Sciences (HIMS), Swami Rama Himalayan University (SRHU), Dehradun, Uttarakhand, India. All clinical samples (N=992) of Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) positive cases of COVID-19 received in the laboratory were cultured and identified using the Vitek-2 automated system and conventional fungal culture. Relevant demographic, characteristics, and clinical outcome data were obtained from records of the patient and recorded in reporting forms and were analysed for the study. Results were analysed with Statistical Package for the Social Sciences (SPSS) version 20.0 and Microsoft Excel 2019.

Results: Overall secondary infection rate of 135 (13.6%) was found among COVID-19 admitted patients. The most commonly isolated bacterial pathogens were Coagulase-negative *Staphylococcus* species (18.52%) and *Enterococcus* species (8.89%). Whereas the most common fungal isolates were *Candida* species (20.75%) and *Rhizopus* (8.15%). In the present study, 60.5% of bacterial pathogens isolated were Multidrug-resistant Organisms (MDRO). Mortality among COVID-19 patients with secondary infection was reported as 53% which was higher than the overall mortality rate of 36% in the same.

Conclusion: A high secondary infection rate, MDRO isolation rate, and high mortality among COVID-19 with secondary infection were reported. This shows the urgent need for reinforcement of infection control practices and strict antimicrobial stewardship policies.

Keywords: Antimicrobial stewardship policy, Coronavirus disease 2019, Multidrug resistant organisms

INTRODUCTION

Secondary infections due to varied aetiology such as bacterial, fungal, and viral are emerging as serious and undesirable consequences of hospitalisation in COVID-19 cases [1]. In a meta-analyses around 23% of secondary infections are estimated for bacterial co-infection and secondary infection, along with increased mortality and morbidity [2,3]. A higher risk of secondary infections in COVID-19 patients is observed more commonly in critically ill ICU patients most probably due to viral-induced and drug-induced immunocompromised compromised state [4]. Despite the high range of prevalence of secondary infection varying from 0.6-50% found in various studies done in China, the USA among these immunocompromised COVID-19 cases, they still appear as an understudied phenomenon [5-20].

During the current times of the pandemic, limited studies have been published on the stratification of admitted patients into different clinical settings and the bacterial and fungal aetiological profile of secondary infections in these patients [21,22]. An increasing number of COVID-19 patients were anticipatory put on empirical antimicrobial therapy in suspicion of the development of secondary infection [1]. This empirical therapy is commonly guided by the Indian Council of Medical Research (ICMR) prepared from antibiogram data from various hospitals to prevent Healthcare Associated Infections (HAI) [1,22]. The émergence of drug-resistant pathogens causing bacterial and fungal infections is a hidden threat lurking among severe cases of this Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus-infected COVID-19 patients as 72% of COVID-19 patients received antimicrobial therapy without following proper antibiotic stewardship policy [21,22]. Amidst high workloads and resources primarily being allocated to COVID-19 diagnosis and management, antimicrobial stewardship efforts were undermined. Also, the use of empirical and broad-spectrum antimicrobial drugs leads to an increase in secondary infections due to MDRO in these patients. There was a decrease in the frequency of screening for carriage of MDROs as resources were focused on SARS-CoV-2 virus detection. These factors also contributed to increased rates of secondary infections in these severely ill patients [21,23].

To meet this lacuna in the knowledge of the same and help understand the burden of secondary infections among COVID-19 patients, the present study was aimed at detecting the secondary infection rate among COVID-19 patients admitted to our hospital and ICU and report the impact on antimicrobial resistance and patient outcome.

MATERIALS AND METHODS

A retrospective study data was collected for a period of three months between April 2021 and July 2021 and analysed in next two months from August 2021 to September 2021 in the Department of Microbiology, Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun, Uttrakhand, India, after obtaining ethical approval from the Institutional Ethics Committee (IEC) no. ECR/483/Inst/UK/2013/RR-16 and proper informed written consent taken from the patients.

Sample size calculation: Convenience sampling method used for sample size calculation i.e. all samples received during these three months from suspected secondary infection from confirmed COVID-19 patients admitted to the hospital.

Inclusion criteria: All clinical samples including Broncho Alveolar Lavage (BAL) fluid, sputum, urine, blood samples, and nasal crust received in microbiology laboratory from COVID-19 admitted patients with secondary pneumonia, urinary tract infection, bloodstream infections of unknown origin, and upper respiratory tract infection.

Exclusion criteria: All clinical samples received in the microbiology lab from admitted patients having infections other than COVID-19.

Data Collection

All clinical samples received in the microbiology laboratory from COVID-19 patients (with an RT-PCR positive report for SARS CoV-2 virus) were included in the study according to inclusion criteria. Relevant demographic, characteristics, and clinical outcome data were obtained from records of the patient and recorded in the performed reporting forms.

Various clinical specimens of COVID-19 positive cases, were received from both wards (187 samples) as well as ICU (198 samples) for both bacterial and or fungal cultures. Clinical samples including BAL fluid, sputum, urine, blood samples, and nasal crust were received and processed immediately as per routine standard operating procedures. Samples received for bacterial cultures were subjected to gram staining and routine culture on Blood and MacConkey agars and incubated overnight at 37°C for isolation of pathogens. While samples received for fungal cultures were subjected to Potassium Hydroxide (KOH) mount and plated onto Sabouraud Dextrose Agar. Isolates recovered were identified using Vitek-2 automated system. As this automated system uses a growth-based technology for identification and also provides Minimum Inhibitory Concentration (MIC) for antimicrobial susceptibility, it was used to identify and report the pathogens and their antimicrobial susceptibility profile.

STATISTICAL ANALYSIS

The SPSS version 20.0 and Microsoft Excel 2019 were used for interpretation and analysis of obtained results. Qualitative data and quantitative data were expressed in terms of percentage and mean respectively.

RESULTS

Out of 8630 sample tested, COVID-19 positivity rate was 34.18% (2950/8630) asymptomatic were 1958 and symptomatic were 992. A total of 992 COVID-19 positive cases were admitted to our hospital and ICU during the study period and rest were sent to home isolation. A total of 385 out of 992 samples had suspected secondary infections with confirmed cases of COVID-19. A total of 135 isolates were recovered from these clinical samples from confirmed cases of COVID-19. An overall secondary infection rate of 13.6% was found which included a bacterial secondary infection rate of 7.2% and a fungal secondary infection rate of 6.4%. Male (64.4%) were more commonly associated with secondary infection in admitted COVID-19 patients as compared to females (35.6%) with a mean age of 52.5 years [Table/Fig-1]. In the present study, it was found that 32.9% of COVID-19 patients with secondary infections were admitted to the ICU whereas 8.2% were from the wards. [Table/Fig-1] also depicts that ICU admitted with COVID-19 patients (32.9%) were more frequently associated with secondary infection as compared to wards (8%). With two consecutive peaks of COVID-19 pandemic in 2020 and 2021, it has also been observed that 61% of MDR pathogenic isolates were seen in 2nd COVID-19 wave while 34% in 1st peak among COVID-19 admitted patients with SIs.

Most commonly pathogens were recovered from the nasal crust (57.6%) followed by blood cultures (29.4%) and urine (22.8%) [Table/Fig-2]. Overall, *Candida* (20.75%) seems to be isolated from all clinical samples followed by CONS (18.52%) with the least frequent were *Enterobacter* and *Pseudomonas* (0.74%) [Table/Fig-3].

Characteristics	Frequency (n)	
Total COVID-19 tested by RT-PCR	8630	
COVID-19 positivity rate (Symptomatic and asymptomatic)	2950 (34.18%)	
Asymptomatic and mild symptomatic (home isolated)	1958 (66.38%)	
Moderate and severe symptomatic (hospitilisation)	992 (33.62%)	
COVID-19 admitted patients (n=992)		
Clinical sample with suspected SIs	385/992	
Pathogenic isolates (Bacterial and fungal)	135/992 (13.6%)	
Bacterial SI rate	71 (7.2%)	
Fungal SI rate	64 (6.4%)	
Sex distribution among COVID-19 admitted patients with SIs 52.5 years (mean age)		
Male	87 (64.4%)	
Female	48 (35.6%)	
COVID patient's area distribution (n=992)	**With SIs**	**Without SIs**
ICU	71/216 (32.9%)	145/216 (67.1%)
Ward	62/776 (8.0%)	714/776 (92%)
MDR bacterial pathogen rates in COVID-19 admitted patient with SIs in 1st and 2nd waves of pandemic		
Wave 1 (January-March 2020)	28/82 (34%)	
Wave 2 (April-July 2021)	43/71 (61%)	

[Table/Fig-1]: Socio-demographic profile of COVID-19 positive patients during the study period.

Variables	Blood	Nasal crust	Respiratory secretions	Urine
Total samples received	163	85	23	114
Number of culture positives	48 (29.4%)	49 (57.6%)	12 (52.2%)	26 (22.8%)

[Table/Fig-2]: Sample-wise culture positives among COVID-19 cases suspected to have secondary infections (N=385).

Isolates	Frequency (%)
Bacteria (n=71)	
Coagulase negative *Staphlococcus* species	25 (18.52)
Enterococcus species	12 (8.89)
Klebsiella species	11 (8.15)
Acinetobacter baumannii	10 (7.41)
Escherichia coli	7 (5.18)
Stenotrophomonas maltophilia	2 (1.48)
Sphingomonas paucimobilis	2 (1.48)
Enterobacter spp.	1 (0.74)
Pseudomonas aeruginosa	1 (0.74)
Fungus (n=64)	
Candida spp	28 (20.75)
Rhizopus spp.	11 (8.15)
Alternaria spp.	7 (5.18)
Aspergillus species	5 (3.70)
Other fungi	13 (9.63)

[Table/Fig-3]: Microbiological profile of secondary infections among COVID-19 patients (n=135).
(Other fungi include *Cladosporium* spp., *Trichophyton* spp., *Fusarium* sp., *Mucor* spp., *Bipolaris* spp., *Conidiobolus* spp.)

In the current study, mortality among COVID-19 patients with secondary infection was 53% higher than the overall mortality rate of 36% in COVID-19 patients [Table/Fig-4]. A higher mortality rate was found among ICU admitted COVID-19 patients with suspected secondary infections (64%) when compared to COVID-19 patients with suspected secondary infections admitted in wards (34%).

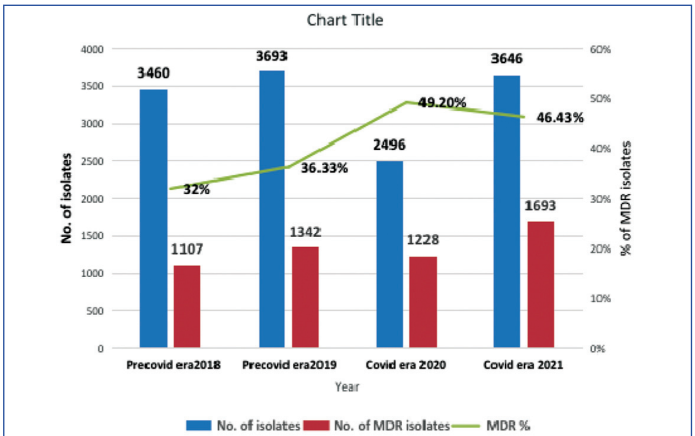
In the present study, it has also been observed that, ampicillin (100%) was the most resistant antibiotic followed by drugs of cephalosporin's class (average 96.4%), and linezolid (100%) was the most sensitive drug among the bacterial isolates [Table/Fig-5]. About 43 (60.5%), out of the 71 bacterial isolates were found MDRO from all samples of COVID-19 patients with suspected secondary infections. A rise in MDRO causing infections was observed during the COVID-19 pandemic as compared to the preCOVID-19 era. 32% and 36.33% of multidrug-resistant strains were recovered in 2018 and 2019 respectively whereas, during the COVID-19 era in the years 2020 and 2021, 49.20% and 46.43% MDROs were reported [Table/Fig-6].

Mortality	Total COVID-19 patient	Mortality in No.	Percentage
Overall	992	357	36
COVID-19 with secondary infections	135	71	53

[Table/Fig-4]: Comparison between overall mortality rate in COVID-19 patients with secondary infections.

Antibiotics	Total tested	No. of resistant isolates	Percentage of resistant isolates
Penicillin	18	16	88.8
Ampicillin	37	37	100
Cefuroxime	71	69	97.1
Ceftriaxone	71	68	96.1
Ceftazidime	52	50	96.1
Cefepime	71	66	92.9
Amoxicillin-clavulanic acid	52	34	65.3
Piperacillin-tazobactum	53	35	66
Cefoperazone-sulbactum	52	33	63.4
Meropenem	54	37	68.5
Imipenem	54	41	75.9
Gentamicin	68	52	76.4
Amikacin	68	38	55.8
Ciprofloxacin	71	66	92.9
Levofloxacin	71	64	90.1
Colistin	42	8	19
Tetracycline	66	62	93.9
Tigecycline	40	6	15
Cholramphenicol	23	9	39.1
Cotrimoxazole	70	56	80
Clindamycin	18	16	88.8
Teicoplanin	33	6	18.1
Vancomycin	33	6	18.1
Linezolid	32	0	0
Fosfomycin	32	3	9.3
Nitrofurantoin	30	6	20

[Table/Fig-5]: Antimicrobial sensitivity pattern of commonly used drug panel against the bacterial isolates (n=71).
All drugs are not tested in all the isolated strains (AST done according to Clinical and Laboratory Standards Institute {CLSI} guideline)



[Table/Fig-6]: Distribution of multi-drug resistant organisms during preCOVID-19 and COVID-19 era.

DISCUSSION

The existing literature available on secondary infections among COVID-19 patients is strongly suggestive of super-infections with varied aetiology globally. Various studies done in other countries like China, the USA, and Italy had variations in secondary infection rates ranging from 0.6-50% either bacterial, viral, or fungal aetiology. In two studies done in the USA, patients show 2.1% and 5.6% SIs, and some Chinese studies show SIs ranging from 4.3-50% [7-20]. ICMR study done across 10 major hospitals shows an average of 3.6% secondary infections ranging from 0.4- to 28.5% [24]. In present study, a secondary infection rate among admitted COVID-19 patients was 13.6%. A similar study from All India Institute of Medical Sciences (AIIMS), India reported a secondary infection rate of around 13% among severe cases of COVID-19 [1]. In a study conducted at Wuhan, a 31% secondary rate was reported among ICU patients and a 10% secondary infection rate was reported overall [6]. In a recent systematic review, the study reported a secondary infection rate ranging from 7-51%, especially in critically ill patients admitted to ICU infected with COVID-19 [25]. In this present study, it was found that 32.9% of COVID-19 patients with secondary infections were admitted to the ICU whereas 8% were from the wards. In a similar study conducted in AIIMS hospital by Khurana S et al., 37% of COVID-19 patients who developed secondary infections were admitted to the ICU [1]. A cumulative incidence of 50% of a patient admitted to ICU had ventilator-associated pneumonia and bloodstream infection were the second most common secondary infection observed ranging from 3.4-50% [26-28]. In the present study also, it has been observed that the common system involved in secondary infection was the respiratory system (52.2%) followed by bloodstream infection (29.4%), this finding found also similar to the Indian Council of Medical Research (ICMR) study with the same frequent system involvement [24].

The present study found that majority of the pathogens recovered from clinical isolates of COVID-19 patients suspected to have secondary infections were multi-drug resistant. MDRO was found in around 60.5% of isolates. In a similar study, a 60% MDR isolation rate was found [29]. In present study, an alarming rise in MDRO during the COVID-19 era including the data for 2020 and 2021 when compared with preCOVID-19 years of 2018 and 2019. ICMR published data summaries a high antimicrobial resistance prevalence among Indian hospitals during even the preCOVID-19 pandemic times. The alarming rise in antimicrobial resistance during the pandemic could be attributed to the increasing pressures to start empirical antimicrobials [30]. Over-prescription and precautionary administration of antimicrobials in patients critically ill patients without bacterial infections was also a leading cause of the rise in antimicrobial resistance during this pandemic and admittedly reported by a group of European clinicians [31].

However, targeted antimicrobial therapy following culture over a prophylactic empirical therapy would allow for a de-escalassions of antimicrobiens and helps to reduce the burden of secondary as well as HAIs due to antimicrobial resistance strains among these critically ill patients.

In the present study, an overall in-hospital mortality rate observed was 36% and 53% in COVID-19 admitted patients with a secondary infection which corresponds to an almost similar study done by Vijay S et al., stated that the mortality among ICU patients was 56.7% against overall mortality of 10.6% in total admitted COVID-19 patient. This means half of the COVID-19 patients who developed secondary infections have succumbed [24]. It also has been observed that the proportion of mortality in ICU (64.3%) was found to be higher than inwards (35.7%) among COVID-19 patients with secondary infections. A similar study found 33% in-hospital mortality among ICU admitted COVID-19 patients with secondary infections [1]. This higher involvement of secondary infection with

COVID-19 and increasing MDR pathogen rates indicates the must necessitate of strict following of hospital infection control guidelines and antibiotic stewardship policy of the hospital and proper supervision by Government authorities over the injudicious or over the counter use of antibiotics.

Limitation(s)

Firstly, as it was a retrospective study, more prospective studies are needed to clarify the true picture of secondary infection and mortality involvement in COVID-19 patients admitted to the hospital. Secondly, molecular characterisation of drug resistant strains was not done in the present study.

CONCLUSION(S)

Increasing secondary infection rate in COVID-19 admitted patients and MDR isolates is a matter of concern. Fear of missing a secondary infection and lack of specific therapy for COVID-19 perhaps lead to an overprescription of antimicrobials. If promptly prioritised inwards and ICUs, reinforcing infection control practices and care bundles to prevent secondary infection could help reduce the burden. Sending appropriate and timely cultures, the use of biomarkers like procalcitonin and galactomannan, and antibiotic time-out at 48 hours of a prescription can help in reducing unnecessary antibiotic prescriptions.

It is our opinion that MDROs screening is the need of the hour as morbidity and mortality are substantially higher in secondary infections caused by them among COVID-19 cases. Appropriate infection control measures for MDROs, if strongly implemented would help in reducing the burden of secondary infections and mortality rates in these cases.

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