Bacterial co-infections and secondary infections and their antimicrobial resistance in Covid-19 patients during the second pandemic wave

Bakterielle Koinfektionen und Sekundärinfektionen und deren Antibiotikaresistenz bei Covid-19-Patienten während der zweiten Pandemiewelle

Abstract

Background: COVID-19 pneumonia with an unusual outbreak is considered a new, global public health threat. Microbiological characterization of co-infections in patients with COVID-19 is important, and antimicrobial use is high. We aimed to describe microbiologically confirmed co-infections and the antimicrobial resistance of the causative pathogens.

Method: From January to December 2020, we tested 1,301 patients who were COVID-19 positive. We received clinical samples (blood, respiratory and sterile body fluids) of COVID-19 patients who were suspected to have bacterial co-infections. Samples were processed and antimicrobial susceptibility testing was performed based on the CLSI recommendation. Demographic, clinical, laboratory and outcome data of those with positive cultures were collected.

Result: A total of 1301 COVID-19 patients (568 from the COVID ward and 733 from ICU) were admitted to the Covid care ward of a tertiary care hospital. 363 samples were sent for culturing and testing antibiotic susceptibility, of which 131 (36%) were found to be culture-positive (90 from ICUs, 41 from wards). Out of the 143 total isolates thus obtained from 131 samples, the majority (62.2%) were Gram-negative bacteria, and most of them were (70.8%) multidrug resistant.

Discussion: Bacterial co-infection in patients with COVID-19 is more commonly reported in the severely ill hospitalized individuals (58%), particularly in the ICU (73.3%) setting. In terms of mortality, almost half of co-infected patients died (51.1%). In most of them, the cause of death was found to be sepsis with post-COVID ARDS (58%).

Conclusion: Co-infection in COVID-19 patients may affect the outcome in terms of increasing the hospital stay.

Keywords: COVID-19, bacterial co-infection, spectrum of pathogens, antimicrobial resistance

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Zusammenfassung

Hintergrund: Die COVID-19-Pneumonie ist eine neue, weltweite Bedrohung für die öffentliche Gesundheit. Die mikrobiologische Charakterisierung von Koinfektionen bei Patienten mit COVID-19 ist wichtig und der Einsatz von Antibiotika ist hoch. Unser Ziel war es, mikrobiologisch bestätigte Koinfektionen und die Antibiotikaresistenz der verursachenden Erreger zu beschreiben.

Methode: Von Januar bis Dezember 2020 wurden bei 1.301 an COVID-19 erkrankten Patienten mit Verdacht auf eine bakterielle Koinfektion klinische Proben (Blut, respiratorische und sterile Körperflüssigkeiten). Die Proben wurden aufbereitet und die Empfindlichkeit gegenüber Antibiotika auf der Grundlage der CLSI-Empfehlung getestet. Für

die Patienten mit positiver bakterieller Kultur wurden demografische, klinische, Labor- und Verlaufsdaten erfasst.

Ergebnisse: Insgesamt wurden 1.301 COVID-19 Patienten (568 auf die COVID-Station, 733 auf die Intensivstation) in das Krankenhaus der Tertiärversorgung aufgenommen. Von 363 untersuchten Proben waren 131 (36 %) kulturell positiv (90 von der Intensivstation, 41 von der COVID-Station). Von 143 Isolaten aus 131 Proben waren 62,2% Gram-negative Bakterien; davon waren 70,8% multiresistent.

Diskussion: Bakterielle Koinfektionen bei Patienten mit COVID-19 wurden häufiger bei schwer kranken Krankenhauspatienten (58%) insbesondere auf der Intensivstation (73,3%) festgestellt. 51,1% der Patienten mit einer Koinfektion verstarb. Bei 58% war die Todesursache eine Sepsis mit post-COVID ARDS (58%).

Schlussfolgerung: Eine Koinfektion kann bei Patienten mit COVID-19 den Krankheitsverlauf verschlechtern und den Krankenhausaufenthalt verlängern.

Schlüsselwörter: COVID-19, bacterielle Koinfektion, Erregersspektrum, Antibiotikarresistenze

Introduction

The SARS–CoV-2 disease has become a public health challenge. SARS-CoV-2 pneumonia was termed "COVID-19" by the WHO on 11th Feb 2020 [1], declaring the novel coronavirus outbreak a public health emergency of international concern [2]. The co-infection/secondary bacterial infections (SBI) of SARS-CoV-2 with microorganisms raise further difficulties of diagnosis, treatment, and prognosis. Co-infection in patients with severe influenza has been reported to be as high as 20–30% [3], [4]. This is associated with a greater severity of illness, greater use of healthcare resources, and increased risk of death. The prevalence, incidence and characteristics of bacterial infection in patients infected with SARS-CoV-2 is not well understood and has been identified as an important knowledge gap [5], [6]. However, little is known about the mechanism by which a virus can predispose the patient to develop a secondary infection which results in longer ICU stays and in-hospital mortality. Further, before the microbiological confirmation of SBIs, the clear majority of COVID-19 patients were given empirical antimicrobial treatment [7]. Hence, it is expected that this increased overuse of empirical antibiotics without their actual need will lead to the emergence of antimicrobial resistance in the future, limiting treatment options to higher class of antibiotics such as colistin and tigecycline.

Aims and objective

Although the burden of Covid co-infection is higher in our developing country, such active surveillance is not being conducted in any large tertiary-care rural hospital in central India. With this background, this study was conducted to determine the etiology and antimicrobial resistance profile of co-infections (at the time of admission) or secondary bacterial infection 48 hrs after hospital admission and to document the subsequent clinical outcomes in hospitalized COVID-19 patients, in order to use this evidence to guide optimal antimicrobial use in COVID-19 patients.

Method

Type of study

Observational cross-sectional study.

Setting

COVID-19 ward and ICU of rural hospital in central India.

Inclusion criteria

All COVID-19 patients with a suspected co-infection or SBI during the study period with positive RT-PCR and clinically positive results from samples collected within 2 days of admission were categorized as co-infection, and those collected more than 2 days after admission as secondary infections.

Exclusion criteria

COVID-19 RT-PCR negative patients, COVID-19 RT-PCR positive Outdoor Patients Department (OPD) patients and culture results recorded as mixed growth or contaminated were excluded.

Implementation

The study was performed during April–July 2021 (2nd wave of the pandemic). Clinical samples consisted of blood, respiratory and sterile body fluids of COVID-19 patients were collected according to recommendations in the personal protective equipment guidelines. The total number of analyzed samples studied was 363. Samples were processed and evaluated by conventional methods.

The growth of bacterial colonies was confirmed by Gram staining and standard biochemical testing. Antimicrobial susceptibility testing was performed based on the CLSI recommendation. As per clinician request the VITEK ID/ AST test system was implemented [8]. Demographic, clinical, laboratory and outcome data of those whose culture was positive were collected, e.g., date of admission, date of culture-positive results, antimicrobial susceptibility profile of isolates, length of hospital stay and patient outcome.

Results

Demographic Details

At our COVID-care facility, 1,301 COVID-19 patients were admitted during the second pandemic wave, out of which 733 (56%) were admitted to the ICU and 568 (44%) to the COVID ward.

During this period, we received 363 clinical specimens (28%): 163 blood cultures, 156 urine cultures, 30 endotracheal aspirates, 9 cerebrospinal fluid samples (CSF) and 5 of pleural fluid, collected and processed using the recommended personal protective equipment guidelines (Table 1). Repeat samples were excluded if similar results were obtained. Also, culture results showing mixed growth or contaminants were excluded. Among these 363 clinical specimens 210 were from the COVID ICU and 153 from the COVID ward.

Overall, 131 cultures were positive (36.1%) and were included, documenting the corresponding demographic data, severity of illness based on ICU admission, outcome measures and length of stay (Table 2). Out of 131 cultures positive samples, 55.7% had a positive blood culture, 13.7% had a positive respiratory culture, 29% had a postivie urine culture, and sterile body fluid cultures were positive in 1.5% patients. 73 (44.7%) of the 163 blood-culture specimens, 38 (24.3%) of the 156 urine specimens, 18 (60%) of the 30 respiratory and 2 (14.3%) of 14 sterile body fluid specimens were positive for bacterial infection (Table 1).

Severity of illness and outcome measures

This was based on admission to ICU and hospital mortality. Out of 1301 total COVID-19 admissions during the second wave, 733 required (56%) ICU admission; of these, 90 (68.7%) were positive for bacterial infections. Overall mortality was 70 (5.4%) among 1,301 patients on the COVID-19 war and 7.6% among the 733 ICU patients.

Etiological profile of secondary infections/co-infections

A total of 363 clinical specimens (blood, respiratory, urine and sterile body fluids) were received for microbiological culture, of which 232 (64%) were culture-negative. Overall, 131 (36%) were culture-positive (Table 3 and Table 4). Out of these 131 patients, 73 (55.7%) had blood stream infections, 38 (29%) had urinary tract infections, and 18 (13.7%) had respiratory tract infections.

A total of 143 significant bacterial isolates was obtained from 131 specimens. 29 coagulase-negative staphylococci and 4 *corynebacterium* species were excluded as common contaminants, due to its absence in repeated samples. The majority (62.2%) were Gram-negative organisms, i.e., 44 (49%) Enterobactericeae, 26 (29.2%) *Acinetobacter* spp., followed by *P. aeruginosa* with 19 (21.3%). Of 54 (37.8%) Gram-positive organisms, 34 (63%) were *S. aureus*.

Antimicrobial resistance (AMR)

Figure 1 presents the percentage sensitivity of Gram-negative bacteria to antibiotics. The dataset comprises 89 cases of Gram-negative bacterial infections. The percentage sensitivity indicates the proportion of cases where the treatment effectively targeted and controlled the Gram-negative bacterial infection. This figure provides insights into the efficacy of interventions against Gram-negative organisms.

Figure 2 portrays the percentage sensitivity of Gram-positive bacteria in response to antibiotics. The dataset used for this analysis consists of 54 cases of infections caused by Gram-positive bacteria.

Discussion

The co-occurrence of bacterial infections alongside COVID-19 has been a subject of significant interest and concern since the emergence of the pandemic. Bacterial co-infections can complicate the clinical course of COVID-19 patients, leading to increased morbidity and mortality.

Table 5 presents a compilation of rates of bacterial co-infection reported in various studies conducted in different regions and time frames. The studies included in Table 5 span a wide range of time frames from the early stages of the pandemic in Wuhan to more recent investigations in 2021. They were conducted in diverse geographical locations, including India, Italy, and Wuhan (China). The studies varied in their sample sizes with patient numbers ranging from hundreds to several thousand. The reported incidence of bacterial co-infections in COVID-19 patients shows considerable variability across studies (Table 5). The rates of bacterial co-infection ranged from as low as 6.8% to as high as 20% [8], [9]. This wide range could be attributed to various factors, such as differences in study populations, patient demo-

Table 1: Distribution of samples according to growth of organisms (n=363)*

Characteristic	% culture positive from samples	ICU		COVID-19 ward	
		total samples	culture positive	total samples	culture positive
Blood culture (n=163)	44.7	115	56	48	17
Urine culture (n=156)	24.3	60	19	96	19
Endotracheal aspirate (n=30)	60	22	13	08	05
CSF (n=09)	14.3	08	01	01	00
Pleural fluid (n=05)		05	01	00	00
Overall culture positive=36% (131 from 363 samples)		210	90 (68.7%)	153	41 (31.2%)
* From 163 blood cultures sent, 73 (55.7%) were positive; 38 (29%) from urine culture, 18 (13.7%) from respiratory samples and 1.5% from sterile fluids were positive.					

Table 2: Demographic profile of 131 patients enrolled in the study

Characteristic		ICU (n=90)	Non-ICU (n=41)	Total (n=131)
Age		55.9±17.7	38.6±17.7	
Gender	male	61	25	86(65.6%)
	female	29	16	45(34.3%)
COVID-19 disease	mild	06	29	35(26.7%)
	moderate	17	7	23(17.5%)
	severe	67	05	72(55%)
Outcome	death	56	14	70(53.4%)
	discharge	34	27	61(46.6%)
Length of stay (days)		13.9	5	

Table 3: Clinical condition in COVID-19 patients with bacterial infections in ICU (n=90)

Risk factor	Number	%
ARDS	40	44.4
Sepsis with shock	24	26.6
Aspiration pneumonia	14	15.5
Diabetic nephropathy	07	7.8
Ventilator associated pneumonia	04	4.4
Meningitis	01	1.1

Table 4: Etiology of bacterial infections in patients hospitalized with COVID-19 (n=143)

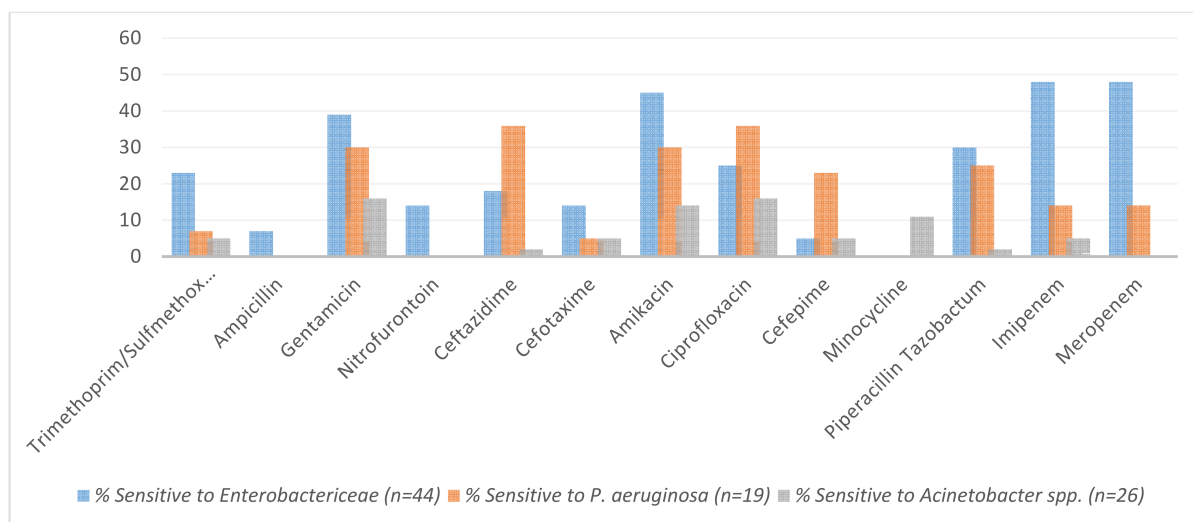| Isolate	No.	%
Gram-negative pathogens	89	62.3
Enterobacteriaceae (*E. coli, Klebsiella spp., Citrobacter spp., Enterobacter ssp.*)	44	49.4
Acinetobacter spp.	26	29.2
Pseudomonas aeruginosa	19	21.3
Gram-positive pathogens	54	37.8
Staphylococcus aureus	34	63
Enterococcus faecalis	13	24
Enterococcus faecium	7	13
Streptococcus pneumoniae	1	2

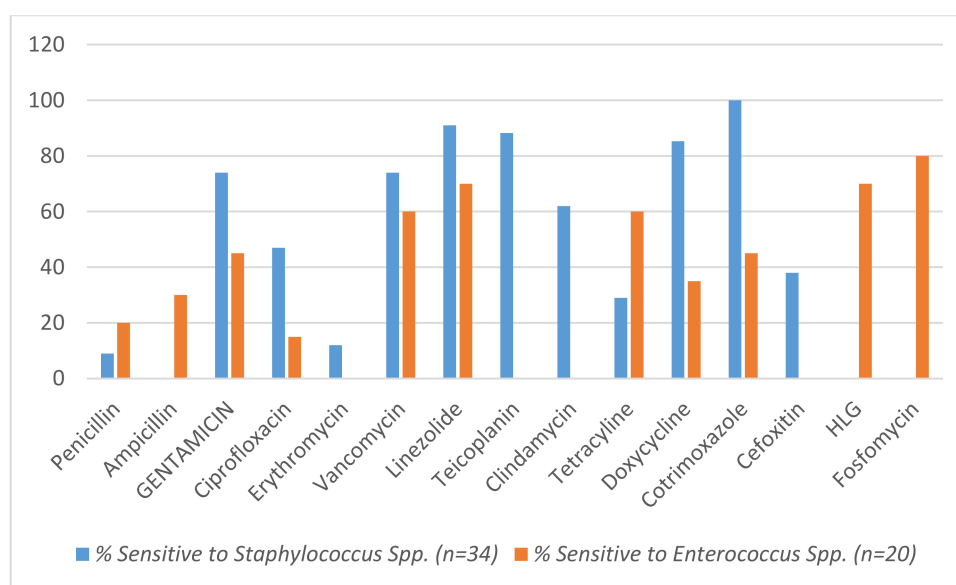Figure 1: Sensitivity (%) of Gram-negative bacteria (n=89)

Figure 2: Sensitivity (%) of Gram-positive bacteria (n=54)

Table 5: Rates of bacterial co-infections reported in the current medical literature for COVID-19 patients

Study years	Total COVID-19 patients	Total samples received	Place of study	Incidence of bacterial infections	Reference
May–Oct 2020	1,184	814	Post graduate Institute of Medical Education & Research (PGIMER) Chandigarh	7.9%	[9]
Apr–Jul 2020	1,179	290	All India institute of Medical Sciences (AIIMS) Delhi	13%	[10]
Jun–Aug 2020	17,534	640	Multicentric under Antimicrobial Resistance Surveil-lance Network from 10 hospitals	20%	[11]
2020			Italy	11%	[5]
Jan–Mar 2020	1,495		Wuhan Union Hospital	6.8%	[8]
Apr–Jul 2021	1,301	363	Mahatma Gandhi Institute of Medical Sciences (MGIMS) Sewagram	**10%**	Our study

graphics, healthcare practices, and diagnostic criteria for identifying bacterial infections.

Geographical differences might contribute to variations in bacterial co-infection rates. For instance, studies conducted in India [8], [10] as well as our study report rates between 7.9% and 13%; in Italy [5] reported an 11% incidence (Table 5). These differences could reflect variations in healthcare infrastructure, clinical management protocols, and prevalence of bacterial pathogens in different regions.

There appears to be no consistent temporal trend in bacterial co-infection rates over the course of the pandemic. Studies conducted early in the pandemic report lower rates compared to those conducted later [10], [11], [9] as does our study. This disparity might be influenced by changing clinical practices, evolving understanding of the disease, and variations in patient populations.

Several limitations should be acknowledged when interpreting the findings from Table 5. The differences in study designs, patient populations, and diagnostic methodologies can introduce biases. The definition of bacterial co-infection might also vary between studies, leading to inconsistencies in reported rates. Additionally, some studies did not provide details on specific bacterial pathogens involved, which hinders a comprehensive analysis of the types of infections.

Understanding the rates of bacterial co-infection in COVID-19 patients is crucial for optimizing patient management and healthcare resource allocation. The variability in reported rates underscores the need for standardized diagnostic criteria and protocols for identifying bacterial co-infections in COVID-19 cases. Further research is warranted to explore factors contributing to regional and temporal disparities and to investigate the impact of bacterial co-infections on patient outcomes.

Conclusion

The findings, presented in Table 5, highlight the diverse landscape of bacterial co-infections in COVID-19 patients across different studies. The variations in reported rates emphasize the importance of cautious interpretation and the need for robust research methodologies to better understand the complex relationship between bacterial co-infections and COVID-19. In India, treatment guidelines for HAIs have been issued by the Indian Council of Medical Research, based on our indigenous antimicrobial resistance data. Antimicrobial stewardship programs must focus on supporting the optimal selection of empiric treatment and rapid de-escalation, based on culture reports.

Notes

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Competing interests

The authors declare that they have no competing interests.

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