Research Article

Prevalence of secondary blood stream infections in patients with SARS-CoV-2 infection in a tertiary care hospital in Sri Lanka: A retrospective analysis

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Abstract

Introduction: Secondary infections are an important cause of morbidity and mortality related to SARS-CoV-2 infection. Early administration of effective antimicrobials improves patient outcome of such infections. In the present study, we investigated secondary blood stream infections (BSI) among COVID-19 patients in Colombo North Teaching Hospital, Sri Lanka (CNTH).

Methods: This is a descriptive study, performed to analyse blood culture positive events retrospectively in patients hospitalized with COVID-19 in our institution from 1st June 2021 to 30th November 2021.

Results: Of a total 434 blood cultures received from SARS-COV-2 positive patients, the overall blood culture positivity rate was 25.3 % (110/434) of which 11.7% (51/434) were clinically relevant bacteraemias. The contamination rate was 13.7% (59/434). Of the 60 isolates from clinically relevant bacteraemias, 60% (36/60) were Gram negative organisms, 31.7% (19/60) were Gram positive organisms and 8.3% (5/60) were *Candida* spp. The most prevalent isolates were *Enterococcus* spp. (20%; 12/60) and *Acinetobacter* spp. (15%; 9/60).

Higher rates of multi drug resistance were observed among Gram negative isolates. The proportion of 3rd generation cephalosporins and ciprofloxacin resistance among enterobacterales was 81.3% and carbapenem resistance among *Acinetobacter* spp. was 77.8%. A primary focus of infection could be identified in only 18 blood stream infections (BSI).

Conclusion: A high rate of significant BSIs was detected in this patient cohort. Blood culture contamination rate among COVID-19 patients was higher than the usual rates in the institution. A

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high number of bacteraemias due to *Enterococcus* spp. and *Acinetobacter* spp. were noted and overall antibiotic resistance among Gram negative organisms was high.

Keywords: SARS-CoV-2 virus, COVID-19, secondary blood stream infections, antimicrobial resistance

Introduction

SARS-CoV-2 virus infection (COVID-19) can present with a myriad of presentations ranging from asymptomatic infection to severe infection. Severe COVID-19 is characterized by respiratory distress syndrome, coagulopathy, hyperferritinaemia and multi organ failure which could include acute cardiac failure, acute kidney injury, acute liver injury and shock. The lymphopenia and dysregulated immune system with aberrant cytokine storm cause significant immunosuppression.[1,2] Administration of steroids and biologic therapy are standard treatment regimens in severe COVID-19 which make the patients further immunosuppressed. On the other hand, most patients with severe disease have pre-existing comorbid conditions adding to their suppressed immune status. Therefore, these patients often require care in intensive or high dependency units and are frequently on invasive respiratory support, and/or renal replacement therapy and harbour central venous and arterial access devices predisposing them to nosocomial infections.

Varying rates of secondary infections were reported following viral respiratory tract infections during the present SARS-CoV-2 pandemic as well as in previous respiratory viral pandemics.[2,3] These infections can be co-infections having dual infections at the time of presentation or superinfections which occur subsequently.[1,4] Secondary infections are a major clinical concern in SARS-CoV-2 pneumonia, causing adverse outcomes including long hospital stays and high mortality rates. However, data published on secondary infections in COVID-19 is scarce in Sri Lanka.

Secondary infections following COVID-19 commonly present as post viral bacterial pneumonias. However, isolation of the causative organisms from sputum or lower respiratory tract is compounded by difficulty in obtaining good quality respiratory samples.[5] Furthermore, result interpretation of them as real causative agents as opposed to upper respiratory tract colonisers is a challenging task too. However, BSIs which could be bacteraemias and/or fungaemias are easier to interpret with available clinical details. The present study was therefore limited to assessment of BSIs. Our institution experienced a high number of COVID-19 patients admitted to the institution at the time we conducted the present study.

Secondary infections were found to be higher than coinfections during the present pandemic and hence over-enthusiastic prescription of empiric antimicrobials at initial presentation was thought to be unnecessary.[5,6] Although the principles of antibiotic stewardship should be considered, in the case of severely ill patients, concern surrounding the pandemic forced clinicians to start treatment with antibiotics.[5] Overall, secondary bacteraemias were found to be common among patients with moderate to severe SARS-CoV-2 infection in studies done in other countries, especially among patients admitted to Intensive Care Units (ICU) and High Dependency Units (HDU).[7] In a study done at IRCCS San Raffaele Hospital, Italy,[6] of the total BSIs (7.9%), the majority (3.5%) were reported among ICU patients. The commonest Gram positive organism in this study was

coagulase-negative *Staphylococcus* spp. (CoNS, 69.7%), and commonly isolated Gram negative organisms were *Acinetobacter baumannii* (30.4%) and *Escherichia coli (*21.7%).[6] Antibiotic resistance was found to be high among the pathogens causing secondary infections.[7,8] The sources of bacteraemia were central line associated blood stream infections (CLABSIs), bacteraemia following secondary pneumonias and bacteraemia without an identified focus.[7] Reported contamination rates, particularly blood stream infections with CoNS, were high among SARS-CoV-2 patients.[1,7]

Methods

This retrospective analysis was undertaken using the microbiology laboratory data base of CNTH, Sri Lanka from 1st June to 30th November 2021. The study group consisted of patients who had moderate to severe COVID-19 admitted for inward care according to the criteria developed by the Ministry of Health, Sri Lanka.[9]

SARS-CoV-2 infection was diagnosed using the real-time reverse transcriptase PCR assay (RealStar® SARS-CoV-2 RT-PCR Kit, Altona diagnostics Hamburg, Germany and AccuPower® SARS-CoV-2 Real-Time RT-PCR kit, Daejeon, South Korea) and/or the lateral flow assay (Standard Q COVID-19 Ag, SD biosensor Inc., Suwon, Korea) on nasopharyngeal and oropharyngeal samples or lower respiratory samples. Blood cultures were ordered upon suspicion of secondary sepsis by the attending physicians or the microbiology team. Blood cultures were performed using automated BACT/ALERT 3D instrument (bioMerieux, Durham, NC, USA). Specimens were processed in accordance with standard operating procedures.[10] Standard microbiological techniques were used for pathogen identification. Antibiotic sensitivities were performed by CLSI disk diffusion method and species identification and MIC of unusual or resistant isolates were performed using BD phoenix instrument (BD Diagnostic Systems, Sparks MD, USA). Susceptibility to colistin was determined using the Stokes method.[10]

Data entered to the WHONET software was retrieved, tabulated anonymously on Excel 2007, and analysed. Isolate identity, their clinical relevance, antimicrobial sensitivity pattern of clinically relevant isolates, demographic data of the patients (age, gender), presence of comorbidities and level of care received at the time of sampling were included in the analysis. Clinical data of patients with positive blood cultures routinely obtained through telephone inquiries or ward visits and entered to the laboratory data base were used to determine the focus of infection.

Detailed inquiries and evaluation of all patients with positive blood cultures were carried out by the microbiology team, and clinical significance and focus of infections were decided taking clinical details and results of other investigations into consideration. All patients with a positive blood culture were followed up by the microbiology team until they were discharged. Decisions on the clinical significance of positive blood cultures with doubtful significance were arrived at through multi-disciplinary discussion with the treating clinical teams.

Duration of hospital stay, particularly ICU or HDU stay before blood culture positivity, the presence of multiple invasive devices, being on invasive therapeutic procedures and immunosuppressive medication and susceptibility pattern of the isolates were considered to identify secondary BSIs.

Same pathogens isolated from the same patient within 7 days were excluded from the analysis. More than one organism isolated during a bacteraemic episode was considered a significant BSI when the clinical details tallied with a true BSI and all the isolates were included for antibiotic susceptibility testing. Infections occurring 48 hours after hospital admission were considered as health care associated infections according to the current CDC definition.[11] To designate an isolate as a contaminant, the patient's clinical information as well as pathogen identity, time to blood culture positivity, and multiple blood culture positivity for the same organism were taken into consideration. An isolate was defined as multi drug resistant (MDR) when it was resistant to 3 or more antibiotic classes.

Results

During the study period, 434 blood cultures were received from patients with COVID-19 after excluding multiple positive blood cultures from the same patient within 7 days. Of these, 110 events of blood culture positivity were identified and enrolled in the analysis. There were 35, 11 and 64 positive cultures from COVID ICU, HDU and COVID wards respectively after excluding multiple blood cultures from the same patient. The median age of the patients with positive blood cultures was 58 (Inter quartile range 53-69) and the majority were males (59.1%; 65/110). All positive samples were received from adults (age 17 years and above).

Overall blood culture positivity rate was 25.3% (110/434) while the clinically relevant bacteraemia rate was 11.7% (51/434) and contamination rate 13.6% (59/434). Of the clinically significant BSIs, 11.8% (6/51) were poly-microbial bacteraemias.

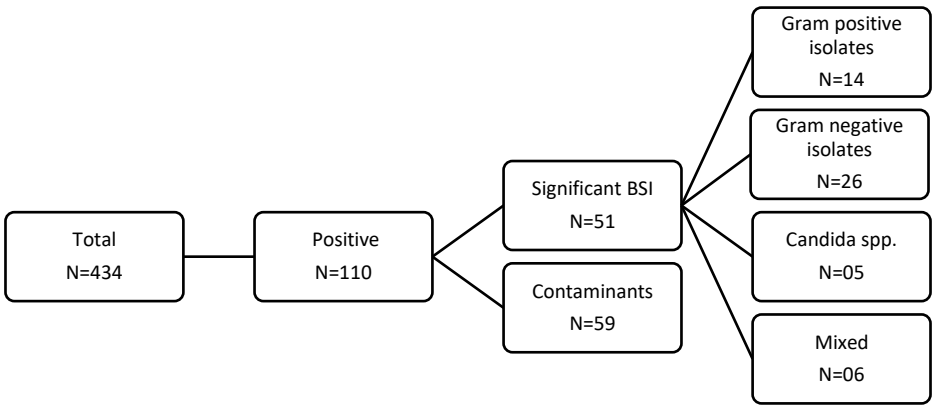

Figure1: Summary of blood culture positive events

In these 51 clinically relevant blood culture positive events, 60 organisms were isolated. The majority of significant isolates (60%; 36/60) were Gram negative organisms and the most prevalent Gram negative isolate was *Acinetobacter* spp. (25%; 9/36).

Of the 19 Gram-positive isolates, 12 were identified as *Enterococcus* spp. (63.2%; 12/19). Details of bacterial isolates are given in Table 1. All patients with candidaemia (8.3%; 5/60) received ICU

care and steroid treatment. One patient with candidaemia was already neutropenic due to chemotherapy when he acquired SARS-CoV-2 infection.

Enterobacterales and *Enterococcus* spp. were isolated in 5 polymicrobial BSIs and enterobacterales and *Pseudomonas* spp. were detected in one episode.

Table 1: Frequency and distribution of clinically relevant isolates and contaminants from blood cultures

Total isolates n=116	**Clinically relevant isolates n=60**		
Gram positive isolates	**n=19**	**n**	**%**
	Staphylococcus aureus (MSSA)	3	5.0
	Streptococcus spp.	2	3.3
	Streptococcus pyogenes	1	1.7
	Enterococcus spp.	2	20.0
	Coagulase negative staphylococcus	1	1.7
Gram negative isolates	**n=36**	**n**	**%**
	Enterobacterales (non-speciated)	9	15.0
	Escherichia coli	3	5.0
	Klebsiella pneumoniae	4	6.7
	Pseudomonas spp.	6	10.0
	Burkholderia gladioli	1	1.7
	Ochromobacter spp.	3	5.0
	Stenotrophomonas maltophila	1	1.7
	Acinetobacter spp.	9	15.0
	Candida spp.	5	8.3
Probable contaminants	**n= 59**		
	Coagulase negative *staphylococcus*	51	86.4
	Enterococcus spp.	1	1.7
	Corynebacterium spp.	2	3.4
	Bacillus spp.	2	3.4
	Mixed growth	3	5.1

All 3 *Staphylococcus aureus* isolates were cefoxitin sensitive and the two *Streptococcus pneumoniae* isolates were sensitive to penicillin according to CLSI breakpoints for non-meningeal isolates. Ten *Enterococcus* spp. isolates were ampicillin resistant, and two isolates resistant to vancomycin (MIC for vancomycin 64 µg/ml) were identified as *Enterococcus faecium.*

Antibiotic susceptibilities of the Gram-negative isolates are given in Table 2. Sensitivity to ceftazidime could not be determined due to the unavailability of ceftazidime discs during the study period. Resistance to all antibiotics were high among *Acinetobacter* spp. which was 77.8% (7/9) for carbapenem, amikacin and cefoperazone-sulbactam and 88.9% (8/9) for ciprofloxacin while all isolates were sensitive to colistin.

Table 2: Antibiotic resistance among the Gram-negative blood culture isolates (%)

Antibiotic	Enterobacterales (n=16)		*Pseudomonas* spp. (total tested=6)		*Acinetobacter* spp. (total tested=9)	
	n	**%**	**n**	**%**	**n**	**%**
3rd gen cephalosporins	13	81.3	N/A		N/A	
Ciprofloxacin	13	81.3	4	66.7	8	88.9
Meropenem/imipenem	8	50	2	33.3	7	77.8
Amikacin	5	31.3	2	33.3	7	77.8
Cefoperazone – sulbactam	N/A		N/A		7	77.8
Colistin	N/A		0	0	0	0

N: number tested; N/A: sensitivity test disk not available

The nosocomial bacteraemia rate was 90.2% (46/51) according to the CDC definition[11]. Only 14 BSIs (nosocomial and community acquired) had a known source of infection as shown in Table 3.

Table 3: Primary focus of clinically relevant bacteraemia

Source of bacteraemia	**Number of BSI n=51**	
	n	%
Community acquired bacteraemia		
Community acquired secondary bacterial pneumonias	4	7.4
Urinary tract infections	2	3.9
Hospital acquired bacteraemia		
Ventilator associated pneumonia associated with BSI	7	13.7
Neutropenic sepsis	1	1.9
Central line colonization	1	1.9
Primary blood stream infections without a known focus	33	64.7

There were 7 ventilator associated pneumonias where the same organism/s were isolated from cultures of tracheal secretion and blood. The single group A streptococcus isolate, two *S. pneumoniae* isolates and one *S. aureus* isolate became positive within 48 hours of admission and were hence considered community acquired coinfections or secondary infections of the respiratory tract. There were 3 CLABSIs, a single central line colonisation, and two *S. aureus* isolates were grown from the central venous line and peripheral blood sent from a single patient which met CLABSI diagnostic criteria. Two BSIs were attributed to urosepsis and the patients had both urosepsis and COVID-19 at the time of admission, and were therefore not considered as secondary infections. In 33 BSIs, the focus of infection was not identified.

Discussion

In the present study we investigated the secondary BSI events in a hospitalised patient cohort who had moderate to severe SARS-CoV-2 infection.

Contamination rates were higher in this patient cohort compared to the usual blood culture contamination rates in the laboratory which was 5.6% in 2019.[12] This was observed in studies done in similar patient populations in other countries, and attributed to the breech of aseptic technique due to the barrier between patients and health care workers wearing personal protective equipment

(PPE).[13] Training on blood culture collection technique while wearing PPE is required to prevent contamination so that wastage of resources can be prevented. High rates of BSI caused by CONS (86.4%) in the category of contaminants was observed in the present study are reported from several other studies among COVID-19 patients.[6,7]

Clinically relevant blood culture positivity (11.7%) was higher than reported in studies done among similar patient cohorts.[3,13] Most of these studies were from high income countries. In a study done in New York, USA comparing BSI rates in COVID-19 positive and negative patients, Sepulveda et al. (2020) reported that only 3.8% of COVID-19 positive patients had positive blood cultures, which was significantly lower than the control group of COVID-19 negative patients.[14] In a study done in six tertiary care hospitals in Sweden, clinically relevant growth was detected in 6.5% of episodes in the COVID-19 group, compared with 10.8% in a control group of COVID-19 negative patients and 10.4% in a historical control group in the previous year.[12] Hughes et al (2020) reported a true bacteraemia rate of 3.2% and classified 6.1% as contaminants in a retrospective observational analysis of COVID-19 positive patients across a multicentre NHS acute trust.[3]

Similar BSI rates among COVID-19 patients were reported in the Asian region. In a study performed in a tertiary care hospital in India, Rajni et al. (2021) reported blood culture positivity of 9.4% among COVID-19 patients, and Li et al. (2020) reported bacteraemia rate of 7.7 % among COVID-19 patients from Wuhan.[15,16] A secondary BSI rate of 8.5% was found in a single-centre retrospective study conducted among SARS-CoV-2 positive patients in an ICU in India.[17]

S. aureus, *S. pneumoniae* and *Streptococcus pyogenes* are important causes of coinfection or secondary bacterial pneumonia following viral respiratory tract infections. These organisms have been reported following influenza and SARS-CoV infection as well as in the current pandemic and noted among our patient cohort as well.[2,4]

High rates of bacteraemia due to *Enterococcus* spp., MDR Gram negative enteric bacilli and *Acinetobacter* spp. were observed in our study, which was similar to findings in other studies.[8,10] Isolation of three *Ochromobacter* spp. which is a ubiquitous bacterium found in hospital environments is noteworthy as this bacterium was not isolated in the historical BSI cohort of our institution in the previous year and non-COVID-19 BSI cohort of the same year (unpublished data). Pasquini et al (2020) reported an increase in the incidence rate of *Enterococcus faecium*, carbapenem-resistant *Klebsiella pneumoniae*, *A. baumannii* and CoNS in blood culture positive COVID-19 patients in four Italian hospitals compared to the pre-pandemic incidence.[18] A study done in France by Amarsya et al. (2022) covering 12 hospitals also showed increased antibiotic resistant strains isolated from COVID-19 patients.[19] Palanisamy et al. (2021) reported 57.8% MDR bacteria in an Indian tertiary care ICU among blood culture positive COVID-19 patients, the majority of which were *K. pneumoniae* and *Enterococcus* spp.[16] A majority of resistant *Acinetobacter* spp. and *Enterococcus* spp. were isolated from ICU and HDU as also observed in previous studies.[9] This high antibiotic resistance is probably due to misuse of third generation cephalosporins and carbapenems as empiric agents in moderate to severe SARS-CoV-2 infection, even in the absence of evidence of secondary bacterial infections. High antibiotic use among COVID-19 patients was reported in studies done previously.[5] Although a limited number of antibiotics are included in the red-light antimicrobial circular issued by the Ministry of Health, Sri Lanka in 2016, large scale implementation of antimicrobial stewardship programmes (ASP) is a

current need in health care institutions to control the observed alarming rate of antibiotic resistance development.

The absence of resistance to colistin in *Acinetobacter* spp. and *Pseudomonas* spp. in our study is an important finding. However, colistin disc diffusion breakpoints are not published in the CLSI disc diffusion breakpoint tables as colistin diffusion in the agar medium is affected by poor diffusion of the large colistin molecule.[20] Therefore, we employed the Stokes comparative method for determination of colistin susceptibility as the above mentioned factors affect both control and test organisms.

In 64.7% of cases, the source of BSI was unknown, which has also been observed in previous studies.[13,16] Buetti et al. (2021) in their multicentre case control study of a French cohort of critically ill COVID-19 patients observed 43 BSIs, 14.9% in the COVID-19 group and 3.4% in the non-COVID-19 group.[21] BSIs of COVID-19 patients were more frequently of unknown source (47.4%). The authors discuss the possibility that coagulopathy associated with SARS-CoV-2 infection, which affects the macro and microcirculation, increases the risk of gut bacterial translocation. In addition, endothelial dysfunctions of the digestive tract causing mesenteric infarctions were associated with increased BSIs. In support of this argument, they state that pathogens from the intestinal microbiota were more frequently observed in BSIs of unknown origin, which was observed in our study as well. However, this observation needs further evaluation.

In our study, most of the patients with an unknown focus were clinically suspected of having secondary bacterial pneumonias needing respiratory support. However, a definite causative relationship could not be determined as sputum samples were not received from most non-intubated patients in the background of discouraging sputum induction in SARS-CoV-2 infection control protocols.

Conclusion

The present study provides useful data on starting empiric treatment when secondary infection is suspected in the event of a further wave of the current pandemic or in future respiratory viral pandemics. It also reiterates the importance of having antimicrobial stewardship programs to restrict unnecessary use of 3rd generation cephalosporins, which was prevalent in COVID-19 treatment units due to the misconception of using triple therapy which includes 3rd generation cephalosporins in moderate to severe SARS-CoV-2 infections.

The present study also highlights the importance of adhering to aseptic procedures in collecting blood for culture and maintaining infection control practices in ICUs which house a group of vulnerable patients who are on life support, including placement of invasive devices.

Limitations

Since the study was performed retrospectively, long term follow-up of patients was not possible which would have provided more data on long term impact, including mortality. As the commonest secondary infection following viral respiratory tract infections is bacterial pneumonia,

frequently without blood stream invasion, if respiratory samples were also included in the analysis, a broader picture of secondary infections could have been obtained.

Declarations

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Conflicts of Interest: There are no conflicts of interest.
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Ethics statement: Ethical approval was obtained from the institutional ethic review committee, CNTH, Ragama (reference number 001912/CNTH/ECC)
Authors' contributions: All authors contributed equally for this work

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