Clinico-microbiological profile of neonatal sepsis among babies born to COVID-19 positive mothers: A study from dedicated COVID tertiary care center

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ABSTRACT

Introduction: Coronavirus disease-19 (COVID- 19) disease, is highly transmissible, has rapidly spread worldwide since December 2019 and caused a wide spectrum of clinical manifestations in humans ranging from common cold to severe acute respiratory syndrome. A major concern of severe acute respiratory syndrome cornonavirus-2 infection is vertical maternal-fetal transmission, though reported sparsely; it remains unclear whether these occurred through the transplacental, transcervical route, or through environmental exposure. **Aim:** The study aims to study the clinico-microbiological profile and COVID status of neonates having sepsis born to COVID-19 positive mothers in a tertiary care COVID-19 hospitals. **Materials and Methods:** Around 50 cases of neonatal sepsis born to COVID-19 positive mothers admitted to neonatal intensive care unit (January to May 2021) at a COVID dedicated tertiary care hospital. Two ml of venous blood drawn aseptically and inoculated aseptically into a brain heart infusion broth containing blood culture bottle. Antimicrobial susceptibility testing was performed on all the bacterial isolates as per the Clinical Laboratory Standard Institute guidelines 2021. **Statistical Analysis**: A $p<0.05$ was considered to be statistically significant. Statistical package for social sciences 19 software was used for statistical analysis. **Results:** Bacteremia was observed in 44 patients (88%), whereas 12% of patients grew yeast. Among the Gram-positive isolates from the blood culture, 80% susceptibility was observed for Teicoplanin and Clindamycin. While 84% of the Gram-negative microorganisms were susceptible to piperacillin with Tazobactam and cotrimoxazole. Of the 6 *Candida* isolates, non-*Candida* albicans species were more common (66 %). **Conclusion:** The current body of evidence from high-burden COVID-19 areas globally suggests that co-infections are common, particularly in severe cases.

Key words: *COVID-19 mothers, Neonatal sepsis, Clinico-microbiological profile*

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a highly contagious RNA virus that was first detected in Wuhan City [1]. It has resulted in 119.2 million infections and 2.64 million deaths by 14th March 2021, globally [2]. India has witnessed 11.35 million infections and 0.15 million deaths during this period [1,2]. COVID-19 disease, is highly transmissible, has rapidly spread worldwide since December 2019 and caused a wide spectrum of clinical manifestations in humans, ranging from a common cold to severe acute respiratory syndrome [3,4]. According to the World Health Organization (WHO) scientific report, the virus can spread through direct close contact, droplets, airborne, and through fomite. The spread of viruses through feces, urine, breast milk, blood, and animal-to-human is less substantiated. Vertical maternal-fetal transmission is a major concern with SARS-CoV-2 infection, and it is unclear whether this occurred via transplacental, transcervical, or environmental exposure [5-9]. The intrauterine transmission of the SARS-CoV-2 virus is still unclear. A few studies have documented vertical transmission and placental transfer as major possibilities [10-14]. There is limited information on the existence of SARS-CoV-2 in the female genital tract, and it may be important for evaluating both vertical and sexual transmission. In a recent Indian study, samples from a COVID infected mother's placenta, cord blood, amniotic fluid, and vaginal secretions tested for SARS CoV-2 were found to be negative [14]. There is, however, no consensus on the mode of delivery and optimal time of delivery in COVID-19 infected women and whether cesarean delivery is the preferred mode to prevent vertical transmission [10,11,15]. It is important to investigate whether and how, SARS-CoV-2 reaches the fetus, to optimize pregnancy management, prevent neonatal infection, improve pregnancy outcomes, and eventually understand SARS-CoV-2 pathophysiology in the fetus and neonate. While ongoing critical scientific evidence is still being ascertained, SARS-CoV-2 is a novel virus requiring a rapid response from health services. Although the primary focus has been on vulnerable groups, particularly the elderly and individuals with underlying medical

conditions, it is possible that pregnant women and newborns are also at higher risk. To date, there have been limited case reports or case series regarding COVID-19 during pregnancy and the possible maternal-fetal transmission and infection among newborns or infants.

In addition, viral respiratory infections are known to predispose patients to bacterial infections, which may worsen the outcome as the disease progresses [16]. As true with other viral pneumonia, bacterial and fungal infections are common complications seen in prolonged hospitalized COVID-19 adult patients. Recent studies documented 3.1–3.5% of bacterial co-infections upon admission in COVID-19 patients, while secondary bacterial infections following hospitalization occurred in 15% of patients [17]. Although COVID-19 has been described as a mild disease in newborns, concern about the implications of the infection among newborns remains high; both in terms of the impact and appropriate care [18-20].

The WHO estimates about 3.3 million neonatal deaths a year, with the majority occurring in developing countries [21]. Septicemia has been reported to occur in 2.3% of intramural live births [22]. Microorganisms implicated in neonatal septicemia (NS) have developed increased drug resistance to the commonly used antibiotics, thus making treatment extremely difficult [17,23,24]. Hence, knowledge of both the common pathogens causing septicemia in neonates and their antimicrobial susceptibility is essential, to select appropriate antimicrobial treatment. To complicate matters further, the antimicrobial susceptibility patterns of pathogens vary geographically and are temporally dependent on local pathogens and the patterns of antibiotics used. In the current pandemic, a higher risk of mortality in COVID-19 patients with bacterial super-infection has been increasingly reported, and several recommendations encourage empirical use of antibiotics in severely ill patients [25]. The lack of information and data in neonates born during the pandemic prompted us to conduct a study on the Clinico-microbiological profile and COVID status of neonates having sepsis born to COVID-19 positive mothers in a tertiary care COVID-19 hospital.

MATERIALS AND METHODS

In the present study, 50 cases of neonatal sepsis born to COVID-19 positive mothers admitted to the Neonatal Intensive Care Unit (NICU) from January to May 2021 at a COVID dedicated tertiary care hospital were enrolled. Two ml of venous blood drawn aseptically from each case was inoculated aseptically into a blood culture bottle containing 10 ml of brain heart infusion broth (1:10), which was incubated at 37°C as per the conventional techniques. The bottles were incubated for 5 days before reporting a negative. A Gram stain and a subculture on blood agar and MacConkey agar were performed at 48 h and 72 h (if sterile at 48 h) from each blood culture bottle. Following that, biochemical tests were done as per standard protocol [22]. Antimicrobial susceptibility testing was performed on all the bacterial isolates as per the Clinical Laboratory Standard Institute guidelines 2021 by the modified Kirby Bauer method [23]. All the isolates of yeast were subjected to Gram staining and were further identified by the germ tube test, growth on Hichrome media, sugar fermentation, and sugar assimilation tests for yeast identification [24,25]. Antifungal susceptibility test (AFST) for yeast was not performed.

The SARS-CoV-2 RT-PCR (real-time polymerase chain reaction) test on nasopharyngeal or oropharyngeal swab samples collected from neonates at birth was used to assess evidence of vertical transmission. The SARS-CoV-2 RT-PCR test was performed in the ICMR approved COVID laboratory, Department of Microbiology, of our tertiary care center. All sample collection, processing, and laboratory testing complied with WHO guidance [26]. All clinical specimens were processed in the biosafety cabinets 2A and adhered to the waste disposal norms of the biomedical waste management guidelines of India.

RESULTS

The study, conducted during a 5 month period from January to May 2021, observed a male predominance (3:1) in neonates with sepsis. The majority of newborns (86%) were <7 days old at birth (Fig. 1). Bacteremia was observed in 44 patients (88%), whereas cultures from 6 patients (12%) grew yeast, though the difference was not statistically significant. (Unpaired t-test, Degree of Freedom: 1, $p>0.372$).

Among the positive blood cultures, Gram-positive and Gram-negative bacteria contributed to 40% (20 isolates) and 48% (24 isolates), respectively, while 12% (6 isolates) of the isolates were *Candida* species (Fig. 2).

The most common etiology for neonatal sepsis was *Klebsiella* species (20%), followed by *Acinetobacter* species (19%), Methicillin sensitive *Staphylococcus aureus* (MSSA; 17%), Coagulase-negative *Staphylococcus* (CONS; 15%), *Candida* species (12%), Methicillin resistance *S. aureus* (MRSA; 9%), *Escherichia coli* (7%), *Enterococcus faecalis* (2.8%), and *Streptococcus species* (2.8%) (Fig. 3).

Of the 6 *Candida* isolates, non Candida *albicans* species were more common (66 %) than *C. albicans* (33%). Of these, *Candida* tropicalis (33%), *Candida glabrata* (16.5%), and *Candida parapsilosis* (16.5%) were the predominant species ($p=0.02$, Mann Whitney U Test; Nonparametric test, Degree of Freedom=1).

Of the 50 samples from neonates with septicemia born to COVID-19 positive mothers, 24 (48%) babies were COVID positive. The risk factors for sepsis among neonates born to COVID-19 positive mothers are shown in Table 1.

Among the Gram-positive isolates from the blood culture, 80% susceptibility was observed for Teicoplanin and Clindamycin each. A lower susceptibility was documented for gentamicin (58%) (Fig. 4).

While 84% of the Gram-negative microorganisms isolated from the blood culture were susceptible to piperacillin, with Tazobactam and cotrimoxazole each. Cefotaxime and Ceftazidime were susceptible to 60% and 55% of isolates, respectively (Fig. 5).

In the present study, Grampositive microorganisms accounted for greater sepsis among the COVID-19 positive cases (45.8%) compared to COVID-19 negative cases (34.6%); though the

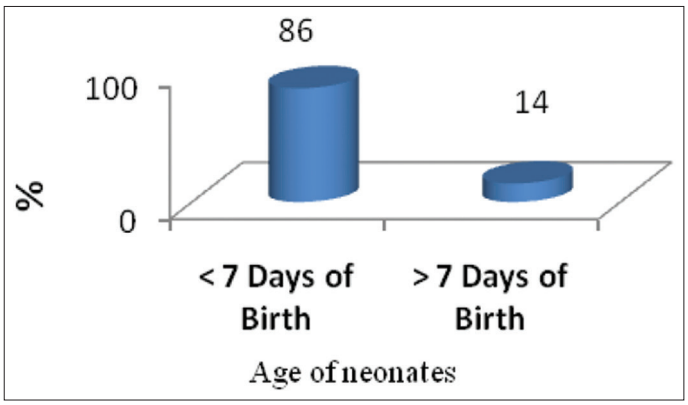

Figure 1: Age of new born in the study group (n=50)

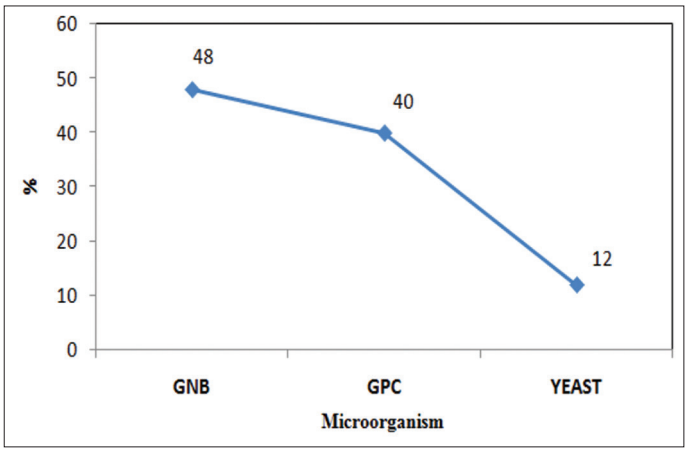

Figure 2: Isolates among positive blood cultures in cases of neonatal septicemia (n=50). GPC: Gram positive cocci, GNB: Gram negative bacilli

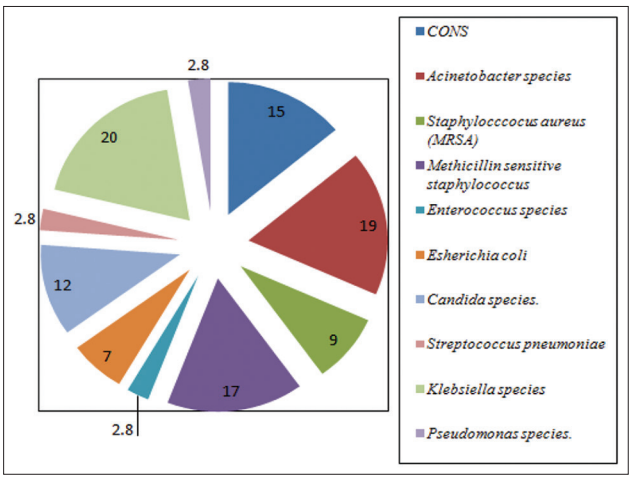

Figure 3: Percentage distribution of blood culture isolates in septic newborns born to COVID19 positive mothers (n=50). *MRSA: Methicillin resistance *Staphylococcus aureus, MSSA: Methicillin sensitive Staphylococcus aureus, CONS: Coagulase negative Staphylococcus aureus*

difference was not statistically significant. Gram-negative bacilli were isolated more frequently in COVID-19 negative cases of NS than in COVID-19 positive cases. The microbiological etiology of newborns with sepsis among COVID-19 positive and COVID-19 negative patients is shown in Table 2.

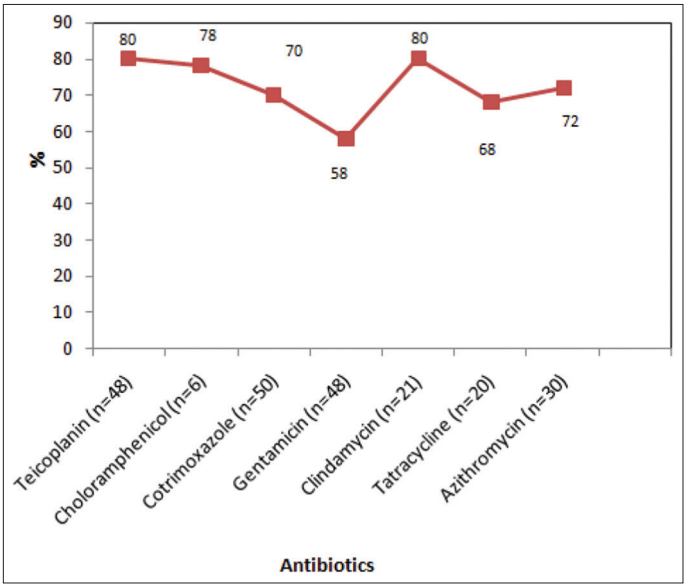

Figure 4: Antibiotics susceptibility pattern among Gram-positive cocci blood culture isolates in neonatal septicemia cases (n=50)

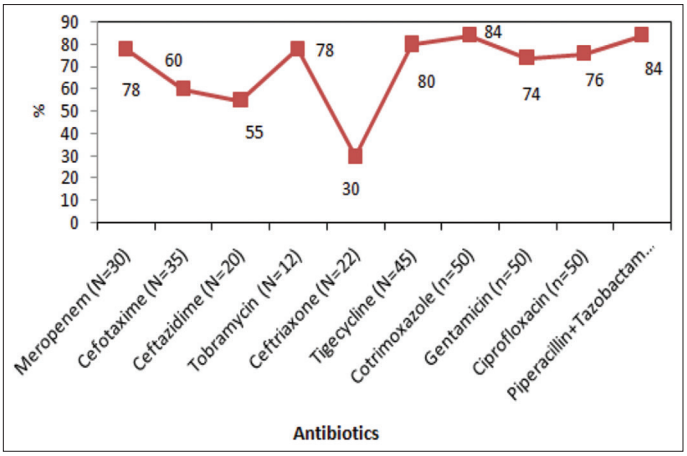

Figure 5: Antibiotics susceptibility pattern among Gram-negative bacilli blood culture isolates from babies with neonatal septicemia (n=50)

None of the risk factors were found significant in COVID-19 positive and negative neonates with sepsis, (Mann Whitney U Test; Degree of freedom=1, $p>0.05$, 95% confidence interval) (Table 3). The overall outcome of the babies born with a COVID 19 positive or negative status was satisfactory and all but 3 (6%) survived.

DISCUSSION

NS is a clinical syndrome of bacteremia characterized by systemic signs and symptoms in the 1st month of life. A high index of suspicion is important in the management of NS because the diagnosis is often delayed, and at times difficult due to delayed clinical manifestation. It is estimated that 20% of all neonates develop sepsis, and NS is responsible for 30–50% of total neonatal deaths in developing countries [19,20]. It is the main cause of infant mortality and morbidity in the NICU, and it often leads to various complications, which not only increase

the hospital burden but also have a serious negative impact on children's physical and mental growth [27,28]. In the present study, 50 blood culture isolates obtained from neonates born to COVID-19 positive mothers, were taken. Males were slightly more affected than females (3:1). However, no effect of gender has been reported on blood culture positivity rate. Our findings correlate with the study done by Sharma *et al*. from Delhi (M: F=2.5:1) [29].

Of the 50 samples from patients with NS born to COVID-19 positive mothers, 24 babies (48%) tested COVID -19 positive. Most neonatal SARS-CoV-2 infections are acquired after birth by horizontal virus transmission from the mother, healthcare workers, or other family members [30]. Limited reports document the potential mechanisms for vertical transmission as placental and umbilical cord during intrauterine life, cervicovaginal secretions during delivery, or through breastfeeding in the postpartum period [29,30]. The source of the infection is often difficult to assess. In utero, infection can be confirmed only if there is (a) "evidence of maternal infection" at any time during pregnancy, (b) "fetal exposure in utero" and (c) "SARS-CoV-2 persistence or exaggerated immune response in the newborn" [30]. For intrapartum and postnatal transmission, the maternal infection must be close to delivery (from 14 days before to 2 days after birth) [30]. A single positive RT-PCR test in a respiratory sample from a newborn can have several conclusions. It may indicate active viral replication or the presence of viral fragments acquired during passage through the birth canal or from external environmental contact soon after birth, or may even be a result of surface contamination that does not necessarily result in neonatal infection [31]. The presence of IgG antibodies in the newborn at birth may simply reflect the transfer of maternal antibodies and does not confirm the diagnosis of intrauterine infection. Consequently, a positive serological test in a newborn at birth always requires confirmation with a molecular test. Therefore, future studies should include SARS-CoV-2 RNA on vaginal samples and include direct testing of intrauterine tissue samples such as amniotic fluid, cord blood, placenta, viral load, and other variables to further determine the risk of COVID-19 vertical transmission to the neonate.

One of the major difficulties in the management of neonatal sepsis is getting an accurate diagnosis. Unlike older patients, newborns have a subtle presentation, and multiple conditions may resemble COVID-19 like symptoms. Auxiliary tests have limited value and are difficult to interpret due to low sensitivity and changing normal ranges during the neonatal period [29]. In the present study, Gram-negative organisms predominated (48%),

Table 1: The demographic profile and risk factors for sepsis among neonates born to COVID-19 positive mothers

Demographic parameters and risk factors among newborns	n=50 (%)
Gender	
Male	24 (48)
Females	26 (52)
Age of Newborn babies	
<7 days of Birth	43 (86)
>7 days of Birth	7 (14)
Clinical parameters	
COVID status of newborns	24 (48)
Small for gestational age	22 (45)
Respiratory distress syndrome	18 (36)
Preterm baby	14 (28)
Meconium stained liquor	10 (20)
Low birth weight baby	10 (20)
Neonatal jaundice	6 (12)
Primigravida mother	6 (12)
Mechanical ventilation	4 (8)
Death	3 (6)
Mean duration of ICU stays in newborns	8 days±5 days

Table 2: Microbiological etiology among cases with COVID-19

Microorganisms	COVID-19 positive cases (n=24)		COVID-19 negative cases (n=26)	
Gram-positive cocci (20)				
Staphylococcus aureus	6 (31.4)	11/24 (45.8%)	4 (15.07)	9/26 (34.6%)
Coagulase negative *Staphylococcus* (CONS)	4 (16.7)		3 (11.5)	
Streptococcus pneumoniae	0		2 (7.6)	
Enterococcus spp.	1 (4.1)		0	
Unpaired t-test, P>0.283, statistically insignificant				
Gram Negative Bacilli (24)				
Escherichia coli	2 (8.3)	10/24 (41.6%)	2 (7.6)	14/26 (53.8%)
Klebsiella pneumoniae	3 (12.5)		6 (23.07)	
Pseudomonas aeruginosa	1 (4.1)		2 (7.6)	
Acinetobacter species	4 (16.7)		4 (15.3)	
Unpaired t test, P>0.583, statistically insignificant				
Yeast (6)				
Candida species	2 (8.3)	2/24 (8.3%)	4 (15.3)	4/26 (15.3%)
Unpaired t-test, P>0.228, statistically insignificant				

***p<0.05 is statistically significant**

Table 3: Neonatal risk factors among COVID positive and negative cases in neonatal sepsis (n=50)

Neonates risk factors	COVID-19 positive newborns n=24 (%)	COVID-19 negative newborns n=26 (%)	Mann Whitney U Test (Non parametric test) Degree of freedom=1 95% Confidence internal
Small for gestational age	12 (50)	10 (38.4)	p=0.31
Respiratory distress syndrome	8 (33.3)	10 (38.4)	p=1.00
Preterm baby	7 (29.1)	7 (26.9)	p=1.00
Meconium stained liquor	5 (20.8)	5 (19.2)	p=1.00
Low birth weight baby	6 (25)	4 (15.3)	p=0.37
Neonatal jaundice	3 (12.5)	3 (11.5)	p=0.31
Primigravida mother	2 (8.3)	4 (15.3)	p=1.00

***p<0.05 is statistically significant**

followed by Gram-positive organisms (40%) and *Candida* species (12%) in NS. Similar studies have reported the same pattern with greater isolation of gram-negative bacilli in hospital settings [32-35]. Among the gram-negative bacteria, we observed *Klebsiella* species (20%), *Acinetobacter* species (17%), and *Escherichia coli* (7%) as the most predominant isolates. As a major cause of NS *Klebsiella* and *Acinetobacter* species are gaining importance as potential pathogens commonly associated with babies on intravenous catheterization and artificial ventilation [36]. Besides these, *Enterobacter* and *Salmonella* species have also been reported quite frequently; because they frequently necessitate prolonged intravenous access, endotracheal intubation, or other invasive procedures that serve as a point of entry for infection [35,37-40]. In our study, among the premature and low-birth-weight neonates, gram-negative sepsis due to *Acinetobacter baumannii* and *Klebsiella pneumoniae* was more common than Methicillin sensitive *S. aureus* (17%), coagulase-negative *Staphylococcus* (15%), and Methicillin-resistant *S. aureus* (9%), similar to other studies [37,41]. Although BSI due to Candida species in the neonate is less frequent, it is often associated with higher morbidity and mortality rates. Among newborns with a birth weight of <1000 g, candidemia has been reported in 4–8% of cases, with 30% mortality [42]. The overall incidence of candidemia in the present study was 12%, though certain studies have reported a higher incidence of candidiemia of up to 20.29% [7,42,43]. The increased use of invasive devices, broad-spectrum antibiotics in neonates have been the major risk factors leading to candidemia in NICU [41,44]. The predominance of non *C. albicans* (66%) over *C. albicans* (33%) was conspicuous in our study, with *C. tropicalis* as the most predominant (33%), followed by *C. glabrata*, and *C. parapsilosis*. A similar study by Zarei et *al.* observed in Iran that non *C. albicans* (63.3%), with *C. tropicalis* in 16%, *C. glabrata* in 10% and *C. krusei* in 6.6% as the common isolates [28].

Increasing antibiotic resistance, especially among gram-negative bacteria, remains a major concern in developing countries [37-40,43,44]. Among the Gram-positive cocci, >60% of strains were resistant to Gentamicin as reported by others [45]. Extensive use of third-generation cephalosporins in emergencies and as empirical therapy has led to the rise in cephalosporin resistance in *S. aureus* and *Enterococcus faecalis*, though susceptibility to vancomycin, teicoplanin, and ciprofloxacin was 100% 80% and 88% respectively in *S.aureus*. In their study, Asrat and Amanuel [46] reported only gentamicin to be relatively effective against gram negatives, while in our study, approximately 74% of strains were sensitive to gentamicin. In the present study, 84% of the isolates were sensitive to piperacillin + tazobactum, 80% to tigecycline, and 78% were sensitive to carbapenem. Cotrimoxazole was 84% sensitive to *Klebsiella* species. *Pseudomonas* species were more than 60% resistant to cotrimoxazole. Multidrug-resistant bacterial strains are emerging as a major problem in the management of sepsis. Improvement in the outcome and successful treatment depends on the early diagnosis of sepsis and the initiation of appropriate and specific antibiotic therapy as per the organism isolated in blood cultures. The etiology pattern has been constantly changing, and the frequent emergence of resistant bacteria compounds the problem further [33].

The current body of evidence from high-burden COVID-19 areas globally suggests that co-infections are common, particularly in severe cases. In a study conducted in Wuhan, of the total 41 patients, co-infections were reported in 31% of the ICU patients and in 10% of the patients admitted to the wards. Preterm birth was found to be the most common adverse pregnancy outcome in patients with COVID-19 [46,47]. In our study, the rate of preterm delivery was 28% of the total 50 newborns born with sepsis. This is certainly significant and clinically relevant when compared to the incidence of preterm delivery in the United States, estimated at 9.9% [47].

In addition, ICMR reports a high prevalence of antimicrobial resistance (AMR) in Indian hospitals in the pre-COVID times. High antimicrobial pressure in the NICU for treating COVID-19 patients with empiric antimicrobials further aggravated the problem of AMR. This is particularly true for COVID-19 centers, which do not have an adequate microbiological backup for routine culture. Various invasive modalities, which would otherwise be used to help diagnose COVID-19 patients, are potential sources of secondary infections. Thus, clinicians often resort to empiric broad-spectrum antimicrobial therapy. The practice of initiating empiric or prophylactic antibiotics often allows the selection of MDR pathogens. On the contrary, clinicians' choice of targeted antibiotic therapy over empiric prophylaxis would be a promising step to prevent the emergence of secondary infections due to MDR pathogens and result in favorable patient outcomes among COVID-19 patients [37].

CONCLUSION

In conclusion, infected infants can shed the SARS-CoV-2 virus through the respiratory tract as well as in stool. Therefore, caregivers should take caution with good hand hygiene, particularly when changing diapers. Prompt recognition of illness in this population is essential to limit further transmission in the community. When handling suspected or confirmed infected mothers, the delivery room or operating room should be specially prepared, preferably with negative pressure when available [48]. Physicians should wear adequate personal protective equipment (PPE). All probable or laboratory-confirmed newborns with SARS-CoV-2 should be isolated or cohorted in a single room (if possible) for at least 14 days. The quarantine room should be equipped, preferably with an isolated air cycle system and negative pressure isolation rooms as recommended. Although the study did not observe any significant difference in the clinical presentation and outcome of newborns with sepsis and COVID-19 positive status versus the non COVID 19 babies, further studies are required to understand the acquisition of SARS CoV2 from mother to child. Standard and additional infection control measures and guidelines should therefore be mandatory in hospitals handling COVID-19 positive mothers and newborns [49].

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