Clinical Practice Guideline

Perinatal-Neonatal Management of COVID-19

Ver.3.0 16 June 2021

Replaces Ver.2.0 of 07 May 2020

National Neonatology Forum, India

Federation of Obstetric & Gynaecological Societies of India

Indian Academy of Pediatrics

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Disclaimer

These guidelines in this document are based on current evidence. With new knowledge, recommendations may change. Users should use these guidelines in accordance with latest government regulations and ICMR advisories.

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Operational Flow Chart for Neonatal Care

Version 2.0 | Updated 15/6/2021

***Suspected** includes:

- Neonates born to mothers with COVID-19 diagnosed within 14 days before or within 2 days after delivery
- Neonates born to mother with suspected COVID-19
- Postnatal exposure to mother or another person with COVID-19
- Symptomatic neonates with onset at or beyond 48 hours of life and presenting with acute respiratory (respiratory distress or apnea with or without cough, with or without fever) or sepsis like illness (fever, lethargy, poor feeding, seizures or diarrhoea).

***Confirmed:** RT-PCR or RAT positive for SARS-CoV-2

COVID-19 status*

- Neither suspected nor SARS-CoV-2 positive → **Manage in usual care areas for neonates**
- Suspected / Confirmed → Sick or gestation <34 weeks

Sick or gestation <34 weeks	No	Yes
Suspected	A	C
Confirmed	B	D

#COVID confirmed neonates can be shifted to usual SNCU/NICU for ongoing intensive care, after two consecutive negative RT-PCR reports

Classify at admission and periodic assessment during course of illness

A — COVID-19 suspected, Stable & gest.≥34 wks

B — COVID-19 confirmed, Stable & gest.≥34wks

Mother sick?

- No: Room-in with mother in **"COVID postnatal ward"**. Allow breastfeeding with droplet and contact precautions. Discharge as indicated with mother.
- Yes: Shift to **"Well-baby COVID ward" or "SNCU"** Feeding: EBM, Donor human milk, formula feed. Discharge as indicated with healthy attendant.

C — COVID-19 suspected, Sick or gest.<34 wks

Shift to **"COVID suspect area" in SNCU/NICU**

If neonate in suspect area tests positive, shift to COVID confirmed ward/NICU.
If stable neonate in ward becomes sick, shift to SNCU/NICU.

D — COVID-19 confirmed, Sick or gest.<34 wks

Shift to **"COVID confirmed area" in SNCU/NICU#**

	A & B	C	D
Area characteristics	**Keep suspected and confirmed neonates/mothers in separate areas/rooms** If not possible, keep in separate corners in the same ward. May create a temporary physical barrier to ensure separation.	**Keep suspected and confirmed neonates in separate areas/rooms** If not possible refer to a nearby hospital with such facility (e.g. COVID hospital).	
	Needs air isolation. If not possible, install exhaust fans to create negative pressure.		
	Entry and exit separate from usual neonatal care areas. Earmarked donning and doffing areas near entry and exit respectively.		
Healthcare provider	Nurse to assist in initiation of breastfeeding. Allow a family member to stay with mother-baby dyad. Nurse for feeding and other care for well-being of baby	Doctors, nurses, and other support staff. Separate set of staff for suspected and confirmed neonates. If not possible, change PPE between the two areas. COVID-19 suspected or confirmed mother or family member not allowed to visit till declared to be cured as per national guidelines. Keep family engaged and informed about neonatal condition by phone/video call.	
Equipment	Crash-cart and resuscitation station, equipment for usual neonatal monitoring and care should be available Equipment and disposables to safely prepare and administer EBM, donor milk or formula Crash-cart and resuscitation station, equipment for usual neonatal monitoring and care should be available	All equipment as per standard of care in SNCU or NICU	All equipment as per standard of care in SNCU or NICU
	Health care providers to wear full set of PPE		
PPE	Mother should wear triple layered mask and perform hand hygiene before breastfeeding		

PERINATAL-NEONATAL MANAGEMENT OF COVID-19

VERSION 3.0

NNF, FOGSI and IAP

16/06/2021

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BACKGROUND

COVID-19 has infected more than 174 million people globally and caused 3.7 million deaths. (1) India is the second worst-hit country, with 29 million cases and 0.36 million deaths. The second wave has caused a massive disruption in the healthcare system and has been more lethal than the first wave. Compared to the first wave, the number of young adults and pregnant women affected with COVID-19 has been higher. The literature suggests that pregnant women are as vulnerable as the general population.(2,3) There has been a lot of advancement in the knowledge and experience regarding management of COVID-19 in pregnant women and neonates. This update provides evidence-based guidance about perinatal-neonatal COVID-19, especially in the Indian context.

This updated evidence-based rapid clinical practice guideline version 3.0 jointly from National Neonatology Forum India (NNF India), Federation of Obstetric and Gynaecological Societies of India (FOGSI), and Indian Academy of Pediatrics (IAP) provides guidance to clinicians and policymakers for the management of pregnant women exposed to COVID19 and their neonates. This document updates and overrides the previous guidelines version 2.0 released on May 7, 2020.

As the situation is evolving and new evidence emerges virtually every day, the users must check for latest updates from authentic sources like Indian Council of Medical Research (ICMR), Ministry of Health and Family Welfare (MOHFW), World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC).

METHODS USED TO DEVELOP THE GUIDELINE

The GRADE approach recommended by WHO was used to develop this guideline.(4) A Guideline Development Group (GDG) comprising of obstetricians, neonatologists and pediatricians was constituted. The GDG drafted a list of questions which are likely to be faced by clinicians involved in obstetric and neonatal care. An e-survey was carried out amongst a wider group of clinicians to invite more questions and prioritize. Literature search was carried out in PubMed using search terms like ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND 2019/12[PDAT] : 2030[PDAT]) OR 2019-nCoV[All Fields] OR 2019nCoV[All Fields] OR COVID-19[All Fields] OR SARS-CoV-2[All Fields]). In addition, websites of all relevant international and national organizations were searched. Guidelines, systematic reviews, trials, reviews and other descriptive reports were reviewed. For PICO questions, the evidence was extracted into evidence profiles. The context, resources required, values and preferences were considered for developing the recommendations.

UPDATED SEARCH

PubMed was searched to identify newly published articles related to pregnancy and neonatal management in the setting of COVID-19 as well as other related articles in the pediatric and adult population. A repository of published literature compiled by the Cochrane Gynaecology and Fertility group was reviewed for additional studies. Guidelines published by Pediatric and Obstetric Societies and bibliographies of relevant articles were also searched. The literature search is updated till 20 May 2021.

COVID-19 AND PERINATAL OUTCOMES

Though the incidence of COVID-19 in pregnancy is similar to the general population, the manifestations are more severe. The proportion of symptomatic and asymptomatic patients depends upon the population studied. Studies using universal screening of pregnant women reported a lower proportion of symptomatic infection. The PregCOV-19 Living Systematic Review reporting on universal screening in pregnancy found an estimated 74% (95% CI 51–93) of women were asymptomatic, while another study from the USA reported that 86% of women who were admitted in labor and who tested positive for SARS-CoV-2 were asymptomatic. (5) On the other hand, in large hospital-based registries where universal screening was not followed, the proportion of symptomatic women varied from 50-70%.(6,7) Around 10-13% of the symptomatic women had severe disease requiring ICU admissions.(6–8) Though publications are still

awaited, there has been a distinct difference in the experience of most centers in India during the second wave. In the first wave of the pandemic, the test positivity rate among hospitalized pregnant women varied from 5% to 12% in the centers following universal screening, whereas it went up to 20% and more during the second wave. During the first wave, only 5-10% of the SARS-CoV-2 positive women were symptomatic and only 1-2% had moderate to severe illness. In the second wave, the percentage of symptomatic women went up to 50-60% with 18-20% having moderate to severe illness.

Maternal COVID status directly affects the mother, fetus, and the newborn infant. As a rule, the adverse effects are much more common among the symptomatic and those with moderate to severe disease.

EFFECT ON PREGNANT WOMEN

Recent large cohort studies report that pregnant women with COVID-19 are at increased risk of not only severe infection (RR: 3.38; 95% CI: 1.63-7.01) but also various pregnancy complication e.g., preeclampsia/eclampsia (OR: 1.21; 95% CI: 1.1-1.3), gestational diabetes, and thrombosis (OR: 3.43; 95% CI: 2.01-5.82).(6,7) These conditions increase the risk of hospitalization, admission to the intensive care unit (RR: 5.04; 95% CI: 3.13-8.10), and death (RR: 22.3; 95% CI: 2.9-172).(6–10) These adverse effects are much more pronounced in the third trimester and in symptomatic women. Even among asymptomatic COVID-positive women, the risk for maternal morbidities and preeclampsia is higher than in non-infected women (RR: 1.33; 95% CI: 1.03-1.73).(8) Increased maternal age, obesity, any pre-existing maternal co-morbidity, chronic hypertension, pre-existing diabetes and preeclampsia were associated with severe COVID-19 in pregnancy.

CLASSIFICATION OF SEVERITY OF ILLNESS IN PREGNANT WOMEN

Severity classification in pregnant women (adapted ICMR/MOHFW guidelines) (11,12)

Table 1: Severity classification in pregnant women (adapted ICMR/MOHFW guidelines)

Severity	Criteria
Asymptomatic	Only test positive; no signs and symptoms
Mild	Upper respiratory tract symptoms &/or fever, WITHOUT shortness of breath or hypoxia
Moderate	Breathlessness / RR ≥24/min OR SpO2 90% to ≤93% on room air
Severe	Breathlessness, RR≥30/min OR SpO2 <90% on room air

Society for Maternal and Fetal Medicine (SFNM) classification: (13)

1. **Asymptomatic disease** is defined as a positive COVID-19 test result with no symptoms.
2. **Mild disease** is defined as flu-like symptoms, such as fever, cough, myalgias, and anosmia without dyspnea, shortness of breath, or abnormal chest imaging.
3. **Moderate disease** is defined by evidence of lower respiratory tract disease with clinical assessment (dyspnea, pneumonia on imaging, abnormal blood gas results, refractory fever of 39.0 °C /102.2 °F or greater not alleviated with acetaminophen) while maintaining an oxygen saturation of greater >94% on room air at sea level.
4. **Severe disease** is defined by a respiratory rate greater than 30 breaths per minute (bpm), hypoxia with oxygen saturation < 94% and a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PF ratio) of less than 300, or greater than 50% lung involvement on imaging.
5. **Critical disease** is defined as multi-organ failure or dysfunction, shock, or respiratory failure requiring mechanical ventilation or high-flow nasal cannula.
6. **Refractory hypoxemia** is defined as persistent, inadequate oxygenation and/or ventilation despite substantial and appropriate measures to optimize it and represents a further escalation of severity on the spectrum of disease.

EFFECT ON FETUS

COVID-19 in pregnancy is associated with increased risk for stillbirth (OR: 2.11; 95% CI: 1.14-3.90), intrauterine growth restriction, and preterm birth (OR: 1.82; 95% CI: 1.38 to 2.39).(6–8,10) The adverse effects are more pronounced in symptomatic women.(8) Available limited data does not support an increase in the risk of teratogenicity with SARS-CoV-2 infection; however, most reports are of infection in the third trimester.(14) Follow-up of pregnancies affected in the first 12 weeks is needed. Drugs (doxycycline, heparin, ivermectin, vitamin D) often used in treatment of COVID-19 have teratogenic potential.(15) Treating physicians should be aware of this and the use of these drugs should be restricted to conditions where the benefit outweighs the risk and that too after written informed consent.

EFFECT ON NEONATE

The neonates born to SARS-CoV-2 positive mothers are at risk of vertical transmission of the infection. However, the incidence of vertical transmission remains low.(2,6,7) Details of neonatal COVID-19 are given in subsequent sections. COVID-19 infection in pregnancy is associated with increased preterm birth (OR: 1.82; 95% CI: 1.38 to 2.39) and prematurity-related complications, low birth weight (OR 1.89, 1.14 to 3.12), and higher neonatal morbidity index (RR: 2.66; 95% CI:1.69-4.18).(2,6–8,10,16) There is no statistically significant effect on neonatal mortality .(6–8,16)

NEONATAL COVID-19

INCIDENCE

A wide range of incidence of neonatal infection has been reported in the literature. Among the neonates born to SARS-CoV-2 positive mothers, the incidence of positive test ranges from 0.5% to 13% (median 2%). (6,7,16) A multicentric study from India (NNF COVID-19 registry) enrolling 1711 neonates (1589 intramural and 122 extramural) reported a 10% positivity rate among intramural neonates.(16) There is limited data on the incidence of SARS-CoV-2 positivity in out-born neonates presenting to the emergency. This variability in reported incidence is due to variation in testing strategies and criteria, type of test, the timing of testing, and population profile.

MODE OF TRANSMISSION

A neonate can acquire SARS-CoV-2 infection in three potential ways:

1. Transplacental passage from mother to fetus (intrauterine infection): relatively rare.
2. Direct exposure to maternal blood or secretions during delivery (intrapartum infection): more likely than the intrauterine transmission.
3. Through aerosol or direct contact from infected mothers or caregivers (including healthcare workers) in the postnatal period (postnatal infection): most likely method of transmission.

Presence of viable SARS-CoV-2 virus in breastmilk and transmission resulting in neonatal infection has not been reported till now.(17) A common dilemma in neonatal COVID-19 is classifying the infection as vertical or horizontal transmission. Some experts have put forth classification schemes, but each has its fallacy and is not universally acceptable.(18,19) Taxonomic classification by Shah et al. is elaborate but challenging to implement in routine practice.(19) A simpler approach can be to classify the infection as perinatal and horizontal transmission.

- *Perinatal transmission* is defined as positive nasopharyngeal RT-PCR in a neonate during first 72 hours after birth. This includes intrauterine and intrapartum transmission. Testing is avoided in the first 12 hours to minimize false positives due to superficial colonization.
- *Horizontal transmission* is considered in a neonate with negative RT-PCR within the first 72 hours who subsequently tested positive any time after 72 hours of birth, irrespective of the mother's SARS-CoV-2 status.

CLASSIFICATION OF NEONATAL COVID-19

Like neonatal sepsis, based on time of onset and possible mode of transmission, the COVID-19 can be early-onset or late-onset.

EARLY-ONSET NEONATAL COVID-19

Early-onset infection is likely to have been acquired intrapartum or in the immediate postpartum period. The onset of illness is within the first week of life (generally 2-7 days). Early-onset COVID is relatively less common, and most of the neonates remain asymptomatic or mildly symptomatic.

LATE-ONSET NEONATAL COVID-19

The onset of illness is beyond 5 to 7 days of life, and most neonates become symptomatic at home after discharge from the hospital. Postnatal transmission from mother or immediate caregivers plays a significant role in late-onset neonatal COVID-19 infection. As the infection is usually diagnosed when the neonate becomes symptomatic, the clinical features are relatively more pronounced as compared to those in early-onset infection.

CLINICAL AND LABORATORY MANIFESTATIONS

Clinical: Most neonates remain asymptomatic or may develop mild symptoms (cough, rhinorrhoea, low-grade fever).(20,21) About 10-15% of symptomatic neonates may develop moderate to severe symptoms like respiratory distress, lethargy, poor feeding, vomiting, diarrhoea, and hemodynamic instability.

Laboratory: Hematological investigations might show leukocytosis, lymphopenia, thrombocytopenia, and elevated inflammatory markers (CRP, procalcitonin, IL-6, ferritin). However, these inflammatory markers are often elevated in the first few days of life due to several perinatal conditions and have wide range of normal values with poorly defined cut-offs. Hence, one should be very careful in their interpretation.

CLASSIFICATION OF SEVERITY OF ILLNESS IN NEONATES

Classification of severity of illness in neonates is given in Table 2.

Table 2: Classification of severity of illness in neonates (adapted from COVID-19 Management Protocol for Pediatric age group by MOHFW, GoI and statement by Indian Academy of Pediatrics version 2.0)

Severity	Criteria
Mild	Fever, rhinorrhea, cough, diarrhea, vomiting AND No tachypnea
Moderate*	Tachypnea (respiratory rate >60/minute) OR hypoxia (SpO_2 90–94%) in room air) AND No signs of severe disease
Severe*	Any of the following: Pneumonia with any of these: SpO_2<90% , grunting or chest retractions CNS features: lethargy, refusal to feed or seizures Severe diarrhea and/or vomiting leading to dehydration Critical disease if any of the following is present ARDS Shock Multiorgan dysfunction syndrome Acute thrombosis **Note: Rule out bacterial pneumonia-sepsis-meningitis which are more likely to cause above mentioned symptoms or signs of moderate to severe disease in neonates.*

MULTISYSTEM INFLAMMATORY SYNDROME (MIS) IN PREGNANT WOMEN AND NEONATES

Many cases of multisystem inflammatory syndrome (MIS) have been reported in adults, though less commonly than in children. (22,23) Pregnant women have also been affected. The typical time interval between SARS-CoV-2 infection and development of MIS in adults varies from 2 to 5 weeks with a median of 10 days. In pregnancy, other than the multiorgan dysfunction, MIS may also adversely affect the fetus.(20,22)

Multisystem Inflammatory Syndrome in Neonates (MIS-N) is a rare effect of maternal COVID-19 infection. The exact pathophysiology of this condition is not known. MIS-N is thought to result from neonatal hyper-immune response to the SARS-CoV-2 specific maternal IgG antibodies transferred across the placenta. Neonates with MIS can become critically ill with severe multiorgan dysfunction, including myocarditis, pericardial effusion, disseminated intravascular coagulation, hypoxemia, acute kidney injury, diarrhoea, necrotizing enterocolitis like illness, and skin ulceration.(23,24) Echocardiography is required to look for coronary aneurysms and myocardial function. The timing of presentation of MIS-N depends upon the timing of maternal SARS-CoV-2 infection. Therefore, it may present in-utero, immediately after birth if the mother was infected in early pregnancy (23) or may present 2-3 weeks after birth if the mother was infected in the later part of the pregnancy.(24)

LOG OF CHANGES

15 JUNE 2021

- Background section: Updated literature and added sections on phenotypes of neonatal infection. Major update
- Practice question 1: Indications and the recommended type of testing have been updated based on current evidence and ICMR recommendations.
- Practice question 2: Indications of admission to hospital and role of teleconsultation have been added. Major update
- Practice question 3: Minor update
- Practice question 4: New question added on use of antenatal steroids in pregnant women with COVID-19
- Practice question 5: Updated literature search. Major update
- Practice question 6: Updated literature search. Major update.
- Practice question 7: New question added on use COVID vaccination in pregnant and lactating women.
- Practice question 8: Minor update
- Practice question 9: Updated literature search. Major update.
- Practice question 10: Updated literature search. Major update.
- Practice question 11: New question added on practice of KMC.
- Practice question 12: Updated literature search. Major update.
- Practice question 13: Updated literature search. Major update.
- Practice question 14: Updated literature search. Indications and the recommended type of testing have been updated based on current evidence and ICMR recommendations.
- Practice question 15: Scope of the question has been expanded and new issues in clinical management have been added. Updated literature search. Major update.
- Practice question 16: Updated literature search.
- Practice question 17: New question added on the follow-up of neonates after COVID.
- Practice question 18: Updated literature search. Major update.
- Practice question 19: New question added on MIS-N.
- Practice question 20: Updated literature search.
- Practice question 21: Minor update.
- Practice question 22: Updated literature search.
- Practice question 23: Updated literature search. Major update.

CLINICAL PRACTICE QUESTIONS FOR OBSTETRICIANS AND NEONATOLOGISTS

Following questions were short-listed:

OBSTETRIC CARE

1. Which pregnant women need testing for COVID-19?
2. Should SARS-CoV-2 positive pregnant women be quarantined at home or admitted in hospital?
3. Where should pregnant women with suspected or active SARS-CoV-2 infection deliver?
4. Should antenatal corticosteroids for fetal lung maturation be administered to SARS-CoV-2 positive pregnant women with threatened preterm birth? **(New question)**
5. What should be the method of induction of labor and mode of delivery in pregnant women with suspected or confirmed SARS-CoV-2 infection?
6. What should be the specific management of SARS-CoV-2 infection in pregnant women?
7. What should be the COVID-19 vaccination protocol for pregnant and lactating women? **(New question)**

NEONATAL CARE

8. What should be specific practices during neonatal resuscitation for delivery of women with suspected or confirmed SARS-CoV-2 infection?
9. Is it necessary to separate the mother and baby if the mother has suspected or confirmed SARS-CoV-2 infection?
10. What should be the feeding policy for stable neonates born to mothers with suspected or confirmed SARS-CoV-2 infection?
11. Should Kangaroo Mother Care be practiced in neonates born to mothers with suspected or confirmed SARS-CoV-2 infection? **(New question)**
12. Should symptomatic neonates with suspected SARS-CoV-2 infection and needing intensive or special care be nursed in common NICU/SNCU or isolation facility?
13. What special precautions should be taken while providing respiratory support to neonates with suspected or confirmed SARS-CoV-2 infection?
14. What should be the COVID testing protocol for neonates?
15. What should be the specific management for neonates with COVID-19?
16. What should be the discharge policy for neonates born to mothers with suspected or confirmed SARS-CoV-2 infection?
17. What should be the follow-up policy for neonates who have recovered from COVID-19? **(New question)**
18. What should be the immunization policy for neonates with suspected or confirmed SARS-CoV-2 infection?
19. What should be the specific management of Multisystem Inflammatory Syndrome in neonates? **(New question)**

GENERAL QUESTIONS

20. What infection control measures should be undertaken in triage, labor and delivery room, and SNCU/NICU?
21. What should be the biomedical waste disposal protocol while managing suspected or confirmed COVID-19?
22. What should be the visitation policy and preventive measures for visitors?
23. What should be the occupational health policy specific to the COVID-19 pandemic?

Practice question 1: WHICH PREGNANT WOMEN NEED TESTING FOR COVID-19?

SUMMARY OF EVIDENCE

In a living systematic review of COVID-19 among pregnant women, Allotey et al. included 192 studies published until 6th October 2020.(5) Most studies reported that RT-PCR of respiratory specimens was used to confirm SARS-CoV-2 (97%, 187/192) infection; five studies reported using SARS-CoV-2 antibodies to confirm COVID-19; 43 studies additionally diagnosed COVID-19 based only on clinical suspicion. The overall rate of COVID-19 diagnosis in pregnant women attending or admitted to hospital for any reason was 10% (95% CI 7% to 12%; 73 studies, 67271 women). However, the rates varied by testing strategy: where universal testing strategy was followed, 7% (95 % CI 5% to 8%; 60 studies, 57144 women) were diagnosed as having COVID-19 compared with 28% (95% CI 15% to 43%; 11 studies, 2436 women) when only pregnant women with symptoms were tested. Among those undergoing universal screening at hospital admission, 75% of those diagnosed with COVID-19 were asymptomatic.

Testing strategy for pregnant women in India is based on ICMR recommendations published on 4th September 2020 and updated on 4th May 2021, and the clinical management protocol for COVID-19 by the Government of India, updated on 25th May 2021.(25,26) The gold standard for the detection of COVID-19 is the RT-PCR Test. However, it has a turnaround time of 18 to 36 hours, depending on the laboratory load. Tests such as TrueNat and CBNAAT are considered equivalent to RT-PCR, have a faster turnaround time, but their availability is limited. The quickest test is the Rapid Antigen Test (RAT), which has a turnaround time of minutes but has a lower sensitivity than the other tests. Recently, the ICMR has also approved a home-based self-testing kit. This is also a variety of RAT. During the second wave of the pandemic, the positivity rate was 20% or more in various parts of the country.(27) Recommendations for testing in pregnant women based on ICMR guidelines are given below.

RECOMMENDATION 1: COVID-19 testing in pregnant women

Testing situation	**Surveillance in containment zones and screening at points of entry**	**Surveillance in non-containment zones**	**Hospital Settings**
Testing in pregnant women	Test irrespective of symptoms	Test if • History of travel to a high-risk area in last two weeks • Symptomatic • Direct contact with a laboratory-confirmed case	All pregnant women in or near labor, who are hospitalized for delivery
Preferred test in order of priority	RAT RT-PCR or TrueNat or CBNAAT	RT-PCR or TrueNat or CBNAAT RAT	RT-PCR or TrueNat or CBNAAT RAT

Test interpretation and action

- If RAT is positive (irrespective of the symptom status), it need not be confirmed by other tests. It is to be taken as COVID-19 confirmed.
- If RAT is negative and the individual is symptomatic, further testing with RT-PCR, TrueNat, or CBNAAT is recommended.
- If the RAT is negative and the individual is asymptomatic, further testing depends on risk status, or the individual may be observed.
- Testing should not be repeated as a discharge criterion.
- For individuals who are hospitalized, testing should not be done more than once a week.

- No emergency procedure (including deliveries) should be delayed for lack of test. Sample can be sent for testing as indicated simultaneously. Pregnant women should not be referred for lack of testing facilities. All arrangements should be made to collect and transfer samples to testing facilities.

Practice question 2: SHOULD SARS-COV-2 POSITIVE PREGNANT WOMEN BE QUARANTINED AT HOME OR ADMITTED IN HOSPITAL?

PICO QUESTION

Among SARS-CoV-2 positive pregnant women which is better: home-quarantine as recommended for non-pregnant individuals versus hospitalization?

SUMMARY OF EVIDENCE

Of the 192 studies including 67,271 pregnant women, no clinical trials have compared specific care including isolation strategies in pregnant women.(5) Testing, isolation and home-based treatment of positive patients is the key measure to curb transmission of SARS-CoV-2. While the Centers for Disease Control (CDC), USA has published guidance for who should be tested, decisions about testing are at the discretion of state and local health departments.(28) The guidelines for high-risk population are extrapolated to pregnant women.

VALUES AND PREFERENCES

No evidence is available about the preference of pregnant women, families, healthcare providers, or policymakers about the isolation of exposed women during pregnancy. While women and their families will likely prefer to remain at home during the quarantine period, they may need close monitoring due to higher risk of complications of COVID-19 among pregnant women.

RESOURCES REQUIRED

Teleconsultation services are required to monitor women in home-isolation while more resources are needed if isolation and quarantine is offered in special facilities.

RECOMMENDATION 2 : Home Quarantine vs. Admission for pregnant women

1. Consider obstetric risk factors, co-morbidities, severity of COVID-19 illness and social conditions for deciding about home isolation or monitoring in a health facility.
2. Pregnant women with any of the following should be admitted in a health facility*:
    i. Obstetric complications needing admission
    ii. Moderate or severe COVID illness
    iii. Mild COVID-19 illness but monitoring by teleconsultation is not available
    iv. Social conditions are not appropriate
3. Pregnant women advised home quarantine should be enrolled in a teleconsultation monitoring program with active surveillance of their condition.

** Refer to Practice Question 6 for detailed recommendations regarding admission*

Practice question 3: WHERE SHOULD PREGNANT WOMEN WITH SUSPECTED OR ACTIVE SARS-COV-2 INFECTION DELIVER?

The Government of India has created three-tiered COVID facilities depending upon disease severity. However, the obstetric needs of pregnant women differ from their medical needs. The designated COVID care facility may or may not have the required obstetric services. Therefore, the choice of the place for care of pregnant women with COVID-19 should also consider the requirements for obstetric and neonatal care.

SUMMARY OF EVIDENCE

The guideline development group looked at the national guidelines on the creation of COVID dedicated facilities (last updated on 7 April 2020).(29) The Ministry of Health and Family Welfare has proposed that in a particular geographical area, dedicated facilities should be identified amongst the public healthcare establishments for COVID-19 suspected and confirmed individuals. These facilities are further stratified according to the infrastructure and level of care into COVID Care Centers (CCC), Dedicated COVID Health Centers (DCHC), and Dedicated COVID Hospitals (DCH). Maternity care services and other specialty services would be available at a DCHC and DCH. If a woman at DCHC needs higher level obstetric or medical care, she should be transferred to pre-mapped DCH.

Large hospitals with adequate space, infrastructure, and logistics can divide the hospital into non-COVID and COVID zones. There should be no or minimal crossover of patients, personnel, and material between the zones. In an ideal setup, there should be three demarcated zones – clean, potentially contaminated (for pregnant women with suspected infection), and contaminated (for pregnant women with proven infection) with exclusive passageways to minimize exposure of individuals to each other once they have been allotted into these zones. Each of these zones should have facilities to deal with outpatient, inpatient care including intensive care, labor room and operation theatre. If possible, each patient should be kept in a separate room with an attached bathroom. If this is not feasible, an adequate distance between the beds should be maintained. Wherever possible, it may be beneficial for the entire contaminated zone to have a negative pressure system to limit the spread of infection.

Every pregnant woman should be triaged at entry and then allotted into one of the zones depending on the presentation. If in a health facility, all asymptomatic pregnant women are being tested as per the ICMR testing strategy, they may be moved to the clean area if they test negative. If a woman who delivers in a non-COVID facility turns out to be SARS-CoV-2 positive, she should be referred to a COVID-19 dedicated facility based on needs of mother and baby, and actions should be taken as per MOHFW's 'Guidelines to be followed on detection of suspect/confirmed COVID-19 case in a non-COVID Health Facility'.(30) Suspect or confirmed COVID-19 pregnant women who have severe or critical illness and need ICU and services of multiple specialists should continue to be cared for in DCH. The obstetric services should be provided on site.

RECOMMENDATION 3: Place of delivery

1. All suspected or confirmed COVID-19 pregnant women should deliver at nearest Dedicated COVID Health Centre (DCHC) or Dedicated COVID Hospital (DCH) as per disease severity, and availability of obstetric and neonatal services.
2. In large facilities, three demarcated zones- clean, potentially contaminated, and contaminated, each housing all the required equipment and services should be organised for the management of non-COVID, suspected and confirmed COVID-19 pregnancies.
3. Every pregnant woman should be triaged at entry and allotted into one of the zones.
4. If a woman who delivers in a non-COVID facility turns out to be SARS-CoV-2 positive, she should be referred to COVID-19 dedicated facility based on the needs of mother and baby.

Practice question 4: SHOULD ANTENATAL CORTICOSTEROIDS FOR FETAL LUNG MATURATION BE ADMINISTERED TO SARS-COV-2 POSITIVE PREGNANT WOMEN WITH THREATENED PRETERM BIRTH?

PICO QUESTION

Does administration of antenatal corticosteroids for fetal lung maturation to SARS-CoV-2 positive pregnant women who are at high risk of preterm delivery affect maternal and perinatal morbidity and mortality?

RATIONALE

1. A single course of antenatal corticosteroids is recommended for pregnant women between 24-34$^{6/7}$ weeks who are at risk of preterm delivery within the next seven days. It is strongly associated with reduction in neonatal mortality and morbidity. (31)

2. Dexamethasone is associated with a reduction in mortality in moderate to severe COVID-19 but might be harmful in patients not requiring oxygen.(32)

3. Repeat doses of corticosteroids in the antenatal period might have an adverse effect in childhood.(33)

CLINICAL DILEMMA

Considering the potential maternal benefits in moderate to severe COVID-19 in pregnant women, dexamethasone is recommended for 10 days or until discharge whichever is earlier.(32) However, there are concerns that prolonged use of dexamethasone may adversely affect the fetal neurodevelopment. Some authors and societies have instead proposed the use of other steroids (hydrocortisone and methylprednisolone) that do not cross the placenta unless steroids are being used for fetal indication.(34,35) On the other hand, it is not known if dexamethasone given for fetal indication to pregnant women with mild COVID-19, can adversely affect the maternal outcome.

SUMMARY OF EVIDENCE

We identified a total of 66 reports of which 24 articles were considered relevant for a full-text read. We did not find any clinical trial comparing the use of steroids with no steroids in the antenatal period or comparing the efficacy and safety of different steroids among pregnant women with COVID-19. Also, we did not find any observational study looking at the safety of dexamethasone use in pregnant mothers in whom it was not required for fetal indications. The trials using corticosteroids enrolled only four pregnant women, and did not provide any evidence for the safety of dexamethasone in pregnant women.(32) Therefore, the numerous recommendations on the use of antenatal corticosteroids in pregnancy with COVID-19 are only consensus-based and are very heterogeneous.(36) We also searched for guidelines from various societies on this aspect . Only one guideline from Australia and New Zealand COVID-19 task force used the GRADE approach. Considering the well-studied and large potential fetal benefits of antenatal steroids and no known harms associated with a short course of steroids to mothers, there is a unanimous recommendation to use them in standard doses for the fetal indication irrespective of mother's COVID status. Among mothers with moderate to severe COVID-19, corticosteroids are strongly recommended for maternal benefit irrespective of fetal gestation. Since, dexamethasone is cheap, easily available, and widely studied drug in moderate to severe COVID-19, most guidelines suggest using it for up to 10 days or discharge whichever is earlier. As COVID-19 is associated with an increased risk of preterm birth, all of them considered using dexamethasone for the first 48 hours (6 mg/dose 12 hourly) if the pregnancy is between 24-34 weeks.(2) However, if corticosteroids are not required for fetal indication, one might consider using alternative agents (like methylprednisolone, prednisolone, or hydrocortisone) that do not cross the placenta. The decision of using other alternatives should be based upon the availability, cost, and individual preference after explaining the risk-benefits of using dexamethasone versus other drugs. In resource-limited settings where the affordability of methylprednisolone or hydrocortisone can be an issue, dexamethasone 6 mg/day for 10 days may be used, if not indicated for the fetus, or 6 mg/dose 12 hourly for four doses followed by 6/mg per day for

the rest of the duration to complete the course, if indicated for the fetus. If methylprednisolone or hydrocortisone are available, affordable, and parents consent against using dexamethasone , one might consider using methylprednisolone or hydrocortisone in equivalent dosage for 10 days or until discharge, whichever is earlier as medically indicated. However, if indicated for fetal lung maturity, it is desirable to use dexamethasone 6 mg/dose 12 hourly for four doses (2 days) and complete rest of the course with methylprednisolone or hydrocortisone.

RECOMMENDATION 4: Antenatal Corticosteroids			
Indication for steroids		**Setting**	**Dose schedule**
Fetal Lung Maturation	**Maternal Covid illness**		
√	**X**	**All settings**	Dexamethasone 6 mg IM every 12 hours for four doses, irrespective of maternal COVID-19 status.
X	√	**Resource limited**	Dexamethasone 6 mg/day PO/IV for 10 days or until discharge, whichever is earlier.
		Resourceful (available, affordable, and parents' consent against using dexamethasone)	Methylprednisolone or Prednisolone or Hydrocortisone in equivalent doses for 10 days or until discharge, whichever is earlier.
√	√	**Resource limited**	Dexamethasone 6 mg IM every 12 hourly for four doses (2 days) followed by Dexamethasone 6 mg/day PO/IV for 8 more days or until discharge, whichever is earlier.
		Resourceful (available, affordable, and parents' consent against using dexamethasone)	Dexamethasone 6 mg IM every 12 hours for four doses (2 days) followed by Methylprednisolone or Prednisolone or Hydrocortisone in equivalent doses for 8 more days or until discharge whichever is earlier.

Practice question 5: WHAT SHOULD BE THE METHOD OF INDUCTION OF LABOR AND MODE OF DELIVERY IN PREGNANT WOMEN WITH SUSPECTED OR CONFIRMED SARS-COV-2 INFECTION?

PICO QUESTIONS

1. Among pregnant women with suspected or confirmed COVID-19 (P), does delivery by cesarean section (I) as compared to vaginal delivery (C) reduce the incidence of perinatal transmission and neonatal COVID in the initial 3-5 days of life (O)?

2. Among pregnant women with suspected or confirmed COVID-19 (P), what is the efficacy and safety (maternal mortality and severe morbidities; preterm delivery; NICU admission, etc.) (O) of early and elective induction before 38 weeks of gestation (I) compared to spontaneous onset of labor or delayed induction at or after 38 weeks of gestation?

3. Amongst pregnant women with suspected or confirmed COVID-19 (P), is mechanical method (I) preferred over pharmacological agents (C) for induction of labor when indicated?

SUMMARY OF EVIDENCE

We found 3111 relevant articles pertaining to pregnancy and COVID-19.

MODE OF DELIVERY

Data over the last 1.5 years has shown that the clinical course of COVID-19 in pregnancy is mild in most cases (86%). It is severe in 9% and critical in 5%.(37,38) At the beginning of the pandemic, there were theoretical concerns of increased risk of vertical transmission of COVID-19 to the neonates by vaginal delivery due to a potential exposure to vaginal secretions in the birth canal. Therefore, there was an increase in the reported incidence of cesarean section in pregnant women with COVID, though more recent registries and cohorts have shown a decline in this trend.(5,39–42) Overall, the incidence of vertical transmission of infection to neonates seems to be very low.(43,44) There have been no trials comparing elective cesarean section with vaginal delivery for prevention of vertical transmission or neonatal morbidities. A systematic review which included case reports, case series, and cohort studies assessed the impact of mode of delivery in reducing the perinatal transmission rates.(45) Only one cohort study (46) among the 68 included studies examined the effect of mode of delivery on neonatal outcomes. We updated the systematic review until May 2021 by using the same search strategy in PubMed (case reports were excluded).

Recent studies have shown that vaginal delivery does not result in increased neonatal morbidity and infection. The severity of illness in the mother is an important factor to be considered while making the choice of timing and mode of delivery. This has been incorporated in the guidelines by various organizations. Most guidelines also recommend vaginal delivery.(3,13,47–50) A recent review of the current practices also advocated that the mode and timing of delivery should follow routine obstetric indications.(51) Thus, it seems reasonable to state that cesarean section should not be performed for prevention of vertical transmission alone. Most organisations, including the ICMR, FOGSI, and Society for Maternal-Fetal Medicine (SMFM) recommend that cesarean section should be considered only in severe/critical disease in pregnant women in whom there is an imminent risk to the mother or fetus.(3,13,47–50)

TIMING OF DELIVERY

No randomized trials have evaluated the effect of timing of delivery on maternal and neonatal morbidities and mortality in pregnant women with COVID. For asymptomatic or mildly symptomatic patients at ≥39 weeks of gestation, induction for delivery can be considered to decrease the risk of worsening maternal status before the onset of spontaneous labor.(13) For women presenting at <39 weeks with non-severe COVID-19, expectant management is advocated if there are no medical or obstetric indications for prompt delivery. In women with some medical/obstetric

complications, the timing of delivery is determined by the usual protocols for the specific medical/obstetric disorder. Till date, there is no consensus on the optimal timing of delivery in critically ill, COVID-positive pregnant women. Increased oxygen consumption and reduced functional residual capacity, which happen usually in pregnancy, may further deteriorate the clinical condition in these women. Although the late third-trimester uterus may account for some mechanical restriction in ventilation, it is unclear whether delivery provides a substantial improvement. There may be a benefit in reducing the physiological demands of pregnancy in certain patients. Delivery is indicated in critically ill pregnant women if delivery is expected to result in the improvement of respiratory failure. The decision should be taken by a multidisciplinary team that includes a critical care specialist, maternal-fetal medicine specialist or a senior obstetrician, neonatologist and family.(52,53) Emergency delivery and pregnancy termination decisions are challenging and are based on many factors: gestational age, maternal condition, and fetal stability. Individual risk-benefit analysis based on potential benefits for mothers and safety to fetus should be considered.(54)

INDUCTION OF LABOR

There are no studies on the efficacy and safety of different methods of induction of labor in pregnant women with COVID-19. Induction of labor for appropriate medical or obstetrical indications in asymptomatic women should not be postponed or rescheduled. Induction can still be conducted as usual, with a combination of 60- to 80-mL single-balloon Foley's catheter for 12 hours and either oral 25 mcg misoprostol initially, followed by 25 mcg every 2/4 hours, or 50 mcg every 4/6 hours (if no more than 3 contractions per 10 minutes or previous uterine surgery), or oxytocin infusion.(55) There is no clear best practice with respect to the choice of agent for cervical ripening. Both mechanical and pharmacological agents are acceptable options.(56)

VALUES AND PREFERENCES

No evidence is available about the preferences of mothers, families, healthcare providers, or policymakers regarding the choice of mode of delivery for pregnant women with COVID-19.

RESOURCES REQUIRED

None, except for those required for supportive and symptomatic care of mothers and their neonates with suspected or confirmed COVID-19.

RECOMMENDATION 5 : Delivery

1. **Mode of delivery**

- Mode of delivery in pregnant women with COVID-19 should be guided by obstetric indications and physiological stability (cardiorespiratory status and oxygenation). SARS-CoV-2 infection itself is not an indication for cesarean section.

  Strong recommendation, based on consensus among experts and the evidence for lack of any beneficial effects of cesarean section in preventing perinatal transmission.

- If a critically ill pregnant woman is having refractory hypoxemia, cesarean section may be indicated for better management of respiratory failure.

2. **Timing of delivery**

- Timing of delivery in pregnant women with COVID-19 should be individualized and based on the disease severity, associated co-morbidities, and the gestational age.

- In asymptomatic/mild disease, delivery should be reserved for appropriate obstetric indications and should not be delayed solely due to SARS-CoV-2 positive status.

- In severe/critical disease, a multi-disciplinary team should assess to make a decision. Delivery is indicated, if it is expected that it may improve the respiratory failure and aid in optimization of clinical status. Pregnancy may be continued if there is no imminent threat to maternal and fetal life.

3. **Induction of labor**

- SARS-CoV-2 infection per se is not an indication for induction of labor.

- Both the indication and the cervical status should be evaluated in SARS-COV-2 positive pregnant women scheduled for labor induction. Those who have an unfavourable cervix (e.g., Bishop score <6) can be induced by mechanical or pharmacological methods as per the hospital protocol.

  Weak recommendation, based on consensus among experts in the absence of evidence for any beneficial effect or harm with the use of any of the options available in this population.

Practice question 6: WHAT SHOULD BE THE SPECIFIC MANAGEMENT OF SARS-COV-2 INFECTION IN PREGNANT WOMEN?

PICO QUESTIONS

1. Among women with mild/asymptomatic COVID 19 infection (P) what is the effect of treatment with one or more antiviral drugs (I) on critical outcomes such as maternal mortality (O), when compared to only supportive care (C)?
2. Among women with moderate/severe COVID 19 infection (P) what is the effect of treatment with one or more antiviral drugs (I) on critical outcomes such as maternal mortality and neonatal mortality rate (O), when compared to only supportive care (C)?
3. Among women with moderate/severe COVID 19 infection (P) what is the effect of prophylaxis for venous thromboembolism (I) on critical outcomes such as maternal mortality (O), when compared to only supportive care (C)?
4. Among women with moderate/severe COVID 19 infection in third trimester (P) what is the effect of delivery on critical outcomes such as maternal mortality and neonatal mortality rate (O), when compared to only supportive care (C)?
5. Among women with moderate/severe COVID 19 infection in third trimester (P) what is the effect of steroids on critical outcomes such as maternal mortality and neonatal mortality rate (O), when compared to only supportive care (C)?

SUMMARY OF EVIDENCE

We identified a living systematic review and meta-analysis by Allotey et al. that included relevant studies published in bibliographic databases and pre-print servers between 1 December 2019, and 6 October 2020.(5) All available guidelines recommend that women with confirmed COVID-19 should be managed based on severity of illness either at home isolation or in hospital. All hospitalized pregnant patients with moderate, severe or critical illness should ideally be managed by a multidisciplinary team comprising obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care specialists at a tertiary care centre with obstetric services and an adult ICU. Pregnant women with COVID are more likely to need ICU admission compared to non-pregnant women. The latest review also showed increased risk of mortality in pregnant women with COVID.(3,5,13,48,57)

ASYMPTOMATIC OR MILD ILLNESS

Home isolation may be suitable for asymptomatic and mildly symptomatic pregnant women. Consider obstetric risk factors, severity of COVID-19 illness and social conditions for deciding about home isolation or monitoring in a health facility (refer to Practice Question 2). All asymptomatic patients should be assessed for their risk for worsening of disease and advised regarding close monitoring for respiratory decompensation which may occur rapidly, infection control and self-isolation for the anticipated duration of illness, and appropriate timing of discontinuation of precautions. Patients should seek emergency medical care if they experience worsening dyspnea, unremitting fever >39°C despite appropriate use of paracetamol, inability to tolerate oral hydration and medications, persistent pleuritic chest pain, confusion, or obstetric complications (e.g., preterm contractions, vaginal bleeding, rupture of membranes).(3) Respiratory rate ≥20 to 24 breaths/minute and/or heart rate >100 beats per minute are also warning signs of patients at risk of clinical deterioration.(58) Women should perform daily fetal movement count and report in case of decreased fetal movement. Home care comprises supportive measures, e.g., hydration, adequate rest, and frequent ambulation with increased activity as tolerated.

MODERATE OR SEVERE ILLNESS

Women with moderate, severe, or critical illness are advised admission in Dedicated COVID Hospital having adult HDU/ ICU with a multidisciplinary team including obstetrician, critical care experts, infectious disease specialists, and trained nursing team.

CRITERIA FOR ADMISSION FOR COVID-19 PREGNANT WOMEN (13)

1. Fever >39°C despite use of paracetamol (which raises concern for cytokine storm syndrome)
2. Moderate or severe illness (refer to background section of the guidelines for classification of illness severity)
3. A co-morbid condition warranting admission (e.g., poorly controlled hypertension or diabetes, preeclampsia, prelabor rupture of membranes, bleeding per vaginum).

All COVID confirmed women getting admitted should be evaluated with investigations like CBC with differential count, Total leukocyte count, LFT, KFT, Blood Sugar, CRP, CPK, PT/PTTK, d-dimer, LDH, Troponin, ferritin, ECG Chest X-Ray/ Chest CT with abdominal shield, if clinically indicated, USG Obstetrics for fetal well-being at admission. For hospitalized women, the need for and frequency of fetal testing depend on gestational age, their vitals and oxygenation status, and comorbidities especially diabetes mellitus. Consider biophysical profile (BPP) once a week and non-stress test (NST) twice a week in stable patients. Chest imaging like X-ray or CT is essential for the evaluation of the unwell woman with COVID-19 and should be performed when indicated, without delay.

THERAPEUTIC CHOICES

Oxygen therapy - Maternal peripheral oxygen saturation (SpO2) should be maintained at ≥95 percent.(13)

Prone position: There is little evidence on the use of prone positioning in pregnancy. However, NIH states that awake prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position or the fully prone position. A review article on prone positioning for pregnant women with COVID-19 provides advice, guidance and an algorithm on how this can be undertaken successfully in the second and early third trimesters. Padding above and below the gravid uterus >24 weeks is desirable to offload the uterus and avoid aortocaval compression.(59)

Antipyretics: Paracetamol is the preferred antipyretic and analgesic agent. ACOG, WHO, and the European Medicines Agency (EMA) recommend the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in COVID-19 patients only when clinically indicated. The lowest effective dose is used, ideally for less than 48 hours and guided by gestational age-related potential fetal toxicity (e.g., oligohydramnios, premature closure of the ductus arteriosus). Low-dose aspirin for prevention of preeclampsia is safe throughout pregnancy.(48,60)

Venous thromboembolism prophylaxis: Pregnancy is widely recognized as a hypercoagulable state. Direct data on risk of venous thromboembolism (VTE) related to COVID-19 are limited but suggest an increased risk in infected pregnant patients compared with uninfected pregnant patients. Pregnancy, reduced mobility, and dehydration can contribute to this risk.(61) There is currently no direct evidence comparing VTE prophylaxis regimens for COVID-19 in pregnancy. According to RCOG guidelines, prophylactic-dose anticoagulation is recommended for pregnant patients hospitalized for moderate to severe COVID-19 and continued for 10 days following hospital discharge, if there are no contraindications to its use. Women with persistent morbidity should be reassessed for longer duration of thromboprophylaxis.(3) Women who are asymptomatic or mildly symptomatic and hospitalized for reasons other than COVID-19 (e.g., labor, preterm prelabor rupture of membranes) do not require anticoagulation, unless antithrombotic therapy had been prescribed during pregnancy for another indication like previous VTE. Decisions regarding VTE prophylaxis in the pregnant and postpartum patient should be individualized, considering concomitant VTE risk factors and timing of delivery.

Corticosteroids: Refer to Practice Question 4

Remdesivir: Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19 . In non-pregnant adults, remdesivir may decrease time to recovery by a few days (hazards ratio (HR) 1.24, 95% CI 1.08–1.42) and time to improvement only slightly (HR 1.17, 95% CI 1.00–1.38). Preliminary reports of remdesivir use in pregnant patients from the remdesivir compassionate use program are reassuring. Among 86 pregnant and postpartum hospitalized patients with severe COVID-19 who received

compassionate use remdesivir, the therapy was well tolerated, with a low rate of serious adverse events.(62) NIH recommends that remdesivir should not be withheld from pregnant patients if it is otherwise indicated.(58)

This guidelines group recommends that remedesivir should not be withheld from pregnant patient if otherwise indicated. Guidelines issued by the government about rationale use of remedesivir should be followed and it should be prescribed only in "select moderate/ severe hospitalized COVID-19 patients on supplemental oxygen".(63)

The interleukin-6 receptor antagonist (anti-IL6) Tocilizumab: The results of the RECOVERY trial and REMAP-CAP provide consistent evidence that tocilizumab, when administered with corticosteroids, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill, rapidly deteriorating with increasing oxygen needs, and have a significant inflammatory response.(32,64) Although data for the use of tocilizumab in pregnancy in this situation are limited, there is currently no evidence that tocilizumab is teratogenic or fetotoxic. Both NIH and RCOG recommend that for women meeting the criteria (hypoxic with systemic inflammation), the use of tocilizumab should be considered after discussion with patient, obstetrician and infection specialists, if the benefits outweigh the risks.(3,58,65)

Convalescent plasma: Nine randomized controlled trials compared convalescent plasma with standard therapy in over 12,800 patients with COVID 19. RECOVERY trial included 11,588 adults with mild to severe COVID-19. In the RECOVERY trial there was no significant difference in the primary endpoint of 28-day mortality in patients receiving convalescent plasma compared with usual care; 1399 (24%) of 5795 patients allocated to convalescent plasma and 1408 (24%) of 5763 patients allocated to usual care died within 28 days (RR 1.00, 95% CI 0.93 to 1.07). When combined with mortality data from the other included trials, results show that compared with standard care, convalescent plasma probably has little impact on death (16 fewer per 1000 patients; RR 0.93, CI 95% 0.79 to 1.10; 12,872 patients in 9 studies). In addition, convalescent plasma probably has little impact on the requirement of non-invasive ventilation and has no impact on the requirement of invasive mechanical ventilation or hospital discharge. Convalescent plasma may increase the incidence of serious adverse events and adverse events. We remain uncertain whether convalescent plasma has an impact on respiratory failure or ARDS, admission to ICU, clinical deterioration, clinical improvement, clinical recovery, negative PCR, time to improvement and time to discharge from hospital. Convalescent plasma has been administered to some pregnant patients with COVID-19 with or without additional drug therapy, however, increasing evidence suggests no clinical benefit.(32,62,65,66)

Monoclonal antibody (Bamlanivimab-etesevimab and casirivimab-imdevimab): NIH recommends Bamlanivimab-etesevimab and casirivimab-imdevimab (a combination of neutralizing monoclonal antibodies) as an option for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization. The drug combination should not be withheld from pregnant patients if they qualify for its use, after a discussion of the potential benefits and theoretic risks.(58) These immunoglobulin G1 (IgG1) antibodies may cross the placental barrier. and there is no information regarding whether the potential transfer of these drugs provides any treatment benefit or risk to the developing fetus.

Indications for termination of pregnancy: For critically ill women, termination of pregnancy may be required in the setting of worsening critical illness and refractory hypoxemia. SMFM recommends to consider delivery in critically ill women if gestation is more than 32 weeks.(13). (for detailed recommendation: refer to Practice question 5)

Vitamin C, Vitamin D and Zinc: There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of vitamin C, Vitamin D and Zinc for the treatment of COVID-19.(58,65)

Hydroxychloroquine, chloroquine, ivermectin and azithromycin: Hydroxychloroquine, chloroquine, ivermectin and azithromycin are not approved by the Food and Drug Administration (FDA) for the treatment of COVID-19.(58,65)

Post discharge follow-up: SMFM emphasizes that patients can deteriorate following discharge. Patients should be instructed to seek care if symptoms worsen. Telehealth monitoring is an option. RCOG recommends reviewing the maternal obstetric status or any growth scan during hospital stay and formulating a plan of delivery and place of birth. Patients often suffer from anxiety and fear and they should be supported by psychological counselling. (26)

VALUES AND PREFERENCES

No evidence is available about the preference of pregnant women, families, healthcare providers, or policymakers about the choice of therapy during active infection. However, potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy and prescribed only in consultation with patient and multidisciplinary team involved in care.

RESOURCES REQUIRED

Dedicated COVID hospitals with ICU facility and trained staff along with facility for telehealth.

RECOMMENDATION 6 : Treatment of pregnant women

Asymptomatic or Mild illness:

1. Home isolation with active surveillance by tele-monitoring OR admission in a health facility based on obstetric risk factors, co-morbidities, and social conditions (see Practice question 2)
2. During home isolation, patients should seek emergency medical care if they experience worsening dyspnea, unremitting fever >39°C despite appropriate use of paracetamol, inability to tolerate oral hydration and medications, persistent pleuritic chest pain, confusion, or any obstetric complication.
3. The use of ivermectin or doxycycline is contraindicated.
4. Vitamin C, Vitamin D and Zinc are not recommended for treatment of COVID-19.

Moderate or severe illness:

1. Admit in dedicated COVID hospital with HDU/ICU
2. *Oxygen therapy*: Maintain SpO_2 >94%. Awake prone positioning is feasible and acceptable.
3. *Corticosteroids***:** Please refer to Practice Question 4
4. *Remdesivir***:** Remdesivir should not be withheld from pregnant patients if it is otherwise indicated as in hospitalized patients requiring oxygen therapy, especially early in disease course. Guidelines issued by the government about rationale use of remdesivir should be followed.
5. *Venous thromboembolism prophylaxis:* All pregnant women with COVID-19 should be assessed for risk of venous thromboprophylaxis and prescribed prophylactic anticoagulation with low molecular weight heparin/ unfractionated heparin (e.g., enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) and continued for 10 days following hospital discharge unless there is a contraindication.
6. *Tocilizumab:* The use of tocilizumab (interleukin-6 receptor antagonist) should be considered for women meeting the criteria i.e., hypoxia and systemic inflammation. Decisions about tocilizumab administration during pregnancy must include shared decision-making between the pregnant individual, family and their health care provider.
7. *Monoclonal antibody:* Monoclonal antibody like Bamlanivimab-etesevimab and casirivimab-imdevimab combination should not be withheld from pregnant patients if they qualify for its use(non-hospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization), after a discussion of the potential benefits and risks.
8. *Convalescent Plasma therapy:* There is no role of convalescent plasma therapy.

Practice question 7: WHAT SHOULD BE THE COVID-19 VACCINATION PROTOCOL FOR PREGNANT AND LACTATING WOMEN?

PICO QUESTIONS

1. Amongst pregnant women (P), what is the efficacy and safety of administering COVID vaccine (I), in terms of incidence of COVID and COVID-related maternal and neonatal complications as well as allergic reactions and serious adverse events (O), compared to not administering it or administration of placebo (C)?

2. Among pregnant women (P), is administration of COVID vaccine at different gestations (I) associated with varying efficacy and safety profile (O)?

3. Amongst all the vaccines available against COVID (I), which has the highest efficacy and safety profile (O) in pregnant women (P)?

SUMMARY OF EVIDENCE

There is a higher risk of hospitalization, requirement of admission to ICU, need for mechanical ventilation and mortality in pregnant women with COVID as compared to non-pregnant or pregnant women without COVID.(7,67–69) In addition, there is also an increased risk of preterm birth in women with COVID 19 during pregnancy when compared with pregnant women without COVID-19.[(7); (5); (44) The issue of vaccination in pregnant women should consider the following for making informed decisions: immunogenicity, efficacy, and reactogenicity (adverse effect profile) in pregnant women naïve to the infection as well as in those who have had COVID-19 in the past (as these individuals may have more systemic and local side effects as well as higher titres of antibody after first dose of vaccine).(70) There are no randomized trials that have evaluated the efficacy or safety of COVID-19 vaccines in pregnant women. One randomized trial, registered in ClinicalTrials.gov (NCT04754594), is enrolling pregnant women at present.(71) Data from the Developmental and Reproductive Toxicity (DART) animal-model studies for the COVID-19 vaccines by Pfizer-BioNtech, Moderna, and Janssen (Johnson & Johnson) have not demonstrated any adverse safety profile in pregnancy. Based on the mechanism of action of these vaccines and the demonstrated safety and efficacy in Phase II and Phase III clinical trials, the safety and efficacy profile of the vaccine for pregnant individuals is expected to be similar to non-pregnant individuals. There are a few observational studies and one registry-based data, but none provides details on the two sub-groups of pregnant women- naïve to COVID vs with past COVID disease.(72–76) Also, the available data is only for the two mRNA vaccines (Pfizer-BioNtech and Moderna) against COVID. No data is available for the safety and immunogenicity of Oxford-AstraZeneca (Covishield) or Bharat-Biotech (Covaxin) vaccines in pregnant women. The mRNA vaccines have been proven to be immunogenic in pregnant women. The reactogenicity and the adverse effect profile do not seem to be any different from non-pregnant women. The CDC v-safe COVID-19 Pregnancy Registry found comparable adverse effects and efficacy profile of the two mRNA vaccines administered to the pregnant women. The two mRNA vaccines – Pfizer-BioNtech and Moderna – appear to have similar reactogenicity and immunogenicity in pregnant women.

Among the choice of vaccines, the mRNA vaccines (vaccines on which surveillance data in pregnant women is available) are not currently available in India. Some of the European countries do not vaccinate population with age less than 55-60 years with Oxford-AstraZeneca vaccine and hence do not recommend its use in pregnant women by extension. In view of the rare risk of Thrombosis with Thrombocytopenia Syndrome (TTS) or vaccine induced thrombotic thrombocytopenia (VITT) with the Oxford AstraZeneca vaccine(5), the Joint Committee on Vaccination and Immunization (JCVI) and the Medicines and Healthcare Products Regulatory Authority (MHRA) in the UK have advised that all people under 40 years of age should not be offered the Oxford AstraZeneca vaccine, and this includes pregnant and lactating women. This rare, but serious and potentially life-threatening, adverse event has also been observed with the Janssen's COVID-19 vaccine. The administration of the Janssen's vaccine was briefly paused for the same reason in the United States but resumed with effect from 23 April 2021. It was stated that women younger than 50 years of age should be aware of the rare risk of blood clot with low platelets post vaccination, and that other COVID-19 vaccines are available wherein this risk has not been observed. Following the reports of TTS after viral vector vaccine in the

developed countries, an in-depth review was conducted by the National AEFI (Adverse Event Following Immunization) Committee in India. The committee found 26 cases of thromboembolic events following the administration of Covishield vaccine as on 3 April 2021, with a reporting rate of 0.61 cases/ million doses which is much lower than the rate of 4 cases/million reported by UK's regulator MHRA, and 10 cases/million reported from Germany. No thromboembolic events were reported following administration of Covaxin. mRNA vaccines, including the recently approved Sputnik V in India, have not reported any cases of TTS. The risk of thromboembolic events in general population is almost 70 per cent less in persons of South and Southeast Asian descent as compared to European descent. The Ministry of Health and Family Welfare (MoHFW) concluded by stating that Covishield continues to have a definite positive risk benefit profile, with tremendous potential to prevent infections and reduce deaths due to COVID-19. Separate advisories are issued to healthcare workers and vaccine beneficiaries to be aware of symptoms suggestive of thromboembolic events occurring within 20 days of administration of COVID-19 vaccines, particularly, Covishield and report preferably to the health facility where vaccine was administered. The major international bodies recommend that providers should discuss the individual risks and benefits of the vaccine during pregnancy. They also recommend routine 'Adverse Effect Following Immunization' (AEFI) surveillance after COVID-19 vaccination in pregnant and lactating women and to publish and disseminate such information.

VALUES AND PREFERENCES

A recent online survey to assess the COVID-19 vaccine acceptance level and potential predictors of acceptance among pregnant women and mothers of young children for themselves and for their children had 17871 respondents from 16 countries, including India (n= 1639).(77) For those who were pregnant (n=5294), the mean gestational age was 20.0 weeks (SD = 9.4). Among pregnant women, 52.0% (n = 2747) intended to receive COVID-19 vaccination during their pregnancy, if an efficacy of 90% were achieved. Vaccine acceptance rate among pregnant women varied substantially by country (range: 28.8–84.4%). COVID-19 vaccine acceptance level was above 80% for pregnant women in Mexico and India. No evidence is available about the preference of healthcare providers, or policymakers about vaccination of pregnant and lactating women in India. The top three reasons for pregnant women to decline COVID-19 vaccination during pregnancy even if the vaccines were safe and free were that they:

1. Did not want to expose their developing baby to any possible harmful side effects (65.9%)
2. Were concerned that approval of the vaccine would be rushed for political reasons (44.9%), &
3. Would like to see more safety and effectiveness data among pregnant women (48.8%)

The higher acceptance among the low- and middle-income countries like India suggests the role played by the historical burdens of other infectious diseases on both the higher perception of risk from COVID-19 and the more positive vaccine attitude. More data has accumulated after this survey was done regarding the higher incidence of morbidity from COVID-19 in pregnancy and safety of the vaccines. It is likely that the acceptance level might have increased now.

RESOURCES REQUIRED

Adequate supply of vaccine and cold chain facility, information leaflets and Adverse Effects Following Immunization (AEFI) Proforma. These pre-requisites are not specific to pregnant women and would require only existing platforms and on-going surveillance.

RECOMMENDATION 7 : COVID-19 vaccination in pregnant and lactating women

1. **Vaccination against COVID-19 should be offered to all pregnant and lactating women, irrespective of the presence of co-morbidities.**

   Strong recommendation, based on consensus among experts and the evidence for lack of any adverse effects in pregnant women vaccinated with mRNA vaccines.

2. **Pregnant and lactating women are to be immunized with any of the vaccines currently available in the country.**

   Conditional recommendation, based on consensus among experts in the absence of evidence for any beneficial effect or harm with the use of any one of the options available in the country.

   Pregnant and lactating women can opt for mRNA vaccines, if and when they are made available, until adequate data on the safety of the currently available (in India) vaccines in this population are generated.

3. **Vaccines can be offered at any gestational age in pregnancy, but the second dose should preferably be completed before the third trimester.**

   Conditional recommendation, based on consensus among experts in the absence of evidence for any beneficial effect and possible side-effects of COVID vaccines at different gestational ages.

   As data on safety of COVID vaccines is still sparse, pregnant women may choose not to take the vaccine in first trimester. Also, as the risk of severe disease is higher in third trimester (after 28 weeks), women should be provided with the option of getting completely vaccinated before 28 weeks.

Practice question 8: WHAT SHOULD BE SPECIFIC PRACTICES DURING NEONATAL RESUSCITATION FOR DELIVERY OF WOMEN WITH SUSPECTED OR CONFIRMED SARS-COV-2 INFECTION?

PICO QUESTIONS

1. For neonates born to women with suspected or confirmed COVID-19, is early cord clamping (ECC) in comparison to delayed cord clamping (DCC) associated with lower incidence of SARS-CoV-2 infection in the neonates?
2. For neonates born to women with suspected or confirmed COVID-19, is skin-so-skin contact immediately after birth in comparison to no skin-so-skin contact associated with higher incidence of SARS-CoV-2 infection in the neonates?
3. For attending resuscitation of neonates born to women with suspected or confirmed COVID-19, do additional steps versus routinely recommended universal precautions to help prevent transmission of SARS-CoV-2 infection to neonates or healthcare providers?

In general, around 10% of neonates are anticipated to require resuscitation including oronasal suction or positive pressure ventilation and a few may require intubation. Neonates born to women with COVID-19 are more likely to be preterm and need resuscitation more frequently.

Neonatal resuscitation should follow the standard Neonatal Resuscitation Protocol (NRP) algorithm.

DELAYED CORD CLAMPING

There is insufficient evidence regarding whether DCC increases the risk of infection. A prospective observational study of 403 pregnant women with COVID-19 compared ECC and DCC in 70 centres in Spain.(78) Of 231 infants in the ECC group two (1.7%) and of 172 infants in the DCC group three (3.6%) tested positive for SARS-CoV-2 by nasopharyngeal PCR test performed within 12 hours of birth.

The recommendations about practicing DCC have varied with different professional organizations and with time.(3,36,79,80) Most common recommendation is to continue practicing DCC unless contraindicated due to specific reasons (other than SARS-CoV-2 infection in mother). On the other hand, a few countries like Russia, Iran and Spain have suggested ECC in COVID-19 mothers and symptomatic COVID suspect mothers but not in asymptomatic and mothers with unknown status. The Chinese recommendation is to do prompt cord clamping in all situations. The World Health Organization recommends continuing DCC as practiced in routine neonatal resuscitation program (NRP).(81)

Due to absence of any evidence indicating increased transmission of infection due to DCC and well-established benefits of DCC, this guidelines group recommends DCC as per neonatal resuscitation guidelines even if mother is SARS-CoV-2 positive, and irrespective her being symptomatic.

SKIN-TO-SKIN CONTACT

Similar to DCC, in absence of evidence to support or refute the practice, existing guidelines vary about the use of skin-to-skin contact (SSC) as part of the routine care at birth in COVID-19 mothers.(3,36,79,80) Countries like UK, Canada, Austria, Australia, Netherlands, Spain Germany and France have promoted SSC in all COVID pregnancies including symptomatic, asymptomatic, suspect and at risk deliveries. Other countries like Belgium and Italy advise against SSC in COVID confirmed women but not in suspect or at-risk women. Countries like Brazil, Israel, Spain, and Russia advise against practicing SSC in all COVID confirmed as well as suspect and at-risk women.

The practice of SSC at birth has several proven benefits for neonates including better temperature control, smoother transition at birth and better breastfeeding outcomes.(82) As stable neonates are also advised rooming-in and

breastfeeding with their SARS-CoV-2 positive mothers, there is no rationale in avoiding a beneficial practice like SSC at birth.

This guidelines group recommends to continue practicing SSC immediately after birth as part of the 'routine care'. During SSC, mother should follow the recommended infection prevention and control measures (hand hygiene, respiratory etiquette and triple-layered mask).

INFECTION PREVENTION DURING RESUSCITATION

In the absence of any clinical trials comparing various approaches to prevent infection during resuscitation, following guidelines are based on viral transmission studies, expert opinion and general infection prevention guidelines by professional organizations:

1. **PPE:** The resuscitation team should wear an N95 mask, face shield or goggles, and full PPE for attending delivery of women with suspected or confirmed SARS-CoV-2 infection.

2. **Resuscitation equipment:** A new set of disposables and disinfected reusables should be used for each delivery. Disposables like endotracheal tubes, suction catheter, orogastric tube, tapes for fixing ET tube, umbilical catheter, syringes placed near the resuscitation area should be discarded even if unused. Reusable equipment should be thoroughly disinfected as per hospital protocol. Wear protective clothing when dealing with contaminated equipment.

3. **Airway:** Perform oral or nasal suction only if indicated to clear the airway.

4. **Respiratory support:** If positive pressure ventilation is needed, self-inflating bag and mask or a T-piece resuscitator with disposable tubing may be used. If a T-Piece resuscitator is used, a disposable circuit should be used. Indications for intubation are as per standard NRP. The use of aerosol boxes during intubation is not recommended in neonates (see details in Practice question 13). The use of filters attached to T-Piece/bag mask devices is not recommended during neonatal resuscitation (see details in Practice question 13)

5. The neonatal resuscitation team should doff the PPE after exiting the delivery area, discard the component in appropriate bins as per disposal policy and perform hand hygiene. Transfer of the neonate to the designated area can be performed by another healthcare worker wearing appropriate PPE. However, if there is a shortage of personnel, the resuscitation team member can doff partially and wear a fresh outer gown and gloves to transport the neonate. If the neonate is on respiratory support, transport personnel should wear an N95 mask.

RECOMMENDATION 8 : Neonatal resuscitation

1. Minimum number of personnel should attend resuscitation (one person in low-risk cases and two in high-risk cases where extensive resuscitation may be anticipated) and wear a full set of personal protective equipment including N95 mask and face-shield/goggle.
2. Mother should perform hand hygiene and wear triple layer mask.
3. Neonatal resuscitation should follow standard guidelines. If positive pressure ventilation is needed, self-inflating bag and mask or a T-piece resuscitator with disposable circuit may be used.
4. Indications for intubation shall not change because of maternal COVID-19 status.
5. Delayed cord clamping and early skin to skin contact should be practiced.
6. Perform oral or nasal suction only if indicated to clear the airway.
7. Endotracheal administration of medications should be avoided.
8. Bathing is not recommended in view of risk of hypothermia and hospital-acquired infections.

Practice question 9: IS IT NECESSARY TO SEPARATE THE MOTHER AND BABY IF THE MOTHER HAS SUSPECTED OR CONFIRMED SARS-COV-2 INFECTION?

PICO QUESTIONS

1. Among neonates born to mothers with suspected or confirmed COVID-19, should routine postnatal care be provided in isolation or by rooming-in with the mother?

2. If isolation from the mother is advised, should the routine postnatal care be provided in a hospital care area or at home with an unexposed healthy family member?

SUMMARY OF EVIDENCE

We found 63 publications evaluating the effect of rooming-in of a neonate born to a COVID-19 positive mother. No clinical trials have compared isolation versus rooming-in of neonates with mothers. A systematic review evaluated neonatal SARS-CoV-2 infections included 74 studies (37 case series, 34 case reports, two retrospective cohort studies, and one cross-sectional study).(83) A total of 176 neonates with COVID-19 were reported cumulatively in these 74 studies. The most common mode of transmission was assigned to be postpartum infection (70.5%). Lack of isolation was found to be significantly associated with late-onset (>72 h after birth) SARS-CoV-2 infection (adjusted OR 6.6, 95% CI: 2.6–16). Evidence from this systematic review was assigned to be of very-low quality (downgraded due to high risk of bias and imprecision).

Data from the NNF Perinatal COVID registry suggests that rooming-in is associated with an increased risk of neonatal SARS-CoV-2 infection (Mantel-Haenszel adjusted RR: 2.65, 95% CI: 1.47 to 4.77, Table 3).(16) However, breastfeeding reduced the risk of neonatal infection. Prabhu et al reported a cohort of 70 pregnant women with COVID-19. (84) If the neonate and mother were stable, they were kept together. Mother wore a mask at all times, followed hand hygiene, and respiratory etiquette, and kept the neonate in an isolette at a distance of 1.8 m when not breastfeeding. None of the neonates tested SAR-CoV-2 positive by RT-PCR performed within 24 h of birth. This study indicates that the postnatal transmission from mother to baby can be reduced by following the infection control practices recommended in the study.

Table 3: Risk of SARS-CoV-2 infection in neonates based on care practice (NNF COVID-19 Registry)(16)

	Mother baby dyad Roomed-in (n=893)	Mother and baby isolated (n=393)	Relative risk (95% Ci)
SARS-CoV-2 positive neonates	111 (12.4%)	29 (7.4%)	Unadjusted: 1.68 (1.14 to 2.49) Adjusted for breastfeeding: 2.65 (1.47 to 4.77)

We also searched for various professional guidelines about rooming-in of neonates with mothers. Almost all professional guidelines have recommended rooming-in except the Chinese guidelines, which recommend avoiding both rooming-in and breastfeeding.(85) These recommendations in favour of rooming-in are guided by three important issues. First, rooming-in is one of the most important interventions to promote the successful establishment of breastfeeding at birth and exclusive breastfeeding at 6 months of age. Second, breastfeeding is the most effective intervention to reduce neonatal mortality. Third, even if rooming-in increases the incidence of neonatal COVID-19, the infection is mostly asymptomatic or mild with excellent outcome.

VALUES AND PREFERENCES

No evidence is available about the preference of mothers, families, healthcare providers, or policymakers about the separation of mother and baby in case of COVID-19 infection. There is expected to be variation in the preferences as the disease is milder in neonates and children. The variation is also evident in the guidelines of different countries with recommendations varying from complete isolation to continuing rooming-in, skin-to-skin contact, and breastfeeding.

RESOURCES REQUIRED

Significant additional resources including healthcare workers and designated area in the hospital are required if baby and mother are to be kept separate. Although these resources will not be needed if mother and baby are roomed-in, mothers especially those who have delivered by cesarean section, need help and assistance in caring for their babies for initial few days. Education and training of mothers to use appropriate mask, follow hand hygiene and respiratory etiquette while caring for their babies is also required. See practice question 10 for detailed discussion of resources required especially when considered in the context of breastfeeding.

RECOMMENDATION 9: Rooming-in of neonates

- Healthy neonates should be roomed-in with their mothers. The mother-baby dyad must be isolated from uninfected mothers and neonates.
- When roomed-in, exclusive breastfeeding must be promoted. Formula feeding and mixed feeding must be avoided.
- Direct breastfeeding should be given. Mother should wash hands frequently including before breastfeeding and wear an appropriate mask. If direct breastfeeding is not feasible due to neonatal or maternal condition, expressed breastmilk may be fed.

Practice question 10: WHAT SHOULD BE THE FEEDING POLICY FOR STABLE NEONATES BORN TO MOTHERS WITH SUSPECTED OR CONFIRMED SARS-COV-2 INFECTION?

PICO QUESTION

For well neonates exposed to SARS-CoV-2 infection from mothers/other relatives/healthcare providers and requiring routine essential newborn care, does feeding expressed breastmilk, donor milk, or formula milk reduces the risk of transmission as well as the incidence of critical outcomes such as neonatal mortality when compared to direct breastfeeding?

SUMMARY OF EVIDENCE

Literature was searched for articles on the transmission of COVID-19/SARS-CoV-2 infection through breastmilk. Following three issues pertain to the use of breastmilk of women with COVID-19 infection:

1. Is virus secreted in the breastmilk and can it transmit infection to the feeding infant?
2. Are antibodies against the virus secreted in breastmilk and do they protect the infant against infection?
3. How these two opposing factors interact and impact the infection and severity of illness in the neonates?

A systematic review by Kumar et al included studies reporting the results of RT-PCR testing for SARS-CoV-2 in breastmilk of mothers with confirmed COVID-19.(17) This review (literature search updated till October 15, 2020) identified 34 eligible studies of which 24 were case reports and 10 were case series or cohort studies. In the 10 studies included in the quantitative synthesis, breastmilk RT-PCR was available for one-third (88/261) of included mothers. Pooled incidence of virus RNA detection was 2.2% (95% CI: 0.0 to 8.8%). Among ten women whose breastmilk tested positive, in eight neonates nasopharyngeal RT-PCR testing was done and five (63%) neonates tested positive. Neonates born to all the ten women had good outcome. Another systematic review by Centeno-Tablante et al included studies which reported transmission of SARS-CoV-2 through breastfeeding in children up to 2 years of age.(86) Primary outcome was SARS-CoV-2 infection within 30 days of receiving breastfeeding or expressed breastmilk from COVID-19 positive mother. This review included 340 studies of which 37 reported analysis of breastmilk samples and 303 reported infections in the eligible subjects but without breastmilk sample testing. Of 68 women in which the breastmilk was tested by RT-PCR, viral RNA was observed in 9 (13.2%) samples. In few women in which repeated testing of breastmilk was done, the presence of viral RNA was transient. The overall evidence generated by these two systematic reviews is of very low certainty due to high risk of bias in the included studies (observational study designs, unadjusted for confounding factors, and no control group in most studies), imprecision, inconsistency, and publication bias. Krogstad et al reported a cohort study of 110 women with SARS-CoV-2 infection.(87) The viral RNA was detected in breastmilk of 9.2% (6/65) women. However, in none of the tested samples, infectious virus or markers of viral replication were found.

In a systematic review, Zhu et al evaluated presence of SARS-CoV-2 genome and antibodies in breastmilk.(88) Among 50 studies included in the review, information about anti-SARS-CoV-2 antibodies was available from 10 studies. A high proportion of breastmilk samples (61/89, 83%, 95% CI: 32% to 98%) were positive for anti-SARS-CoV-2 antibodies. IgA was the predominant antibody type. Among women in which breastmilk antibodies were found, only 3 (5%) neonates tested positive. The duration between onset of maternal symptoms and detection of antibodies varied from 3 to 79 days. The overall evidence generated by this systematic review is also rated to be of very low certainty due to high risk of bias in the included studies (observational study designs, unadjusted for confounding factors, and no control group), imprecision, and publication bias.

The NNF COVID registry reported outcome of 1330 intramural neonates born to mothers with COVID-19.(89) Of these, information about use of breastmilk was available in 1281 neonates (Table 4). No association was observed between breastmilk feeding and RT-PCR status of neonates (RR: 0.98, 95% CI: 0.63 to 1.54). After adjusting for

rooming-in status, use of breastmilk was associated with a reduced incidence of COVID-19 infection in neonates (Mantel-Haenszel adjusted RR: 0.45, 95% CI: 0.23 to 0.87).

Table 4: Risk of SARS-CoV-2 infection among neonates based on the mode of feeding (NNF COVID-19 Registry)

	Breastfed (n=1099)	Not breastfed (n=182)	Relative risk (95% Ci)
SARS-CoV-2 positive neonates	119 (10.8%)	20 (11.0%)	Unadjusted: 0.98 (0.63 to 1.54) Adjusted for rooming-in: 0.45 (0.23 to 0.87)

We also searched the literature for existing guidelines on postnatal care, including breastfeeding in neonates born to mothers with suspected/confirmed COVID-19. All guidelines advise continued breastfeeding with most also recommending skin-to-skin contact and rooming-in.

Overall, very low-quality evidence suggests that SARS-CoV-2 viral RNA is present in 2.2 to 13.2% breastmilk samples. However, the presence of viral RNA is transient and does not equate with infectious form of the virus. Very low-quality evidence also suggests that women with COVID-19 start secreting antiviral antibodies in the breastmilk during or shortly after the acute infection. These antibodies are of IgA type which may have protective effect on the neonate. Moderate-quality evidence from NNF registry suggests that use of breastmilk may protect against infection with SARS-CoV-2. Based on the limited evidence available, the COVID-19 is unlikely to be severe in the neonates.

Milk donation: Based on the available data on other coronaviruses, it is likely that the process of pasteurization can destroy SARS CoV-2 is present in breastmilk. However, the European and the Human Milk Banking Association of North America, recommend that mothers with active COVID-19 infection should not donate milk.

VALUES AND PREFERENCES

No evidence is available on the preferences of mothers, families, and healthcare providers regarding the mode of feeding in asymptomatic exposed neonates in the postnatal period. The preferences and values are likely to be varied given that (a) the SARS-CoV-2 virus has been detected in a small proportion of breastmilk samples, (b) the COVID-19 disease is unlikely to be severe in neonates and children, and (c) the potential benefits of direct breastfeeding in reducing the neonatal and infant mortality, particularly in low- and middle-income country settings. Given the benefit-harm ratio, professional organizations, including the World Health Organization and the Government of India, recommend continued rooming-in, skin-to-skin contact, and breastfeeding among neonates born to COVID-19 positive mothers.

RESOURCES REQUIRED

Significant resources are required if neonates are to be separated from their mothers with suspected or confirmed infection. Separate air isolated neonatal care areas for stable COVID suspected and confirmed neonates will need to be maintained with all equipment, disposable supplies, medicines, and trained healthcare providers in each area for providing essential neonatal care. Besides, arrangements need to be made for either the safe expression of breastmilk or safe formula milk preparation and administration. It will entail a significant burden on the available resources.

Rooming-in will also require resources preferably single rooms with enough space for keeping the mother-baby dyad or in a ward with recommended physical separation between two beds. Services of nurses trained in essential newborn care and lactation support and laboratory support for jaundice management will need to be organized in the dedicated COVID health centers and hospitals. A healthy family member, if available, can be trained to provide support to mother and baby under the supervision of nurses. Round-the-clock coverage by pediatricians will also need to be arranged.

If expressed breast milk is used because of prematurity or sickness in baby or mother, nursing support will be required to help and support milk expression. Resources will be required for safe collection and transport several times a day, without contamination.

RECOMMENDATION 10 : Breastfeeding

1. **Stable neonates exposed to mothers or other persons with SARS-CoV-2 infection should be roomed-in with their mothers and be exclusively breastfed.** For supporting lactation, nurses trained in essential newborn care and lactation management should be provided. A healthy willing family member who is not positive for SARS-CoV-2, is not in direct contact with persons with suspected or confirmed infection and is asymptomatic may be allowed to stay with the mother-baby dyad to assist and provide support for breastfeeding.

2. **If rooming-in is not possible because of sickness in the neonate or the mother, the neonate should be fed expressed breastmilk** (EBM) of the mother by a nurse or a trained healthy family member as described above.

   Strong recommendation based on consensus among experts in the absence of evidence for any beneficial effect or harm in the risk of COVID-19 following direct breastfeeding or expressed breastmilk feeding.

Conditions to be met for safe breastfeeding

- Mothers should perform hand hygiene frequently, including before breastfeeding and touching the baby.
- Mothers should practice respiratory hygiene and wear a triple-layered mask while breastfeeding and providing care to the baby; they should routinely clean and disinfect the surfaces.
- Mothers can express milk after washing hands and wearing a mask. If possible, a dedicated breast pump should be provided. If not, it should be decontaminated as per protocol. This expressed milk can be fed to the baby without pasteurization. The collection and transport of EBM should be done very carefully to avoid contamination.

3. **Mothers are not eligible to donate milk in any of the following COVID-19 related situations in addition to standard criteria**
   - SARS-CoV-2 positive till she is declared free of infection.
   - History of having stayed or transited in a containment zone during the previous 14 days.
   - History of close contact with a confirmed or suspected case of COVID-19 in previous 14 days.
   - Suffering from symptoms like cough, fever, sore throat, running nose till found to be SARS-CoV-2 negative on nasopharyngeal sample RT-PCR.
   - Worked in or attended a healthcare facility with a case of confirmed SARS-CoV-2 infection.

Practice question 11: SHOULD KANGAROO MOTHER CARE BE PRACTICED IN NEONATES BORN TO MOTHERS WITH SUSPECTED OR CONFIRMED SARS-COV-2 INFECTION?

PICO QUESTION

Among stable low birth weight neonates born to mothers with suspected or confirmed COVID-19 (P), is no Kangaroo Mother Care (I) better than Kangaroo Mother Care (C) for reducing the risk of transmission of SARS-CoV-2 infection (O)?

SUMMARY OF EVIDENCE

There are concerns of horizontal transmission of SARS-CoV-2 infection from mother to neonate, though the risk is very low. In our literature search, we could not find any trials comparing no KMC versus KMC in stable LBW infants born to COVID mothers who are otherwise eligible for KMC. However, KMC is an evidence-based intervention with a significant beneficial reduction in neonatal mortality, nosocomial infections and hypothermia (moderate-quality evidence).(90) A recent large randomized controlled trial from low- and middle-income countries has shown that immediate KMC in stable infants with a birth weight between 1000 to 1799 g reduces the neonatal mortality.(91) The risk of horizontal transmission of SARS-CoV-2 infection from mother to neonates is low with appropriate precautions, and even if it happens, a majority of neonates either remain asymptomatic or have mild illness. A recent modelling estimate has shown that the survival benefit of KMC is 65-fold higher than the mortality risk of COVID-19 if the mother to baby transmission were to be 100%. Assuming a more realistic estimate of 10% transmission, the benefit ratio of KMC would be 630 fold.(92) Therefore, it is strongly recommended to practice KMC in stable LBW neonates born to COVID mothers who are otherwise eligible for KMC.

RECOMMENDATION 11: Kangaroo Mother Care

1. Kangaroo Mother Care should be provided to stable low-birth-weight neonates who are otherwise eligible, irrespective of mothers' COVID status. KMC can be initiated as early as the mother's medical condition allows and continued as indicated in usual circumstances.
2. If mother is not able to provide KMC due to her medical condition, the father of the neonate or another healthy family member who is not symptomatic and is tested to be SARS-CoV-2 negative can provide skin-to-skin contact. Frequent change of such persons providing KMC should be avoided.
3. Persons providing KMC should follow respiratory etiquettes, wash hands frequently including before and after KMC and wear a triple-layered mask.

Practice question 12: SHOULD SYMPTOMATIC NEONATES WITH SUSPECTED SARS-COV-2 INFECTION AND NEEDING INTENSIVE OR SPECIAL CARE BE NURSED IN COMMON ROOM NICU/SNCU OR ISOLATION FACILITY?

PICO QUESTION

Should symptomatic neonates with suspected SARS-CoV-2 infection (due to perinatal/postnatal exposure/from an area with high test positivity rate) needing intensive or special care be nursed in common room NICU/SNCU or isolation facility?

SUMMARY OF EVIDENCE

A symptomatic neonate may be suspected to have SARS-CoV-2 infection in the following three scenarios:

1. Born to mother with suspected or confirmed SARS-CoV-2 infection
2. Postnatal exposure to another person with SARS-CoV-2 infection
3. Presents to hospital from an area or in a time-period with high test positivity rate (during a 'wave' of the pandemic)

No randomized trials have been conducted to compare nursing in shared room NICU/SNCU versus in Isolation facility for symptomatic neonates. A review of the evidence shows that neonatal infections are overwhelmingly horizontal, with very few confirmed cases of vertical transmission. There are limited studies on the source of infection in the neonate, and they are difficult to ascertain. Very scanty information about transmission from neonate to caregivers or other neonates is available in the published literature. Cases from of neonatal nosocomial SARS-CoV-2 transmission attributable to healthcare workers have been documented in Spain and Romania.(93–96) Similar findings were reported by an Indian study that described a cohort of 21 SARS-CoV-2 positive neonates.(97) A report of horizontal transmission of SARS-CoV-2 from asymptomatic children with confirmed infection to other children and adults in care facilities further supports the possibility of horizontal transmission.(98) Therefore, like for other age groups, there is a need for an isolation facility to prevent potential transmission of infection from symptomatic neonates with suspected COVID-19 to other neonates and care providers.

RECOMMENDATION 12 : Care area for neonates

1. Symptomatic neonates with suspected SARS-CoV-2 infection should be isolated from other healthy mothers and neonates and cared for according to recommended infection prevention and control practices.
2. The care area for suspected cases should be separate from that of confirmed cases.
3. If a suspected case is confirmed by RT-PCR or RAT, the neonate should be moved to the designated care area for COVID-19 confirmed neonates and children.
4. If SARS-CoV-2 infected neonates continue to need hospital care, two consecutive negative RT-PCR reports should be documented before transfer to normal SNCU/NICU.
5. Symptomatic neonates with suspected SARS-CoV-2 infection who test negative should undergo repeat testing after 24-48 h, as per testing protocol (see Practice Question 14) before being shifted to normal SNCU/NICU.

Practice question 13: WHAT SPECIAL PRECAUTIONS SHOULD BE TAKEN WHILE PROVIDING RESPIRATORY SUPPORT TO NEONATES WITH SUSPECTED OR CONFIRMED SARS-COV-2 INFECTION?

SUMMARY OF EVIDENCE

There is limited evidence to support one mode of respiratory support over another for severe COVID-19 disease in children. During the early stages of the pandemic, adult guidelines favoured an early intubation strategy due to fear of the aerosol spread of the virus during non-invasive ventilation. With the emergence of more safety data with non-invasive ventilation, adult guidelines advocate a more conservative approach and awake-proning when appropriate.(99,100) Guidelines for the respiratory management of COVID-19 in children are provided by many organizations, including the European Society of Pediatric and Neonatal Intensive Care (ESPNIC)(101), the Intensive care chapter of the Indian Academy of Pediatrics(102), and an international collaboration of pediatric intensivists.(103) The International collaborative guidelines classified each recommendation as Strong, Weak, Best practice, or Insufficient evidence based on available evidence and consensus among experts. The authors acknowledge that an Evidence to Decision framework (EtD) could not be followed due to the paucity of relevant evidence in pediatric patients. This guideline extrapolated the available recommendations in children to the neonatal age group due to limited evidence.(104)

RISK OF AEROSOLIZATION FROM RESPIRATORY EQUIPMENT

All forms of respiratory support (HFNC, CPAP, BiPAP, bag-valve-mask ventilation) are at risk of generating aerosols and healthcare providers must ensure that airborne precautions and proper PPE are used.(105) Procedures including intubation, extubation, bronchoscopy, open tracheal suctioning, and chest compression may also generate aerosols and appropriate PPE should be used. In older children and adults, a surgical mask placed over HFNC could be an effective strategy to mitigate droplet dispersion in COVID-19.(106) However, comparative data are lacking in young infants generally managed on lower flow rates of HFNC and lower CPAP pressures, which could influence both aerosol generation and dispersion. One exploratory study in neonates without COVID-19 noted that neonates on respiratory support generated minimal aerosols.(107)

USE OF PLEXIGLASS OR AEROSOL BOXES

During intubation, the use of a plexiglass box or aerosol boxes were noted to minimize aerosol spread in benchtop experiments. However, the box may restrict hand movement and requires training before use. Operators may be required to abandon the use of the box should airway management prove difficult. In a systematic review Sorbello et al analyzed 52 papers reporting the use of aerosol boxes.(108) The majority were expert opinions, small case series, technical descriptions and small-sample simulation studies. The use of these barrier devices added to the complexity of airway procedures especially during airway emergencies. Concerns include restrictions imposed by the barrier on the operator, or the ability of an assistant to help, patient injuries, compromise of PPE integrity, lack of evidence for added protection of healthcare providers (including secondary aerosolization upon barrier removal), and lack of cleaning standards. The use of enclosure barriers may give a false sense of security in the use of adequate PPE. The guideline group recommends that that the use of plexiglass or aerosol boxes should be avoided until adequate validation studies are reported.

USE BACTERIAL/VIRAL FILTER (HEPA; HIGH-EFFICIENCY PARTICULATE AIR)

Filters in the path of exhaled gas in mechanical ventilator or positive pressure ventilation device are recommended in adults to decrease aerosolization risk. This filter should ideally be replaced every 8-12 hours. Even the smallest filter occupies a dead space volume of 8-10 ml, higher than the tidal volume in most neonates. If used, the only suitable position to place this filter in neonate is in expiratory limb. This will not increase dead space but increases risk for prolonged Te, high PEEP, and circuit block. The expiratory limb must be heated and pressure should be measured at Y-

piece. Such filters should be used only with ventilators fulfilling these conditions. Use of viral filters on T-Piece or bag and mask device introduces resistance, dead space and can cause obstruction if contaminated with secretions.(109)

RECOMMENDATION 13 : Respiratory support for neonates

1. Mode of respiratory support

- In neonates with hypoxemia and minimal respiratory distress, supplemental oxygen therapy by low-flow nasal cannula (<2 L/min) can be used when SpO2 is <90% and targeted to achieve pre-ductal SpO2 of 90-95%.
- Neonates with respiratory distress [tachypnea (>60/min) and any of the following-cyanosis (SpO2 < 90%), chest retractions or grunting], should receive non-invasive ventilation such as high flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV) based on availability, familiarity and expertise as well as the underlying lung condition.
- Early mechanical ventilation may be offered in case of failure of the non-invasive mode.

2. Mechanical ventilation

- A lung-protective ventilation strategy is advised during mechanical ventilation, and ventilator settings should be individualized based on the lung condition.

3. Staff protection during respiratory support

- Personnel performing aerosol-generating medical procedures (AGMPs), including intubation and extubation, must wear full PPE with N95 masks and eye and face protection.
- Intubation should be done by a trained and skilled healthcare provider. For non-emergent intubations, pre-medication should be used to decrease the probability of aerosol generation. Cuffed endotracheal tubes may offer an advantage.
- Minimize endotracheal tube disconnections.
- In-line or closed suction devices should be preferred.
- The area providing respiratory support should preferably be a negative air pressure area.
- The use of filters attached to T-Piece/bag-mask devices is not recommended during neonatal resuscitation.
- The use of aerosol boxes during intubation is not recommended in neonates.

Practice question 14: WHAT SHOULD BE THE COVID TESTING PROTOCOL FOR NEONATES?

PICO QUESTIONS

1. Among neonates born to mothers with confirmed COVID-19 within 14 days before or 2 days after delivery, does universal testing after birth for SARS-CoV-2 infection compared to testing only symptomatic neonates affects neonatal outcomes (early neonatal infection diagnosed by positive RT-PCR in the first week of life and neonatal mortality)? ***(Scenario-1: Possible perinatal transmission).***

2. What should be the testing strategy for neonates exposed postnatally to persons with suspected or confirmed SARS-CoV-2 infection? ***(Scenario-2: High-risk contact)***

3. What should be the testing strategy for neonates presenting with symptoms suggestive of SARS-CoV-2 infection at or beyond 48 hours of age? ***(Scenario-3: Symptomatic neonate presenting to a health facility)***

SUMMARY OF EVIDENCE

We identified a living systematic review and meta-analysis by Allotey et al (1).(5) that included relevant studies published in bibliographic databases and pre-print servers between December 1, 2019, and October 6 2020. We also looked at the guidelines published by various organizations regarding neonatal COVID-19 management in the respective websites and at a review comparing different guidelines.(110) The salient findings from the existing literature are:

- On an average, 4% of neonates tested COVID-19 positive after birth (28/666 neonates; data from 49 studies that included information on the mode of delivery and infant infection status for 655 women and 666 neonates).(111) The risk of positive SARS-CoV-2 RT-PCR in neonates was comparable between vaginal and cesarean deliveries (2.7 % vs. 5.3%; OR 0.49 (95% 0.21 to 1.14).

- Pregnant women with COVID-19 are at 1.5 times (95% CI 1.14 to 1.91; 18 studies, 8549 women) higher risk of preterm births than those without COVID.(5) Also, 33% of neonates (95% CI 24% to 43%) require NICU admission – 5-fold greater odds of requiring NICU care than those born to COVID negative mothers. In such a scenario, testing neonates would serve two purposes: 1) explain the cause of symptoms in neonates, 2) end isolation measures in asymptomatic infants.

- Most guidelines suggest universal testing of all neonates born to mothers with COVID-19, regardless of the symptoms. Some countries (Australia, Argentina, Brazil, The Netherlands, Norway, the United Kingdom) recommend testing only the symptomatic infants.(5) The Centers for Disease Control (CDC) suggest that testing can be prioritized for neonates with symptoms and those requiring intensive care or prolonged hospitalization in resource-limited settings.

- RT-PCR test using nasopharyngeal swab is the test suggested by all the guidelines.

- The optimal timing of testing is unclear and variable.

The online survey by NNF between July to August 2020 also showed wide variability in the testing strategies for neonates.(112) All hospitals (n=45) that participated in the survey reported testing neonates born to mothers with COVID-19 once or at multiple time points; 9 (20%) tested neonates at birth, 18 (40%) by 24 hours, 16 (36%) by 48 hours, and 49% between days 5-7. While 44% did not repeat testing, others repeated it after varying periods irrespective of the initial results. Most hospitals (97%) used RT-PCR tests on oro-nasopharyngeal swabs. About a quarter (11; 25%) of the hospitals tested all neonates presenting to a health facility with symptoms, while others selectively tested them based on specific criteria like a history of contact or symptomatology.

To inform decision-making, the Guideline Development Group looked at studies from LMIC countries, especially India reporting on the neonatal outcomes of mothers with COVID-19 and the testing strategies reported in the studies. The salient findings are:

1. RT-PCR was the method used to diagnose COVID-19 in mother and neonate in all the studies
2. The first testing was done closer to 24 hours of age in the majority (although with some variation among studies)
3. RT-PCR test was not repeated after the initial test in all single-center studies. In the report by Nayak et al.(41) the test was repeated on day 7 of life among neonates admitted to COVID NICU with an initial negative RT-PCR. This facilitated transfer of these neonates to a non-COVID hospital.
4. The incidence of COVID-positive cases varied from 0% to a max of 16%.

We also looked at recently published cohort or registry data from HICs on the risk of SARS-CoV-2 infection among neonates born to COVID-19 mothers. Similar to data from LMICs, RT-PCR of the nasopharyngeal swab was the test reported by all. The timing of the test was variable or not reported. However, repeat testing was variable, with one-third to a half undergoing repeat testing.(113–115) The rate of SARS-CoV-2 positivity among neonates was similar, varying from 0% to a max of 9.5%.

With the recent surge in COVID-19 cases, the Indian Council of Medical Research (ICMR) (28) has updated the testing guidelines to optimize the RT-PCR testing facilities. The recent guidelines suggest the following:

- RT-PCR test must not be repeated in any individual who has tested positive once either by RAT or RT-PCR.
- No testing is required for COVID-19 recovered individuals at the time of hospital discharge

RECOMMENDATION 14 : COVID-19 testing in neonates

- RT-PCR for SARS-CoV-2 is the test of choice. However, if RT-PCR is not available, point of care (POC) tests can be used for triaging and rapid diagnosis. POC tests include TruNat/CBNAAT or Rapid antigen test (RAT).
- These tests should be done on combined naso-oropharyngeal swab. Tracheal samples can be used for testing if the neonate is intubated.
- When the index of suspicion is high, a negative RAT needs to be confirmed with RT-PCR.
- Serologic testing (total, IgM or IgG antibody levels) is not recommended to diagnose acute infection in neonates.

- A positive result by RTPCR or TruNat/CBNAAT or RAT is confirmatory. Any individual who has tested positive by a POC test need not undergo RTPCR for confirmation.

Scenario	Recommendations	
	Timing of test	**Repeat testing**
Suspected perinatal transmission: (Mother with COVID-19 detected within 14 days before or within 2 days after delivery)	Between 24-48 hours of age. Rooming-in should not be postponed if testing is delayed. In case of early discharge, take a pre-discharge sample.	A repeat test is desirable at 5-7 days of age (or earlier if neonate becomes symptomatic). Repeat testing can help to prevent transmission from the neonate (who is likely to be asymptomatic even if infected) to other family members.
History of exposure to persons with COVID-19 (including mother or family member or healthcare provider)	Asymptomatic high-risk contacts to be tested once between day 5-10 of coming in contact	-
Symptomatic neonates (irrespective of history of exposure) with onset at or beyond 48 hours of life and presenting with **acute respiratory** (respiratory distress or apnea with or without cough, with or without fever) **or sepsis-like illness** (fever, lethargy, poor feeding, seizures or diarrhoea).	At the time of the first evaluation. Immediate RAT, if available, can help decide the transfer of the neonate to an appropriate area.	If the index of suspicion is high and initial test is negative, repeat in 24-48h. If the neonate requires ongoing hospital care because of prematurity and its complications, documentation of negative RT-PCR is desirable before shifting to a non-COVID area.

Practice question 15: WHAT SHOULD BE THE SPECIFIC MANAGEMENT FOR NEONATES WITH COVID-19?

PICO QUESTIONS

A. What investigations should be conducted in neonates with COVID-19?

B. What is the role of specific treatment in symptomatic neonates with suspected or confirmed infection with SARS-CoV-2?

   i. Among neonates with suspected or confirmed COVID-19 (P), what is the effect of treatment with one or more antiviral drugs (I) on critical outcomes such as in-hospital mortality and neonatal mortality rate (O), when compared to only supportive care (C)?

   ii. Among neonates with suspected or confirmed COVID-19 (P), what is the effect of treatment with chloroquine or hydroxychloroquine (I) on critical outcomes such as in-hospital mortality and neonatal mortality rate (O), when compared to only supportive care (C)?

   iii. Among neonates with suspected or confirmed COVID-19 infection (P), what is the effect of treatment with adjuvant therapies including, corticosteroids, intravenous gamma globulin, and interferon (I) on critical outcomes such as in-hospital mortality and neonatal mortality rate (O), when compared to only supportive care (C)?

A. WHAT INVESTIGATIONS SHOULD BE CONDUCTED IN NEONATES WITH COVID-19?

SUMMARY OF EVIDENCE

There is a lack of robust data on routine clinical laboratory tests that need to be performed in neonates and children with confirmed COVID-19.(116) A systematic review of COVID-19 in the pediatric population reported deranged blood counts, inflammatory markers, and coagulation abnormalities.(117) In this review, 66 pediatric studies reported increased C-Reactive Protein (CRP) (54%), serum-ferritin (47%), lactate dehydrogenase (LDH) (36%) and d-dimers (35%) as the most common abnormalities followed by elevated erythrocyte sedimentation rate (ESR), lymphopenia, procalcitonin. However, individual studies had inconsistently reported these parameters. Also, data on the correlation of the abnormal parameters with sickness and the information on the timing of the various tests in the disease course is lacking. Chest radiographic abnormalities were noted in 44% of 4670 children with COVID-19.(117) Of these, ground-glass opacities were most common (27%). Given the limited data on laboratory investigations, the Guideline Development Group recommends the following based on consensus.

RECOMMENDATION 15A

Investigations for COVID-19 in neonates

1. In neonates with suspected or confirmed but asymptomatic or mild COVID-19, no "routine" laboratory testing aside from RT-PCR for SARS-CoV-2 is recommended.

   Weak recommendation, based on consensus among experts

2. In neonates with symptomatic and moderate or severe COVID-19 illness, the relevant biochemical, hematologic, and coagulation tests may be performed to obtain information on the severity, progression, and complications of COVID-19 illness and/or to rule out co-existing illness like sepsis, asphyxia, or meconium aspiration syndrome.

   Weak recommendation, based on consensus among experts

Laboratory testing is essential in neonates presenting with signs and symptoms of MIS. (Refer to recommendations on MIS in practice question 19)

B. WHAT IS THE ROLE OF SPECIFIC TREATMENT IN SYMPTOMATIC NEONATES WITH SUSPECTED OR CONFIRMED INFECTION WITH SARS-COV-2?

SUMMARY OF EVIDENCE

We found a recent systematic review on the clinical features, management, and treatment of pediatric COVID-19 infection.(117) The review included 129 studies from 31 countries comprising 10,251 children. Of the 129 studies, 11 had reported neonatal COVID-19 cases. The salient findings of the review on neonatal management are provided in the supplementary material.

No clinical trials have compared the effect of different antivirals, other drugs like chloroquine or hydroxychloroquine, or adjuvant treatment including corticosteroids and intravenous gamma globulin in the neonatal and pediatric population. Guidelines from various organizations) do not recommend using antiviral or adjuvant drugs in neonates <3.5 kg due to lack of representation of this population in trials and concerns of safety and efficacy in this age group.

A randomized evaluation of COVID-19 therapy (RECOVERY trial) currently recruits neonates and infants with a post-menstrual age of ≤44 weeks with COVID-19 pneumonia.(118) The trial entry criteria are COVID-19 suspected or confirmed case with pneumonia AND any one of the following:

1. Significant increase in respiratory support to maintain oxygen saturation within accepted limits that is new or above a baby's baseline
2. Signs of sepsis with shock
3. Encephalopathy
4. Multiorgan failure

Intervention arm receives moderate dose of hydrocortisone (0.5 mg/kg every 12 hours for 7 days and 0.5mg/kg OD for 3 days). At present, no other drug is being tested as a part of a randomized trial in neonates. However, the use of remdesivir has been reported in 2 neonates, both of whom improved and tolerated the treatment well.(119,120)

The living guidelines for therapeutic interventions in COVID-19 by WHO include 16 trials with 2407 participants.(121) The network meta-analysis provided relative estimates of effect for important outcomes in patients randomized to receive systemic corticosteroids vs. standard care (8 trials enrolling 7184 critically ill or hospitalized patients). Trials varied in their choice of steroid-dexamethasone, hydrocortisone, methylprednisolone, and their dosage regimens (duration of therapy 5-14 days). Among patients with critical COVID-19 systemic steroids compared to standard care resulted in a reduction in mortality at 28 days after illness (RR 0.79; 95% CI, 0.7 to 0.9, moderate certainty) and need for mechanical ventilation at 28 days (RR 0.74; 95% CI, 0.59 to 0.93, moderate certainty). There was no difference in the incidence of gastrointestinal bleeding (RR 1.06; 95% CI, 0.85 to 1.33, low certainty) and super-infections (RR 1.01; 95% CI, 0.9 to 1.13, low certainty). However, a higher incidence of hypernatremia (RR 1.64; 95% CI, 1.32 to 2.03, moderate certainty) and hyperglycemia (RR 1.16; 95% CI, 1.08 to 1.25, moderate certainty) was noted. Similar results were found among patients with severe COVID-19 who received systemic steroids compared with standard care. There was no mortality benefit in the non-severe COVID-19 patients; instead, a potential increase of 3.9% in mortality was observed in this group of patients.

The Indian Academy of Pediatrics has recently published guidelines for the management of COVID-19 in children from 1 month to 19 years of age.(122) The illness severity for children with COVID-19 has been classified as mild, moderate, and severe (see Background section).

The IAP recommends administering intravenous dexamethasone to children (1 month to 19 years) with moderate (who have SpO2 ≤94%) and severe disease. The dose recommended is 0.15mg/kg once daily for 5-14 days.(122) On a note to compare, the RECOVERY trial's intervention is hydrocortisone 0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days (equivalent to a total of 0.3 mg/kg of dexamethasone)

Dose equivalence: A dose of 0.15 mg/kg dexamethasone is equivalent to 3.75 mg/kg hydrocortisone, 0.8 mg/kg methylprednisolone and 1mg/kg prednisolone.

RECOMMENDATION 15B

Treatment of COVID-19 in neonates

1. Specific anti-COVID-19 treatment -remdesivir, lopinavir/ritonavir, chloroquine/ hydroxychloroquine, ivermectin, or interferon- is not recommended in symptomatic neonates with confirmed or suspected COVID-19.

   Strong recommendation AGAINST, based on consensus among experts and the evidence for lack of any beneficial effects in adults with COVID-19.

2. Use of adjunctive therapy such as intravenous gamma globulin is not recommended in symptomatic neonates with confirmed or suspected COVID-19 (other than in the scenario of suspected MIS).

   Strong recommendation AGAINST, based on consensus among experts in the absence of evidence for any beneficial effect and possible side-effects with the use of immunoglobulin in this population.

3. Use of systemic corticosteroids may be considered in neonates with severe or critical COVID-19 requiring mechanical ventilation, in whom alternate causes such as sepsis have been ruled out.

   Conditional recommendation, based on consensus among experts in the absence of evidence for any beneficial effect or harm with the use of any of the options available in this population but beneficial effects in adults.

   Dose: Dexamethasone: 0.15mg/kg once daily for 5-14 days (as an alternate, 3.75 mg/kg hydrocortisone or 0.8 mg/kg methylprednisolone or 1 mg/kg prednisolone can be considered)

VALUES AND PREFERENCES

No evidence is available about the preferences of mothers, families, healthcare providers, or policymakers regarding the utility of specific treatment strategies for symptomatic COVID-19 in neonates.

RESOURCES REQUIRED

Management of neonates with COVID-19 needs significant resources including trained healthcare workers, monitoring equipment, respiratory support modalities, equipment for supportive care (e.g. radiant warmers and infusion pumps) and drugs. Allocation of additional resources and demarcation of dedicated areas in NICU/SNCU for care of COVID-19 neonates requires significant planning and ongoing evaluation.

Practice question 16: WHAT SHOULD BE THE DISCHARGE POLICY FOR NEONATES BORN TO MOTHERS WITH SUSPECTED OR CONFIRMED SARS-COV-2 INFECTION?

PICO QUESTION

Among stable neonates exposed to SARS-CoV-2 infection from mothers/other relatives/ healthcare providers and requiring routine newborn care (P), what is the efficacy and safety of early discharge (I) on the incidence of critical outcomes such as neonatal mortality (O) when compared to delayed discharge from the health facility (C)?

SUMMARY OF EVIDENCE

Of the 136825 articles on COVID-19, 12 had addressed the issue of discharge policy in neonates. None of these were clinical trials that examined the beneficial effects or safety of different discharge criteria among neonates exposed to SARS-CoV-2 infection or confirmed COVID-19. Hence, we examined all the cohort studies and the neonatal COVID registries to identify the discharge criteria and post-discharge outcomes, if reported, among neonates born to mothers with confirmed COVID-19. A total of 7 cohort studies (6 prospective and one retrospective study) reported the perinatal and neonatal outcomes in women with pregnancy and COVID-19 .(16,113,123–127) Discharge criteria for stable neonates born to mothers with confirmed COVID-19 varied among the studies depending on the testing strategy and local guidelines. The guidelines group also searched the literature for existing guidelines on discharge criteria for neonates born to mothers with suspected/confirmed SARS-CoV-2 infection. None of the guidelines have followed the GRADE approach. Also, none of them have addressed this issue clearly in their recommendations.

VALUES AND PREFERENCES

No evidence is available on the preferences of mothers, families, healthcare providers, or policymakers regarding the discharge criteria of the asymptomatic exposed neonates in the postnatal period. The preferences and values are likely to be varied given the differences in the unit policies regarding isolation of the exposed neonates (home isolation vs. facility isolation, isolation with affected mother vs. with a healthy unexposed family member).

RESOURCES REQUIRED

Significant resources are required if a decision is made to delay the discharge of the exposed neonates, to ensure isolation for 10-14 days – from the health facility. Conversely, if the neonates are roomed-in with their mothers or cared for by a trained family member, they can be discharged early to home. In that case, the resources required will be minimal. However, it may pose additional concerns of continued exposure to infection (if rooming-in with the mother) and compromise in the care of the neonate (if taken care of by the family member).

RECOMMENDATION 16 : Discharge policy for neonates

1. Stable neonates exposed to SARS-CoV-2 infection and roomed-in with their mothers may be discharged along with their mothers.

   Weak recommendation, based on consensus among experts based on the incubation period of SARS-CoV-2 infection in adults and older children

2. Stable neonates in whom rooming-in is not possible because of the sickness in the mother and who are being cared by a trained family member, may be discharged from the facility by 24-48 hours of age.

   Weak recommendation, based on consensus among experts in the absence of evidence for any beneficial effect or harm with early discharge following exposure to COVID-19

Remarks

- *Early discharge to home should be followed by telephonic follow-up or home visit by a designated healthcare worker.*
- *Mothers and family members should be counselled regarding the danger signs.*
- *If the neonate develops any danger signs during home isolation, he/she should be taken to a designated hospital facility for assessment and COVID-19 testing, if indicated.*
- *Mothers and family members should wash their hands frequently including before touching and feeding the baby.*
- *Mothers should practice respiratory hygiene and wear a triple-layered mask while breastfeeding and providing care to the baby; they should routinely clean and disinfect all the surfaces.*

Practice question 17: WHAT SHOULD BE THE FOLLOW-UP POLICY FOR NEONATES WHO HAVE RECOVERED FROM COVID-19?

PICO QUESTIONS

1. What should be the post-discharge follow-up policy for neonates with COVID-19?
2. What should be the follow-up policy for neonates born to mothers with COVID-19 who test negative during birth hospitalization?

SUMMARY OF EVIDENCE

Most existing guidelines are based on consensus or expert opinion and generally state follow-up of neonates born to COVID-19 positive mothers (regardless of infant's status) for at least 14 days after discharge.(128–133) Based on local available support home visits by a midwife, in-person visits with a local provider, a hybrid model of teleconsultation followed by personal visits or teleconsultation alone has been suggested. Common issues in the postnatal period (weight loss, neonatal jaundice, feeding issues) need to be addressed as well as those specific to SARS-CoV-2 infection (generally presenting with respiratory symptoms).

Studies have reported variable follow-up of the neonates born to SARS-COV2 positive mothers. Most studies from high-income countries have followed up neonates for 2-4 weeks using telehealth facility(134) or specialized follow-up clinics(115) or a hybrid of telehealth and in-person visits.(135) Most studies reported that SARS-CoV-2 exposed neonates discharged home with a positive mother do well. Farghaly et al noted that neonates of SARS-CoV-2-positive mothers were ten times more likely to be symptomatic at the 2-week follow-up, although symptoms were not related to COVID-19.(136) Marín Gabriel et al noted that 10% of neonates under follow-up required hospital visits at a median age of 14 days for various symptoms, including colic, jaundice, conjunctivitis, etc.(137) Neonates also presented with fever or common cold symptoms suspicious for COVID-19 but turned out negative by RT-PCR. Only 40% were exclusively breastfed, and 25% were on formula feeding, signifying feeding issues. Angelidou et al noted that 18% of neonates under follow-up required emergency room or non-scheduled visits for various symptoms.(138)

Studies from LMICs provide limited data on follow-up. Nayak et al, Anand et al, Kalamdani et al, and Nanavati et al, used telephonic follow-up and reported neonates to be well.(125,126,139,140) Charki et al from Karnataka reported on outcomes of 28 neonates who visited physically for follow-up at one month.(141) One infant required readmission for pneumonia and was COVID-19 positive by RT-PCR.

Ongoing studies: The Brazilian PROUDEST (Pregnancy outcomes and Child Development Effects of SARS-COV-2 infection study) is a multicentric, prospective cohort study designed to elucidate the repercussions of COVID -19 for the global health mothers and their children.(142) This has a sub-study called "BORN," a long-term follow-up study that aims to assess the offspring of women who enrolled in the main study. The follow-up is planned from birth up to 5 years of age. It includes two comparison groups; group A (exposed; n=300) comprises children born from SARS-CoV-2-exposed pregnancies, and group B (controls; n=300) comprises children born from non-exposed mothers.

RECOMMENDATION 17 : Follow-up policy for neonates

1. All neonates born to mothers with COVID-19 (regardless of the neonate's COVID status) should be followed up for at least 14 days and preferably till 28 days of life.

   Strong recommendation, based on consensus among experts (Not GRADED)

2. Telephonic follow-up or physical visit with a nearby pediatrician as per convenience can be chosen. At least one contact during this period should be scheduled.

   Strong recommendation, based on consensus among experts (Not GRADED)

Remarks

The incubation period of SARS-CoV-2 is similar for children and adults, at 2-14 days with an average of 6 days. Hence the minimum period of follow-up offered should be 14 days. The follow-up should address common neonatal problems, including feeding issues, jaundice, gastrointestinal symptoms, as well as possible symptoms or complications related to COVID-19.

Practice question 18: WHAT SHOULD BE THE IMMUNIZATION POLICY FOR NEONATES WITH SUSPECTED OR CONFIRMED SARS-COV-2 INFECTION?

PICO QUESTIONS

1. What should be the immunization schedule for neonates born to mothers with SARS-CoV-2 infection?
2. What should be the immunization schedule for neonates at risk of immunosuppression under the following situations?
    i. Neonates born to SARS-CoV-2-positive mothers who received immunomodulatory drugs (Tocilizumab) in the antenatal period.
    ii. Neonates who received Intravenous immunoglobulin or steroids for severe COVID-19 or MIS.
    iii. Neonates who received immunomodulatory drugs (e.g., Tocilizumab) for their management.

No clinical trials or specific information is available about vaccination of these neonates. Indian Academy of Pediatrics Committee on Vaccines & Immunization recommends continuing all immunizations during the pandemic.(143) Due to the risk of acquiring severe infection, live vaccines are contraindicated in immunosuppressed individuals. Individuals receiving high-dose steroids (2 mg/kg/day prednisolone equivalent) for two weeks or more are considered immunosuppressed. The neonates born to mothers receiving biological immunomodulatory drugs might be immunosuppressed for 6-12 months based on the medication used.(144) The same holds for the neonate self who received these agents.

SUMMARY OF EVIDENCE

We did not find any studies assessing immunogenic response to live/killed vaccines in the population mentioned above. In addition, we searched the CDC and AAP website for recommendations but did not find any clear guidance over the same. Therefore, we extrapolated the guidance from AAP (Red Book edition 32) and CDC (Pink Book edition 13) provided for other immunosuppressed conditions.(144,145)

1. Neonates who received Intravenous Immunoglobulin (IVIG)- Can continue their routine immunization schedule (as per national guidelines) once IVIG is discontinued.
2. Neonates who received dexamethasone 0.15mg/kg/day (equivalent to 1 mg/kg prednisolone) for ten days- As the dose is less than 2 mg/kg prednisolone equivalent, they are not considered immunosuppressed. They can continue their routine immunization schedule (as per national guidelines) once steroids are discontinued. In exceptional situations, when the neonates received a higher dose (≥2 mg/kg per day of prednisone equivalent) for 14 days or more, live-virus vaccines should not be administered until four weeks after discontinuation of treatment.
3. Neonates born to COVID-positive mothers who received immunomodulatory drugs (e.g., Tocilizumab) for their management: Tocilizumab (IL-6 receptor inhibitor) is the commonest used biological agent COVID-19. Studies assessing the effect of Tocilizumab on the immunological response against live influenza vaccine, pneumococcal polysaccharide vaccine, and tetanus toxoid in rheumatoid arthritis patients did not observe any significant impact on immunogenic response or adverse events related to the vaccine.(146–148) Therefore, the guidelines recommend that live influenza vaccines can be given to the patients who received Tocilizumab. Data on neonatal immunosuppression secondary to maternal tocilizumab intake is lacking. However, considering that the live influenza vaccine can be safely given to patients on Tocilizumab, we suggest continuing the routine immunization schedule (as per national guidelines) of the infant.

4. Neonates who received Tocilizumab for their management: Based on limited data from adults (mentioned above), Tocilizumab is unlikely to blunt the immunogenic response in the neonate. Therefore, all inactivated/sub-unit vaccines can be safely given. Three live vaccines (BCG, OPV, rotavirus) are given in the first six months. We suggest using BCG and IPV (instead of OPV) in these neonates, considering the disease burden. OPV can be safely administered after six months from the last dose of the Tocilizumab. We suggest avoiding the Rotavirus vaccine unless the physician feels that the risk of getting a diarrhoeal disease outweighs the potential hazard of vaccine-induced severe rotavirus infection.

RECOMMENDATION 18 : Immunization policy for neonates

1. Follow routine immunization policy in healthy neonates born to mothers with suspected/confirmed COVID-19.

2. In neonates with suspected/confirmed infection, vaccination should be completed before discharge from the hospital as per existing policy. (Pl. see special situations below)

3. **Special situations:**

   A. ***Neonates who received intravenous immunoglobulin (IVIG) or postnatal steroids in standard dose for a shorter duration (5-10 days):*** Continue their routine immunization schedule (as per national guidelines) once IVIG/steroids are discontinued.

   B. ***Neonates born to SARS-CoV-2 positive mother who received Tocilizumab in antenatal period:*** Continue their routine immunization schedule (as per national guidelines).

   C. ***SARS-CoV-2-positive neonates who received Tocilizumab for their own illness:*** Continue their routine immunization schedule (as per national guidelines) except using IPV instead of OPV and avoiding rotavirus vaccine unless the risk of getting a diarrheal disease is extremely high.

Practice question 19: WHAT SHOULD BE THE SPECIFIC MANAGEMENT OF MULTISYSTEM INFLAMMATORY SYNDROME IN NEONATES?

PICO QUESTIONS

1. In which neonates should MIS-N be suspected and what should be the diagnostic criteria?

2. Among neonates with the MIS-N, what is the effect of treatment with one or more immunosuppressive drugs (immunoglobulin, steroids) or immunomodulators (I) on critical outcomes such as in-hospital mortality and neonatal mortality (O), when compared to only supportive care (C)?

SUMMARY OF EVIDENCE

We retrieved 2554 articles published in 2021 and 7224 articles published in 2020. Of these, 363 full-text articles were reviewed to answer the above practice questions. Multisystem inflammatory syndrome in children (MIS-C) is a rare severe hyper-inflammatory condition that typically occurs 2–6 weeks after acute SARS-CoV-2 infection in children and adolescents. It is also known as pediatric inflammatory, multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). First described in children in April 2020, little is known about similar occurrences in neonates. The case definitions used by various organizations to label MIS-C are provided in Table-5.

Table 5: Case definition of MIS-C

Organization	Case definition
Centers for Disease Control (CDC), USA(149)	1. Age younger than 21 years 2. Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours 3. Inflammatory markers include one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin 4. Hospital admission 5. Multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, or neurological) 6. No plausible alternative diagnosis 7. Either laboratory confirmation of SARS-CoV-2 infection by RT-PCR, serology, or antigen test or known COVID-19 exposure within 4 weeks before symptom onset.
World Health Organization(150)	Children and adolescents 0–19 years of age with fever ≥ 3 days **AND** two of the following 1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands, or feet). 2. Hypotension or shock. 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP), 4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers). 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain). **AND** Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. **AND** No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. **AND**

	Evidence of COVID-19 **(**RT-PCR, antigen test, or serology positive) or likely contact with patients with COVID-19.
Royal College of Paediatrics and Child Health (RCPCH)(151)	1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) AND 2. Evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder) This may include children fulfilling full or partial criteria for Kawasaki disease. 3. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus 4. SARS-CoV-2 PCR testing may be positive or negative

MANIFESTATIONS AND OUTCOMES OF CHILDREN WITH MIS

Literature since April 2020 has noted that children can develop MIS-C after exposure to COVID-19 or after an asymptomatic illness. MIS-C typically manifests 3–4 weeks after SARS-CoV-2 infection, and this is why many children had positive antibodies to SARS- CoV-2 but negative RT-PCR at the time of MIS-C presentation.

MULTISYSTEM INFLAMMATORY SYNDROME IN NEONATES (MIS-N)

Data on MIS-N in neonates are limited and restricted to case reports). In the present scenario, the case definition, investigations, and management are extrapolated from pediatric literature. Godfred-Cato et al.(152). reported that infants (<12 months of age) accounted for only 4% (85/2060 cases <21 years) of the MIS-C patients reported to CDC's national surveillance system between May 2020–January 2021. Infants had a milder course of MIS-C than older children. Common presentations were rash (62.4%), diarrhoea (55.3%), and vomiting (55.3%). Other findings included hypotension (21.2%), pneumonia (21.2%), and coronary artery dilatation or aneurysm (13.9%). Laboratory abnormalities included elevated C-reactive protein, ferritin, d-dimer, and fibrinogen. Around 98% tested positive for current or past infection with SARS CoV-2 (RT-PCR was positive in 32%, serology was positive with negative RT-PCR in 36%, and 27% both serology and RT-PCR were positive). Among therapy, 73% received intravenous immunoglobulin and 67% steroids, 76% anti-platelet drugs, and a third received anticoagulants. Only one neonate out of 85 died (mortality 1.2%).

VALUES AND PREFERENCES

No evidence is available about the preferences of mothers, families, healthcare providers, or policymakers regarding the utility of specific treatment strategies for MIS temporally related to COVID-19 in neonates.

RESOURCES REQUIRED

Resources are needed for specialized laboratory investigations and echocardiography to offer supportive therapy, including mechanical ventilation and hemodynamic monitoring. Immunoglobulin therapy is costly and requires careful administration. Neonates with suspected or probable MIS should preferably be managed in neonatal intensive care units of tertiary care settings.

RECOMMENDATION 19 : MIS in neonates

1. The WHO case definition for multisystem inflammatory syndrome in children (MIS-C) related to COVID-19 can be extrapolated to neonates until more information is available.

   Weak recommendation, based on consensus among experts due to limited neonatal data

   Remarks: *Fever is an uncommon manifestation in neonates, and the criteria of fever for ≥3 days may not be applicable to neonates.*

2. A 2-tiered approach – proposed by the American College of Rheumatology for management of multisystem inflammatory syndrome in children (MIS-C) –may be used in neonates until more information is available.

   Weak recommendation, based on consensus among experts due to limited neonatal data

3. The current management strategies used for the management of MIS in children – including intravenous immunoglobulin, methylprednisolone, and aspirin and enoxaparin – may be adopted in neonates as well, until more information is available.

   Weak recommendation, based on consensus among experts and derived from pediatric recommendation in the absence of evidence in the neonatal age group.

4. Neonates with suspected MIS should be managed at tertiary care hospitals. Multidisciplinary management in consultation with cardiology is recommended.

Investigations

Tier-1: Complete blood count, differential counts, electrolyte levels, renal function tests, urinalysis, liver function tests, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), and testing for SARS-CoV-2 (RT-PCR, antibody or antigen test)

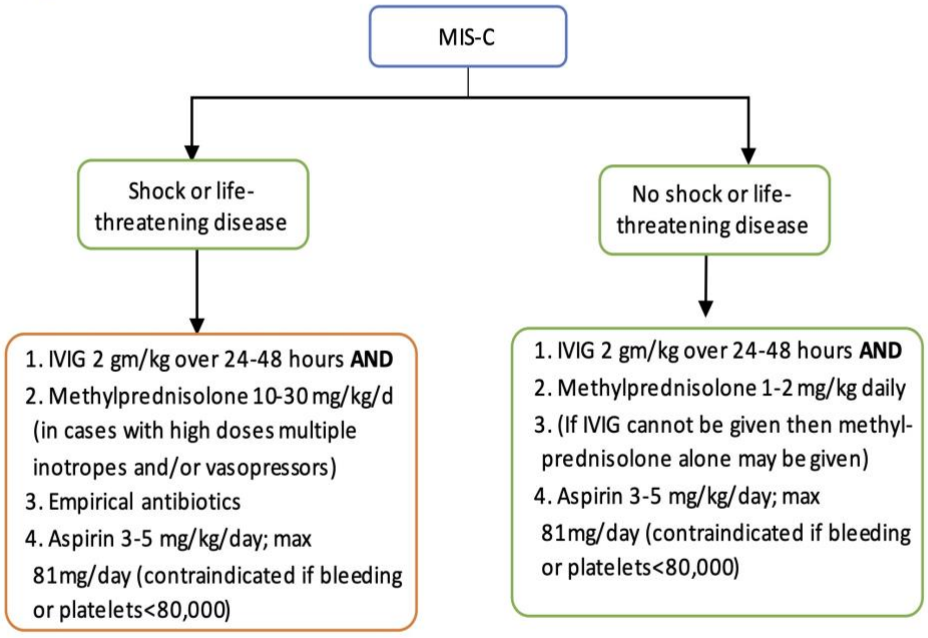
Positive Tier-1 screen (BOTH 1 &2 should be present):

1. CRP> 5 mg/dL or ESR > 40 mm per hour
2. At least one of these: Absolute lymphocyte count<1000/µL, Platelet < 150,000/µL, Na < 135 mEq/L, Neutrophilia, Hypoalbuminemia.

Tier-2: (Done if Tier-1 screen is positive or life-threatening presentation and clinical suspicion of MIS-C)

Cytokine panel (IL-6, TNF alpha, IL-10), coagulation studies (prothrombin time/INR, partial thromboplastin time, D-dimer), ferritin, troponin, NTproBNP chest radiograph, ECG, and echocardiogram

Management



Coronary aneurysm (Z score>10) or thrombosis or LVEF<35%	Enoxaparin 1mg/kg BD SC
Steroids	Taper methylprednisolone to oral dexamethasone after 3-5 days. Taper and stop over 3-5 weeks
Echo	At 1-2 weeks and 4-6 weeks
No response	Ongoing fever and or significant end organ dysfunction or significantly elevated inflammatory markers. Repeat IVIG in consultation with experts.

Figure 1: Investigations and management of Multisystem inflammatory syndrome related to COVID-19 in neonates.
Adapted from Statement by Indian Academy of Pediatrics (April 2021) COVID-19 management for 1 Month - 19 Years Old(122)

Practice question 20: WHAT INFECTION CONTROL MEASURES SHOULD BE UNDERTAKEN IN TRIAGE, LABOR AND DELIVERY ROOM, AND SNCU/NICU?

PICO QUESTIONS

1. What precautions healthcare workers need to follow while working in triage, labor and delivery room, and SNCU/NICU to prevent transmission of SARS-CoV-2 infection to self, other healthcare providers and patients?

2. What environmental disinfection is needed to prevent transmission of SARS-CoV-2 infection to other patients or healthcare providers in triage, labor and delivery room, and SNCU/NICU?

SUMMARY OF EVIDENCE

PERSONAL PROTECTION

SARS-CoV-2 can be transmitted through aerosols (size <5 µm, travel >1 m), droplets (size >5 µm and travel <1 m), or contaminated surfaces or supplies. Therefore, protection against infection needs both standard (to reduce the risk of transmission through contact with body fluids) and transmission-based (to reduce the risk from droplets/aerosols) precautions.

A Cochrane systematic review with literature search updated till 20 March 2020 evaluated type of full-body PPE, method of donning or doffing and training methods.(153) A total of 24 studies with 2278 participants were included in the review. Evidence was judged to be of very-low certainty due to high risk of bias and indirectness (simulation studies studying contamination rather than infection). Powered air-purifying respirator mask was associated with lower risk of contamination as compared to N95 mask (RR: 0.27; 95% CI: 0.17 to 0.43). However, these were more difficult to don than N95 masks. Sealed gown-glove combination, fit around the neck, wrists and hands, and added tabs to grab on the gowns were associated with less contamination. Following of CDC guidelines for donning and doffing was associated with lower risk of contamination. Spoken instructions during the doffing, computer simulation and video lectures were associated with improved doffing/donning practices. In another umbrella review published more recently, Griswold et al evaluated the effects of different PPEs on the risk of COVID-19 infection.(154) This review was for health personnel caring for trauma surgery patients, but evidence from other healthcare settings was also considered. Two systematic reviews included in the above mentioned umbrella review, both following the GRADE methodology and therefore of high-quality inform the recommendations made in the current guidelines.(155,156) In the review by Chu et al, high certainty evidence indicated that use of N95 and surgical mask was associated with lower risk of infection (adjusted OR: 0.15, 95% CI: 0.07 to 0.34).(155) N95 masks were associated with lower risk (RR: 0.43; 95% CI: 0.29 to 0.64) of infection than surgical masks with wearing N95 masks preventing 73 extra (95% CI: 46 to 91) clinical infections per 1000 HCWs compared to surgical masks.(156) Eye protection reduced the risk of infection (adjusted OR: 0.22; 95% CI, 0.12 to 0.3).(155) Physical distancing of 1 m or more was associated with lower transmission of infection than a distance of less than 1 m (adjusted OR: 0.18, 95% CI: 0.09 to 0.38).(155)

Following recommendations are based on the literature review and guidelines of Centre for Disease Control (CDC) (157):

1. **For all care areas including where patients not suspected to have COVID-19 infection are being care for:**

    i. All eligible healthcare workers, frontline workers and citizens should be vaccinated against SARS-CoV-2 infection.
    ii. All patients and relatives should wear well-fitting face masks.
    iii. All healthcare workers should wear well-fitting face masks including when in duty rooms or in areas with co-workers.
    iv. Hand hygiene as recommended during routine non-COVID care should be followed.

v. Arrange patient flow and care setting to allow a distance of 1 meter between two persons.
vi. If the health facility is in area with moderate to high community transmission rate, HCW should follow universal and transmission-based precautions including wearing of N95 mask and eye protection.

2. **Additional precautions for care areas with suspected or confirmed COVID-19 patients**

vii. HCW should wear N95 or higher-level respirator, gown, gloves, and eye protection. Eye protection should be by a full face shield or goggles.
viii. HCW should perform hand hygiene by using 60-95% alcohol-based hand rub or washing hands with soap and water for at least 20 seconds. Hand hygiene should be performed before and after all patient contact, contact with equipment, patient bed or any other potentially infectious material, and before putting on and after removing PPE, including gloves.
ix. Equipment used in the area should be dedicated and not mixed with non-COVID care areas.
x. Strategies to ensure that the healthcare personnel follow the recommended precautions and correctly adhere to donning and doffing steps include – education using videos and posters, easy availability of PPE supplies, and spoken instructions during doffing.

If it is an emergency and there is limited PPE, it should be allocated to the workers who are caring for confirmed COVID-19 pregnant women or those who present with symptoms suggestive of acute respiratory illness or those who are close contacts of confirmed cases or are from areas with high test positivity rate. The procedure of wearing (donning) and removing (doffing) of the PPE as recommended by CDC should be strictly followed.(157)

Sequence of wearing PPE (donning): Before wearing the PPE for managing a suspected or confirmed COVID-19 case, proper hand hygiene should be performed. The gown should be donned first. The mask or respirator should be put on next and properly adjusted to fit; remember to fit check the respirator. The goggles or face shield should be donned next and the gloves are donned last. Keep in mind, the combination of PPE used, and therefore the sequence for donning will be determined by the precautions that need to be taken.

Steps in removing PPE (doffing): Wearing the PPE correctly will protect the healthcare worker from contamination. After the patient has been examined or desired procedure is performed, the removal of the PPE is a critical and important step that needs to be carefully carried out to avoid self-contamination because the PPE could by now be contaminated. The gloves are removed first because they are considered a heavily contaminated item. Alcohol-based hand rub should be used before removing the gloves. Dispose of the gloves in a biohazard bin. After the removal of gloves, hand hygiene should be performed again, and a new pair of gloves should be worn to further continue the doffing procedure. Using a new pair of gloves will prevent self-contamination. Unbuttoning of the backside of the gown should be performed by an assistant. Removal of the gown to be performed by grabbing the backside of the gown and pulling it away from the body. Single-use gowns can be disposed of; reusable gowns have to be placed in a bag or container for disinfection.

ENVIRONMENTAL DISINFECTION

Of 1363 articles found, no clinical trials were found comparing different disinfection procedures. However, we found 44 systematic reviews evaluating in-vitro inactivation of the virus in different scenarios. Of these 3 most recent systematic reviews were used to build evidence for this practice question.(158–160)

SARS-CoV-2 is inactivated by traditional surface disinfectants used in the NICU including chlorine-based disinfectants, alcohol, detergents, glutaraldehyde, iodine-containing detergents, hydrogen peroxide compounds and household bleaches. The World Health Organization recommends the use of 70% ethyl alcohol to disinfect small areas between uses, such as reusable dedicated equipment and 0.5% sodium hypochlorite (equivalent to 5000 ppm) for disinfecting surfaces. CDC refers to the products approved by the Environmental Protection Agency for disinfection. These products include ethyl alcohol, hydrogen peroxide, or sodium hypochlorite.

VALUES AND PREFERENCES

No evidence is available about the preference of nurses, sanitation workers, healthcare providers, or policymakers for a specific disinfectant. The recommended preparations are used routinely, and it can be presumed that their use is acceptable.

RESOURCES REQUIRED

Adequate supply of N95 masks, PPE, full face shields or goggles and alcohol-based hand rub is needed to comply with these recommendations. Additional training of the healthcare providers is needed before they are posted to perform duties in the COVID areas. No new disinfectants or related resources are required. Healthcare facilities need to ensure an adequate supply of the recommended disinfectants. Although healthcare workers have previous experience of using these disinfectants, refresher training, supervision, and ready reference tools (like posters) should be ensured.

RECOMMENDATION 20A

Personal Protection

1. Irrespective of the COVID infection status, all patients and accompanying family members should wear fitting facemasks.
2. Hospital patient areas should be organized to maintain a distance of at least 1 m between two persons.
3. Healthcare workers providing care in non-COVID areas should wear fitting facemasks at all times including when in duty room or in areas with other co-workers. If health facility is located in an area with test positivity rate more than 10%, healthcare workers providing care even in non-COVID hospital areas should wear N95 mask, gown and eye protection.
4. When providing healthcare to women in labor with suspected or confirmed COVID-19, follow the standard universal precautions to prevent contact with body fluids. In addition, use personal protective equipment (PPE) to prevent acquiring infection through respiratory droplets. The PPE should include masks such as N95 and face protection by a full-face shield or goggles.
5. Reception and triage should be in the same room that is to be used for admission in labor and delivery. Ideally, this should be a room with negative pressure (If not available, exhaust fans can be installed).
6. There should be a restriction on the number of attendants and non-essential staff into the room.
7. There should be facilities for health care providers to safely donn and doff PPE when entering and exiting the COVID care area.

RECOMMENDATION 20B

Environmental disinfection

Disinfection of surfaces in the childbirth/neonatal care areas for patients with suspected or confirmed SARS-CoV-2 infection is not different from those for usual labor room/OT/NICU/SNCU areas and include the following:

- Wear personal protective equipment before disinfecting.
- If equipment or surface is visibly soiled, clean with soap and water solution or soaked cloth as appropriate before applying the disinfectant.
- 0.5% sodium hypochlorite (equivalent to 5000 ppm) can be used to disinfect large surfaces like floors and walls at least once per shift and for cleaning after a patient is transferred out of the area.
- 70% ethyl alcohol can be used to disinfect small areas between uses, such as reusable dedicated equipment.
- Hydrogen peroxide (dilute 100 ml of H_2O_2 10% v/v solution with 900 ml of distilled water) can be used for surface cleaning of incubators, open care systems, infusion pumps, weighing scales, standby equipment-ventilators, monitors, phototherapy units, and shelves. Use H_2O_2 only when equipment is not being used for the patient. For ensuring the efficacy of disinfection with H_2O_2 use the contact period recommended by manufacturer. Usually, a contact period of 1 hour is required.

Practice question 21: WHAT SHOULD BE BIOMEDICAL WASTE DISPOSAL PROTOCOL WHILE MANAGING A SUSPECTED OR CONFIRMED CASE OF COVID-19?

PICO QUESTION

What should be the biomedical waste disposal protocol while managing a suspected or confirmed case of COVID-19?

SUMMARY OF EVIDENCE

SARS-CoV-2 is highly infectious and has the potential to spread through direct, indirect, or close contact with infected people (airborne or droplets). Respiratory secretions or droplets expelled by infected individuals (fomites) have viable viruses and can contaminate surfaces and objects. The fomites are in high concentration in health care facilities where COVID-19 patients were being treated. Therefore, to prevent the spread of infection through the biomedical waste (BMW) generated in the COVID-19 facility, appropriate handling, and disposal of BMW is of utmost importance.

Biomedical Waste Management (BMWM) in a healthcare facility is governed by the state or central rules. In India, all healthcare facilities are legally bound to comply with the rules formulated by Central Pollution Control Board (CPCB). Therefore, we searched for the latest guidelines from CPCB for Handling, Treatment, and Disposal of Waste Generated during Treatment/Diagnosis/Quarantine of COVID-19 Patients. To supplement them with the recent advancement in the knowledge about COVID-19 transmission, we looked for World Health Organization and CDC guidelines on handling BMW generated from COVID-19 facilities.

The latest revision of CPCB guidelines (Version 4) was published on July 17, 2020.(161) We extracted relevant information applicable to neonatal facilities and summarized it here: These are the additional steps to be followed in addition to existing practices under BMW Management Rules, 2016.

1. Keep separate color-coded bins (with foot-operated lids)/bags/containers in the wards and maintain proper segregation of waste as per BMWM Rules, 2016.
2. To ensure adequate strength and prevent leakage, double-layered bags (using 2 bags) should be used for the collection of waste from COVID-19 wards.
3. The bags/containers used for collecting biomedical waste from COVID-19 wards should be labelled as “COVID-19 Waste”.
4. The basic rules for segregation and collection of waste from COVID-19 are the same as BMWM Rules, 2016 (Table 6).
5. The BMW collected from the COVID facility should be stored separately in bins labelled “COVID-19” before handing over the same for final disposal.
6. Maintain separate records of waste generated from COVID-19 isolation wards.
7. Depute dedicated sanitation workers trained for handling COVID-19 waste for storage and transport of BMW generated from the COVID facility. They must wear a full personal protective equipment.
8. Use dedicated trolleys and collection bins in COVID-19 isolation wards. The inner and outer surface of containers/bins/trolleys used for storage of COVID-19 waste should be disinfected with 1% sodium hypochlorite solution daily.

Table 6: Guidance for segregation of BMW at generating point

Category of Waste	Colour code of Bag/Bin
Used Personal Protective Equipment (Goggles, face-shield, splash-proof apron, Plastic Coverall, Hazmat suit, gloves), contaminated Intravenous tubing's, bottles, catheters, and urobag.	**RED**
Used Personal Protective Equipment (Mask, cap, shoe-cover, disposable linen Gown, non-plastic, or semi-plastic coverall), tissues, toiletries, diapers, cotton swabs, blood bags.	**YELLOW**
General solid waste (wrappers of medicines /syringes, fruit peel offs, empty juice bottles or tetra packs, used water bottles, discarded papers, carton boxes of medicines, empty bottles of disinfectants, etc.)	**BLACK**
Glass vials (broken or intact)	**BLUE**
Metallic sharp waste (Needle, scalpel, blade)	**WHITE**

RECOMMENDATION 21: Biomedical waste disposal

1. Facilities caring for suspected or confirmed case of COVID-19 should follow the most recent state/national biomedical waste guidelines.
2. All waste must be segregated at the site of generation itself and should be collected in designated colored bins/bags.
3. All bins/bags must be labelled "COVID-19" for easy identification and appropriate handling.
4. Designated sanitation workers trained in handling COVID-19 waste should be deployed for storage, transport and disposal of BMW generated from COVID facility.

Practice question 22: WHAT SHOULD BE THE VISITATION POLICY AND PREVENTIVE MEASURES FOR VISITORS?

SUMMARY OF EVIDENCE

Family integrated/participatory care is an integral part of neonatal intensive care. However, due to the COVID-19 pandemic, most units restricted the entries of caregivers to limit the transmission. A global survey from 277 facilities reported a significant reduction in parental presence and their participation in clinical rounds.(162) Almost 50% of units reported reductions in therapy services, lactation and social worker support. As NICU admission of a baby itself causes enormous stress in parents, their restricted access further worsened it (162,163). Moreover, restricting access was associated with decreased breastmilk use and increased lactation failure. None of the studies compared the effect of restricted versus routine NICU visit policies over horizontal transmission rates. However, compared to the pre-COVID era, the restricted policy was associated with increased parental stress, lactation failure, and decreased breastmilk feeding and kangaroo mother care rates.

Many units adopted a telemedicine facility (video calls, routine updates on baby's clinical status, daily counselling, and emotional support) in case parents could not visit NICU [2]. Questionnaire-based screening at the entrance to avoid the entry of suspect/confirmed COVID-19 has been followed to curtail horizontal transmission.(162)

For asymptomatic parents, unrestricted access as per pre-pandemic levels is recommended. All visitors to NICU should be provided appropriate PPE and should be explained all hygiene measures. To ensure uniformity, the NICU/SNCU should develop local policy and display it at the entrance.

RECOMMENDATION 22 : Visitation policy

1. Families of suspected and confirmed COVID-19 mothers and neonates should receive informed healthcare. They should be aware of and understand the isolation, monitoring, diagnostic, and treatment plans of the mothers/babies and be given a periodic update about the health condition. Alternative methods of interaction with families like video calls should be utilized to supplement.
2. NICU/SNCU should develop a local visitation policy and display it at the entrance.
3. Visitors to routine childbirth/neonatal care areas should be screened for symptoms of COVID-19. Persons with suspected or confirmed COVID-19 should not be allowed entry in the childbirth/neonatal care area.
4. All visitors to NICU should be provided appropriate PPE and should be explained all hygiene measures.
5. For neonates roomed in with mother having suspect/confirmed COVID-19, one healthy family member following contact and droplet precautions may be allowed to stay with her to assist in baby care activities.
6. Visitation policy for mother with COVID-19 to see her neonate admitted in NICU/SNCU :

   Mother may be allowed to visit if she fulfills all of these:

   - A minimum of 10 days have passed since symptoms first appeared (up to 20 days in case of severe to critical illness or are severely immuno-compromised), AND
   - Resolution of fever without the use of antipyretics for at least 72 hours, AND
   - Improvement (but not necessarily full resolution) in respiratory symptoms

Practice question 23: WHAT SHOULD BE THE OCCUPATIONAL HEALTH POLICY SPECIFIC TO THE COVID-19 PANDEMIC?

SUMMARY OF EVIDENCE

Healthcare workers being the frontline care providers are at risk of acquiring the COVID-19 infection at their workplaces. Recommendations under the Practice question 19 in these guidelines list the appropriate precautions to be taken to prevent the transmission of infection by using of appropriate personal protective equipment. In addition, the healthcare workers should follow the guidelines as currently recommended by the Government of India and/or respective state governments.

Literature was reviewed about efficacy of different chemoprophylaxis approaches in prevention of infection among healthcare workers. Bartoszko et al in a living systematic review and network meta-analysis evaluated and compared the effects of drug prophylaxis on SARS-CoV-2 infection.(164) Evidence of high certainty indicates that hydroxychloroquine has minimal to no effect on admission to hospital or mortality. Evidence of moderate certainty also indicates that it does not reduce the risk of laboratory confirmed SARS-CoV-2 infection and may lead to increased adverse effects leading to drug discontinuation. Evidence of very low certainty indicates that ivermectin does not prevent laboratory confirmed SARS-CoV-2 infection.

Currently approved COVID-19 vaccines are effective against preventing infection with mRNA-based vaccines showing 94.6% (95% CI 93.6%-95.4%) efficacy and adenovirus-vectored COVID-19 vaccines showing 80.2% (95% CI: 56%-93%) efficacy in phase II/III RCTs.(165) Specifically among healthcare workers, the surveillance data shows that mRNA based vaccines have 82% and 94% (similar to point-estimate of the above mentioned systematic review) efficacy with one and two doses respectively.(166)

Following recommendations are based on the current guidelines of the Ministry of Health and Family Welfare and the literature reviewed.

PROPHYLAXIS

1. Hydroxychloroquine or ivermectin chemoprophylaxis is not associated with reduced risk of laboratory-confirmed infection and is therefore not indicated.
2. All eligible healthcare workers, frontline workers and citizens should be vaccinated against SARS-CoV-2 infection.
3. If possible, pregnant healthcare workers should not be posted in areas where suspected or confirmed COVID-19 patients are cared for.

SUSPECTED COVID INFECTION

- If HCW have symptoms suggestive of COVID-19 (e.g., fever, cough, cold, nasal discharge, anosmia, etc.) they should isolate themselves promptly and get tested.
- If tested positive, HCW should continue isolation and appropriate treatment based on the MOHFW/ ICMR guidelines for mild/moderate/ severe disease. As per current guidelines, those with mild disease can return to work 10 days since the onset of symptoms provided it has been 3 days since they have been afebrile. Those who are asymptomatic can join after 10 days from the date of the positive swab. Repeat RT PCR testing is not required.(167)
- Health care workers with symptoms suggestive of COVID-19 and negative RT PCR should continue to isolate themselves till symptom resolution or till an alternative diagnosis is made. A repeat RT-PCR may also be done as indicated clinically.

EXPOSURE TO COVID

- If the HCW has exposure to a COVID-19 case, the exposure should be classified as low-risk or high-risk exposure. (168)
  - High-risk exposure:
    - HCW or other person providing care to a COVID-19 case or lab worker handling respiratory specimens from COVID-19 cases without recommended PPE or with possible breach of PPE
    - Performed aerosol generating procedures without a proper PPE.
    - HCWs without mask/face-shield/goggles having face to face contact with COVID-19 case within 1 meter for more than 15 minutes or having accidental exposure to body fluids
    - HCW with household member having COVID-19
  - Low-risk exposure: Contacts who do not meet criteria of high risk-exposure
  - If the exposure is low-risk then no quarantine or testing of the HCW is required and the HCW can continue to work with proper PPE and monitor self for symptoms and test/ isolate when symptoms appear.
  - For high-risk exposures the policies vary. In the ICMR advisory of June 2020, such HCW were quarantined for 1 week and tested after 1 week. If they tested positive, they were managed as an asymptomatic positive case as discussed above. If they tested negative, they would continue to remain isolated for another week and then return to work.

Mental health support should be provided to the HCW and the yearly occupational health check-ups should continue.

RECOMMENDATION 23 : Occupational health policy

1. Hydroxychloroquine or ivermectin chemoprophylaxis is not indicated.
2. All eligible healthcare workers, frontline workers, and citizens should be vaccinated against SARS-CoV-2 infection.
3. If possible, pregnant healthcare workers should not be posted in areas where suspected or confirmed COVID-19 patients are cared for.
4. Healthcare professionals working in any childbirth or neonatal area should promptly isolate, get tested, and report to their supervisor if they have symptoms suggestive of COVID-19. Such healthcare professional should not be put on clinical duty and should be replaced by a healthy healthcare professional to maintain appropriate patient-provider ratio.
5. Healthcare professionals with exposure to SARS-CoV-2 virus should undergo risk assessment and must be classified as high- or low-risk exposure.
6. No quarantine is needed for low-risk exposure and healthcare professionals can continue working while self-monitoring for appearance of any symptoms suggestive of COVID infection.

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