



The Turkish Neonatal Society proposal for the management of COVID-19 in the neonatal intensive care unit

Yenidoğan yoğun bakım biriminde COVID-19 yönetimi: Türk Neonatoloji Derneği önergesi

Ömer Erdeve¹, Merih Çetinkaya², Ahmet Yağmur Baş³, Nejat Narlı⁴, Nuray Duman⁵, Mehmet Vural⁶, Esin Koç⁷

¹Division of Neonatology, Department of Pediatrics, Ankara University Faculty of Medicine, Ankara, Turkey

²Division of Neonatology, Department of Pediatrics, University of Health Science Faculty of Medicine, İstanbul, Turkey

³Division of Neonatology, Department of Pediatrics, Yıldırım Beyazıt University Faculty of Medicine, Ankara, Turkey

⁴Division of Neonatology, Department of Pediatrics, Çukurova University Faculty of Medicine, Adana, Turkey

⁵Division of Neonatology, Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey

⁶Division of Neonatology, Department of Pediatrics, İstanbul Cerrahpaşa University Faculty of Medicine, İstanbul, Turkey

⁷Division of Neonatology, Department of Pediatrics, Gazi University Faculty of Medicine, Ankara, Turkey

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Abstract

Due to immaturity of immune function and the possibility of mother-fetal vertical and aerosol transmissions, neonates are particularly susceptible to the new coronavirus (SARS-CoV-2). Perinatal-neonatal departments should cooperate closely and take integrated approaches, and neonatal intensive care units (NICU) should prepare emergency plans for the coronavirus disease 2019 (COVID-19) as far as possible, so as to ensure the optimal management and treatment of potential victims. During the epidemic of COVID-19, the emergency response plan for the NICU should be based on the actual situation, including diagnosis, isolation, and treatment, as well as available equipment and staffing, and take into account the psychosocial needs of the families and neonatal care staff. In this context of the COVID-19 pandemic, the Turkish Neonatal Society has proposed a protocol with the evidence available at the time of preparation to handle neonates with SARS-CoV-2 infections and outbreaks in NICUs. We hope that this proposal can provide valuable information so medical workers do not have to enter the battlefield alone. At this moment, sharing resources, experiences and lessons, regardless of who you are, is our only chance to win.

Keywords: Coronavirus, COVID-19, guideline, neonatal intensive care unit, newborn, SARS-CoV-2

Öz

Yenidoğanlar, bağışıklık sisteminin immatüritesi ve anne-fetal vertikal ya da damlacık yolu ile bulaş nedenlerinden dolayı yeni koronavirüse (SARS-CoV-2) özellikle duyarlıdırlar. Virüsten etkilenecek muhtemel bireyler için perinatal-neonatal üniteler yakın iletişim içerisinde olmalı ve ortak hareket etmelidirler. Yenidoğan yoğun bakım birimleri koronavirüs 2019 hastalığı (COVID-19) için acil eylem planlamalarını en kısa sürede hazırlamalıdır. Yenidoğan yoğun bakım birimlerinin COVID-19 epidemisi sırasındaki acil eylem planları o anki tanı, izolasyon ve tedavi ile ilgili bilgiler, eldeki ekipman ve personel durumu ve personel ile ailelerin psikososyal gereksinimleri gözeticilerle hazırlanmalıdır. Türk Neonatoloji Derneği, COVID-19 pandemisi konusunda günümüze kadar olan verileri derleyerek yenidoğanlarda SARS-CoV-2 enfeksiyonu ve ünitelerde salgına yönelik bir önerge hazırlamıştır. Bu önergenin, sağlık çalışanlarına değerli bilgiler sunmasına ve bu mücadelede kendilerini yalnız hissetmemelerine yardımcı olmasını umuyoruz. Günümüz şartlarında kim olursak olalım kaynaklarımızı, tecrübelerimizi ve öğrendiklerimizi paylaşmak kazanmak için tek şansımız olarak gözükmektedir.

Anahtar sözcükler: COVID-19, coronavirus, rehber, SARS-CoV-2, yenidoğan yoğun bakım birimi, yenidoğan

Corresponding Author/Sorumlu Yazar: Ömer Erdeve E-mail/E-posta: omererdeve@yahoo.com

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Introduction

A new coronavirus (SARS-CoV-2) was highlighted at the end of 2019 in China and is spreading widely throughout the world. The coronavirus disease 2019 (COVID-19) is a new respiratory disease and its pandemic has affected hundreds of thousands of people all around the world. Most often originating with a mild infectious syndrome, associating mild symptoms (fever, cough, myalgia, headache and possible digestive disorders) to different degrees, COVID-19 can cause serious pulmonary pathologies and sometimes death (1–3).

Due to the immaturity of immune function and the possibility of mother-fetal vertical and aerosol transmissions, newborns are particularly susceptible to SARS-CoV-2. Perinatal-neonatal departments should cooperate closely and take integrated approaches, and neonatal intensive care units (NICU) should prepare emergency plans for COVID-19 as far as possible, so as to ensure the optimal management and treatment of potential victims. During the epidemic of COVID-19, the emergency response plan for the NICU should be based on the actual situation, including diagnosis, isolation, and treatment, as well as available equipment and staffing, and take into account the psychosocial needs of the families and neonatal care staff (2, 3).

The first COVID-19 case was reported on March 11th, 2020, in Turkey. Turkey is a country where 1.2 million infants are born annually. In this context of a COVID-19 epidemic in a country with a high birth number, the Turkish Neonatal Society (TNS) has established a ‘Task Force on the Management of Suspected or Confirmed COVID-19 in Newborns,’ which works in coordination with Ministry of Health COVID-19 Scientific Committee, and has proposed a protocol with the evidence available at the time of preparation to handle newborns with SARS-CoV-2 infections and outbreaks in NICUs. Today, with the spread of the infection, experiences are the most valuable sources of information and the most important weapon for medical workers on the frontline. We hope this proposal can provide valuable information for all countries so medical workers do not have to enter the battlefield alone. Due to the limited cases and clinical evidence in neonatal COVID-19, recommendations should be modified based on accumulated clinic evidence and experience. At this moment, sharing resources, experiences and lessons, regardless of who you are, is our only chance to win (4).

COVID-19 in Pregnancy

Pregnant women seem to be more vulnerable to viral infections due to partial immune suppression. Some viral

infections such as influenza, pandemic H1N1, hepatitis E, Ebola, Lassa fever, and herpes simplex were reported to affect pregnant women more severely. It is also well known that viral infections during pregnancy may have adverse effects on both mother and newborns (5–8).

Fever, dry cough, fatigue, myalgia, and sore throat are the main clinical findings of COVID-19 in pregnant women during the last trimester. Peripheral white blood cell counts are either normal or decreased and the lymphocyte count may be reduced. Mild thrombocytopenia, and elevated levels of liver enzymes, creatine phosphokinase, and C-reactive protein have been reported (8). Chest computed tomography (CT) is recommended in suspected cases because the sensitivity of CT was reported to be as high as real-time polymerase chain reaction (RT-PCR) (9). Viral nucleic acid detection of SARS-CoV-2 using RT-PCR has been considered as the reference standard diagnostic tool. Specimens from saliva, nasopharyngeal and oropharyngeal swabs, sputum, endotracheal aspirate, or bronchoalveolar lavage, urine, and stool should be evaluated using RT-PCR. Repeated testing may be required to confirm the diagnosis. Samples should also be tested for other common respiratory viruses. Serology as a diagnostic procedure should be used only if RT-PCR is not available. Supportive, antibacterial, antiviral and corticosteroid therapies may be performed in pregnant women with COVID-19 by a multidisciplinary team in a designated hospital, and these patients should be followed up in a negative pressure isolation ward (8).

There are no data regarding the effect of COVID-19 in the first trimester of pregnancy. Premature rupture of membranes (PROM), preterm delivery, fetal tachycardia, and fetal distress are the major complications associated with COVID-19 in the third trimester. No maternal death has been reported to date. Nearly half of women (47%) infected with SARS-CoV-2 had preterm delivery. Fetal growth was reported as unlikely to be affected (10). Currently, there is no evidence for transplacental transmission because amniotic fluid, cord blood, neonatal throat swab, and breast milk sample analyses were found to be negative for SARS-CoV-2 according to the very limited data (11).

Delivery Room Management

In the presence of available data, we recommend that delivery decisions should be made in conjunction with a neonatologist or pediatrician. Timing and mode of delivery should be determined by an obstetrician in terms of obstetric indications (6, 12). However, most pregnant women with SARS-CoV-2 infections delivered by cesarean section in China (12). Although viral shedding during vaginal delivery and the presence of vertical transmission still compose the main unknown issues, a new case report sug-

Keypoints for perinatal COVID-19	
Prenatal	Postnatal
<ul style="list-style-type: none"> • Due to immaturity of immune function and the possibility of mother-fetal vertical and aerosol transmissions, neonates are particularly susceptible to the SARS-CoV-2 • The perinatal-neonatal departments should cooperate closely and take integrated approaches • Nearly half of women (47%) infected with COVID-19 had preterm delivery • Viral shedding during vaginal delivery and presence of vertical transmission still compose the main unknown issues • The delivery should be performed in an isolated negative pressure room including all protective equipment in the operating room or delivery room. • As vertical transmission has not been excluded, the possible perinatal transmission of SARS-CoV-2 either by respiratory droplets and/or vaginal secretions during vaginal delivery should be kept in mind 	<ul style="list-style-type: none"> • NICUs should prepare emergency plans for COVID-19 to ensure the optimal management of potential victims • The assigned team should coordinate the hospitalization and maintenance of the patient with suspected COVID-19 • In the presence of high-risk factors, it is recommended that the newborn should be admitted and taken into an isolation ward in the NICU as soon as possible • Samples of the patient should be taken by staff that is trained and designated by the NICU • Newborns may be born prematurely and the most common non-specific initial symptoms include respiratory distress, shortness of breath, cyanosis, increased heart rate, lethargy, fever, feeding intolerance and vomiting • The SARS-CoV-2 has not been detected in breast milk, but the choice to breastfeed should be the mother's and the families • There is no effective anti-coronavirus treatment yet and treatment is generally supportive

gested the possible vertical transmission of SARS-CoV-2 from an infected mother to the newborn in utero (13).

The delivery should be performed in an isolated negative pressure room including all protective equipment in the operating room or delivery room. The minimum number of medical staff should attend the delivery and use all available personal protective equipment (PPE) including gown, N95 masks, goggles, and gloves during delivery. The TNS does not recommend delayed cord clamping to minimize the risk of possible perinatal transmission, and to perform resuscitation as stated in the Neonatal Resuscitation Program. The possible perinatal transmission of SARS-CoV-2 either by respiratory droplets and/or vaginal secretions during vaginal delivery should be kept in mind because vertical transmission has not been excluded. These newborns should also be washed and/or cleaned after delivery, if possible. In the presence of limited data, isolation and temporary separation of an ill mother and her infant may be offered as an important strategy to prevent neonatal infection perinatally. Newborns born to women with suspected or confirmed COVID-19 should be carefully evaluated by neonatologists and/or pediatricians (8, 10).

Neonatal Transport

Infants, whether symptomatic or asymptomatic should be taken into an isolated room to perform routine postnatal care with a separate transport incubator. If there is a need for an ambulance, it should be equipped with

special transfer incubators for newborns, transport ventilators, monitoring equipment, transport supplies, and first aid medicine. The cab and the car should be strictly sealed and isolated, and the car should be equipped with PPE, disinfectant solution, and rapid hand disinfectant. The ambulance should be disinfected before and after transfer. Any accompanying medical staff must wear PPE (14, 15).

Neonatal Intensive Care Unit Management

Patient admission and isolation

The assigned team (responsible physician and nurse) should coordinate the hospitalization and maintenance of the patient with suspected COVID-19. In the presence of high risk factors including prenatal and postnatal maternal fever, twin pregnancy, PROM, premature birth, low birth weight or small for gestational age, it is recommended that the newborn should be admitted and taken into an isolation ward in the NICU as soon as possible. If the isolation rooms are full, one of the intensive care rooms can be allocated for the cohort of patients with COVID-19. The infant should be placed in an incubator instead of radiant warmer during postnatal care facilities (15, 16).

Maternal separation may cause anxiety to parents and maternal depression. All of the above situations should be communicated to and fully understood by parents. So-

cial workers or supportive consultants can provide help to facilitate communication (15).

General rules for the staff

It would be appropriate to ensure that as many healthcare providers as possible wear professional medical uniforms (scrubs); to wash scrubs or clothes used at the hospital at a minimum of 60°C in a washing machine with regular detergent, and not to take them out of the workplace/hospital; to shave or trim facial hair; do not wear facial piercings that may prevent the use of face masks; do not wear accessories that may complicate the hand washing procedure such as watches, rings, and bracelets at the hospital; to keep nails short and long hair tied; to have dedicated footwear for the working period at the hospital, which should remain at the hospital, and removing 'outside' shoes before entering the home; to wash the face, hands, and forearms below the wrist before leaving the hospital; to wipe cell phones with disinfectants or warm soapy water; do not keep a stethoscope around the neck, and wipe them at regular intervals; do not use the medical or non-medical devices commonly between different units unless necessary; and to limit human traffic among healthcare providers as much as possible (4, 15, 16).

Procedures in the NICU

Access to the patient's room and the NICU should be limited. Only personnel in charge of patient care and who are required to enter the room should be allowed and PPE should be available at the door entrance. Staff that perform examinations, treatments, and personal care should wear gloves, insulating gowns, goggles/face protectors, and medical masks. When donning and doffing PPE, care should be taken to follow the put-on/take-off order. Particular attention should be paid to removing the mask last after leaving the patient's room and then to ensure hand hygiene. During procedures that may cause aerosolization, care should be taken to ensure that there are no people other than the healthcare personnel in the patient room, the door should be closed during the procedure, and the door should be kept closed for a while after the procedure. In patients under non-invasive/invasive respiratory support treatment, respiratory isolation measures should be followed and N95 masks should be used instead of surgical masks (4, 15, 16).

Samples of the patient should be taken by staff that have previously been trained and designated by the NICU. The sample should be taken under proper conditions and kept in the refrigerator (between 2–80°C) and delivered to the relevant laboratory. Staff performing invasive procedures (aspiration, intubation, respiratory sample) must use disposable waterproof gowns, N95 masks, gog-

gles/eye protection, and gloves. Hand hygiene should be attained before and after gloves. Jumpsuit, bonnet, and foot protection can be used on the basis of the condition of the patient, especially in cases where intensive contact with body fluids and secretions may occur. Ensure that samples are correctly labeled, the request forms are completed correctly, and clinical information is provided (15, 16).

Medical materials to be used must be patient-specific, not be taken out of the room, and material sharing among patients must not be allowed. Portable X-ray, echocardiography, and ultrasound used for the patient, and the transport incubator used for patient transfer are cleaned and disinfected according to the rules determined in accordance with the infection control directives of the NICU. In order to dispose of used PPE, there should be two separate double-bagged medical waste bins both at the entrance of the patient room and in the room. It should be known that virus infection continues longer with patient stool (4, 15).

COVID-19 in the Newborn

The number of neonates has been increasing day by day as COVID-19 spreads widely and rapidly throughout the world. After two separate reports including 9 and 10 infants born to mothers with COVID-19 infections, the largest series of 33 infants with early-onset sepsis born to mothers with COVID-19 has been published recently (12, 17, 18). The TNS recommends similar definitions used by the Chinese Expert Consensus for Neonatal COVID-19 as follows: newborns born to mothers with a history of COVID-19 between 14 days before delivery and 28 days after delivery, or newborns directly exposed to those infected with COVID-19 including family members, caregivers, medical staff, and visitors regardless of the presence of symptoms are defined as suspected COVID-19 cases. Newborns who have positive respiratory tract or blood tests are defined as confirmed COVID-19 case (15).

The limited number of neonatal case series show that infants may be born prematurely and the most common non-specific initial symptoms include respiratory distress, shortness of breath, cyanosis, increased heart rate, lethargy, fever, feeding intolerance, and vomiting. Although the clinical symptoms and neonatal outcomes seem to be mild and favorable in infants born to COVID-19-positive mothers, one infant has died of multiple organ failure and disseminated intravascular coagulation. Therefore, the TNS recommends close monitoring of vital signs, and respiratory, cardiovascular, and gastrointestinal symptoms. Laboratory examinations including complete blood

count, liver function tests, creatine phosphokinase, and lactate dehydrogenase may be normal. Analysis with RT-PCR should be performed for upper and lower respiratory tract, blood, and stool samples for the confirmation of COVID-19, and should be repeated in case of suspicion. Chest radiography, lung ultrasonography, and chest CT may reveal findings of neonatal pneumonia (12, 15–19).

Breastfeeding

Breast milk provides vital protection against viral and bacterial infections. In limited studies on mothers with COVID-19, the virus has not been detected in breast milk. However, we are not completely sure that virus cannot be transmitted via breast milk. The World Health Organization, Centers for Disease Control and Prevention, and the Academy of Breastfeeding Medicine state that mothers with COVID-19 can breastfeed (20–22). They recommend that while taking all precautions to avoid spreading the virus to the newborn, it is still reasonable for the mother to choose to breastfeed or provide expressed milk for her infant. On the other hand, Wang et al. (15) wrote a letter regarding the proposal for the prevention and control of the coronavirus in newborn infants and recommended avoiding breastfeeding by mothers with COVID-19 until recovery.

The TNS proposes that the choice to breastfeed should be the mother's and the families. The decision may be given individually based on the mother's health status. Mothers should be encouraged to express their breast milk to establish and maintain milk supply. While feeding at the breast, all possible precautions should be taken to avoid contamination of the virus, including careful handwashing and wearing a face mask. If milk is expressed with a breast pump, the mother should wash her hands before touching the pump or bottle, and after each pumping session, the pump should be disinfected as per the manufacturer's instructions. These recommendations may need to be updated based on new clinical evidence and experience for breastfeeding.

Treatment

A multidisciplinary approach including specialists of neonatology, pediatrics, pediatric infectious diseases, and radiology, as well as nurses and other auxiliary health personnel should be exercised. Supportive treatments such as oxygen therapy, fluid-electrolyte treatment, total parenteral nutrition support if necessary, and advanced respiratory support if necessary (non-invasive/invasive with exhalation filter) are used on a need basis. In the presence of serious acute respiratory distress syndrome, high-dose pulmonary surfactant, inhaled nitric oxide, and high-frequency oscillatory ventilation can be administered. Re-

nal replacement therapy and extracorporeal membrane oxygenation are other supportive treatments. However, evidence-based data on surfactant, inhaled nitric oxide, various ventilation methods, renal replacement therapy, and extracorporeal life support are limited (15–19).

As yet, there is no effective anti-coronavirus treatment. A case series from China did not report any data on any antiviral therapy in newborns. We suggest a case-by-case approach for drug therapy in management. Turkish Ministry of Health Scientific Committee on COVID-19 has reported a list of drugs including oseltamivir, hydroxychloroquine, azithromycin (beyond first month) and lopinavir-ritonavir combination (in infants beyond postnatal 15 days), which can be used in severe cases. Both azithromycin and hydroxychloroquine can prolong the QT interval. The efficacy and safety of a lopinavir-ritonavir combination in newborns aged <14 days are not known. The treatment regimens may change according to new available data from trials and experience. Unnecessary use of broad-spectrum antibiotics should be avoided and antibiotics should be used in the presence of secondary bacterial infection evidence in accordance with the NICU's treatment protocols (15–19, 23).

Discharge Criteria

Patients can be discharged if the following requirements are met (15, 24):

1. If the RT-PCR tests of the suspected mother and infant are negative, and the infant is asymptomatic.
2. If the newborn has asymptomatic infection: upper airway specimens (nasopharyngeal and pharyngeal swabs) should be collected and tested every two days until two consecutive results show negative for SARS-CoV-2. Stool may be collected and tested every two days until two consecutive results show negative for SARS-CoV-2.
3. If the newborn has mild infection: the temperature of the patient should be normal for more than three days, symptoms should improve, and specimens collected from the upper airway secretion (nasopharyngeal and pharyngeal swabs) should show negative for SARS-CoV-2 twice, consecutively (with at least a 24-hour interval). Stool may be collected and tested every two days until two consecutive results show negative for SARS-CoV-2.
4. If the newborn has severe infection: the temperature should return to normal for more than three days, symptoms should improve, and pulmonary imaging should show inflammation disappearing. Specimens collected from the upper respiratory tract (nasopharyngeal and pharyngeal swabs) and lower respiratory tract should show negative for SARS-CoV-2 twice,

consecutively, with at least a 24-h interval. Stool may be collected and tested every two days until two consecutive results show negative for SARS-CoV-2.

In cases of infection in the newborn, the infant should be quarantined for a minimum of two weeks at home. If this is not possible, discharge may be postponed with an individual decision.

Procedures for Handling Bodies of Deceased Suspected or Confirmed Patients and Autopsy

Staff must make sure that they are fully protected by wearing work clothes, disposable surgical caps, disposable gloves and thick rubber gloves with long sleeves, medical disposable protective clothing, medical protective masks (N95) or powered air-purifying respirators, protective face shields, work shoes or rubber boots, waterproof boot covers, and waterproof aprons or waterproof isolation gowns. All openings or wounds the patient may have, such as mouth, nose, ears, anus, and tracheotomy openings, must be filled using cotton balls or gauze dipped in 3000–5000 mg/L chlorine-containing disinfectant or 0.5% peroxy-acetic acid. The corpse must be wrapped with a double-layer cloth sheet soaked with disinfectant, and packed into a double-layer, sealed, leak-proof corpse wrapping sheet soaked with chlorine-containing disinfectant. The body should be transferred by the staff in the isolation ward of the hospital via the contaminated area to a special elevator, out of the ward, and then directly transported to a specified location for cremation by a special vehicle as soon as possible. A final disinfection of the ward and the elevator must be performed (4).

Autopsy is of great significance to the elucidation of the pathologic changes, pathogenesis, and cause of death of COVID-19, and can provide a theoretical basis for more scientific and accurate prevention and control of the outbreak (25). The Guide to the Forensic Pathology Practice on Death Cases Related to COVID-19 has been developed in China, and includes information on the background investigation of the cases, autopsy room requirements, personal prevention and protections, external examinations, autopsy, auxiliary examinations, and so on. This guide can be used as a reference by forensic and pathologic examination institutions, as well as examination staff (26).

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