Novel Coronavirus 2019 (2019-nCoV) Infection: Part I - Preparedness and Management in the Pediatric Intensive Care Unit in Resource-limited Settings

Namita Ravikumar¹, Karthi Nallasamy¹, Arun Bansal¹, Suresh Kumar Angurana¹, Basavaraja GV², Manu Sundaram³, Rakesh Lodha⁴, Dhiren Gupta⁵, and Muralidharan Jayashree¹ for the Intensive Care Chapter of Indian Academy of Pediatrics

From Division of Pediatric Critical Care, Departments of Pediatrics, ¹Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India; ²Paediatric Intensive Care Unit, Indira Gandhi Institute of Child Health, Bangalore Karnataka, India; ³Division of Critical Care Medicine, Sidra Medicine, Doha, Qatar; ⁴Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India; and ⁵Paediatric Intensive Care Unit, Sir Ganga Ram Hospital, New Delhi, India.

Correspondence to: Dr Arun Bansal, Professor, Department of Pediatrics, Advanced Paediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India. drarunbansal@gmail.com

Received: March 26, 2020; Initial review: March 28, 2020; Accepted: March 31, 2020.

The year 2020 started with the emergence of the 2019 novel corona virus (2019-nCoV) as a threat to the world; shortly afterwards the World Health Organization (WHO) declared it a pandemic. Having begun in China, globalization and travel led its spread all over the globe, overwhelming the healthcare resources and resulting in high mortality and morbidity. About 5% of adults, especially those with co-morbidities, were critically ill and required intensive care management for acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. Children account for about 1-2% of the total cases, and 6% of these fall under severe or critical category requiring pediatric intensive care unit (PICU) care. Diagnosis involves a combination of clinical and epidemiological features with laboratory confirmation. Preparedness strategies for managing this pandemic are the need of the hour, and involve setting up cohort ICUs with isolation rooms. Re-allocation of resources in managing this crisis involves careful planning, halting elective surgeries and training of healthcare workers. Strict adherence to infection control like personal protective equipment and disinfection is the key to contain the disease transmission. Although many therapies have been tried in various regions, there is a lack of strong evidence to recommend anti-virals or immunomodulatory drugs.

Keywords: COVID-19, Guideline, Pandemic, SARI, Treatment.

Published online: March 29, 2020; PII: S097475591600151

Burden

Global: Till March 26, 2020, a total of 416,686 confirmed cases from 197 countries with 18,589 deaths have been reported by WHO. China has reported the maximum cases with a total of 81,869, followed by Italy with 69,176 cases. However, mortality is more in Italy with 6,820 (9.9%) deaths followed by China having 3,287 (4%) deaths. The United States of America has surpassed Spain and Germany over the last few days with 51,914 cases and 673 deaths [3].

Indian scenario: A total of 606 cases with 10 deaths have been reported from India as on March 26, 2020 as reported by the WHO. Among these cases, only one child from Kerala has been tested positive.

Epidemiology

The 2019-nCoV belongs to a group of enveloped positive-sense RNA viruses in the family, Coronaviridae with 4 genera viz., alpha, beta, gamma and delta. Human coronaviruses (HCoV) belong to alpha and beta genus...
and are mostly implicated in endemic respiratory infection with mild severity [4]. However, the novel coronaviruses infecting humans namely, SARS-CoV, MERS-CoV and SARS-CoV-2 are believed to have originated from bats with few intermediate hosts like civet cats, camels and pangolins [5]. RNA viruses mutate faster than DNA viruses, single-stranded viruses mutate faster than double-strand virus, and genome size appears to correlate negatively with mutation rate.

**Transmission Characteristics**

It is speculated that it originated in bat (genetic character matches to bat corona virus) then it got transmitted to pangolins, or scaly anteaters. Humans seem to be accidental host who got this virus from pangolins in Wuhan seafood market. Human to human transmission of COVID-19 started in Wuhan city, Hubei Province of China where it was initially labelled as ‘Pneumonia of unknown etiology’. Epidemiological investigation of early transmission dynamics revealed that 55% of the cases of COVID-19 during December, 2019 were linked to the hunan seafood wholesale market. The mean incubation period has been reported to be 5.2 days with the 95th centile being 12.5 days. The main modes of transmission include droplet and fomites followed by airborne transmission. Reproduction number of nCoV-19 is between 2.2 to 3.6, which is comparable to SARS-CoV but higher than MERS-CoV[6].

**Less severe affection in children:** Children less than 10 years of age accounted for 1% of the total cases [1]. The median age among pediatric cases was 6.7 years [7]. The lesser proportion of severe cases among children has been attributed to lesser opportunities for exposure and immaturity of angiotensin converting enzyme 2 receptors, which are proposed to be the binding sites for coronaviruses [8,9].

**Case Fatality Rate**

The overall case fatality rate as per China Centre for Disease Control and Prevention (CDC) is 2.3%, which is much lower compared to SARS (9.6%) and MERS (34%) but significantly higher compared to the latest H1N1 influenza pandemic (0.001 – 0.007%)[1]. However, as per WHO, the global case fatality rate is as high as 4.4% with absolute number of deaths already higher than the total fatality of SARS and MERS combined [10]. The case fatality reported from Italy is 7.2% which has gone up to 9.8% as per WHO (as on March 26, 2020) [11].

**CLINICAL MANIFESTATIONS**

The common clinical features reported in the critically ill patients include fever (98%), cough (77%), dyspnea (63%), malaise (35%), myalgia, headache, nausea, vomiting and diarrhea [12]. A prospective study from China involving 171 children with confirmed COVID-19 reported fever (41%) with a median duration of 3 days (1-16), cough (48%), pharyngeal erythema (46%) tachypnea (28%) and diarrhea (8.8%). The cohort had 15% asymptomatic, 19% upper respiratory infection, and 65% pneumonia. Only 3 children (1.7%) required care and mechanical ventilation. All three of them had comorbidities, and one died [7].

**ICU Requirements in COVID**

The severe and critical categories require admission and management in ICU. Among adults, 7% of patients admitted with SARS-CoV-2 pneumonia required ICU care. The mean age of these ICU patients was 60 years with male: female ratio of 2:1 and 50% had chronic illness. Majority had Multi-organ dysfunction syndrome (MODS) with ARDS (67%), acute kidney injury (29%), liver dysfunction (29%) and cardiac injury (23%). Of the ICU admissions, 71% required mechanical ventilation, 35% vasoactive support, 17% renal replacement therapy and 11% ECMO. Mortality was as high as 61% among the critically ill [12]. As per unpublished data from Italy, 16% of admitted patients with COVID-19 needed ICU care [13]. In the Chinese pediatric cases, 5.9% of all pediatric cases belonged to the severe or critical categories. Based on the experience in managing community-acquired pneumonia, high-risk pediatric population includes children with underlying conditions such as congenital heart disease, broncho-pulmonary hypoplasia, airway/lung anomalies, severe malnutrition, and immunocompromised state; however, more information is needed in the setting of COVID-19 [2].

**DIAGNOSIS**

Case definitions for suspected, probable and confirmed COVID-19 cases as given by WHO are in **Box I** [16]. The largest series on children analyzing suspected and confirmed COVID cases is from the electronic data base of Chinese CDC [17]. Cases were suspected based on the presence of clinical features and exposure history. They also identified high-risk cases and categorized into groups based on severity (**Box II**).

Laboratory testing of suspected cases is based on clinical and epidemiological factors. Screening protocol should be adapted to local situation and may change with the evolution of the outbreak scenario in the local population. Recent testing strategy in India (as on March 20, 2020) given by ICMR is as per algorithm in **Fig. I**[18]. Specimen handling for molecular testing would require Biosafety 2 (BSL-2) or equivalent facilities.
Attempts to culture the virus require minimum of BSL-3 facilities [19].

**Type of Sample**

*Upper respiratory specimens*: nasopharyngeal and oropharyngeal swabs; both swabs are placed together in a viral transport medium and transported to the laboratory in ice.

*Lower respiratory specimens*: sputum and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease (obtained with aerosol precautions)

**Confirmatory Tests**

(a) Respiratory tract or blood samples tested positive for 2019-nCoV nucleic acid using Real-time Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR)

(b) Genetic sequencing of respiratory tract or blood samples is highly homologous with the known 2019-nCoV, but this is not done routinely.

Serological tests may help in epidemiological investigation but there could be cross reactivity with other coronaviruses. Viral isolation is not done routinely for diagnosis. Rapid diagnostic test kits like Xpert Xpress
SARS-CoV-2 by Cepheid has been approved by the US-FDA (United States Food and Drug Administration) for Emergency Use Authorization (EUA) and RealStar SARS-CoV-2 RT-PCR kit 1.0 by Altona Diagnostics and Patho Detect by MY LAB have been approved by ICMR[20,21].

Ancillary Investigations

Complete blood count: Lymphopenia was seen in 85% of critically ill adults, suggesting it a marker of severe disease while among the overall pediatric cases, it was seen in 3.5%[7,12].

Infection markers: Elevation of C-reactive protein (CRP) was reported in 20% and procalcitonin in 64% of cases [7].

Radiological findings: Chest radiography (CXR) or computed tomography (CT) are not recommended as a routine for children but only in specific cases presenting with pneumonia and/or acute respiratory distress syndrome (ARDS). Parenchymal abnormalities with peripheral consolidations on CXR have been reported in a small case series from Korea [14]. Ground glass opacities (32%), local patchy shadows (18%) and bilateral patchy shadows (12%) on CT chest were the common findings in children [7]. Bilateral pneumonia (75%), unilateral pneumonia (25%) and multiple mottling and ground-glass opacity (14%) were reported based on CXR and CT findings from adult patients in Wuhan, China [15].

Laboratory markers of organ dysfunction: Elevation of transaminases is seen in 12-14% and d-Dimer in 14% cases [7].

PREPAREDNESS AND ADMINISTRATIVE CONCERNS FOR ICU

A phased and tiered plan for ICU during the pandemic needs to be made based on the assessment of healthcare burden and resource utilization [13,22,23].

Intensive care units: Create cohort intensive care units where critically ill confirmed COVID-19 patients will be managed. This would be a different area from where other PICU patients are being managed in order to reduce transmission within the hospital. In addition, a separate area should be developed where suspected COVID-19 patients will be managed. With increasing burden of patients, general beds may have to be converted to ICU beds and provided with suitable infrastructure. Predictive models based on local epidemic need to be developed for expected number of patients as well as need of equipment.

Setting up of isolation rooms: Negative pressure isolation is the standard recommendation for management of a suspected or proven COVID-19 patient. However, in case of non-availability of these rooms, use single rooms with separate air outlet/exhaust, preferably on the higher floor of the building. These rooms should be equipped with resuscitation trolley, essential drugs, multipara monitor and ventilator. Positive pressure rooms
like operation theatres are not suitable for airway management as aerosol generation is higher.

Reducing the ICU burden: All elective non-urgent admissions and surgeries need to be halted during the outbreak in order to rationalize resource-utilization, and ensure adequate back-up to handle the crisis.

Re-allocation of staff: During the crisis, there may be acute shortage of critical care specialists and nursing staff. It is essential to identify staff from respiratory medicine, infectious disease and other units who may be trained in infection control, personal protective equipment (PPE) use and management of critically ill patients.

Rotation of staff and reserve for back-up: Adequate reserve of healthcare providers needs to be ensured as a back-up in case of emergencies or healthcare professionals falling sick. The team members should be working on rotation (in a shift of 4-7 days) with adequate rest in between.

Training of all staff: All those who are likely to come in close contact with the patient or are handling equipment, surroundings, and waste management should receive training regarding infection control including correct technique of donning and doffing of PPE and disinfection of surfaces and equipments. Proper training and a written plan (Standard Operating Procedure) should be there for waste disposal.

Rational use of PPE: In view of current global shortage, WHO has formulated guidelines for the rational use of PPE. This includes co-ordination of PPE supply chain management mechanism, appropriate PPE use based on indication, minimizing the need of PPE by bundling activities, using physical barriers and telemedicine where appropriate, and restricting visitors [24].

MANAGEMENT IN RESOURCE-LIMITED SETTINGS

Triage and Transport

A dedicated area for screening and triaging of patients with suspected COVID-19 is essential. Once the patient fits to the case definition and requires admission, unnecessary movement must be avoided and minimum staff should accompany the patient. Ensure that the patient (if self-breathing) and the accompanying persons should be on a 3-ply surgical mask.

ICU Management

Severe and critical cases need ICU care for monitoring, ventilation and organ support therapy.

Severe acute respiratory illness (SARI): SARI is defined by the presence of cough and fast breathing plus at least one of the following [25]: (i) Oxygen saturation ($\text{SpO}_2$) <90%, (ii) severe chest indrawing and grunting, and (iii) altered mental status.

SARI is the most common indication for ICU transfer and most guidelines are similar to management of any viral pneumonia with ARDS with an emphasis on minimizing risk of transmission to others, especially healthcare workers [26,27]. The details on the management of SARI are given in Part II of this write-up and Table I.

Septic shock: Management of septic shock in COVID is not very different from the routine. However, the Surviving Sepsis Campaign (SSC) guidelines for COVID-19 recommend conservative fluid strategy, avoiding colloids as resuscitation fluid, and to use low dose steroids in catecholamine refractory shock [28]. In children, epinephrine is the first vasoactive of choice for septic shock.

Co-infections: Co-infections like secondary bacterial pneumonia are common, especially in children (50%) and addition of broad spectrum antibiotic to cover gram positive, gram negative, and staphylococcal infection is recommended [29].

Myocarditis: Cardiogenic shock with elevations in hypersensitive Troponin-I have been seen in 12% of patients. Management includes inodilators like milrinone, diuretics, immunomodulators (methylprednisolone and IVIG) and circulatory support with ECMO (extracorporeal membrane oxygenation) have also been used in a few cases [30,31].

Acute kidney injury: This has been reported in 7% and renal replacement therapy may be necessary [32].

Supportive care: This includes conservative fluid management, nutrition, appropriate sedo-analgesia, and prevention and treatment of healthcare associated infections.

Specific Therapy

Although no definitive therapy till date has proven benefit for SARS-CoV2, antiviral drugs like Remdesivir, Lopinavir/Ritonavir are being used in over 50% of the critically ill adults based on in vitro viral inhibition and recovery in SARS and MERS but there is no strong evidence [33–36]. Chloroquine has been found to increase endosomal pH and hinder virus cell fusion and also interfere with ACE2, a receptor for binding of SARS-CoV2 [37]. A combination of hydroxychloroquine and azithromycin showed reduction in viral load [38].
Interferons, IVIG, and convalescent plasma from recovered SARS patients are other tested treatment options [39]. Vaccination for RNA viruses (measles, influenza, polio) has shown higher titers of neutralizing antibodies against SARS-CoV [40] (Table II). Based on the current experience, we may use broad spectrum antibiotics, oseltamivir, protease inhibitors, hydroxychloroquine and azithromycin. Lopinavir/Ritonavir should be avoided in combination.

**Course and Recovery**

In adult patients with COVID-19 pneumonia, onset of symptoms to respiratory failure takes an average of 7 days with peak severity at 10 days. Signs of improvement start occurring by day 14. However, at the time of reporting of most studies, many patients were still admitted and their course needs to be followed to know the exact prognosis [40].

**INFECTION PREVENTION AND CONTROL**

In the intensive care setting, disinfection of high-touch surfaces like monitors, ventilator screen, other equipment, resuscitation trolleys etc are essential and need to be carried out every 4 hours.

**Surface decontamination:** Alcohol (e.g. isopropyl 70% or ethyl alcohol 70%) can be used to wipe down surfaces where the use of bleach is not suitable for e.g. Mobiles, laptops, keys, pens etc.

*Disinfection:* Freshly prepared 1% sodium hypochlorite should be used as a disinfectant for cleaning and disinfection with at least 10 minute contact period.

*Aerosol:* Ensure room disinfection within 20 minutes of any procedure generating aerosol.

*Social distancing:* Maintain at least 1 meter distance unless required for examination or procedure.

*Contact and droplet precautions:* minimize direct contact, ensure hand hygiene, and cough etiquette.

**Healthcare Worker (HCW) Risks**

Apart from risks related to droplet spread and from contaminated surfaces, ICU professionals face the challenge of acquiring infection during aerosol generating procedures (see table in Part II). HCW should wear a medical mask and gown when entering a room where patients with suspected or confirmed COVID-19 are admitted and use full personal protective equipment (PPE), which includes N95 mask, goggles or face shield, cap, full sleeve gown and shoe cover, when performing aerosol-generating procedures [41]. The entire PPE is

### Table I Treatment Based on Severity of Disease in Proven Coronavirus Disease-19 (COVID-19)

| Symptomatic proven case | Admit in | Treatment | Discharge |
|-------------------------|----------|-----------|-----------|
| Mild                    | Designated COVID isolation room | Symptomatic treatment | Discharge if 72 h afebrile or 7d after symptom onset and two samples negative 24 h apart followed by home quarantine for total 14 d |
| Moderate                | Designated COVID isolation room | Supportive care, oxygen Oseltamivir | Clinical improvement and two negative nCoV PCR tests 24 h apart |
| Severe                  | COVID ICU | Provide nasal prong oxygen Escalate to invasive ventilation if worsening Avoid HFNC/NIV Oseltamivir Ritonavir/Lopinavir OR Hydroxychloroquine Supportive care | Clinical improvement and two negative nCoV PCR tests 24 h apart |
| Critical                | COVID ICU | In addition to the above: Intubate based on clinical/blood gas/radiological features Use all airborne precautions Ventilation ARDS protocol Other organ support Once improving, wean from ventilator and extubate as per protocol | Clinical improvement and two negative nCoV PCR tests 24 h apart |

HFNC: High-flow nasal cannula, NIV: Non-invasive ventilation, ICU: intensive care unit, ARDS: Acute respiratory distress syndrome.
| Antiviral drugs | Drug class | Drug name; stage | Mechanism | Dose | Additional points | Evidence |
|----------------|------------|------------------|-----------|------|-------------------|----------|
| Nucleoside analogue | Ribavarin; Pneumonia | Inhibits RNA synthesis and viral replication | IV 8 mg/kg 8 hourly × 14 d | Side effects: | Hemolytic anemia, Hypocalcemia, Hypomagnesemia May increase viral load in combination with steroid | In vitro studies SARS data Not recommended |
| Neuraminidase inhibitor | Oseltamivir; Pneumonia | Reduces viral replication | <12 mon: 6 mg/kg/ dose BD >12 mon: <15 kg: 60 mg/d 15-23 kg: 90 mg/d 23-40 Kg: 120 mg/d >40 kg: 150 mg/d Given PO/BD for 5 d (max dose 150mg) | If co-infection with influenza suspected | MERS-CoV data |
| Protease inhibitor | Lopinavir/ Ritonavir; Early ARDS | Inhibit CoV main protease required in replication | Low dose: 200/100 mg BD High dose: BD for 6-15 d 14 d-12 mon: 16 mg/kg/dose < 15 kg: 12 mg/kg/dose 15-40 kg: 10 mg/kg/dose (Based on Lopinavir) >40 kg: 400/100 mg Given PO/BD for 5-14 d (Max dose Lopinavir 400 mg / ritonavir 100 mg) | | In-vitro studies SARS data [33] Weak recommendation [44] |
| Adenosine analogue | Remdesivir; Pneumonia | Incorporates into viral RNA and leads to premature chain | Adult dose: 200 mg IV on d 1 followed by 100 mg daily ×5-10 d | Avoid in children, pregnant, renal and hepatic impairment | In vitro studies [35] Case report in US [36] On-going trials termination |
| Aminoquinoline | Chloroquine Hydroxy-chloroquine; Pneumonia | Increases endosomal pH and hinders virus cell fusion Inhibits viral binding to ACE-2 Immunomodulatory effect | CQ: 10 mg/kg base stat followed by 5 mg/kg base BD HCQ: 8 mg /kg loading dose, then 4 mg/Kg / dose PO /BD: 5 d (max dose 400mg) Prophylaxis 400 mg BD on d 1 then 400 mg weekly | Inhibits pneumonia exacerbation Negative conversion Shortens disease | Unpublished data [45] Ongoing phase III trial for prophylaxis and reducing transmission ICMR recommendation for prophylaxis |

Contd....
| Drug class               | Drug name; stage | Mechanism                  | Dose                          | Additional points                                                                 | Evidence                                                                 |
|-------------------------|------------------|---------------------------|-------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| **Immuno-modulators**   |                  |                           |                               |                                                                                  |                                                                           |
| Corticosteroids         |                  | To suppress cytokines     | 1-2 mg/kg/day × 5-7 d         | Delays clearance of viral RNA                                                     | Reduced duration of supplemental oxygen and radiological improvement [46] |
|                         |                  | storm, HLH                |                               |                                                                                  | SSC guidelines recommend use in ARDS but meta-analysis in viral pneumonia- harm > benefit [28] |
|                         | Methylprednisolone; Pneumonia ARDS |                           |                               |                                                                                  |                                                                           |
|                         |                  |                           |                               |                                                                                  |                                                                           |
| Immunoglobulin          |                  | Immunomodulator           | 1-2 g/kg over 2-5 d           | After all therapies failed                                                         | Critically ill SARS [47]                                                 |
|                         | IVIG/Convalescent plasma; Critical stage |                           |                               |                                                                                  |                                                                           |
| **Immuno-modulator and antiviral** |                  |                           |                               |                                                                                  |                                                                           |
| Interferon-α; Early phase of URTI, Pneumonia | Reduces viral load | Nebulization of 200,000 - 400,000 IU/kg (2-4 µg/kg) in 2 mL sterile water BD for 5-7 d | Weak recommendation [48]                                                          |                                                                                 |
| Interferon-α2b spray; Close contacts URTI | Reduces viral load | 1-2 sprays (8000 IU/spray) on each side of the nasal cavity, 8-10 sprays on the oropharynx, once every 1-2 hrs for 5-7 d |                                                                                  |                                                                                 |
| **Immunotherapy**       |                  |                           |                               |                                                                                  |                                                                           |
| Interleukin -6 inhibitor | Tocilizumab; Cytokine release syndrome | Immunosuppression          | <30 kg - 12 mg/kg/dose >30 kg - 8 mg/kg/dose IV BD as infusion 1-2 d (max dose 800 mg) | For HLH and cytokine storm                                                   | On-going clinical trials                                                  |
|                         |                  |                           |                               |                                                                                  |                                                                           |
recommended to be used for 4-6 hours and changed earlier if there is any soiling. Team should not include staff vulnerable to infection like immunocompromised person, pregnant ladies, age >60 years or those with co-morbidities. In the event of exposure and manifestation of infection, management as per guidelines as well as psychosocial support needs to be ensured. Adequate communication, education and adherence to strict personal protection can minimize the risk of transmission to HCW [26]. ICMR recommends prophylactic use of hydroxychloroquine 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks for HCW managing suspected or confirmed COVID-19 patients [42].

Special Considerations for Resuscitation

It is important to minimize the number of people inside the room during high aerosol generating events like cardiopulmonary resuscitation. One airway specialist, one nurse/doctor for chest compression and one nurse for medication are essential. Other assistants may remain outside the room and may enter only if necessary after donning full PPE. Hand bagging needs to be avoided. During any disconnection from ventilator, endotracheal (ET) tube needs to be clamped and/or viral filter attached to the ET tube. In case re-intubation is required, follow the standard procedure described (see Part II in this issue).

CONCLUSION

The COVID-19 pandemic caused by 2019-nCOV has become a serious concern for mankind all over the world. It has challenged and overwhelmed the existing intensive care facilities globally. SARI is the most common indication for intensive care management and is associated with high mortality. The disease so far appears to be less common in children and seems to have a milder course. Preparation for handling crisis during this outbreak is essential for early identification, stratification and management of cases. Prevention by ensuring strict infection control practices minimizes transmission to other patients and healthcare workers, especially in intensive care units.

Contributors: NR, KN, AB, SKA: substantial contribution to the conception and design of the work (ii) drafting the work (iii) final approval of the version to be published (iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; GVB, MS, RL, DG, MJ: substantial contributions to the acquisition and interpretation of data for the work (ii) revising it critically for important intellectual content (iii) Final approval of the version to be published (iv) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding: None; Competing interests: None stated.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in China: Summary of a report of 72,314 cases from the Chinese center for disease control and prevention [published online ahead of print]. JAMA. 2020;10.1001/ jama.2020.2648. Available from: https://jamanetwork.com/ journals/jama/fullarticle/2762130. Accessed March 25, 2020.
2. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts’ consensus statement. World J Pediatr (2020). doi:10.1007/ s12519-020-00343-7. Accessed March 25, 2020.
3. Coronavirus disease 2019 [Internet]. [cited 2020 Mar 26]. Available from: https://www.who.int/emergencies/diseases/ novel-coronavirus-2019.
4. de Wilde AH, Snijder EJ, Kikkert M, van Hemert MJ. Host factors in coronavirus replication. Curr Topic Microbiol Immunol. 2018;419:1–42.
5. Paules CI, Marston HD, Fauci AS. Coronavirus infections—More than just the common cold. JAMA. 2020;323:707–8.
6. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhuan, China, of novel coronavirus–infected pneumonia. N Engl J Med. 2020; 382:1199-207.
7. Lu X, Zhang L, Du H, Zhang J, Li Y, Qu J, et al. SARS-CoV-2 Infection in Children. New England J Med. 2020. Available from: https://www.nejm.org/doi/full/10.1056/ NEJMc2005073. Accessed March 24, 2020.
8. Lee P-I, Hu Y-L, Chen P-Y, Huang Y-C, Hsueh P-R. Are children less susceptible to COVID-19? J Microbiol Immunol Infect. 2020. Available from: https://www.sciencedirect.com/ science/article/pii/S1684118220300396?via%3Dihub. Accessed March 24, 2020.
9. Li W, Moore MJ, Vasilieva N Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426:450-54.
10. Mahase E. Coronavirus: covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. BMJ. 2020;368:m641. Available from https:// www.bmj.com/content/368/bmj.m641. Accessed March 29, 2020.
11. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. Published online March 23, 2020. doi:10.1001/jama.2020.4683. Accessed March 29, 2020.
12. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhuan, China: A single-centered, retrospective, observational study. Lancet Respiratory Medicine. 2020. Available from: https://doi.org/10.1016/ S2213-2600(20)30079-5. Accessed March 29, 2020.
13. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: Early experience and forecast during an emergency response. JAMA. Published online March 13, 2020. doi:10.1001/jama.2020.4031. Accessed March 29, 2020

14. Yoon SH, Lee KH, Kim JY, Lee YK, Ko H, Kim KH, et al. Chest radiographic and CT findings of the 2019 Novel Coronavirus Disease (COVID-19): Analysis of nine patients treated in Korea. Korean J Radiol. 2020;21:494-500.

15. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395:507-13.

16. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports-48. Accessed March 29, 2020.

17. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics. 2020; doi: 10.1542/peds.2020-0702. Accessed March 29, 2020.

18. Indian Council of Medical Research. Revised Strategy of COVID19 testing in India (Version 3, dated 20/03/2020). Available from: https://icmr.nic.in/sites/default/files/upload_documents/2020-03-20_covid19_test_v3.pdf. Accessed March 29, 2020.

19. World Health Organization. (2020). Laboratory testing for COVID19. Available from: https://www.who.int/iris/handle/10665/331329. Accessed March 30, 2020.

20. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected Interim guidance. WHO/2019-nCoV/IPCPPE_use-2020.1-eng.pdf. Accessed March 29, 2020.

21. Indian Council of Medical Research. Press Release on “Fast Track Approval for Indian COVID-19 Testing Kits for Commercial Use.” Available from: https://www.icmr.nic.in/content/press-release-fast-track-approval-indian-covid-19-testing-kits-commercial-use. Accessed March 29, 2020.

22. The Australian and New Zealand Intensive Care Society (ANZICS). COVID-19 Guidelines Version 1. Available from: http://www.icmr.nic.in/content/press-release-fast-track-approval-indian-covid-19-testing-kits-commercial-use. Accessed March 30, 2020.

23. Xie J, Tong Z, Guan X, Du B, Qui H, Slutsky AS. Critical care crisis and some recommendations during the COVID-19 epidemic in China. Intensive Care Med. 2020. Available from: https://doi.org/10.1007/s00134-020-05979-7. Accessed March 29, 2020.

24. Available from: https://apps.who.int/iris/bitstream/handle/10665/331215/WHO-2019-nCoV-IPCPPE_use-2020.1-eng.pdf. Accessed March 29, 2020.

25. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected Interim guidance. WHO/2019-nCoV/clinical/2020.4. Accessed March 29, 2020.

26. Murthy S, Gomersall CD, Fowler RA. Care for Critically Ill Patients With COVID-19. JAMA. Published online March 11, 2020. doi:10.1001/jama.2020.3633. Accessed March 29, 2020.

27. Brewster DJ, Chrimes NC, Do TBT, Fraser K, Groomboodirect.com, Higgins A, et al. Consensus statement: Safe Airway Society principles of airway management and tracheal intubation specific to the COVID-19 adult patient group. Med J Aust. March 16, 2020. Accessed March 29, 2020.

28. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. https://doi.org/10.1007/s00134-020-06022-5. Accessed March 29, 2020.

29. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID 19 infection: Different points from adults. doi.org/10.1002/ppul.24718. Accessed March 29, 2020.

30. Hongde Hu, Fenglian Ma, Xin Wei, Yuan Fang. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin, Eur Heart J. 2020; ehaa190. https://academic.oup.com/europarl/advance-article/doi/10.1093/europarl/ehaa190/5807656. Accessed March 29, 2020.

31. Zeng J, Liu Y, Yuan J, Wang F, Wu W, Li J, et al. First case of COVID-19 infection with fulminant myocarditis complication: Case report and insights [Pre-print]. Preprints 2020, 2020030180. Available from https://www.preprints.org/manuscript/202003.0180/v1. Accessed March 29, 2020.

32. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.

33. Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MML, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: A multicentre retrospective matched cohort study. Hong Kong Med J. 2003;9:399–406.

34. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New Eng J Med. 2020 [Online early]. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2001282. Accessed March 29, 2020.

35. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269-71.

36. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Graviss EA,钉钉. Coronaviruse/situation-reports-48. Accessed March 29, 2020.

37. Vincent M, Bergeron E, Benjannet S, Erickson B, Rollin P, Ksiazek T, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:69.

38. Gautret P, Parolaoa P, Hoanga V, Meddeba L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID 19: Results of an open label non randomized clinical trial. Int J Antimicrob Agent. 2020 [Online early]. Available from: http://www.sciencedirect.com/ science/article/pii/S0924857920300996. Accessed March 29, 2020.
9. Wang BX, Fish EN. Global virus outbreaks: interferons as 1st responders. Semin Immunol. 2019;43:101300. Available from http://www.sciencedirect.com/science/article/pii/S1044532319300065. Accessed March 29, 2020.
10. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol. 2020;92:479-90.
11. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on chest ct during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Available from: https://pubs.rsna.org/doi/10.1148/radiol.2020200370. Accessed March 29, 2020.
12. World Health Organization. Advice on the use of masks in the community, during home care and in healthcare settings in the context of the novel coronavirus (COVID-19) outbreak [internet]. Available from: https://www.who.int/publications-detail/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak. Accessed March 25, 2020.
13. Indian Council of Medical research. Recommendation for empiric use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection [internet]. Available from: https://icmr.nic.in/sites/default/files/upload_documents/HCQ_Recommendation_22March_final_MM.pdf. Accessed March 25, 2020.
14. Wang XF, Yuan J, Zheng YJ, Chen J, Bao YM, Wang YR, et al. Clinical and epidemiological characteristics of 34 children with 2019 novel coronavirus infection in Shenzhen [English abstract]. Zhonghua Er Ke Za Zhi. 2020;58:E008. [Retracted].
15. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020;14:72-3.
16. Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China [pre-print]. Available from: https://doi.org/10.1101/2020.03.06.20032342. Accessed March 29, 2020.
17. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19[Published online ahead of print]. Lancet Infect Dis. 2020;S1473-3099(20)30141-9. Available from: https://doi.org/10.1016/S1473-3099(20)30141-9. Accessed March 29, 2020.
18. Jin Y, Cai L, Cheng Z, Cheng H, Deng T, Fan Y, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military Med Res. 2020;7: 4. Available from: https://mmrjournal.biomedcentral.com/articles/10.1186/s40779-020-0233-6. Accessed March 29, 2020.