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COVID - 19

ORIGIN OF PANDEMICS***Gouri Rao Passi**

Abstract: *The incidence of infectious disease outbreaks is increasing over time. This article presents an overview of some major pandemics. The majority of them are zoonoses and the causes underlying spillovers to humans are analysed. Degradation of wild life habitats, intensive animal husbandry and changing land use are some important causes. The concept of “One Health” is highlighted.*

Keywords: *Pandemics, Wild life, One health.*

Currently, the world is in the throes of a pandemic of unprecedented magnitude. Looking back sometimes not only clarifies the future and also helps us to look forward with confidence into the future.

History books abound with tales of pandemics. A prominent story is that of the Black Death. In October 1340 AD, twelve trading ships from Central Asia, weighed anchor in the Sicilian port of Messina. Port authorities panicked when they found most of the sailors on board dead and the rest afflicted by a terrifying new disease. They had nodules breaking out using blood and pus. Though the ships were ordered to summarily leave, it was too late. The infection had set foot in Europe and in five years a third of Europe's population was wiped out.

This was the bubonic plague, caused by *Yersinia pestis*. Its natural reservoir is the rat but other animals like dogs, cats and camels can also be infected. The vector which transmits it from rat to rat is the flea. Poor sanitary conditions and congested surroundings set the stage for spillover to humans. On a positive note, the plague pandemics led to the birth of widespread public health measures and the first example of quarantine.¹

An important question haunts mankind today. Are pandemics just random events or is the incidence of

novel infectious diseases burgeoning over time? Jones et al., analyzed a database of 335 infectious disease outbreaks between 1940 and 2004. They found that outbreaks have risen significantly over time after taking care of reporting bias. Importantly, 60.3% are zoonoses and the vast majority (71.8%) originated in wildlife. They also identified certain global ‘hotspots’ where they are most likely to begin.²

A careful analysis of the influenza epidemics sets the stage for a deeper understanding of why diseases sometimes go out of control. In the last 100 years there have been 4 major pandemics in humans - “Spanish” influenza, H1N1 (1918), “Asian” influenza, H2N2 (1957), “Hong Kong” influenza, H3N2 (1968) and Swine flu Mexico/USA, H1N1 (2009). The deadliest was the Spanish flu which killed 40 million people and infected a third of the world's population between 1918-1919.³ Genetic testing and phylogenetic analysis of the influenza viruses from the fixed and frozen lung tissue of the 1918 epidemic victims have revealed that it originated from avian influenza viruses.

Repeated investigations have shown that the natural reservoir of influenza viruses are wild water fowls. But these viruses regularly undergo antigenic drift and shift. The drift is due to mutations in the single stranded RNA of the virus. Because the RNA polymerase of these viruses lacks proof reading capacity, all RNA viruses are prone to multiplicative errors. The antigenic drift helps the virus evade host immunity and is responsible for annual outbreaks. However, pandemics occur due to antigenic shifts. The influenza virus has two viral proteins, namely hemagglutinin (HA) and neuraminidase (NA) which get attached to the sialic acid on the human epithelial cells glycoprotein. They have alpha-2,6 residues while birds have alpha-2,3 residues. Interestingly, pigs have both. As influenza virus has a segmented genome, pigs act as reassortment vessels where genes of avian influenza viruses mix resulting in antigenic shifts and develop capability to infect humans by reassortment.⁴

The innovative influenza virus is relentlessly evolving new strategies to infect humans and the humans are fighting back. In 1997 a global web-based surveillance system called FluNet was established. Data of the various influenza

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subtypes isolated is continually entered here by various countries. According to data collected, vaccines effective against the predicted strains are annually manufactured just before the flu season. It also predicted pandemics such as the 2009 H1N1 outbreak which was rapidly evaluated and contained after just a few cases were detected in Mexico and USA.

In the mid 1990's, investigations into a mysterious illness which killed horses and their caretakers in Australia identified a new virus called the Hendra virus (HeV).⁵ A serological study in horses failed to show any significant antibodies implying that they were not the primary reservoirs. A careful study of 46 animal species finally clarified that fruit bats were the reservoirs.⁶

When the virus spreads to horses, they not only acted as amplifying agents but further spread it to humans. Since then bats have been repeatedly identified as the reservoir for a series of zoonoses including the Nipah virus, Ebola, SARS-CoV-1 and now the SARS-CoV-2 (COVID-19).^{7,8} The extraordinary characteristics of bats need detailing. Bats form the largest aggregation of mammals on the planet around up to a million members. They are greatly vilified in common folklore but vital to maintaining nature's balance. They control insect populations, reseed cut forests, pollinate plants and scatter nutritious guano to enrich the soil. Less known fact is that they act as reservoirs for more than 200 viruses.⁹

Their large breeding grounds, long life spans and ability to fly long distances all contribute to harbouring and spreading viruses. There is intense research into why bats are such rich reservoirs of viruses. Delay in recruitment of B and T lymphocytes suggests that the immune system in bats has evolved to favour incomplete viral clearance to evade immune mediated morbidity and mortality.¹⁰

Bats played a crucial role in the occurrence of the Nipah virus epidemic in Malaysia in September 1998. It began as an unexplained acute febrile encephalitis in pig farmers of Malaysia with a mortality rate of 40%. But a zoonosis was suspected in view of the preceding epidemic of barking cough and encephalitis in pigs in the same area. Virus isolation in the CSF of patients and fruit bats in nearby orchards and forests helped to piece together the parts of the puzzle.¹¹ It is edifying to note that the story started much earlier and natural climatic variations, human behaviour, diminishing forest cover, bats, pigs and our intensive animal husbandry practices by human all played a role.

In 1997, there was an unusually hot summer due to the El Nino Southern Oscillation effect. In Indonesia the

traditional slash and burn cultivation triggered huge fires. A severe haze enveloped the entire surrounding areas. Forest trees failed to flower and fruit. Unable to feed in the forests, fruit bats had to look towards greener pastures. They flocked to cultivated fruit orchards often adjacent to pig farms, a burgeoning industry in Malaysia. Pig feed was contaminated with bat excrements. The pigs passed it further to the pig farmers and were an intermediary amplifying host. Pigs exported to Singapore infected abattoir workers sparking risks of global spread.

The epidemic sent shock waves all over South East Asia. Abattoirs in Singapore and Malaysia were shut down. One million pigs were culled in Malaysia and the rest of the pigs were kept under close surveillance. An international team of virologists, epidemiologists and public health experts were instrumental in finally quelling the outbreak.¹¹

Later, during outbreaks of Nipah in Bangladesh, by using infrared cameras, it was revealed that bats whose natural habitats had been disturbed had started frequenting forest fringes to eat date palm sap. The contamination of the date palm sap which was collected by the village people to make tari (fermented date palm juice) led to transmission of the virus to humans without any other animal intermediary.¹²

In 2018, prompt action by public health experts and the administration helped to halt the Nipah virus encephalitis in Kozhikode, Kerala after an outbreak involving 18 people with 88.8% mortality. The virus was again isolated in bats of neighbouring forests and transmission occurred probably during cleaning of an unused bat infested well or perhaps, visits to the forest by the locals.¹³

The first pandemic of the 21st century was due to SARS- CoV-1 in 2002. The severe acute respiratory syndrome (SARS) infected 8422 patients in 29 countries with 916 deaths.¹⁴ Painstaking epidemiological tracing identified that the first patients were in Guangdong province of China. A single patient who travelled from there to Hong Kong and stayed in a hotel on February 22, 2003 managed to infect 10 more people living in the hotel by aerosols generated. This led to international spread when guests flew back home to Canada, Singapore, Hanoi, etc. The reservoir of the SARS CoV-1 virus was again traced to bats. There was probably an intermediary host, either the Himalayan Palm Civets or raccoon dogs linked to a live animal market in Shenzhen, China.

A closely related outbreak in April 2012 of severe acute respiratory infections in a hospital in Jordan needs

mention. Of the 11 people infected, 8 were health care workers and two of them died. In September 2012 the etiological agent was identified as a novel corona virus and the infection was named the Middle East Respiratory Syndrome (MERS).¹⁵ Subsequently, there were several other small outbreaks in Saudi Arabia as well as certain countries in Europe. In view of the annual Haj pilgrimage attracting 2 million people from 182 countries, there was an urgent evaluation for any pandemic potential. Detailed epidemiological studies to find the animal host identified that 22.8% of dromedary camels tested in Saudi Arabia harboured the virus and camel shepherds were at high risk for infection. Mathematical modelling by Breban, et al showed that the R_0 (the number of secondary cases) was below 1 and hence pandemic potential was low¹⁶ and this has been borne out with time. Between 2012 and December 2019 about 2502 patients have been infected with MERS with a case fatality rate of 34.4%.¹⁷

The details of the current novel SARS-CoV-2 epidemic is still evolving. Chinese authorities announced a cluster of pneumonia of unknown etiology on 31st December 2019 in Wuhan province. Most had an association with a local sea food market which sold wild animals also. By 7th January 2020, the infectious agent had been identified as a novel corona virus (2019 nCoV). Human to human transmission was soon confirmed with a R_0 of 2-3.5.¹⁸ Wuhan's gargantuan population, widespread trade and travel connections and presence of asymptomatic carriers are some of the reasons for the consequent malignant global spread. The natural reservoir has again been traced to bats with the possible animal intermediary being the pangolin.⁸

Hidden behind each outbreak is an urgent lesson for mankind. The recurrent patterns are obvious. Most deadly emerging infectious disease outbreaks are zoonotic in origin. New outbreaks are inevitable because of the constant evolution of organisms. Excessive replicative errors in RNA viruses are the reason why they are the commonest novel infections to emerge.¹⁹

Animals in the wild coexist harmoniously with deadly viruses. The association probably goes back to millions of years. Nuclear gene analysis has dated bats to the Eocene period 50 million years ago. Viruses which evolved with them probably used key cellular receptors some of which have been conserved in later mammals like humans.²⁰ Hence, it is easy for viruses to cross infect man.

Finally, one needs to ask - why do spillovers occur and why are they increasing over time? There are two parts to the problem - 'the spark' where the spillover starts and the 'spread', determines how it transforms into a pandemic.

The natural habitats of wild animals are shrinking. They are being forced to migrate to newer areas often near human settlements. The reasons are protean with wanton destruction of forests, unprecedented changes in land use, intensified agricultural practices due to an explosive growth in human population and their need are just to name a few.²¹ Intensive animal husbandry such as poultry farming and pig farming increase the risk of spillover of new viruses from animals.²² Yet another hotspot for spillovers include wet markets where animals are slaughtered in unhygienic conditions. Certain diseases like Ebola are linked to hunting and eating of wild meat.²³

The rapid spread across countries is linked to the large scale movements of people, livestock, food and goods as well as ubiquitous air travel due to tourism in today's world.²⁴ The human population is predicted to cross 10 billion by 2050. It has increased from 1 billion in the beginning of the 20th century to 6 billion by the turn of the century.² Urban spaces are overloaded and it takes just a spark to unleash a wildfire.

Cataloguing problems without contemplating solutions is a recipe for disaster. So, what must be done to reduce the risk of further inevitable outbreaks? We need to solve it at many different levels. Public health experts, ecologists, scientists, economists and sociologists and all mankind need to come together.

Short term solutions include monitoring emerging infectious diseases in both wild animals and livestock with systems such as the Global Early Warning System (GLEWS) developed by the Food and Agriculture Organization-World Organisation for Animal Health formerly the Office International des Epizooties (OIE) - World Health Organization (FAO-OIE-WHO), streamlining the animal husbandry industry and wet markets, strengthening core public health services, increasing pandemic preparedness and developing a surge capacity to scale up delivery of health interventions, if required.

Long term solutions include conservation of forests, wild life and other complex ecosystems. The solution lies in the concept of 'One Health'.²⁵ We need to understand that the health of humans is inextricably linked to that of all other animals, organisms, plants and the entire biosphere. The economy of unjustified overconsumption needs questioning. Each one of us has a role in nurturing the planet.

400 years ago, John Donne rightly said, "No man is an island. Every man is a piece of the continent. So never send to know for whom the bell tolls. It tolls for thee."

Points to Remember

- *World had constantly faced pandemics, the most prominent being black death caused by bubonic plague in 1340, causing death of one third of European population in a span of five years, which led to the birth of widespread public health measures and the first example of quarantine.*
- *Bats have played a crucial role in the appearance of many virus epidemics involving, Nipah virus, Ebola, SARS-CoV-1 and now the SARS-CoV-2 (COVID-19).*
- *Bats not only play a vital role in maintaining nature's balance, but also act as reservoirs for more than 200 viruses.*
- *Hidden in each outbreak is an urgent lesson for mankind that the natural habitats of wild animals are shrinking. They are being forced to migrate to newer areas often near human settlements.*
- *Long term solutions include conservation of our forests, wild life and other complex ecosystems. The solution lies in the concept of "One Health". We need to understand that the health of humans is inextricably linked to that of all other animals, organisms, plants and the entire biosphere.*

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COVID - 19

CORONA VIRUS: WHAT DO WE KNOW?***Jaydeep Choudhury******Dhanalakshmi K**

Abstract: *Coronavirus causes a wide variety of diseases in various animal species. It is known to cause innocuous respiratory infections and occasional viral diarrhea in humans. Pandemic caused by SARS-CoV-2 (a beta corona virus) is a third spill over in two decades of an animal corona virus to humans. It uses ACE2 receptors for cell entry. Active viral replication has been proved in the cells of human respiratory tract, conjunctiva and gastrointestinal tract contributing to multiple routes of transmission. Peak viral load is noted at the time of presentation which explains the transmission even in pre-symptomatic stage. R_0 is expected to be around 2 to 3, which explains the higher pandemic potential. The virus persists on inanimate objects for a variable period of time depending on the infectious dose, temperature and humidity.*

Keywords: *Coronavirus, Basic reproductive number, Viral load, Replication sites, Infectivity, Stability.*

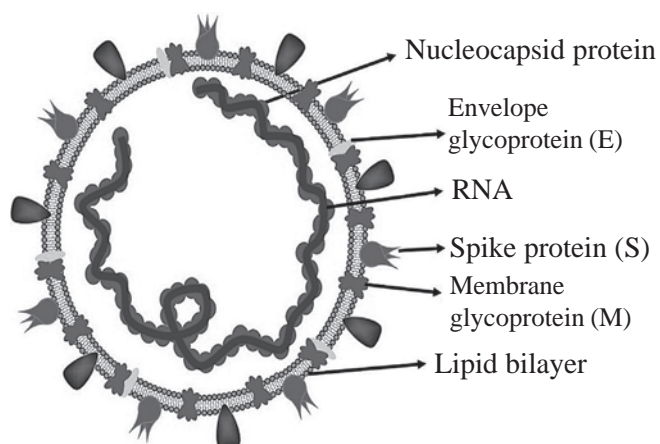
The Coronavirus family comprises of two subfamilies, Coronavirus and Torovirus. The Coronavirus subfamily is divided into four genera, alpha, beta, gamma and delta. Human Coronaviruses (HCoV) belong to alpha and beta genera. Following corona viruses are found to have the pandemic potential i) SARS-CoV-1, ii) MERS and iii) SARS-Cov-2, this is the virus responsible for the current pandemic. The first HCoV isolation was reported in 1965. The first epidemic of HCoV, Severe Acute Respiratory Syndrome (SARS) was reported in 2002. Middle East Respiratory Syndrome (MERS) was the next major HCoV outbreak which occurred in 2012. In various

animal species, a wide variety of diseases for causes. In chicken, it causes bronchitis and nephrosis. Manifestations in pigs include gastroenteritis and encephalitis. In dogs, turkeys and calves, enteritis is the usual presentation. While hepatitis and encephalitis in rats, peritonitis in cats, pneumonia and hepatitis in whales of the diseases in different species. It has got varied manifestations in bats with multiple strains.¹ Recent available literature is reviewed for better understanding of the nature of virus and viral dynamics which will be useful for improving clinical care and containment of the disease.

Human corona viruses

Coronaviruses are medium to large enveloped RNA viruses. It has a characteristic widely spaced, petal shaped surface projections, making the virus look like solar corona. The viruses are heat labile and also vulnerable to lipid solvents and alkaline pH.

Coronavirus is positive sense, single stranded RNA of 30 kilobases in length. (Single stranded RNA viruses are classified as positive or negative depending on the sense or polarity of the RNA. The positive-sense viral RNA genome can serve as messenger RNA and can be translated into protein in the host cell). It is the largest known viral RNA.² Structurally a nucleoprotein (N)

**Fig.1. Human Coronavirus - Structure**

Source: Shereen M A, Khana S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020; 24:91-98.

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surrounds the RNA genome and together they appear as a coiled tubular helix inside the bilayer lipid envelope, which anchor membrane (M), envelope (E) and spike (S) protein. A subset of corona viruses (specifically the members of beta corona virus) have a shorter spike-like surface protein called hemagglutinin esterase (HE).

While replicating, the virus attaches to the cell membrane by HE or S protein in the spikes. Some of the viruses use angiotensin-converting enzyme 2 (ACE 2) as the cellular receptor. Next the penetration occurs due to fusion of the viral envelope with plasma membrane. A large polyprotein is formed, cleaved into 15 or 16 nonstructural proteins and a replication complex is formed, following which the transcription is initiated. Virions are assembled by budding into cytoplasmic vesicles and released by cell lysis.

Epidemiology

Coronavirus infection may occur throughout the year, more cases are seen around winter months. It contributes to about 35% of upper respiratory infection during peak activity. Occasionally there may be outbreaks of infections. Reinfection is common which may be due to rapid diminution of antibody level after infection.²

Age

Among patients with common cold across all age groups, 2-10% are due to human corona viruses. Asymptomatic and symptomatic infections occur at all ages.

Transmission of HCoV

Infections occur through respiratory route. Aerosols are generated during cough, sneeze or even while talking. It consists of saliva and nasopharyngeal secretions that are contaminated with infectious agents. The droplets can be propelled for some distance depending upon their size and force of expulsion. The expelled droplets can land directly on the conjunctiva, oro-respiratory passage or skin of a close contact.

Small droplets less than 5µm can travel rapidly and to some distance depending upon the external environment. During dry season with less humidity, the moisture in these particles evaporate to produce droplet nuclei which are light and can remain airborne for a long time. Respiratory droplets can also contaminate inanimate objects. Touching these objects with contaminated fingers following cough or sneeze can transmit infection.

In healthy children, HCoV replicates only in the upper respiratory tract. The incubation period is generally 2 days

and the infection lasts for about a week. Infection in immune-compromised children may be severe.

Manifestations of HCoV

(a) Upper respiratory tract infection: HCoV often presents like an undifferentiated acute respiratory tract infection. Rhinorrhea, sore throat, cough, malaise, headache and fever are the usual features.

(b) Lower respiratory tract infection: HCoV is the third most common etiology of viral pneumonia and bronchiolitis after respiratory syncytial virus (RSV) and parainfluenza virus. It may also precipitate acute asthma. HCoV may affect neonates and clinically present with apnea, hypoxia and bradycardia.

(c) Enteric infection: There are reports of nursery outbreaks of severe diarrhea and necrotizing enterocolitis (NEC) related to HCoV.¹

(d) Neurologic diseases: HCoV is linked to neurological diseases like acute disseminated encephalomyelitis (ADEM), multiple sclerosis and polyradiculitis.

Severe acute respiratory syndrome (SARS)

SARS CoV-1 was first identified in China in November 2002 and subsequently it spread throughout the world. The epidemic lasted till the summer of 2003, the last known case occurred in summer of 2004. It accounted for 774 deaths (9.6% mortality) all over the world.³

SARS-CoV was classified as beta coronavirus lineage B. It originated in animals, most probably bats and then spread to exotic animals which were consumed by human in China. Humans were affected subsequently through an intermediate host, probably palm civet or raccoon dog. The viruses have been noted to mutate frequently and infect new species. SARS-CoV virus was transmitted by aerosols. It uses angiotensin-converting enzyme as a cellular receptor.²

In children, the disease manifested with fever, cough and systemic influenza like symptoms. Some children had diarrhea also.¹ Pneumonia developed in few children, mostly adolescents. Chest radiology showed ground glass opacities with peripheral consolidation. Maternal SARS-CoV infection resulted in maternal and fetal morbidity and mortality.

Lymphopenia with normal or decreased neutrophil count is the usual finding in peripheral blood examination. Neutrophilia is associated with poor outcome.² CPK, LDH and SGOT are usually abnormal. Reverse transcription polymerase chain reaction (RT-PCR) specific for

SARS-CoV in respiratory secretions is the confirmatory investigation. There is no specific treatment. Prevention is the mainstay. The epidemic was controlled by massive efforts at case identification and containment.

Middle east respiratory syndrome (MERS)

The first case of MERS was in Saudi Arabia reported in June 2012. Later it spread to different parts of the world. The virus was named MERS-CoV. Globally it accounted for 609 deaths (36% mortality).⁴

MERS-CoV was classified as beta coronavirus lineage C and is closely related to bat coronaviruses.

All MERS-CoV infections were traced to middle east countries, mainly Saudi Arabia.^{4,5} Initial transmission pattern of the virus showed reproductive coefficient (R_0) less than 1, which indicates low pandemic potential. Later, in one outbreak, superspreading was observed where one patient infected 80 individuals.² Mean incubation period was 5 days with a range of 2 to 14 days.

Patients suffering from MERS present with fever, chills, sore throat, cough, arthralgia and myalgia. They often develop dyspnea and rapidly progress to pneumonia. Many patients required ventilator support. Some presented with nausea, vomiting and diarrhea. Renal failure,

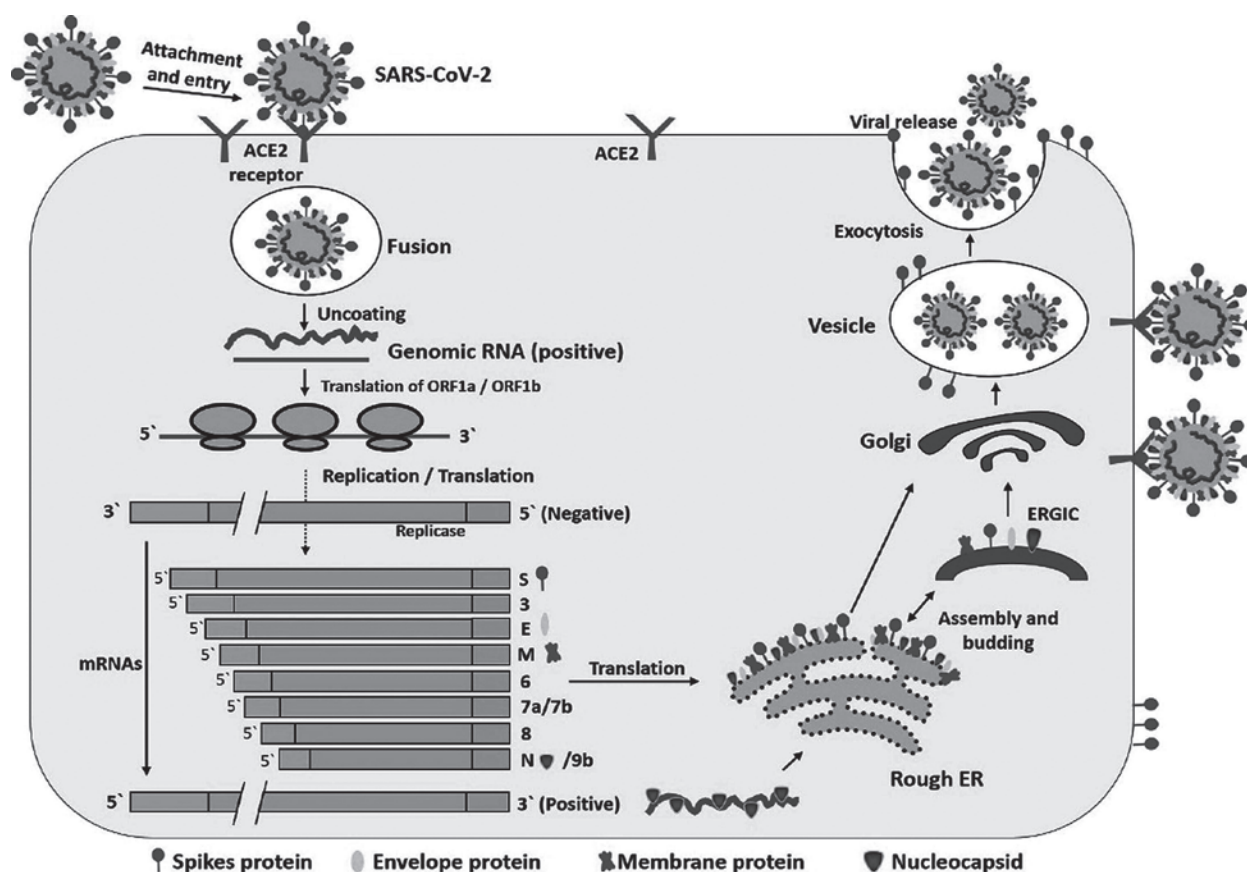


Fig 2. Life cycle of SARS CoV2 in host cells (begins its life cycle when S protein binds to the cellular receptor ACE2. After receptor binding, the conformation change in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway. Then SARS-CoV-2 releases RNA into the host cell. Genome RNA is translated into viral replicase polyproteins pp1a and 1ab, which are then cleaved into small products by viral proteinases. The polymerase produces a series of sub genomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins. Viral proteins and genome RNA are subsequently assembled into virions in the ER and Golgi and then transported via vesicles and released out of the cell. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER-Golgi intermediate compartment).

Source: Shereen MA, Khana S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission and characteristics of humancoronaviruses. *J Adv Res* 2020; 24:91-98.

pericarditis and ARDS have been reported. Children and adolescents with MERS, occasionally, have been asymptomatic or mildly symptomatic.¹

Both SARS and MERS have presented with similar clinical features. But patients with MERS have a shorter time from onset of illness to clinical presentation, enhanced requirement for ventilatory support and higher case fatality rate.⁴

SARS-CoV-2

The current pandemic caused by SARS -CoV-2 which emerged initially in Wuhan, China is rapidly spreading and so far has affected 216 countries with 3,00,441 deaths (as on May 16, 2020).⁶ It was initially named as 2019 novel coronavirus because of the incomplete match between the genomes of this and other (previously known) coronaviruses.⁷ This pathogen was later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group and the disease was named coronavirus disease 2019 (COVID-19) by the WHO.⁸ The incubation period of SARS-CoV-2 is estimated to be between 1 and 14 days, with a median of 5 to 7 days.⁹

Phylogenetic analysis of the SARS-CoV-2 genome indicates that the virus is closely related (with 88% identity) to two bat-derived SARS-like coronaviruses collected in 2018 in eastern China (bat-SL-CoVZC45 and bat-SL-CoVZXC21) and genetically distinct from SARS-CoV (with about 79% similarity) and MERS-CoV.⁷ Even though findings suggest that bats might be the original host of this virus, further studies are needed to elucidate whether any intermediate hosts have facilitated the transmission of the virus to humans.^{7,10}

Viral dynamics of SARS-CoV-2

Viral load from respiratory samples

In an analysis of a cohort of 23 patients with confirmed COVID-19 infection, peak viral load was highest at the presentation ($5.2 \log_{10}$ copies per ml) even when the disease is mild, explaining the high contagiousness of the disease.¹¹ Viral load gradually declined over second week. The relationship between the viral load, severity of the disease and mortality is yet to be ascertained. The reported median viral load of $1 \log_{10}$ was higher in severe cases than mild cases and the difference was not significant.¹¹

In another study from Germany of nine virologically confirmed cases, pharyngeal viral shedding was very high during the first week of symptoms (peak at day 4) and gradually declined (Box 1). The swabs taken after day 5 had a detection rate of only 39.93%¹²

Box 1. Viral RNA load from upper respiratory samples¹²

Peak on day 4	: 7.11×10^8 copies/swab
Average till day 5	: 6.76×10^5 copies/swab
Average after day 5	: 3.4×10^5 copies/swab

Viral load from lower respiratory samples (sputum)

Maximum viral load	: 2.35×10^9 copies/ml
Average	: 7.00×10^6 copies/ml

Infectivity and replication sites

Presence of viral subgenomic mRNA indicates actively infected cells since subgenomic mRNA is transcribed only in infected cells.¹² When samples from the upper respiratory tract were analyzed the presence of high viral load proved that active viral replication is happening. Active viral replication was noted till day 5 of symptom onset and no subgenomic mRNA was identified after that.¹²

Similarly, active viral replication from lower respiratory samples (sputum) was obvious from Day 4 to Day 9 (which was evident from the levels of viral subgenomic mRNA). Decline in viral load occurred from Day 10 to Day 11. When analyzing the genotypes from throat and sputum, the presence of genotype distinct serotypes support the fact that viral replication is happening in the throat rather than shedding of the virus to throat from lung.¹² A recent study showed SARS-CoV-2 infected the ciliated, mucus-secreting, club cells of bronchial epithelium and alveolar cells in the lung, where gas exchange takes place.¹³ It replicates more effectively in the bronchi similar to MERS. They also proved infection and replication of the virus in the conjunctiva and gastrointestinal tract.¹³ High expression of ACE2 receptors are also shown in the brush border of intestinal enterocytes^{14,15} and significant titres of virus particles were detected. This could explain the subset of patients with gastrointestinal symptoms. Thus transmission through eyes and faeco-oral route serves as additional routes of infection, which are relevant for the infection prevention and control.

Apart from the detection of viral mRNA from respiratory samples, stool and conjunctiva, it was also isolated from blood, urine and saliva.¹⁶⁻¹⁸ From the available evidence, active viral replication was detected in airways, alveolar epithelium, conjunctiva and gastro intestinal tract.

Duration of viral shedding

Duration of viral shedding by repeated viral cultures is warranted to ascertain the period of infectivity.

Presence of viral mRNA does not always mean active viral replication and infective potential. SARS CoV-2 RNA has been detected for 20 days or longer in one third of cohorts analysed and no association was seen between prolonged detection of viral RNA and the severity of illness.¹¹

In an attempt to understand the infectivity and duration of viral shedding, live virus isolation was attempted multiple times from various clinical samples.^{11,12} During the first week of symptoms, live virus was readily isolated from significant fraction of samples (16.66% of swabs and 83.33% of sputum).¹² After 8 days of symptom onset, no isolate was obtained from respiratory samples in spite of ongoing high viral loads. Generally, shedding of viral RNA from sputum outlasted the onset of symptoms. In most of the patients where symptoms wane at the end of first week, viral mRNA was detected from the upper respiratory samples and continued well into the second week and from sputum and stool, it can be detected till third week.¹² Considering the above factors, if the patients are clinically stable, home isolation can be offered to those presenting after 10 days of symptoms. Understanding this viral dynamics is important, because it was insisted that two negative swabs taken 24 hours apart were needed for discharge, but because of this intermittent shedding of viral mRNA (which need not be infectious) discharge criteria has been revised.¹²

Basic reproductive number - R_0

To calculate the degree of contagiousness or transmissibility of the coronavirus (infectivity), epidemiologists use different mathematical formulae to calculate the infectivity index. For this purpose, “basic reproductive number” R_0 (pronounced as R naught or R zero) is used. It is defined as the average number of new infections generated by an infectious person in a totally naïve (uninfected) population.¹⁹ It determines the herd immunity threshold and therefore the immunization coverage required to eliminate the disease. If R_0 is >1 , the number of people infected is likely to increase and if R_0 is <1 , transmission is likely to die out.

A study from Wuhan reported R_0 for SARS-CoV-2 to be 2.68 based on the imported cases from Wuhan to other cities.²⁰ A retrospective analysis from 12 different studies, quoted an average R_0 of 3.28 and median of 2.79.¹⁹ In general, R_0 for COVID-19 is expected to be around 2 to 3. The difference in R_0 in various studies is because of different calculation methods and the calculations were done during various stages of the epidemic. R_0 estimates by WHO ranges from 2 and 2.5 which is higher than both SARS (1.7-1.9) and MERS (<1), suggesting the higher pandemic potential of SARS CoV -2.²¹⁻²⁵

Household transmission of SARS-CoV-2

One of the important aspects of the virus transmission is its transmissibility among household members.²⁶ The study from Wuhan¹⁹ enrolled 85 patients with confirmed COVID-19 and their close contacts were 155 in total.²⁰ Secondary attack rate was 30% among household members. Among the close contacts, infection rate was 38% for household with 1 contact, 50% for household with 2 contacts and 31% for households with 3 contacts.²⁰

Another report, from analysis of cases from 20 provinces outside of Hubei in China found 1183 case clusters, out of which 64% of the clusters have been within the familial household.²⁷

Analysing the outbreak in cruise ship Princess Diamond off the Japanese coast, where initially 10 people were confirmed with COVID-19 and all others were quarantined for 14 days, 19% (both passengers and crew) were found to be infected when tested later.^{28,29} Thus, when compared with secondary attack rate among the household contacts for MERS which is 5% and for SARS-CoV which is 10.2%. The higher secondary attack rate for SARS-CoV-2 could explain the higher speed of spread and ever increasing quantity of cases when compared to the other two corona viruses.^{30,31}

Virus survival on different surfaces and environmental conditions

Though droplet transmission plays a major role in the transmission of SARS-CoV-2, aerosol (particle size $<5\mu\text{m}$) and fomite transmission is possible since the virus can remain infectious in aerosol for hours and on surfaces upto days (depending on the inoculum shed).³² As per the recent report published, the virus remained viable in aerosol for 3 hours.³³ Viruses were applied to different objects, maintained at 21 to 23°C with 40% relative humidity over 7 days and time for significant reduction in TCID₅₀ (Tissue culture infectious dose) was noted. SARS-CoV-2 is more stable on plastic and stainless steel than on copper and card board. The results are shown in Table I.³⁴

Stability at different temperatures

As per another recent work, SARS-CoV-2 is found to be highly sensitive to heat and at 4°C there was only around 0.7 log unit reduction on day 14, but at 70°C, the inactivation time was reduced to 5 minutes.³³ They investigated the stability of the virus at 22°C with a relative humidity of 65%. Virus stability on various surfaces is given in Table II.³⁴

In a retrospective analysis, human coronaviruses persist for a short time at temperature of 30°C or more.³⁵

Table I. Virus stability on surfaces (21 to 23°C with 40% humidity for 7 days) incubated at 21 to 23°C and 40% relative humidity over 7 days)³⁴

Surfaces	Time for significant reduction in viral titres	Reduction in TCID ₅₀
Plastic	72 hours	10 ^{3.7} to 10 ^{0.6} per milliliter of medium
Stainless steel	48 hours	10 ^{3.7} to 10 ^{0.6} per milliliter of medium
Copper	4 hours	No viable virus was detected after 4 hours
Card board	24 hours	No viable virus was detected after 24 hours
Aerosol	3 hours	10 ^{3.5} to 10 ^{2.7} TCID ₅₀ per litre of air

Thus the stability of the virus varies under different environmental conditions such as varying temperatures and humidity. In tropical countries like India with temperature nearing 40°C during summer and with average humidity of 60-70%, the viral survival on different surfaces needs to be studied.

Environmental contamination in health care premises

Many health care workers are affected by COVID-19 and hospitals are becoming the epicenter for human-to-human transmission. Recently, in a field investigation surface swabs were collected in various hospital environments and they were analyzed for the presence of SARS-CoV-2 RNA. The most contaminated objects were self service printers (20.0%), desktop/keyboard (16.8%) and door knobs (16%). Among personal protective equipments, hand sanitizer dispensers (20.3%) and gloves (15.4%) were the most contaminated objects.³²

Frequently touched surfaces in the health care settings are therefore a potential source of virus transmission. Hence, to decrease the viral load in frequently touched surfaces in the immediate patient surroundings, appropriate disinfectants should be used. Surface disinfection with 0.1% sodium hypochlorite or 62-71% ethanol significantly reduces coronavirus infectivity on surfaces within 1 minute

Table II. Virus stability on surfaces (22°C with 65% humidity)³⁴

Surfaces infectious	Time at which no virus was isolated
Printing and Tissue paper	After 3 hours
Treated wood & cloth	Day 2
Glass and bank note	Day 4
Plastic and Stainless steel	Day 7

exposure time.³² WHO recommends 70% ethyl alcohol to disinfect small surface areas and equipment between usage such as reusable equipment (e.g. thermometer).

Immunogenicity

IgM and IgG antibodies against SARS-CoV-2 internal nucleoprotein (NP) and surface spike protein receptor binding domain (RBD) correlated with neutralising activity.¹¹ There are many factors which affect the antibody production including age, nutritional status, severity of the disease, certain medications or infections like HIV which suppress the immune system.³⁶⁻³⁸ Antibody levels do not correlate with clinical course or disease severity.¹¹ Seroconversion occurred after 7 days in 50% and by day 14 in majority of the patients.¹² SARS-CoV-2 infections are somewhat unusual because IgM and IgG antibodies arise nearly simultaneously in serum within 2 to 3 weeks after illness onset. Thus, detection of IgM without IgG is uncommon.³⁹ In some patients with confirmed COVID-19 disease by RT-PCR, antibody responses were weak, late or absent.^{37,38,40} Antibodies may also cross react with other human coronaviruses.^{37,41,42.}

Because of the variable sensitivity and specificity, antibody testing cannot be used to diagnose COVID-19. Some clinicians make a presumptive diagnosis of recent COVID-19 disease in cases where molecular testing was negative but where there was a strong epidemiological link to COVID-19 infection and paired blood samples (acute and convalescent) showing rising antibody levels.⁴³ Since the appropriate antibody response happens only in the recovery phase, use of it for clinical intervention or to interrupt the disease transmission is minimal. Lastly, whether detection of antibodies could predict if an individual is immune to reinfection with the COVID-19 virus is still under debate and there is no evidence till date to support this.⁴³

Tests to detect antibody responses to COVID-19 in the population will be critical to support the development

of vaccines and for understanding the extent of infection among people who are not identified through active case finding and surveillance efforts, the attack rate in the population and the infection fatality rate.⁴³

Herd immunity (herd effect, community immunity, population immunity, social immunity)

Herd immunity is a form of indirect protection from infectious disease that occurs when a large percentage of a population has become immune to an infection. Immunity can be achieved either through vaccination or by contracting the infection and over a period of time natural immunity develops. When a significant proportion of the population are immune, the spread of the disease slows down or stops thereby providing a measure of protection for individuals who are not immune.

Some individuals cannot become immune because of their underlying immunodeficiency state or because of immunosuppressive medications and for this group of individuals, herd immunity offers protection. Newborn infants also cannot be vaccinated, because of their immature immune system and also the acquired antibodies from mother renders the vaccine ineffective. Once the herd immunity reaches a threshold, it helps in elimination of the disease and if the elimination was achieved globally, it results in disease eradication.

Herd immunity threshold (HIT) or herd immunity level (HIL)

When a critical proportion of the population becomes

immune, the disease may no longer persist in the community.^{44,45} Herd immunity threshold, in a given population, is the point where the disease reaches an endemic steady state, which means that the infection level is neither growing nor declining exponentially. The threshold can be calculated from the effective reproductive number R_e , which can be obtained by taking the product of basic reproductive number R_0 (average number of new infections caused by an infectious case in the susceptible population) and S , the proportion of population who are susceptible to the infection. R_0 is a measure of contagiousness, so low R_0 values are associated with lower HITs, whereas higher R_0 values result in higher HITs.^{45,46} For example, if the R_0 is 2, the HIT for a disease is theoretically only 50%, whereas a disease with an R_0 of 10 the theoretical HIT is 90%.⁴⁵

The estimated R_0 and HIT of various infectious diseases is listed on Table III.

When the effective reproduction number (R_e) is reduced to below 1 new individual per infection, the number of cases occurring in the population gradually decreases until the disease has been eliminated.^{45,46,47} If the R_e increases to above 1, the disease is actively spreading through the population and infecting a larger number of people than usual.⁴³⁻⁴⁶ If a population is immune in excess of that disease's HIT, the number of cases reduces at a faster rate.^{47,48} So far, eradication programs based on the concept of herd immunity with reliance on vaccines have been globally successful in the case of smallpox and rinderpest, and are currently underway for poliomyelitis.⁴⁹

Table III. Estimated R_0 and HIT of various infectious diseases^{22,50-54}

Disease	R_0	HIT
Measles	12-18	92-95%
Pertussis	12-17	92-94%
Diphtheria	6-7	83-86%
Rubella	6-7	83-86%
Small pox	5-7	84-86%
Polio	5-7	84-86%
Mumps	4-7	75-86%
Influenza (influenza pandemics)	1.5-1.8	33-44%
Ebola (out break in West Africa)	1.5-2.5	33-60%
SARS (2002-2004 out break)	2-5	50-80%
COVID-19 (COVID-19 pandemic)	1.4-3.9	29-74%

With regard to COVID-19 pandemic, the variables that determines the herd immunity to contain the outbreak are

- i) R_0 : Even though various studies quote different R_0 , considering the average of 2.2, 60% of the population needs to have protective antibodies.⁵⁵
- ii) Whether the total measurable antibodies were the same as protective, virus neutralizing antibodies.⁵⁵ Even if it is protective, how long is the immunity to COVID-19 likely to last? -these questions have to be addressed.
- iii) For effective herd immunity, immune response of the individuals plays an important role. Studies in COVID-19 shows that 10-20% have little or no antibody response.⁵⁶
- iv) No effective vaccine is available, with more than 100 candidate vaccines in development and few in phase 1 or phase 2 trial to assess the safety and immunogenicity.⁵⁵

A large population based seroprevalance data is needed to ascertain the extent of population exposed and is potentially immune to the virus. With the current knowledge, there is uncertainty about the immunological correlates of protective antibodies and how much proportion of the population needs to be immune for the herd immunity effect.

Points to Remember

- *Coronavirus family includes SARS-CoV-1, MERS and SARS-CoV-2, the currently circulating virus.*
- *There are multiple routes of transmission for SARS-CoV-2 (respiratory, conjunctival, feco-oral routes).*
- *Peak viral load has been demonstrated at the time of presentation.*
- *No live virus was demonstrated from the respiratory tract after 8 days and hence infective potential gradually declines after 10 days.*
- *Basic reproductive number R_0 is around 2 to 3, suggesting the higher pandemic potential of SARS-CoV-2.*
- *PCR positivity does not always imply active infection, since it cannot distinguish live and dead virus.*
- *Serology is mainly useful for epidemiological surveillance.*
- *Herd immunity will play a role in interruption of the pandemic, but currently difficult to ascertain due to lack of information on the seroprotection levels of the population and the non-availability of vaccine.*

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CLIPPINGS

Seroprevalence of novel coronavirus disease (COVID-19) in Kobe, Japan.

A cross-sectional serologic testing for SARS-CoV-2 antibody was done on 1,000 samples from patients at outpatient settings who visited the clinic from March 31 to April 7, 2020, stratified by the decade of age and sex. There were 33 positive IgG among 1,000 serum samples (3.3%, 95%CI: 2.3-4.6%). By applying this figure to the census of Kobe City (population: 1,518,870), it is estimated that the number of people with positive IgG be 50,123 (95%CI: 34,934-69,868). Age and sex adjusted prevalence of positivity was calculated 2.7% (95%CI: 1.8-3.9%) and the estimated number of people with positive IgG was 40,999 (95% CI: 27,333-59,221). These numbers were 396 to 858 fold more than confirmed cases with PCR testing in Kobe City.

Conclusions: This cross-sectional serological study suggests that the number of people with seropositive for SARS-CoV-2 infection in Kobe, Japan is far more than the confirmed cases by PCR testing.

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COVID - 19

**PATHOPHYSIOLOGY OF COVID-19:
KNOWN AND UNKNOWN****Suhas V Prabhu**

Abstract: *The corona virus disease 2019 caused by severe acute respiratory syndrome corona virus-2 starts as a respiratory infection but can progress to multi-organ involvement with some very unique and unusual clinical presentations. This can appear at times puzzling and can account for significant morbidity and mortality. Understanding the pathophysiology of this disease can help reveal the various mechanisms of the progress of the disease and can explain the clinical symptoms and offer hope for prevention and treatment modalities.*

Keywords: SARS-CoV-2, COVID-19, Pathophysiology, Children.

The severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) that originated in China towards the end of December 2019 has spread rapidly all over the world and hence labelled as the corona virus disease 2019 (COVID-19) pandemic. This virus belongs to the Corona group, which commonly causes minor upper respiratory tract infections in both children and adults. The SARS-CoV-2 however is a new mutant with specific features which are different from the other Corona viruses. These are:

1. A novel mutation increasing susceptibility (that makes practically every human susceptible).
2. An easy transmissibility (that has caused rapid spread worldwide).
3. An unusual pathophysiology with involvement of many systems of the body beyond the respiratory tract (that has contributed to different clinical presentations and higher morbidity and mortality).

The focus here is to elaborate on the third feature i.e., the unusual pathophysiology. It offers an insight into the

mechanisms of damage caused by the virus and the disruption of the host systems, which can explain the clinical features of the disease and may help in finding appropriate treatment modalities. However, since this is a new disease, few well documented studies are available. With the rapid spread and high morbidity and mortality associated with this pandemic, the efforts of researchers and clinicians have naturally been focused on risk stratification, prevention of transmission, treatment methods and of course the race to find a vaccine. It is but natural that there are very few peer reviewed published studies on the pathophysiology or autopsy findings of this novel disease. It is an evolving field and hence including the phrase “Known and Unknown” in the title is justified.

The pathophysiology of the disease has several facets but essentially the disease occurs in three stages (Fig. 1).

Stage I. Entry of the virus and early replication

During the first week, when the virus gets inoculated, it establishes itself inside the host. The route of infection is through the mucosa, usually of the upper respiratory tract. The conjunctiva is also a suspect portal of entry. The virus is believed to gain entry by attachment to a metallo-peptidase named angiotensin-converting enzyme receptor (ACE2 receptor). Studies on the earlier SARS virus had shown that the S1 domain of the spike protein of the virus binds well to the ACE2 receptor.¹ In fact, the SARS-CoV-2 virus has a 10-20 times higher affinity to these receptors compared to the earlier SARS virus. This receptor has therefore been described as the functional receptor for SARS-CoV-2. It is uncertain whether the SARS-CoV-2 virus has any other receptor for entry. CD209L has been proposed as an alternative receptor, but confirmation is lacking.²

The importance of this hypothesis is that drugs that alter the receptor to prevent attachment by the virus can be potentially used in the prevention and treatment of COVID-19. Examples of drugs that can change the glycosylation of these receptors and reduce viral entry in vitro are chloroquine and hydroxychloroquine (HCQ) and an initial small uncontrolled study with HCQ had shown clinical promise.³⁻⁵ Although the genes for the ACE2 receptor are present in all human cells, they are expressed

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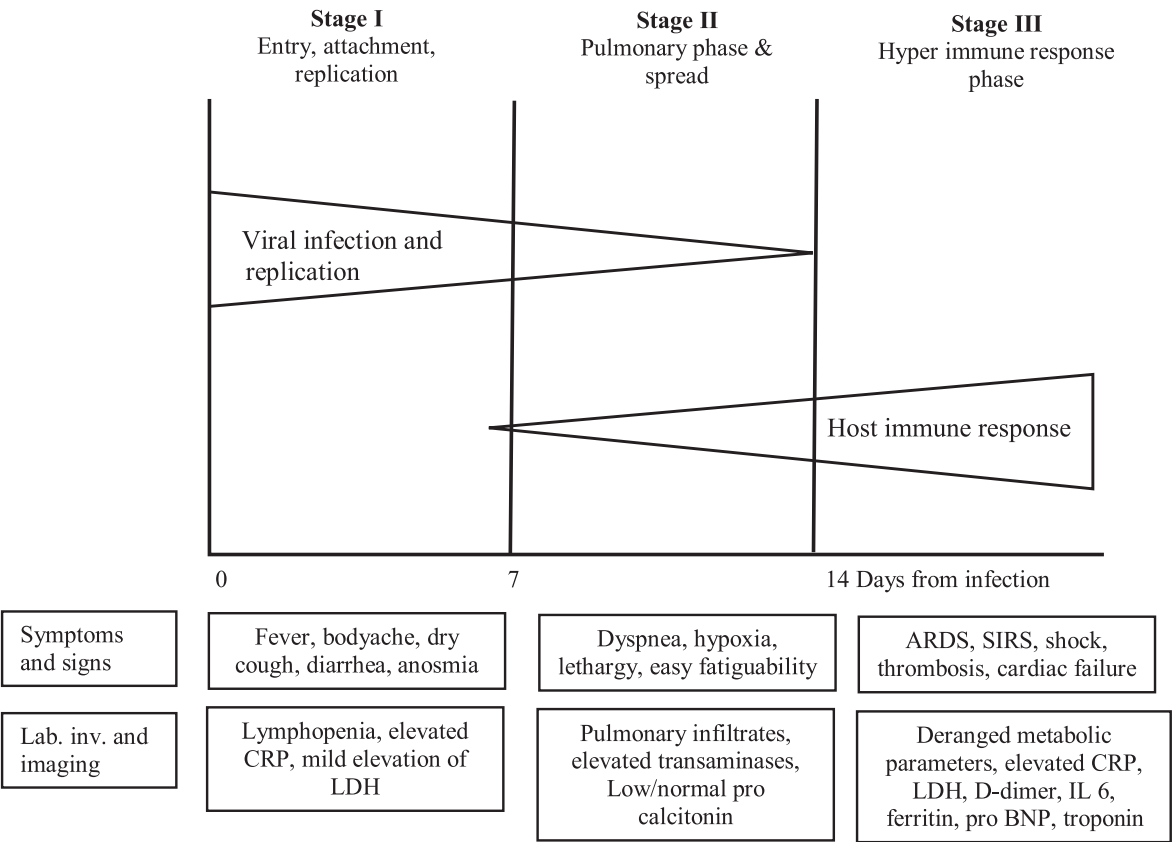


Fig.1. Stages of COVID-19 infection

only in specific tissues of the body and in high amounts in the oral and nasal mucosa and the gastro-intestinal epithelium. This is the reason why the virus is easily able to enter the human host through these routes. Once attached, the virus is able to enter the cells by a process of endocytosis. In vitro electron microscopy studies clearly show hundreds of viral particles clustered around the cilia and in double walled vacuoles within the cytoplasm of epithelial cells derived from the respiratory tract.

Another very remarkable finding is the surface expression of ACE2 protein on lung alveolar epithelial cells and in the endothelial cells of arteries and veins in all organs. This has great relevance to the two important clinical features of the disease i.e. pneumonia and coagulopathy. Lymphoid cells in the lymph nodes, thymus, bone marrow and spleen are surprisingly devoid of ACE2 so there must be an alternative (but yet unknown) mechanism for the hallmark lymphopenia that is seen even in the early stage of the illness.¹ Although the expression of ACE2 metallo-protein in gustatory and olfactory receptor cells has not been specifically studied, it is likely that they are located in the mucosal lining of these organs as they are contiguous. So, they can be invaded by the virus causing the two rather specific symptoms of COVID-19 namely the loss of sensation of smell and taste.

ACE2 receptors are also expressed in the arterial, venous endothelial cells and arterial smooth muscles of organs like heart, liver and brain and these can be affected by the infection.¹ The testis is another particular organ with high levels of ACE2 receptors. They possibly serve as a reservoir for the virus which accounts for the delayed clearance and higher mortality seen in males compared to females. Another reason could be the higher expression of ACE2 receptors in males compared to females.⁶ Some studies have also shown that pre-existing heart disease leads to a higher expression of ACE2 receptors on the myocardium which may account for the higher cardiac complications and mortality in this group. This is reflected in higher levels of circulating ACE2 receptors in the male gender especially with pre-existing heart disease like cardiac failure.⁷

In the first stage of the disease, the virus is just getting a foothold and multiplying in the mucosa, near the entry site, which is the incubation period and the infected person remains asymptomatic. This period lasts from 2 to 7 days with a mean of 4-5 days. The symptoms then start and consist of fever (which may be high or even completely absent), constitutional symptoms like headache, body ache, dry cough, throat pain, anosmia, ageusia and diarrhoea. The laboratory findings in this stage (that last about a week)

are lymphopenia, moderately elevated CRP and modest elevation of LDH. However, some individuals and especially children can remain almost totally asymptomatic all through the illness.

Stage II. Spread to lungs and other systems

By the second week, the virus is able to spread to the lungs which has rich expression of ACE2 receptors and hence pneumonia is the most common pathology. The primary involvement is the ACE2 receptor expressing alveolar type II cells, generally at the periphery of the lung.² A larger lung alveolar surface area is involved in coronavirus infection than in bronchopneumonia, due to ubiquitous expression of ACE2 on type II pneumocytes.⁸ Alveolar type II cells perform many critical functions that include production of pulmonary surfactant, airway epithelial barrier stabilization, immune defence and airway regeneration in response to injury. As the SARS-CoV-2 replicates within these type II cells, the affected cells undergo apoptosis and release a large number of viral particles to infect the neighbouring cells. Spread to surrounding lung is relatively prevented by ciliary activity.

Poor muco-ciliary clearance in the elderly is probably responsible for the higher incidence of pulmonary complications in older population. Chronic damage to the ciliary lining of the respiratory tract by habitual smoking may similarly account for the higher morbidity in smokers. Children normally have a robust muco-ciliary action and are therefore less likely to have COVID pneumonia unless they have pre-existing conditions like cystic fibrosis, bronchiectasis or diabetes with consequent reduced muco-ciliary clearance. This has been validated by clinical data. In a multi-centric cross sectional study in North America on 46 children requiring ICU admission, 83% of them had some co-morbidity or pre-existing chronic illness, generally cardio-pulmonary or diabetes mellitus. Twenty four patients (>50%) had one comorbidity, 8 had two and 9 had three or more concomitant co-morbidities.⁹

With progressive loss of type II alveolar cells, surfactant production is affected and micro-atelectasis occurs causing the streaky shadows seen on chest imaging by radiography or CT and finally a ground glass appearance. The alveolar type II cells are also the precursors of the type I cells that maintain the integrity of the alveolar lining and permit gaseous exchange. Hence the end result when the alveolar type I cells get involved is impaired gaseous exchange leading to hypoxia. The pathological result of SARS and COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. Aberrant healing of alveolar

lining may lead to scarring and fibrosis that may present as ARDS. This can prolong the need for ventilatory support into the third week overlapping with the hyperimmune stage III of the disease with its attendant complications. Recovery requires a vigorous innate and acquired immune response and epithelial regeneration. This may be defective in the elderly and result in longer duration of sub-optimal lung function with consequent very gradual and incomplete recovery of the lung capacity.

The pneumonia of COVID is thus different in severity and course from the exudative consolidation seen in bacterial infections like pneumococcus. A productive cough therefore is not commonly seen (unless there is a secondary bacterial invasion) and the only symptom may be a progressive shortness of breath with general lethargy and fatigue from the slowly increasing hypoxia.

Another intriguing observation in COVID-19 disease is that the hypoxia is not usually accompanied by air hunger; instead, a paradoxical feeling of calm and well-being may result. This phenomenon has been coined 'silent or happy hypoxia'. The etiology of this observation is not clear at present. Certain structural viral proteins attacking porphyrin moiety of hemoglobin has been postulated as a possible reason, but has not been substantiated by evidence.¹⁰

Spread of the virus to many other organs like liver, kidney and brain may start in the second week. This is believed to be via the bloodstream and has been documented in Chinese studies.¹¹ The actual pathophysiology in these organs in the current COVID-19 epidemic has not yet been elucidated as there are no studies on histopathology from these organs. Many of the postulates are based on the studies of the earlier SARS epidemic due to a Corona virus of the same group.

In the most comprehensive study of cardiac involvement in patients who died from the earlier SARS epidemic, viral RNA was detectable in a third of post-mortem cardiac tissues and was associated with both decreased ACE2 expression and increased macrophage infiltration.^{11,12}

Hepatic involvement is common and leads to elevated liver transaminases and occasional cases present with jaundice. Neurological symptoms, although uncommon can signal invasion of the virus into the CNS and the patient can present with altered sensorium, seizures and neurological deficit. Renal dysfunction is common but this may be as a result of circulatory problems and not due to viral invasion of the kidney. This is buttressed by the fact that RT-PCR studies for SARS-CoV-2 in the urine have

failed to identify the virus.¹¹ Also, changes in these vital organs would be compounded by problems in blood supply due to cardio-respiratory failure, shock and the vasculopathy / coagulopathy. Autopsy findings have shown ischemia, infarction and effects of shock.

Surprisingly, many children may have little or no respiratory involvement and present with only extra-pulmonary findings. Some have predominant gastro-intestinal symptoms like diarrhea and vomiting, even intussusception and intestinal gangrene and others have only neurological findings like convulsions and altered sensorium without any cough or dyspnea.^{12,13} Why this happens only in the pediatric age group baffles many and may be related to the different pattern of distribution or expression of ACE2 receptors.

What is also unclear is the rate of resolution of these pathological changes in various organs and whether there are any residual lesions. This is particularly important in commonly involved organs like the lungs. The reported very gradual recovery of elderly adults with long lasting shortness of breath and dyspnea on minor exertion probably indicate an incomplete recovery of normal gas exchange in the alveoli due to persistent residual fibrosis.

Stage III. Hyperimmune response phase

This stage is not seen in all patients. A majority of patients and an even higher percentage of children seem to recover after stage II or even directly after stage I. This has been the case right from the earliest studies from China. Initial data of 72,314 cases from Wuhan presenting for medical care, showed only 1.3% of them were aged below 20 years and a subsequent report of 171 children younger than 16 years hospitalized in Wuhan province reported that only 3 required ICU care with a single fatality.¹³⁻¹⁵ Thus, particularly in pediatric age group, it is only in a minority of cases where there is a progression to this stage with peculiar features and is possibly related to an abnormal or variant host immune response. It is this stage specific to Corona virus that is responsible for the severe morbidity and mortality and hence needs to be addressed. The host immune system comes into play by the end of the second week or so. This is correlated by the presence of IgM antibodies by 5 to 8 days and IgG antibodies in a majority of cases by 10-14 days. Further pathophysiology possibly results from a complex interplay between the direct effects of the virus and the host immune reaction.

A few peculiar clinical situations described so far in the current COVID-19 epidemic are discussed below.

Vasculopathy/Coagulopathy: Virchow's triad delineating the pathophysiology of intravascular thrombosis proposes that it can occur as a result of three factors: a) reduction in blood flow (stasis), b) vascular endothelial injury (leading to triggering of the coagulation cascade) and c) hypercoagulable state due to alterations in the blood constituents.

All three factors are in part responsible for causing the reported complications of thrombosis and embolism in COVID-19. The reduced blood flow is secondary to the cardiac decompensation seen as a part of the systemic inflammation response syndrome (SIRS) or septic shock in severely ill patients. The vascular endothelium is probably damaged directly by the virus via the ACE2 receptors with subsequent triggering of the coagulation cascade. Elevated levels of antiphospholipid antibodies have been found in some patients with COVID-19 in the third week but the correlation with coagulopathy is not clear.¹⁵ The laboratory evidence for the onset of the coagulopathy is the elevation of D-dimer levels which reflects ongoing activation of the hemostatic and thrombolytic system. Deep vein thrombosis in the lower half of the body is the commonest affliction seen followed sometimes by pulmonary embolism. Small pulmonary vessel thrombosis and hemorrhages seen in SARS-CoV-2 reflect pulmonary involvement and possibly add to the deranged respiration and gaseous exchange.¹⁴ Part of the CNS and other organ dysfunction may also be caused by arterial thrombus due to endothelial injury, stasis and hypercoagulable state.

Intravascular clots in COVID-19 can essentially occur in any vessel, arterial or venous. Sudden cardiac death seen in some adults who appeared to be recovering from respiratory failure with decreasing oxygen requirement could be due to acute myocardial infarction occurring from thrombosis in the cardiac circulation. Involvement of these parts of the circulation has been reported to happen more commonly in adults than in children. In contrast, in children, vasculitis/coagulopathy changes have been described more often in the peripheral circulation like the tips of the toes and fingers. Lesions such as purpura, skin necrosis, subcutaneous hematoma and local infarction causing chilblain like lesions on the tips of the fingers and toes (called "COVID toes") have been described, initially from Europe but later on elsewhere too.¹⁶ Clinical importance of this pathophysiology is the possible role of anticoagulants like low molecular weight heparin in preventing or treating these complications.

Cytokine storm

It is well known that sepsis syndrome complicating any infection, bacterial or viral is a complex interplay of

pathogenic effects of the infective agent as well as the host response. It is no different for COVID-19. While the clinical course of the disease in children may be mild, the immune response starting towards the end of the second week can contribute to peculiar clinical presentations and contribute to mortality. It is quite likely that the resulting organ dysfunction is mediated by excessive release of a number of cytokines and these are involved in the pathophysiology of the acute respiratory distress syndrome (ARDS) and the sepsis syndrome described earlier.

But additionally, a specific multisystem inflammatory syndrome has been described to occur in children with COVID-19.¹⁷⁻¹⁹ IL-2, IL-6, IL-7, IL-10, granulocytic colony stimulating factor (GCSF) and TNF- α are some of the cytokines with high levels recorded in these cases.²⁰ But one of the key cytokines in this process is IL-6 and some studies have shown positive correlation of this agent with disease severity.²¹ The multisystem inflammatory syndrome presents with features similar to Kawasaki disease with constitutional features, limb sparing conjunctivitis, cracked lips, even skin rashes and brawny edema of peripheries and multi-organ dysfunction including fluid refractory shock. Hypoalbuminemia and pleural / pericardial effusions have been described in some cases. Laboratory evidence of high acute phase reactant levels (ESR, pro-calcitonin, CRP), IL-6 and ferritin (moderately elevated) is always present in these cases and markers of cardiac damage like troponin and N-terminal pro B type natriuretic peptide (NT-pro-BNP) may also be elevated. Late thrombocytosis, the hallmark of Kawasaki disease is however absent. In such a situation, anti-inflammatory agents like methylprednisolone, intravenous immunoglobulin and monoclonal antibodies like Tocilizumab which is specific antagonist for IL-6 have been used with some clinical success.²¹

Several explanations have been proposed for the relatively lower morbidity and mortality observed in children as compared to adults with COVID-19. These include the following:

- i) The first possibility is that the expression level of ACE2 may differ and ACE2 expression may be lower in pediatric population.
- ii) The second possibility is that children have a qualitatively different response to the SARS-CoV-2. Severe COVID-19 infection in adults is characterized by a massive proinflammatory response or cytokine storm that results in ARDS and multi-organ dysfunction (MODS). Ageing is associated with increasing proinflammatory cytokines that govern

neutrophil functions and have been correlated with a severe illness.

- iii) The third possibility is that the simultaneous presence of other viruses in the mucosa of lungs and airways in young children compete with SARS-CoV-2 virus and limit its growth. But we do not have studies to prove this right now.

Rather a combination of these factors may cause less severe COVID-19 in children.²¹

The pathophysiological mechanisms underlying SARS-CoV-2 infection is an unfolding story and the last words on the clinical features, pathophysiology and its implications for treatment of COVID-19 are yet to be written. Hence it would be prudent to stay abreast of the burgeoning evidence emerging in this long drawn pandemic.

Points to Remember

- *The pathophysiology of SARS-CoV-2 infection appears to be unique with involvement of many systems of the body beyond the respiratory tract.*
- *The disease progresses through three stages - virus entry and replication, spread to lungs and other organs followed by a hyperimmune response.*
- *Only a minority of children progress to the hyperimmune response stage.*
- *Vasculopathy / Coagulopathy is responsible for the complications of thrombosis and embolism in COVID-19.*
- *Difference in expression level of ACE2 and qualitative response to SARS-CoV-2 can explain the clinical differences observed in children.*
- *Multisystem inflammatory syndrome due to cytokine storm may present with features of Kawasaki disease.*

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CLIPPINGS

FDA authorizes first next generation sequence test for diagnosing COVID-19

Using next generation sequencing the test can detect genomic sequence of the virus from the respiratory secretions from which one can understand if and how viruses mutate.

COVID - 19

CLINICAL FEATURES AND DISEASE STRATIFICATION OF COVID-19 IN CHILDREN

***Arun Wadhwa**

Abstract: *We are in the midst of a pandemic caused by novel virus SARS-Cov-2 with no sign of abating. The clinical features have been ranging from asymptomatic to severe respiratory distress leading to death. Fortunately, children have been less affected in terms of both morbidity and mortality. Although the signs and symptoms are similar to adults, a smaller number of children tend to be symptomatic. Some children however have been reported with unusual skin lesions or vasculitis like syndrome and also recently an overlap of Kawasaki and toxic shock like syndrome named as Pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2. The common presentations in children and their difference from adults are discussed.*

Keywords: Covid-19, SARS-CoV-2, Clinical features, Children.

In the later part of 2019, a novel coronavirus infection emerged in Wuhan, Hubei province, China. It was linked to animal-to-human transmission in local wet markets. Subsequently, human-to-human transmission of the virus commenced, resulting in widespread respiratory illness in Wuhan and other areas of the Province.¹ The virus then spread across China and then to other nations across the globe. On February 11, the World Health Organization named the virus SARS-CoV-2 and the syndrome was named COVID-19, or coronavirus disease 2019.² Although not as lethal as the severe acute respiratory syndrome (SARS) outbreak in 2003, COVID-19 is still characterized by severe respiratory illness and significant mortality, especially among the elderly and individuals with underlying co-morbid conditions such as cardiac and respiratory diseases, diabetes and hypertension.¹ As of 28th May 2020, more than 5.69 million cases have been reported

across 188 countries and territories, resulting in more than 3,55,000 deaths and 1.56 million people have recovered too.³

As COVID-19 is a new disease, many aspects such as to how it spreads is not proved conclusively.⁴ The infection is spread during close contact, often by small droplets produced during coughing, sneezing, or talking.⁴ The droplets are transmitted and cause new infection, when inhaled by people in close contact (1 to 2 meters / 3-6 feet). They are also produced during breathing out, but as these droplets are relatively heavy, they usually fall to the ground or surfaces.⁴ Loud talking releases more droplets than normal talking.⁵ Although not proven crying in children has also been postulated to release droplets.⁶

After the droplets fall on floor or surfaces, they can still infect other people, if they touch these contaminated surfaces and then touch their eyes, nose or mouth with unwashed hands.⁴ On surfaces, the amount of active virus decreases over a period of time until it can no longer cause infection. However, the virus has been found to survive on various surfaces for some time - for example copper or cardboard for a few hours, and plastic or steel for a few days.⁷

Sputum and saliva carry large amounts of virus.^{4,7} Some medical procedures which produce aerosol like dental procedures may result in the virus being transmitted easier than normal.^{4,7} Although COVID-19 is not a sexually transmitted infection, kissing, intimate contact and fecal oral routes are suspected to transmit the virus.⁸

The incubation period for COVID-19 is from 2 to 14 days, with an average of 4-6 days. 97.5% of people who develop symptoms, do so within 11.5 days of infection.⁹ The virus is most contagious during the first three days after onset of symptoms, spread can occur even two days before symptoms appear (pre-symptomatic transmission) and in later stages of the disease. A section of infected people do not develop noticeable symptoms at any point of time. These asymptomatic carriers tend not to get tested, and their role in transmission is not yet fully known.¹⁰ However, preliminary evidence suggests they may contribute to the spread of the disease.

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Symptoms and signs - adults

Fever is the most common symptom, although some older people and those with other health problems experience fever later in the disease. In one study, 44% of people had fever when they presented to the hospital, while 89% went on to develop fever at some point during their hospitalization.¹¹

Other common symptoms include cough, loss of appetite, fatigue, shortness of breath, sputum production, and muscle and joint pains.¹¹ Symptoms such as nausea, vomiting, and diarrhea have been observed in varying proportions.¹² Less common symptoms include sneezing, runny nose or sore throat¹³ (Table I). Some patients in China initially presented with only chest tightness and palpitations.¹⁴ A decreased sense of smell (hyposmia) or disturbances in taste (hypogeusia) may occur.¹⁵ Severity of symptoms tend to be more in patients with underlying medical conditions.

According to Centre for disease control (CDC), Atlanta, USA, people with these symptoms or combinations of symptoms may have COVID-19: Cough with shortness of breath or difficulty in breathing: Or at least two of the following symptoms: Fever, chills, repeated shaking with chills, muscle pain, headache, sore throat, new loss of taste or smell.¹⁶

Risk scoring

In collaboration with the National Health Commission of China, and based on a retrospective cohort of 1590 patients with COVID-19 from 575 hospitals, a high-risk score has been developed for adults.¹⁷ The score provides an estimate of the risk that a hospitalized patient with COVID-19 will develop critical illness. Critical illness was defined as the composite measure of admission to the intensive care unit, invasive ventilation or death. The mean

age of patients in the cohort was 48.9 years (57.3%) were men. 72 potential predictors were evaluated, ten variables were found to be independent predictive factors and were included in the risk score: chest radiographic abnormality, older age, hemoptysis, dyspnea, unconsciousness, more number of comorbidities, cancer history, increased neutrophil-to-lymphocyte ratio, elevated lactate dehydrogenase and direct bilirubin. The score has been translated into an online risk calculator that is freely available to the public (<http://118.126.104.170/>).

Covid-19 in children

Pediatric cases of COVID-19 have been reported but there are relatively fewer cases among children compared to adult patients. It was 2% in the United States, 2.2% in China, 1.2% in Italy and 0.8% in Spain of confirmed cases who were below 18 years of age.¹⁸ Most of the children had exposure to household members with confirmed COVID-19.

The predominant signs and symptoms of COVID-19 reported to date among all patients are similar to other viral respiratory infections, including fever, cough and shortness of breath. Although these signs and symptoms may occur at any time during the overall disease course, children with COVID-19 may not initially present with fever and cough as often as adult patients.¹⁸ Data from China suggest that pediatric COVID-19 cases might be less severe than adults and that children might experience different symptoms than do adults.^{19,20} These findings are largely consistent with a report on pediatric COVID-19 patients aged <16 years in China, which found that only 41.5% of pediatric patients had fever, 48.5% had cough and 1.8% were admitted to an ICU.¹⁸ A second report suggested that although pediatric COVID-19 patients infrequently have severe outcomes, the infection might be more severe among infants. The same report detected no substantial difference in the number of cases among males and females.²⁰

Age distribution

Data from 1,49,760 laboratory-confirmed COVID-19 cases in the United States occurring during February 12-April 2, 2020 were analyzed. Among 1,49,082 (99.6%) reported cases for which age was known, 2,572 (1.7%) were among children aged <18 years (the median age being 11 years).²¹ Nearly one third of reported pediatric cases (32%) occurred in children aged 15-17 years, followed by those in children aged 10-14 years (27%). Among younger children, 15% occurred in children aged <1 year, 11% in children aged 1-4 years and 15% in children aged 5-9 years. Among 2,490 pediatric COVID-19 cases

Table I. Symptoms in adults¹¹

Symptoms	Range
Fever	83–99%
Cough	59–82%
Loss of appetite	40–84%
Fatigue	44–70%
Shortness of breath	31–40%
Coughing up sputum	28–33%
Muscle aches and pains	11–35%

for which sex was known, 57% occurred in males; among cases in adults aged ≥ 18 years for which sex was known, 53% were males.

Symptoms and signs

In the same US study, complete data on signs and symptoms of COVID-19 were available for 291 of 2,572 (11%) pediatric cases and 9.6% cases among adults aged 18-64 years. Among the children with available information, 73% only had symptoms of fever, cough, or shortness of breath compared with 93% of adults aged 18-64 years. Among those with known information on each symptom, 56% of pediatric patients reported fever, 54% reported cough, and 13% reported shortness of breath, compared with 71%, 80%, and 43% respectively, reporting these signs and symptoms among patients aged 18-64 years (Table II). Myalgia, sore throat, headache and diarrhea were also less commonly reported by pediatric patients.²¹ These data support previous findings that children with COVID-19 might not have reported fever or cough as often as adults.¹⁸

Hospitalization in children

Information on hospitalization status was available for 29% (745 of 2572) cases in children aged <18 years and 31% cases in adults aged 18-64 years. Among children

with COVID-19, 147 (estimated range = 5.7%–20%) were reported to be hospitalized, with 15 (0.58%–2.0%) admitted to an ICU. Among adults aged 18-64 years, the percentages of patients who were hospitalized (10%–33%), including those admitted to an ICU (1.4%–4.5%), were higher. Whereas most COVID-19 cases in children are not severe, serious COVID-19 illness resulting in hospitalization still occurs in this age group. Children aged <1 year accounted for the highest percentage (15%–62%) of hospitalization among pediatric patients with COVID-19. Among 95 children aged <1 year with known hospitalization status, 59 (62%) were hospitalized, including five who were admitted to an ICU. The percentage of patients hospitalized among those aged 1-17 years was lower (estimated range = 4.1%–14%), with little variation among age groups.²¹

Among 345 pediatric cases with an underlying condition, 80 (23%) had at least one underlying condition. The most common underlying conditions were chronic lung disease including asthma 40(50%), cardiovascular disease 25(31%) and immunosuppression 10(13%). Among the 295 pediatric cases for which information on both hospitalization status and underlying medical conditions was available, 28 of 37 (77%) hospitalized patients, including all six patients admitted to an ICU, had one or more underlying medical condition; among 258 patients who were not hospitalized, 30 (12%) patients had underlying conditions.²¹ Three deaths were reported among the pediatric cases included in this analysis; however, review of these cases is ongoing to confirm COVID-19 as the likely cause of death. In the present analysis, the predominance of males in all pediatric age groups, including patients aged <1 year, suggests that biologic factors might play a role in any differences in COVID-19 susceptibility by sex.

In a study of 20 children admitted in Wuhan children's hospital during the early part of the pandemic, 7 had a previous history of congenital or acquired diseases, which may indicate that children with underlying diseases may be more susceptible to COVID-19 infection.²² It was noted that the procalcitonin (PCT) was elevated in 80% cases in this study, with or without coinfection, which was not common in adult patients. Co infection was however noted in 8/20 (40%) indicating it is probably more common in pediatric patients.²³

Relevance of Pediatric COVID presentation

This preliminary examination of characteristics of COVID-19 disease among children in the United States and China suggests that children do not always have fever or cough as reported signs and symptoms. Although most

Table II. Signs and symptoms among 291 pediatric (age <18 years) and 10,944 adult (age 18–64 years) patients with laboratory-confirmed COVID-19 - United States, February 12–April 2, 2020²¹

Sign/Symptom	No. (%) Pediatric	with sign/symptom Adult
Fever, cough, or shortness of breath	213 (73)	10,167 (93)
Fever	163 (56)	7,794 (71)
Cough	158 (54)	8,775 (80)
Shortness of breath	39 (13)	4,674 (43)
Myalgia	66 (23)	6,713 (61)
Runny nose	21 (7.2)	757 (6.9)
Sore throat	71 (24)	3,795 (35)
Headache	81 (28)	6,335 (58)
Nausea/Vomiting	31 (11)	1,746 (16)
Abdominal pain	17 (5.8)	1,329 (12)
Diarrhea	37 (13)	3,353 (31)

cases reported among children to date have not been severe, clinicians should maintain a high index of suspicion for COVID-19 infection in children and monitor for progression of illness, particularly among infants and children with underlying conditions. As persons with asymptomatic and mild disease, including children, are likely playing a role in transmission and spread of COVID-19 in the community, social distancing and everyday preventive behaviors are recommended for persons of all ages to slow the spread of the virus, protect the health care system from being overloaded and protect older adults and persons of any age with serious underlying medical conditions.^{11,22}

Dermatological manifestations

Five skin conditions associated with coronavirus have been identified by dermatologists and deserve special mention. A research carried out on 375 patients in Spain²⁴, aimed to build a picture of how the disease might manifest with skin symptoms. The Spanish dermatologists were asked to identify patients who had an unexplained skin “eruption” in the last two weeks and who had suspected or confirmed Covid-19. Five different lesions were identified. Lesions were classified as acral areas of erythema with vesicles or pustules (Pseudo-chilblain, 9%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%). Vesicular eruptions appear early in the course of the disease (15% before other symptoms). The pseudo-chilblain pattern frequently appears late in the evolution of the COVID-19 disease (59% after other symptoms), while the rest tend to appear with other symptoms of COVID-19. Severity of COVID-19 shows a gradient from less severe disease in acral lesions to most severe in the other groups. Results are similar for confirmed and suspected cases. Alternative diagnoses were discussed but seem unlikely for the most specific patterns (pseudo-chilblain and vesicular). These may help clinicians approach patients with the disease and recognize pauci-symptomatic cases.²⁴

Course of the disease

The disease can have a very variable course, from asymptomatic to life threatening. All the various determinants of this variability have not been worked out yet. A typical course can be described as below.²⁵ Symptom onset is preceded by an incubation period from the day of contact which ranges from 1 to 14 days with median estimates of 5 to 6 days.

Day 1: Patients start having fever. They may also experience fatigue, muscle pain, and a dry cough. A small

minority of them may have had diarrhea or nausea one or two days before the onset of symptoms.

Day 5: Patients may have difficulty breathing specially if they are older or they have a preexisting health condition.

Day 7 is the average time the patients are admitted.

Day 8. At this point patients with severe illness develop ARDS. If the disease worsens patients are generally admitted to the ICU by day 10.

Day 14-17 is the usual time the patient is discharged from the hospital.

The child has to be restricted from mixing with other family members, especially the elderly, during the course of the disease and even later. The duration of quarantine can be time based, symptom based or test based.²⁶ The patient should be quarantined for 14 days after recovery. Recovery is when 3 days (72 hours) have passed after resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath) and at least 10 days have passed since symptoms first appeared. In test-based strategy, resolution of fever without the use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath) and negative results of at least two consecutive respiratory specimens collected more than 24 hours apart are considered as indicators of recovery.

Disease stratification

The decision to manage a pediatric patient with mild to moderate COVID-19 in the outpatient or inpatient setting should be decided on a case-by-case basis. Pediatric healthcare providers should consider the patient's clinical presentation, requirement for supportive care, underlying conditions and the ability for parents or guardians to care for the child at home.¹¹

Severe COVID-19 in children is rare. The largest review of children with COVID-19 included 2143 children in China. Only 112 (5.6%) of 2143 children had severe disease (defined as hypoxia) and 13 (0.6%) children developed respiratory or multiorgan failure or ARDS.³³ Emergency signs and symptoms include difficulty in breathing, persistent chest pain or pressure, new confusion, blue lips or face. If there are any of these signs or symptoms the child should be admitted immediately. Any child without these symptoms but has a chronic medical condition such as heart disease, lung disease or on chemotherapy should also be admitted.¹¹ Classification based on the severity of illness is summarized in Box 1.

Box.1 Definitions of clinical types of COVID-19 in pediatric patients³⁸**Mild disease**

- Upper respiratory symptoms (eg, pharyngeal congestion, sore throat and fever) for a short duration or asymptomatic infection
- Positive RT-PCR test for SARS-CoV-2
- No abnormal radiographic and septic presentation

Moderate disease

- Mild pneumonia
- Symptoms such as fever, cough, fatigue, headache, and myalgia
- No complications and manifestations related to severe conditions

Severe disease

Mild or moderate clinical features, plus any manifestations that suggest disease progression:

- Rapid breath (≥ 70 breaths per min for infants aged <1 year; ≥ 50 breaths per min for children aged >1 year)
- Hypoxia
- Loss of consciousness, depression, coma, convulsions
- Dehydration, difficulty feeding, gastrointestinal dysfunction
- Myocardial injury
- Elevated liver enzymes
- Coagulation dysfunction, rhabdomyolysis and any other manifestations suggesting injuries to vital organs

Critical illness

Rapid disease progression, plus any other conditions:

- Respiratory failure with need for mechanical ventilation (eg, ARDS, persistent hypoxia that cannot be alleviated by inhalation through nasal catheters or masks)
- Septic shock
- Organ failure that needs monitoring in the ICU

In the absence of studies involving large number of children and considering the fact that the incidence and as well as proportion of critically ill children is too little, assessment of physiological status will give a guidance on disease stratification as given in Box 1 .

Complications**Respiratory**

In some people, COVID-19 may cause viral pneumonia. In those most severely affected, COVID-19 may rapidly progress to acute respiratory distress syndrome (ARDS) causing respiratory failure, septic shock, or multi-organ failure and death.²⁹ Complications associated with COVID-19 include sepsis, abnormal clotting and damage to the heart, kidney and liver. Approximately 20-30% of people who present with COVID-19 demonstrate elevated liver enzymes more frequently seen in severe cases.³⁰ Neurological manifestations include seizures, stroke, encephalitis and Guillain-Barré syndrome.³¹ Cardiovascular related complications may include heart failure, arrhythmias, thrombosis and myocarditis.³²

Inflammatory syndrome

A growing number of hospitals in the U.S. and U.K. have reported cases with presentation similar to Kawasaki Disease.³³ Symptoms of these children include fever, rash, eye irritation, swollen lymph nodes and/or swelling of the hands and feet. The link between Kawasaki syndrome and COVID-19 is still not well established. The UK Kawasaki Disease Foundation released a statement saying that many children with the disease tested negative for COVID-19 and there is no current evidence of any increased incidence or greater susceptibility to COVID-19 infection for children who had Kawasaki Disease in the past.³⁴

Though COVID in children presents with milder symptoms and less complications, the hospitalization and ICU admission are relatively more in infants and those with existing health conditions within the pediatric age group. The pediatrician has to be aware of certain atypical manifestations such as dermatological lesions and inflammatory syndromes which may be related to SARS-CoV-19 infection.

Points to Remember

- *Children are less often involved compared to adults.*
- *The pediatric patients may be asymptomatic or show mild non-specific viral symptoms like fever, cough and cold.*

- *Some may present with skin lesions or vasculitis.*
- *High index of suspicion is required in view of non-specific mild illness in pediatric age group.*
- *Children less than three years should be carefully monitored for deterioration as they may not be able to communicate worsening.*

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CLIPPINGS

Consensus statement on chest imaging in pediatric COVID-19 patient management: Imaging findings and imaging study recommendations.

CXR: In the clinical experience of this expert panel of pediatric chest radiologists, both unilateral and bilateral opacities have been observed in pediatric COVID-19, although bilateral opacities are more typical and may show patchy opacities with peripheries and lower lung zone predominance. Bilateral peripheral and/or subpleural ground-glass opacities and/or consolidation are suggestive of COVID-19 pneumonia. However, other viral or atypical pneumonia would also be differential considerations. Less sensitive than CT in detecting lung parenchymal opacities. CXR is considered the most appropriate first step in imaging evaluation

CT chest: Bilateral and subpleural ground-glass and/or consolidative opacities often in the lower lobes of lungs. The "halo" sign, which describes a focal consolidation with a rim of surrounding ground-glass opacity, has been reported in up to 50% (10/20) of cases. The "halo" sign is generally observed early in the disease course (early phase) and progresses to ground-glass (progressive phase) and eventually develops into consolidative opacities (developed phase). Peribronchial thickening and inflammation along the bronchovascular bundle are observed more frequently in the pediatric population compared to adults. Fine mesh reticulations and crazy paving sign have also been reported. These CT findings are not pathognomonic. Thus the American College of Radiology currently recommends against using CT as a first line screening test to diagnose COVID-19 because of the risk of radiation and states that chest CT should be reserved for symptomatic hospitalized patients with specific clinical indications.

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COVID - 19

NEUROLOGICAL ASPECTS OF COVID-19 IN CHILDREN

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Abstract: *Children with COVID-19 infection may present with various neurologic manifestations. Although several neurological findings have been documented, it is not clear whether they are causally attributable to SARS-CoV-2 or just occur incidentally in children with COVID-19 infection. During the epidemic period of COVID-19, when seeing patients with neurologic manifestations, clinicians should consider SARS-CoV-2 infection as a differential diagnosis to avoid delayed diagnosis and lose the chance to treat and prevent further transmission. This article documents the various neurological features that have been reported till date due to COVID infection in children.*

Keywords: *Neurological manifestation, COVID -19, Children.*

Children under 19 years of age represented only 2% of total diagnosed cases of COVID-19 in a large cohort of 72,314 patients from China.¹ While studies in adults report up to 36.4% incidence of neurologic symptoms in COVID-19, there are no published cohorts describing neurological complications of COVID-19 in children with exception of a few case reports / series.² Moreover, whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is coincidental or causative for the

described neurological manifestations, is also unclear. Two routes of entry into the central nervous system have been suggested- hematogenous and via the cribriform plate. Both direct virus-induced injury and immune-mediated damage have been thought to underlie the pathogenesis of neurological complications.

Neurological manifestations

The neurological manifestations reported with COVID-19 in children include few reports of paroxysmal events (including seizures) over a wide age range encompassing a newborn and an adolescent with status epilepticus.³⁻⁵ A premorbidly normal 11 year-old boy without any prior history of seizures, presented with status epilepticus. He had a striking absence of typical respiratory symptoms except fever recorded at admission. The status epilepticus required four antiepileptic drugs. Electro-encephalography (EEG) revealed frontal intermittent delta activity and cerebrospinal fluid examination (CSF) was suggestive of meningitis/encephalitis.³ His computed tomography (CT) brain was normal. Similarly, paroxysmal events have been described in a 26 day-old neonate and 6 week-old infant, who presented with fever and mild respiratory symptoms.^{4,5} Evidence of abnormal EEG and uprolling of eyeballs in the infant points towards seizures, however normal EEG and termination of episode with stimulation raises the suspicion of non-epileptic events in the case of newborn. The CSF examination was normal in these 2 cases.

Whether COVID-19 was the culprit or an incidental finding in above cases is not clear as neither SARS-CoV-2 was demonstrated in CSF nor it was the sole pathogen detected in the respiratory samples (positive for rhinovirus/enterovirus also in case of infant and adolescent). Another report describes vague findings of axial hypotonia with drowsiness, moaning sounds in four infants (<3 months) presenting with fever and mild respiratory symptoms.⁶ Co-existing fever and dehydration suggested by presence of mottled skin (present in 3 out of 4 children) cannot be refuted as possible causes for these non-specific signs. Interestingly, all these children had a favorable outcome with complete recovery without any antiviral/immunomodulatory therapy.

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Similar to adults, neurologic manifestations such as dizziness, headache, encephalopathy, myositis, taste and smell impairment, etc. may be seen in adolescents.² Most of these manifestations (except taste and smell impairment) were associated with severe COVID-19 in adults which are rare in children. While cerebrovascular events (both ischemic and hemorrhagic) have been associated with severe disease and lymphopenia in adults, there are no reports of cerebrovascular events in children. The striking absence of literature on cerebrovascular events in children may probably be due to the presence of proactive anti-thrombotic factors in young age and absence of comorbidities like atherosclerosis and hypertension. Other rare associations of COVID-19 in adults include Guillain Barre syndrome, meningoencephalitis, acute necrotizing encephalopathy and ataxia.⁷ These findings have not been reported in children to date except a solitary case of suspected encephalitis in an adolescent described above.³

The basis of diagnosis in these cases was RT-PCR of nasopharyngeal swab specimen for SARS-CoV-2 which appears to be a useful investigation for confirmation of COVID-19 even in children with neurological presentation. Considering the hazards of aerosol generation and low yield, CSF examination may not be a practical investigation.

Considerations in children with neurodevelopmental disorders (NDD)

Severity of the COVID-19 infection represents a major challenge to patients already afflicted with chronic and possibly acute neurological diseases and their caregivers. Children with chronic neurodevelopmental disorders (NDD) are a vulnerable population in this regard due to limited understanding of the mode of spread of COVID-19, inevitable dependency on caregivers for personal hygiene and care, and limited access to health-care facilities. Also, the NDDs are quite prevalent and afflicted children often have multiple comorbidities such as spasticity, movement disorders, gastroesophageal reflux, seizures, etc. which need to be looked after. Besides, children with specific neurological disorders may require immunosuppressive therapy such as steroids which may act as a double-edged sword. Therefore, policy-making and resource allocation should be consciously aimed at providing optimal care to children with NDDs.

There is a rising concern about initiating and continuing immunosuppressive therapies like adrenocorticotrophic hormone (ACTH) or steroids in

children with infantile spasms, Duchenne muscular dystrophy (DMD), etc. Current guidelines advocate continuing standard therapy (steroids / ACTH/ Vigabatrin) for infantile spasms.⁸ Similarly children with DMD can continue steroids which may be converted to stress dose in case of acute illness based on the judgement of treating physician.⁹ Intravenous immunoglobulin (IVIg) and azathioprine may also be initiated and continued with routine precautions and careful monitoring of lymphocyte counts in the case of azathioprine.¹⁰ However, the risk-benefit ratio should be carefully considered before rituximab initiation.¹⁰

Children with disabilities and their families frequently require medical support as compared with typically developing children. Also, their rehabilitation needs may further be heightened with lockdowns due to restricted mobilization and closure of special schools and early intervention centers. Continual provision of medical services (including rehabilitation) by telemedicine is the need of the hour.

Conclusion

A high index of suspicion and characterization of clinical features by the neurologists on the frontline are key to diagnosis which should be aided by the provision of appropriate PPE. For outpatient care and rehabilitation of children with NDD, teleconsultation may be a beneficial approach.

Points to Remember

- *Neurological manifestations are reported in pediatric COVID-19 albeit in lower frequency than that in adults.*
- *Symptoms range from mild ones like headache to full blown meningoencephalitis.*
- *Whether the SAR-CoV-2 virus is the etiologic or an incidental accompaniment is yet to be elucidated.*

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CLIPPINGS

Ignaz Semmelweis : Father of hand hygiene.

Handwashing has been a central component of personal hygiene for many years. However, the link between handwashing and health was first made by Ignaz Semmelweis, a Hungarian doctor working in Vienna General Hospital, who is known as the father of hand hygiene. In 1846, he noticed that the maternal mortality in / doctor-run maternity ward in his hospital were much more than the adjacent midwife-run maternity ward. He investigated and noticed that doctors often visited the maternity ward directly after performing an autopsy. Based on this observation, he developed a theory that those performing autopsies got ‘cadaverous particles’ on their hands, which they carried from the autopsy room to maternity ward and this is responsible for fatal puerperal fever. Midwives were not exposed to these particles.

As a result, Semmelweis imposed a new rule mandating handwashing with chlorine for doctors. The rates of death in his maternity ward fell dramatically from 10 percent to 2 percent This was the first proof that cleansing hands could prevent infection. However, the innovation was not popular with everyone. In 1861 he published his principal work - The Etiology, Concept, and Prophylaxis of Childbed Fever. Later he was dismissed from the hospital for political reasons, harassed by the medical community and contemporaries. Later abandoned by his wife, believing that he was losing his mind, and in 1865 he was committed to an asylum. He died there of septicemia only 14 days later, possibly as a result of being beaten up by guards. He died for the cause he promoted.

Only years after his death, Louis Pasteur developed the germ theory of disease, offering a theoretical explanation for Semmelweis’s findings. After 150 years, it was the Semmelweis University (SU) in Budapest that first adapted a digital tool to teach hand disinfection technique. Now washing hands with soap and water is universally agreed to be the most effective method to prevent the spread of the new coronavirus, SARS-CoV-2,

Global Handwashing Partnership. <http://globalhandwashing.org/abouthandwashing/historyofhandwashing/> Accessed on 14th June 2020.

COVID - 19

DIAGNOSIS OF COVID-19 IN CHILDREN***Tanu Singhal**

Abstract: *The world is facing an unprecedented crises with the advent and spread of COVID-19. Fortunately children are less affected. Diagnosis begins with identifying the right suspect which in turn depends on local prevalence of infection and contact history. In high burden areas any acute illness with or without fever can be COVID-19. The gold standard for diagnosis is RT-PCR in respiratory specimen. Correct collection and transport of specimen is important. Since the sensitivity of RT-PCR is at best 70%, a negative test does not rule out the diagnosis. Sick children may have lymphopenia and elevated CRP, D-dimer, ferritin, CPK, LDH, IL-6. CT chest is more sensitive than CXR and may be abnormal even in those who are asymptomatic or have mild symptoms. The role of serologic tests in children at this time is limited to diagnosis of pediatric multi system inflammatory syndrome.*

Keywords: SARS-CoV-2, COVID-19, Children, Diagnosis.

COVID-19 has been ravaging the world since the past four months with devastating consequences.¹ Globally more than 6 million people have been affected and almost 4,00,000 lives lost.² Fortunately, disease in neonates, infants and children has been mild with less morbidity and mortality.³ However, unusual manifestations such as the pediatric multi system inflammatory syndrome (PIMS) are now being reported.⁴ It is possible that with the evolution of the pandemic, there may be a change in the spectrum and severity of disease in children and recognition of new manifestations. In this article we shall discuss the diagnosis of COVID-19 in general, with focus on children.

When to suspect?

The definition of 'Suspect COVID-19' will vary with the local prevalence and contact history. With widespread closure of schools and day care centres and lockdowns

since the onset of the pandemic, children are most likely to get infected from household contacts. Hence, history of sick family members is important. In published reports from China, a significant percentage of children with COVID-19 were infected from household contacts.⁵ The common manifestations which merit evaluation for COVID-19 in the context of epidemiologic and contact history include:

- Any acute illness with no other explainable cause
- Fever with or without associated respiratory/gastrointestinal manifestations
- Runny nose, sore throat, cough, loss of sense of taste or smell
- Myalgia, fatigue
- Abdominal pain, diarrhea and vomiting
- Irritability, drowsiness, seizures, stroke
- Breathlessness, tachypnea, hypoxia
- Manifestations of pediatric multi system inflammatory syndrome including fever, conjunctivitis, rash, hypotension

Asymptomatic household contacts of COVID-19 positive patients should be tested once between day 5 and 10 of exposure as per recent ICMR guidelines.⁶ Similarly newborns born to mothers who were COVID-19 positive within 2 weeks of delivery or those who have been in contact with COVID-19 infected family members should be tested at birth and then before discharge.⁷

Diagnosis

The diagnosis of COVID-19 in the right clinical setting can be confirmed only by molecular tests as per current guidelines. Other laboratory tests and radiology offer supportive evidence. The role of antibody test is limited. Viral cultures are usually performed only for research purposes. Genome sequencing is also a research tool to determine viral virulence, aid in vaccine development and understanding epidemiologic characteristics of the virus such as circulation of the virus/place of origin.⁸

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Molecular tests (Nucleic acid amplification tests/ NAAT)⁹

Basis

NAAT tests conducted on respiratory secretions are currently the gold standard for diagnosing COVID-19. The most common NAAT assays in commercial use are the RT-PCR tests. These tests have two targets. The first screening gene is the generic coronavirus gene coding for either the spike protein (S), nucleocapsid protein (N), envelope protein (E) or membrane protein (M). The second target is the gene specific to COVID-19 which could be the gene coding for RNA dependent RNA polymerase or spike protein (S) or the open reading frame, ORF 1 or 2. Hence, the sensitivity of kits may vary depending on the target genes used. The common kits in use in India are Altona Real star CoV-2 real-time PCR kit, Thermo TaqPATH COVID-19 and the indigenous Mylab PathoDirect COVID-19 kit. All these tests require first DNA extraction and then PCR. They need batching of samples, technical expertise and the testing time is 4-6 hours. Since most laboratories run only a few batches per day, the turn around time may actually be 24-36 hours depending on when the sample is submitted. Cepheid the manufacturers of Xpert MTB/ Rif have developed a RT-PCR assay for SARS-CoV-2 called Xpert Xpress SARS-CoV-2 which does not require separate DNA extraction and hence can deliver results within 2 hours after submission of the sample. It also does not need technical expertise and can be run as an individual test and samples need not be batched. It is particularly useful when rapid results are needed.

The tests are semi quantitative in nature wherein, the viral load can be estimated from the cycle threshold (Ct) i.e. the number of cycles that need to be run to amplify the RNA. The usual cut off for most test kits is 40 (for the Xpert Xpress kit it is 45). If the cycle threshold is above the cut off, test is negative. The lower the Ct, the higher is the viral load. The Ct values also tend to correlate with infectivity. High Ct values are associated with non viable virus and low risk of transmission. However these Ct values are assay dependent and have been variably reported as >24/ >34 between different assays¹⁰

Collection of samples

The molecular test is performed on respiratory secretions which can be collected from the upper respiratory (nasal swab, oropharyngeal swab, nasopharyngeal swab) or lower respiratory (sputum, endotracheal aspirate, bronchoalveolar lavage) tracts. The person collecting the swab should wear proper personal

protective equipment (PPE) including eye protection, N 95 mask, gloves and gown while collecting the specimen. The samples have to be collected by synthetic swabs and immersed in viral transport medium and transported on ice. Saliva is also being evaluated and found comparable in efficacy to other respiratory specimens and obviates the need for swab sticks and the transmission risks associated during collection.¹¹ If the samples are not processed immediately, they should be frozen at -20°C.

Sensitivity

Sensitivity of the molecular methods is difficult to assess since they themselves are the gold standard for diagnosis. The sensitivities reported in literature are based on test positivity in clinically suspect cases with epidemiologic, contact and radiologic corroboration.

The sensitivity of the molecular tests depends on many factors including the site of collection, method of collection/ transport and duration of illness prior to collection. A study from China which evaluated 1000 swabs from multiple sites reported the best sensitivity from lower respiratory tract specimens (bronchoalveolar lavage 90%, sputum 70%) followed by nasopharyngeal swabs (50%) and lowest from nasal and oropharyngeal swabs (20-30%).¹² The sensitivity is higher in the early phase of the illness and decrease as the illness progresses, particularly after the first week. The tests are often negative in children and adolescents with the Kawasaki disease like multisystem inflammatory syndrome.⁴

While there is scanty data about the sensitivity in children, one study from China that evaluated more than 2000 children with suspect COVID-19 disease reported virologic positivity only in 33% of the cases.¹³ Children with high clinical suspicion of the disease but initial negative molecular tests should be treated as COVID-19. Tests can be repeated on a daily basis in suspect cases. If lower respiratory samples are available, they should be tested. However, doing bronchoscopies for getting access to lower respiratory specimens for diagnostic purposes is not recommended as these are invasive requiring technical expertise, aerosol generating procedures and associated with heightened risk of transmission to health care workers.

Specificity

The RT-PCR tests are highly specific. However, since they detect only RNA sequences of the virus, they can remain positive for weeks and months. Therefore in children who are asymptomatic and test positive on throat swab (such as before elective surgeries) it cannot be inferred when they were infected and whether they are

currently infectious or not. Therefore positive results should be interpreted with caution in patients who are asymptomatic and have no history of close contact with COVID-19 patients. This is also true for children who have tested positive in the past and then are readmitted with some acute illness and test positive again. These were earlier attributed to reinfections but now it is well established that COVID-19 produces at least short term immunity against the virus.¹⁴ Hence, these children who retest positive after recovery should not be managed/isolated as COVID-19.

Repetition of molecular tests

As discussed earlier, molecular tests can remain positive for a long time after infection, even weeks and months. Earlier, it was assumed that the patient is infectious as long as SARS-CoV-2 RNA is detectable in the upper respiratory tract and deisolation required demonstration of two negative swabs 24 hours apart.¹⁵ However, this approach resulted in multiple tests and prolonged hospital stay and was very resource intensive.¹⁶ Meanwhile, it was reported that viable virus was seldom cultured after 7-10 days of the illness if the patient had recovered.¹⁷ Hence, now as per new national guidelines, patients with COVID-19 can be deisolated once 10 days have elapsed from the time of symptom onset and three days since clinical recovery, whichever is longer.¹⁸ However, there is little information about infectivity in patients with severe and protracted illness and current guidelines recommend demonstrating one negative swab prior to discharge in severe cases.¹⁸

Hematologic and biochemical parameters

The changes in hematologic and biochemical parameters in COVID-19 have been extensively studied. These studies have been mainly in hospitalized adults and abnormalities depend on the severity of disease.¹⁹ ²⁰ The white blood cell count is usually normal or low with lymphopenia and elevated absolute neutrophil: lymphocyte ratio. The platelet counts are normal or mildly decreased. There is elevation of C reactive protein but procalcitonin is normal. In patients with severe disease there is elevation of creatine phosphokinase (CPK), lactate dehydrogenase (LDH), D-dimer, ferritin and interleukin-6 (IL-6). There may be mild derangement of liver enzymes, elevation of creatinine and prolongation of prothrombin time/activated partial thromboplastin time. There may be elevation of troponin in some patients indicating myocardial involvement. In children, there is less derangement of the hematologic and biochemical parameters discussed above.²¹ This may also be related to the fact that the disease is less severe in children.

Hence, it is reasonable to say that these tests are primarily of value to assess the severity of COVID-19 and do not really aid the diagnosis of the disease. Poor prognostic markers in adults have been absolute lymphocyte count of < 1000, absolute neutrophil count: absolute lymphocyte count of > 3.5, elevation of CRP beyond 100 mg/ L, increase in D-dimer to more than 6 times normal and levels of IL-6 beyond 7-10 times normal.¹⁹

The pediatric multi system inflammatory syndrome is associated with marked rise in inflammatory parameters. These children have usually an elevated white cell count with neutrophilia and lymphopenia, but normal/ low platelet counts.⁴ The latter is unlike Kawasaki disease where platelet counts increase progressively. These children have high erythrocyte sedimentation rate and high CRP levels. There is mild derangement of the liver enzymes. These children also show other laboratory abnormalities like raised triglycerides, fibrinogen, ferritin and D-dimer and elevated troponin I. Hyponatremia was also a common feature. Some of these children also had elevated levels of IL-6. The ECHO in some showed evidence of coronary artery aneurysms and reduced ejection fraction.

Radiology²²

Chest radiology plays an important diagnostic role in COVID-19 disease. However, radiology in COVID-19 presents logistic challenges due to transmission risks to health care workers and radiation risks to the patients.

The CxR's are usually normal in mild/ early disease. In those with severe disease, it is abnormal with bilateral infiltrates and sometimes complete white out of the lungs.



Fig. 1. CT scan of a mildly symptomatic child showing a peripheral ground glass opacity



Fig.2. CT image in a child with severe COVID-19 disease

CT scans of the lungs are infinitely more sensitive than CxR. Some series reported abnormal CT scans in 20% of children who were clinically asymptomatic. In those who had symptoms, chest CTs were abnormal 2/3rd of the time.²² Disease could be bilateral/ unilateral with predominant involvement of lower lobes than the upper lobes and lesions more peripheral than central. The most common radiologic finding is that of ground glass opacity (Fig.1). Other findings include consolidations, crazy paving pattern and the halo and reverse halo signs. Findings can be severe in patients with clinical evidence of pneumonia and hypoxia (Fig.2). Pleural effusions were rare. As compared to adults, CT findings are less common and less severe in children which basically correlates with the fact that disease is less severe in children. Symptomatic adults had abnormal CT, 90% of the times unlike children, where the CT was abnormal 60% of the time. Also, adults were more likely to have bilateral involvement unlike children where almost half the times there was unilateral involvement. Some studies in adults reported superior sensitivity of CT scan as compared to RT-PCR in diagnosis of COVID-19.²³ This was however not observed in children.

Point of care lung ultrasound is also emerging as a useful diagnostic investigation in COVID-19.²⁴ Since the lesions are peripheral in COVID-19 they are readily picked up by lung USG and termed as straight beam sign.

Serologic diagnosis^{9,25,26}

Kinetics of immune response

COVID-19 is associated with a gradual development of an immune response. IgM antibodies appear 1-2 weeks after infection almost followed immediately by IgA antibodies and then IgG antibodies between 2-3 weeks.

However, the immune response is not uniform in all individuals and severe infections are associated with stronger immune responses. People with mild disease or those who are asymptomatic may not develop an immune response at all. This is possibly attributed to the innate immune response wiping out the virus before the adaptive immune response can kick in.

Detection of immune response

It is expected that IgM detection should be more useful since these antibodies appear early; however IgM antibodies cross react with other circulating coronaviruses. On the other hand, IgG response though a little delayed persists for a long time and is more specific. Detection of virus neutralizing antibodies by special assays is the best approach since these antibodies correlate with future protection. However, viral neutralizing assays are only possible in research laboratories. IgA antibodies are also reliable but are not included in most commercial kits.

Several antibody detection kits that are based on principle of enzyme-linked immunosorbent/ Chemiluminescence immunoassay (ELISA/ CLIA) have been developed that detect both IgM and IgG antibodies or combined antibodies or only IgG antibodies. They differ in sensitivity and specificity and in-house validation of kits is strongly recommended. Rapid serologic tests based on lateral flow assays have been developed. These can give the results within 10-15 minutes but have not been validated sufficiently and are possibly less sensitive than ELISA.

Clinical application of serologic tests

While serologic tests hold great promise, they have not been commonly used in the clinical setting. Indications of these tests include:

- Diagnosis of COVID-19 infection in those patients who have COVID-19 like illness and who test negative by RT-PCR methods. These tests could thus prove useful in those who present with prolonged symptoms when the viral shedding is less. This is especially the case in the multi system inflammatory syndrome where RT-PCR is negative but antibody tests are positive.
- To estimate the prevalence of infection in population and health care workers. This would indirectly help in assessment of herd immunity and effectiveness of infection control measures in hospitals. Recent studies also indicate that infection with COVID-19 leads to short term protection against reinfections.¹⁴ If more evidence accumulates that presence of antibodies equates with protection against future infection,

deployment of such people in front line work would also be possible.²⁷ The main drawback of this approach is that mildly symptomatic people or those who have been asymptomatically infected may not mount a detectable immune response and thus test falsely negative. Hence, absence of antibodies does not indicate absence of previous infection.

- To estimate the level of protection given by convalescent plasma before transfusion to patients with COVID-19. Ideally the titre of neutralizing antibodies should be determined but these assays are not always universally available.

Conclusion

COVID-19 is challenging our lives and resources like never before. Currently, the most common cause of fever with or without any other focus is COVID-19. While we can draw comfort from the fact that children tend to have milder disease as compared to adults, diagnosis of COVID-19 in them is equally important. The RT-PCR in appropriately collected nasopharyngeal swab is the diagnostic method of choice. False negative results can be seen in 30-50% of the cases. Hematologic and biochemical markers and radiology play a supporting role and help in assessment of disease severity. The role of antibody tests is yet to be elucidated.

Points to Remember

- *The gold standard test for diagnosis of COVID-19 at this time is RT-PCR in respiratory tract specimens.*
- *The sample has to be collected and transported properly.*
- *A negative RT-PCR does not rule out the diagnosis of COVID-19.*
- *Presence of lymphopenia, high CRP/ ferritin/ D-dimer/ CPK/ LDH may indicate severe disease.*
- *CT may be useful in the right clinical setting for quick triaging of suspect cases and evaluation of RT-PCR negative cases.*

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CLIPPINGS

A new therapeutic strategy in severe COVID-19.

Patients with severe COVID-19 have a hyperinflammatory immune response suggestive of macrophage activation. Bruton tyrosinase kinase (BTK) regulates macrophage signaling and activation.

Acalabrutinib, a selective BTK inhibitor, was administered off- label to 19 patients hospitalized with severe COVID-19 (11 on supplemental oxygen; 8 on mechanical ventilation), 18 of whom had increasing oxygen requirements at baseline. Over a 10-14 day treatment course, acalabrutinib improved oxygenation in a majority of patients, often within 1-3 days, and had no discernible toxicity. Measures of inflammation-C-reactive protein and IL-6-normalized quickly in most patients, as did lymphopenia, in correlation with improved oxygenation. At the end of acalabrutinib treatment, 8/11(72.7%) patients in the supplemental oxygen cohort had been discharged on room air and 4/8 (50%) patients in the mechanical ventilation cohort had been successfully extubated, with 2/8(25%) discharged on room air. Ex vivo analysis revealed significantly elevated BTK activity, as evidenced by autophosphorylation and increased IL-6 production in blood monocytes from patients with severe COVID-19 compared with blood monocytes from healthy volunteers.

These results suggest that targeting excessive host inflammation with a BTK inhibitor is a therapeutic strategy in severe COVID-19 and has led to a confirmatory international prospective randomized controlled clinical trial.

Roschewski M, Lionakis MS, Sharman JP, Roswarski J, Goy A, Monticelli MA, Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. Science Immunology 05 Jun 2020:Vol. 5, Issue 48, eabd0110 DOI: 10.1126/sciimmunol.abd0110.

COVID - 19

MANAGEMENT OF COVID-19 IN COMMUNITY AND NON-ICU SETTINGS

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Abstract: *Coronavirus disease 2019 (COVID-19) caused by SARS-COV-2 is rarer in children compared to adults. Most countries have reported an incidence of 1- 2%. Whether this reflects 'lower susceptibility' or 'higher proportion of asymptomatic infection in this age group' is not really known. Nevertheless, severe manifestations and deaths are increasingly reported in children. They can act as a source of infection for adults and health care workers, as they cannot follow cough etiquettes as efficiently as adults. Here, we provide a brief overview of pre-ICU management perspectives of COVID-19 disease in children.*

Keywords: COVID-19, Children, Management.

When to suspect COVID-19 in children

The reported incidence of COVID-19 in most countries is 1- 2%.¹ All symptomatic (fever /cough/ shortness of breath) children who have undertaken international travel in the last 14 days, symptomatic contacts of laboratory-confirmed cases, children hospitalized with severe acute respiratory illness (SARI) (fever and cough with onset within last 10 days and requires hospitalisation as defined by WHO) and asymptomatic direct and high-risk contacts of a confirmed case need to be considered as COVID-19 suspect. One needs to remember that indications to clinically suspect COVID-19 was derived predominantly from the adult database. The symptomatology is getting broadened over time as there are multiple documentations of heterogeneous presentation including multisystem inflammatory syndrome, acute heart failure, acute abdomen, etc.

These pieces of information need to be interpreted in concurrence with the epidemiological pattern in the specific geographical area.

Clinical features of COVID-19

The incubation period ranges from 2 - 14 days. Asymptomatic infections have been reported in 4% of children. Illness often starts with mild symptoms like fever, dry cough and sore throat. Fever is seen in about 41% of pediatric patients. 10% of patients may present with GI symptoms like diarrhea and vomiting, while rhinorrhea is relatively rare, being seen in around 7.6% of patients.¹ Patients may also complain of myalgia, headache and fatigue. Clinical syndromes associated with COVID-19 infection include mild, uncomplicated illness with fever, sore throat, malaise, cough, diarrhea or vomiting, mild pneumonia, severe pneumonia, ARDS, sepsis and shock with multi-organ involvement currently labelled as inflammatory multisystem syndrome, temporally associated with SARS-CoV-2.

Clinical progression and heterogeneity in clinical presentation

Around 81% of COVID-19 infections in adults are mild; 14% have moderate to severe symptoms, with 5% of patients having critical illness requiring ICU admission.³ Studies in children have reported fewer severe (5% vs 14%) and critical cases (0.6% Vs 5%) (compared to adults).² Hospitalization is more common in children under one year of age and in those with comorbidities. The clinical course may be hyper-acute with rapid onset of fever and breathlessness or moderate with slower progression of symptoms and later recovery or biphasic with late progressive worsening and multi-organ involvement including ARDS, sepsis and septic shock.⁴

Multisystem inflammatory syndrome in children (MIS-C) or Pediatric Multisystem Inflammatory Syndrome temporally associated with SARS-CoV-2 infection, (PIMS-TS): This may occur weeks after a patient is infected with COVID-19. Some patients may have been infected asymptotically also. Patients present with high persistent fever with multi-organ involvement like cardiac, gastrointestinal, renal, hematologic, dermatologic or neurologic with elevated inflammatory markers.⁵

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Management of children with COVID-19

Community management

All children suspected of having COVID-19 exposure or infection with mild symptoms should be advised quarantine in COVID-19 isolation centres, if available or they may be advised home quarantine.

Home quarantine : Patients should preferably stay in well ventilated single rooms with attached bathrooms. If another person other than care taker of a small child needs to share the room, he should maintain a distance of one metre at all times. He/she should stay away from older adults, pregnant ladies, other children and patients with comorbidities. They should practice strict personal hygiene, including hand hygiene and wearing of masks. They should not share utensils or clothes with other members of the family. Masks used by patients /close contacts during home care should be disinfected using ordinary bleach solution (5%) or sodium hypochlorite solution (1%) and then disposed of either by burning or deep burial.⁶

Family members cleaning the room or handling soiled linen should wear disposable gloves and wash hands with soap and water after removing gloves. Clean frequently touched surfaces with 1% sodium hypochlorite solution and toilet seats with household bleach or phenolic disinfectants. Wash linen separately with detergent and dry. Patients should seek medical advice if any COVID-19 infection symptoms appear including fever, cough, diarrhoea, vomiting or breathlessness and all close contacts in such a situation should be home quarantined (for 14 days). This may be followed up for an additional 14 days or till the report of such case turns out negative on lab testing. Asymptomatic direct and high-risk contacts of a confirmed case should be tested once between day 5 and day 14 after contact.

Hospital management

Triage

Hospitals should preferably establish a 3 tier triage system. History of 'international travel' or 'travel to hotspot areas in the last 14 days' or 'contact with suspected or confirmed cases' should be elicited at the point of the first contact (out-patient counter or registration desk) and all those with positive history should be directed to the COVID-19 isolation area. All patients coming to the emergency or OPD should also be similarly triaged at the entry point for respiratory symptoms and triple-layer surgical mask offered to patient and caretaker of all suspected cases and directed to the designated COVID-19 isolation areas. In the COVID-19 isolation areas, the patient should be triaged for the severity of the infection (Box 1).

Box.1 Triage questions

1. Has someone in your close family returned from a foreign country? Yes/No
2. Is the patient under home quarantine as advised by the local health authority? Yes/No
3. Have you or someone in your family come in close contact with a confirmed COVID-19 patient in the last 14 days? Yes/No
4. Do you have fever? Yes/No
5. Do you have cough /sore throat? Yes/No
6. Do you feel shortness of breath? Yes/No

Clinical categorisation for planning therapy

All children with suspected COVID-19 infection should be categorized into three categories.

Category A patients (mildly symptomatic patients)

These patients can be sent home or to COVID-19 care centres with supportive care. Avoid using non-steroidal anti-inflammatory drugs other than paracetamol. Advice regarding prevention and treatment of dehydration with ORS and appropriate use of other home available fluids in case of diarrhea and vomiting. Patients should be clearly instructed about danger signs and the occurrence of any new symptom or worsening of existing symptom warrants review. These patients should be reviewed every 24-48 hours. Telemedicine facilities may be used for reviewing mildly symptomatic patients. Patients may be offered zinc 2mg/kg/day, (maximum 20 mg) especially in the presence of diarrhea. All category A patients with a history of contact with a confirmed case of COVID 19 should be tested for COVID 19 with a nasopharyngeal swab.

Box.2 Clinical categories of COVID-19

Category A

Mild sore throat, fever, cough, rhinorrhea, diarrhea, vomiting.

Category B

Fever, severe sore throat, increasing cough. Category A symptoms in children with chronic heart, kidney, lung, neurological or liver disease and children on long term steroids, congenital or acquired immunosuppression.

Category C

Altered sensorium, respiratory distress, $\text{SpO}_2 < 94\%$, breathlessness, cyanosis, inability to feed, seizures, hypotension.

Category B patients (moderate symptoms/ patient with comorbidities)

Admission: These patients may be preferably admitted in isolation wards and nasopharyngeal swabs sent for confirmation of disease. Children with comorbidities also should be admitted in isolation wards. If the health care system is overburdened, those without comorbidities and danger signs can be admitted at COVID-19 care centres or advised to self-quarantine at home with follow up and low threshold for admission in case of worsening of symptoms.

Treatment: They may be started on oseltamivir 3mg/kg/dose BD if they fulfil the criteria for treatment of Influenza like illness (ILI). WHO clinical case definition “An acute respiratory illness with a measured temperature of $\geq 38^{\circ}\text{C}$ and cough, with onset within the past 10 days”. Antibiotics as per clinician’s discretion to cover community-acquired pneumonia including atypical pneumonia may be offered. Once swab report is available and the diagnosis confirmed, oseltamivir might be stopped and the patient started on hydroxychloroquine 6.5mg/kg/dose BD on day one followed by 3.25mg/kg/dose BD for four more days along with zinc 2mg/kg/day.⁷

Category C patients (severe and critical disease)

Category C patients require admission and treatment in high dependency units or ICU’s according to severity of illness.

Admission in ward

- Presence of tachypnea (respiratory rate: <2 months ≥ 60 /minute; 2-11 months ≥ 50 /minute; 1-5 years ≥ 40 /minute) without lower chest indrawing or danger signs like lethargy, altered sensorium, inability to feed, convulsion, etc.
- Children with high risk for severe disease with mild symptoms: children with congenital or acquired heart disease, chronic lung, liver, kidney or neurological disease, children on immunosuppressive drugs, congenital or acquired immunodeficiency
- SpO_2 90 - 94% without retractions and danger signs.

Admission in high dependency unit (HDU)

- SpO_2 less than 94% with ≤ 2 site retractions
- Children with comorbidities with a saturation of less than 94% or tachypnea.
- $\text{SpO}_2 < 90\%$ without increased work of breathing.
- Children with tachypnea with lower chest in drawing/grunt.

- Presence of danger signs like inability to feed, altered sensorium, seizure etc. without evidence of shock or other organ involvement (these children may need transfer to PICU early for close monitoring if symptoms persist).

Admission in PICU

- Moderate to severe ARDS ($\text{PaO}_2/\text{FiO}_2$ (P/F) ratio less than 200 / oxygenation index (OI) < 8 / Oxygen saturation index as measured by $\text{FiO}_2 \times \text{mean airway pressure}$)/ SpO_2 values (OSI) < 7.5 while on CPAP of minimum 5 cm
- $\text{SpO}_2 < 94\%$ with increased work of breathing (> 2 site retraction/ paradoxical breathing / see saw breathing / head bobbing etc.)
- Suspecting atypical presentation of COVID, i.e., Kawasaki disease (KD) like illness, multisystem inflammatory disorder etc.,
- Shock
- Multi-organ dysfunction
- Need for mechanical ventilation
- Transfer from ward or HDU for close monitoring / mechanical ventilation

Management of admitted patients

General measures

- Symptomatic treatment: Avoid giving NSAIDs other than paracetamol for fever. Provide oral bronchodilators or MDI with spacer and mask for children with wheeze.
- Antibiotics and antivirals may be given as per clinicians discretion to cover community-acquired pneumonia, including atypical infections and influenza.
- Ensure euvolemia and advice adequate fluid and feed intake.

Monitoring

- Vital signs - HR, RR, SpO_2 , BP
- Work of breathing (retractions, use of accessory muscles, grunting, head bobbing, air hunger, large tidal volume breaths)
- Oxygen requirement

Laboratory investigations

Routine investigations: CBC with differential count and ESR, RFT, LFT, coagulation profile, urine routine and

send these in all admitted patients. Unlike adult patients with COVID-19, there have been no consistent leukocyte abnormalities reported in pediatric patients. Only 3.5% of pediatric cases showed lymphopenia.¹ Chest X-ray may show patchy infiltrates consistent with viral pneumonia and chest CT scans may show nodular ground-glass opacities.

Biomarkers in sick children : CRP, LDH, D-dimer, CPK, ferritin, troponin I, elevated transaminases, prothrombin time, NT-ProBNP, BUN, creatinine. Send these in patients with severe or critical disease admitted in HDU or PICU and those with worsening respiratory status.

Complications

COVID-19 infection primarily causes upper respiratory infection followed by pneumonitis of varying severity. Some patients progress to develop hyperinflammatory syndrome due to cytokine storm clinically presenting with features of KD, cytokine release syndrome or infection associated HLH often leading to multi-organ failure. Pointers towards hyperinflammatory syndrome include -

1. Persistent high fever or reappearance of fever.
2. Rising CRP especially more than 100- 200 mg/L
3. Doubling of ferritin in 24 hours or very high ferritin levels (> 2000 - 10,000mcg/L)
4. Falling counts
5. Rising or falling ESR
6. Rising CPK, LDH
7. New-onset shock especially with elevated trop I (also rule out Kawasaki disease with shock syndrome)

COVID-19 pneumonitis : Hypoxia in COVID is multifactorial. Two basic types of lung phenotypes have been described: the L type and H type lung. These two phenotypes are not mutually exclusive; they may indicate lung in different stages of evolution of the disease. Increased work of breathing contributes to lung damage by increasing patient self-inflicted lung injury (P-SILI) and is responsible for the transition from L Type to H Type (Table I).⁸

Oxygen therapy in COVID-19 infection

All areas where patients with SARI are cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, simple face mask, non-rebreathing mask).

- Give supplemental oxygen therapy immediately to patients with SARI and respiratory distress, hypoxemia, or shock.
- Target $\text{SpO}_2 \geq 94\%$ during resuscitation and $> 90\%$ for patients on oxygen therapy and those recovering from pneumonia without respiratory distress.⁶
- Nasal prongs or cannula are preferred in children as it may be better tolerated. Offer a surgical mask or hood covered by a surgical mask to decrease the risk of aerosolization and droplet spread.
- If on prongs and SpO_2 less than 90% with minimal respiratory distress, options include
 - a) Face mask at flow $> 5\text{LPM}$ (FiO_2 40 - 60%)
 - b) Oxygen hood at flow $> 5\text{LPM}$ (FiO_2 30-90%)
 - c) Venturi mask (28-60% FiO_2)

Table I. L type and H type lung characteristics

L type lung characteristics	H type lung characteristics (typical ARDS lung)
• Good lung compliance	• High elastance
• Low elastance	• Low compliance
• Low ventilation-perfusion ratio due to abolition of hypoxic vasoconstriction or pulmonary thrombophlebitis leading to pulmonary thrombosis	• Wet lung
• Low lung recruitability as the amount of non-aerated lung less	• High right to left shunt
• Relatively dry lung	• Higher lung recruitability as the amount of non-aerated lung is higher due to damage to the alveolar basement membrane and loss of surfactant.

d) Non-rebreathing mask at flow 10-15 LPM (FiO₂ 80-90%).

- If the flow of 15 LPM oxygen achieves saturation of > 95%, it indicates the shunt fraction is mild. Failure to accomplish this indicates a moderate-severe shunt fraction. These children should be closely monitored for deterioration and respiratory support should be escalated as per need.
- Heated humidified high flow nasal cannula (HFNC) may be used preferably over CPAD/BIPAP if the target saturation is not achieved with above oxygen delivery devices. It should be used only in patients with hypoxemic respiratory failure. It increases the risk of aerosolization, but the risk is less than that for other NIV.
- Switch on the machine only after fixing the nasal cannula.
- Start at 0.5 - 1litre per kg per minute and increase up to 2 litre/kg/minute if needed.
- Use minimal flow that makes the baby comfortable.
- Target SpO₂ 90 - 94%
- Monitor HR, RR, SpO₂ and work of breathing. Monitor closely, if no response in 1- 2 hours will need escalation of support.

NIV CPAP: It may be offered only in selected patients with hypoxemic respiratory failure. The failure rate with NIV is very high, especially in de-novo respiratory failure, so these patients need close monitoring.

- Use of conventional ventilators for NIV with non-vented oronasal masks/helmets preferable.
- Avoid using dedicated NIV with single limb and vented masks as the risk of aerosolization is very high.
- Connect a bacterial/viral filter at exhalation port
- Use the lowest possible PEEP to achieve targets.
- Monitor closely for deterioration and intubate if the patient deteriorates or there is no improvement in 1 hour or delivered tidal volume is more than 9.5ml/kg with increased work of breathing as P- SILI may damage the lung further.
- Placing of the aerosol box with ports covered by the surgical mask may decrease the risk of aerosolization.

Specific therapy

No specific antiviral therapy is proven to be effective as per currently available literature. Drugs being used in clinical trial settings include

- Hydroxychloroquine / Chloroquine
- Lopinavir / Ritonavir
- Remdesivir
- Nitazoxanide
- Ivermectin

Hydroxychloroquine : 6.5mg /kg /dose (Max 400 mg) PO BD day 1 followed by 3.25mg per kg PO BD (max 200mg/dose) for 4 days. Usual treatment is for 5 days, but in select patients with extended ventilation or profound immunosuppression, duration may be extended to 10 days. Retinopathy, rash, nausea, glucose fluctuations and diarrhoea include adverse events associated with HCQ therapy. GI symptoms can be mitigated by taking HCQ with food. Avoid taking hydroxychloroquine with antacids and separate administration by at least 4 hours.

Contraindications: QT prolongation > 500 ms, porphyria, myasthenia gravis, retinal pathology, epilepsy. If baseline QT prolongation is present, take frequent ECG.

Chloroquine: 10 mg /kg chloroquine sulphate base stat followed by 5 mg per kg 12 hours later and then 5 mg/kg/ dose BD for four more days. Adult dose: Chloroquine sulphate base 600mg stat followed by 300 mg 12 hours later followed by 300mg BD for four days.

Lopinavir / Ritonavir

This may be considered on a case to case basis in severe disease (SpO₂ <94% in room air or requiring supplemental oxygen, mechanical ventilation or ECMO) not responding to chloroquine after written consent and medical board concurrence and dose is given in Box 3.

Box.3 Dose of Lopinavir/Ritonavir

- 14 days to 6 months : 16mg/kg/dose PO BID (based on lopinavir component)
- < 15kg : 12 mg/kg/dose PO BID (based on lopinavir component)
- 15-25 kg: 200 mg/50 mg PO BID
- 26-35 kg: 300 mg/75 mg PO BID
- >35 kg: 400 mg/100 mg PO BID
- Adult dose : 400/100 PO BID

Duration of treatment : 14 days or 7 days after becoming asymptomatic.

Adverse events: Hepatotoxicity, pancreatitis, diabetes, QT prolongation, lipid elevations.

Remedesivir

Not currently freely available in India. EUA (emergency use authorisation) has been granted by FDA for use in children and adults with severe disease.

Dose : 5mg/kg IV (max. 200mg) loading dose over 30 - 120 minutes on day 1 followed by 2.5mg/kg (max.100mg) IV OD on days 2- 4.

Duration of treatment: Usual duration 5 days. If no clinical improvement, duration may be extended to total 10 days.

Infection prevention and control perspectives in COVID-19 scenario

Infection prevention and control (IPC) measures are of paramount importance in managing patients with COVID-19 infection.

Triage area

- Encourage all patients to wear masks. All suspected patients and caretakers should be provided with a triple layer surgical mask and advice patients to keep 1-metre distance between them. Advice patients to perform hand hygiene after coming in contact with respiratory secretions. Health care workers in the triage area should wear N95 masks, face shields, gowns and gloves.
- Apply droplet precautions when working within 1 - 2 metres of the patient using a triple-layer mask and face shield or goggles.
- Use PPE while entering the room with a triple layer mask, gown and goggles and remove when leaving.
- Use dedicated /disposable equipment when possible.
- Aerosol precautions should be taken while doing aerosol-generating procedures by donning complete PPE, including N95 mask.⁶
- Disinfection of equipment, cleaning of patient's surrounding and safe disposal of waste are also part of IPC measures.

Hand hygiene

Perform hand hygiene with alcohol-based hand rub for 20 seconds or wash hands with soap and water for 40 seconds before and after touching patient, using washrooms, taking food, donning and doffing of PPE including mask and also after coughing, sneezing, handling garbage, touching mask or soiled PPE.

Patient placement

- If single rooms are available, admit patients in a single room.
- If single rooms are not available, patients with the same etiological diagnosis can be grouped. If the etiological diagnosis is not confirmed, patients with a similar clinical diagnosis and epidemiological risk factors can be grouped with spatial separation of 1 meter between beds.⁶
- Isolation ward should have separate entry and exit and should not be located with post-surgical wards /dialysis units/SNCU labour rooms.
- There should be a double door entry with a changing room and nursing station.
- All healthcare workers should use PPE (triple layer surgical mask, eye protection, gloves, gown and shoe cover) when entering a patient room and remove PPE when leaving.
- If possible, use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers). Equipment which is reused should be disinfected appropriately.
- Place an appropriate container with a lid outside the door for equipment that requires disinfection or sterilization.
- Avoid patient movement and transport unless necessary.
- Aerosol-generating procedures (i.e. open suctioning of the respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation) whenever possible, should be done in adequately ventilated single rooms, preferably negative pressure rooms with minimum of 12 air changes per hour or at least 160 litres/second/patient in facilities with natural ventilation. These rooms may have stand alone air-conditioning. These areas should not be a part of the central air-conditioning. If air-conditioning is not available negative pressure could also be created through putting up 3-4 exhaust fans driving the air out of the room. These procedures should be done after donning complete PPE, including gloves, long-sleeved gowns, eye protection, and fit tested particulate N 95 masks.
- Used PPEs should be disposed of as per the bio-medical waste management guidelines. Ensure these bins (dirty) are inside the isolation areas.

Cleaning and disinfection of the environment

1% freshly prepared sodium hypochlorite solution can be used as a disinfectant for cleaning and disinfection. A contact time of at least 10 minutes is recommended. 70% alcohol-based disinfectants may be used for disinfecting surfaces where bleach is not suitable (e.g. metals). Wear heavy-duty/disposable gloves, disposable long-sleeved gowns, eye goggles or a face shield, and triple-layer surgical mask while cleaning the area. Wipe all frequently touched areas (e.g. doorknobs, lift buttons, handrails, armrests, tables, keyboards, switches, etc.) every 3 - 4 hours. Low touch areas like wall and mirror should be wiped daily once. Clean toilet surfaces with 1% sodium hypochlorite solution or chemical disinfectant. Wash linen/fabrics preferably using the hot water cycle. For hot-water laundry cycles, wash with detergent or disinfectant in the water at 70°C for at least 25 minutes. Discard cleaning items made of cloth and absorbent materials, e.g. mop head and wiping cloths, into biohazard bags after cleaning and disinfecting each area. Wear a new pair of gloves and fasten the double-bagged biohazard bag with a cable tie. Buckets can be disinfected by soaking in disinfectant or bleach solution or rinsing in hot water before filling.

Transport of infectious patients⁹

Transport of infectious patients should be limited to movement considered medically essential by the clinician. The patient should be dressed in a mask and gown and covered in a sheet. For quarantine isolation, the patient may be transported in a fully enclosed transport cell or isolator with a filtered air supply and exhaust. The transport personnel should remove existing PPE, clean hands and apply clean PPE before transporting. The destination unit should be notified before transport. It is preferable to transport patient through service or staff corridors than public corridors. The nominated lift and corridor should be isolated from public and staff before transport and should be cleaned following transit of an infectious patient.

Planning inter-facility transfer of COVID-19 patients

Ideally, there should be ambulances specifically identified to transport COVID-19 patients. It may be needed to transport patients from home to hospital or from one hospital to another. Ambulance staff should be trained about common infection prevention and control practices, including the use of personal protective equipment (Box 4).

Box 4. Rational use of PPE for inter hospital transport

- Driving the ambulance (Low risk) - Triple-layer surgical mask gloves
- Transporting patients, not on any assisted ventilation (Moderate risk) - N-95 mask Gloves
- Management of SARI patient while transporting (High risk) - The full complement of PPE
- When aerosol-generating procedures are anticipated

Before transport

Both the emergency medical technician (EMT) and driver of an ambulance should wear PPE while handling, managing and transporting the COVID-19 identified/suspect patients. Patient and attendant should be provided with a triple layer mask and gloves. Only one caregiver should be allowed to accompany a patient. The identified health facility should be contacted beforehand for facility preparedness and readiness. Treatment summary, vitals at reference and referral indication should be documented

Management on board

Monitor vitals during transport. Give supplementary O₂ at 5 L/min and titrate flow rates to reach target SpO₂ ≥90%. If a patient is on a ventilator, follow ventilator management protocols.

Post transport

At the receiving hospital, hand over the patient and details of medical interventions if any, during transport. PPEs should be taken off as per protocol followed by hand washing. The biomedical waste generated (including PPE) should be disposed of in a biohazard bag (yellow bag). Inside of it should be sprayed with sodium hypochlorite (1%) and after tying the exterior should also be sprayed with the same.

Disinfection of ambulance

All surfaces that may have come in contact with the patient or materials contaminated during patient care (e.g. stretcher, rails, control panels, floors, walls and work surfaces) should be thoroughly cleaned and disinfected using 1% sodium hypochlorite solution. Clean and disinfect reusable patient-care equipment before use on another patient with an alcohol-based rub. Cleaning of all surfaces should be done morning, evening and after every use with soap/detergent and water.

Points to Remember

- *COVID-19 is rarer in children (1- 2%).*
- *All suspected of having COVID-19 exposure or infection with mild symptoms should be advised quarantine at home or in isolation centres.*
- *All children with suspected COVID-19 infection should be categorized into three categories, Category A, B and C.*
- *Category C is a child with critical symptoms like altered sensorium, shock or respiratory distress or a $SpO_2 < 94\%$.*
- *Both clinical and laboratory monitoring are essential at periodic interval to decide escalation or deescalation of therapy.*
- *Non invasive ventilatory support is preferred unless child deteriorates, where intubation and mechanical ventilation is needed.*
- *Even though there are no proven drugs, those tried in clinical trial settings include hydroxychloroquine / chloroquine, lopinavir / ritonavir, remdesivir, nitazoxanide and ivermectin.*
- *Safety of the health care workers and others are important at every stage right from triage, admission areas and during transport.*
- *Hand hygiene, proper donning and doffing of the PPEs and environmental cleaning are extremely important.*

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CLIPPINGS

Tears do not carry corona.

COVID-19: Low risk of coronavirus spreading through tears.

While researchers are certain that coronavirus spreads through mucus and droplets expelled by coughing or sneezing, it is unclear if the virus is spread through other body fluids, such as tears. Today's just-published study offers evidence that it is unlikely that infected patients are shedding virus through their tears, with one important caveat. None of the patients in the study had conjunctivitis, also known as pink eye. However, health officials believe pink eye develops in just 1 percent to 3 percent of people with coronavirus. The study's authors conclude that their findings, coupled with the low incidence of pink eye among infected patients, suggests that the risk of virus transmission through tears is low.

American Academy of Ophthalmology: COVID-19: Low risk of coronavirus spreading through tears. ScienceDaily, 25th March, 2020. Available from www.sciencedaily.com/releases/2020/03/200325143826.htm. Last accessed on 14th June, 2020.

COVID - 19

CRITICAL CARE MANAGEMENT OF PEDIATRIC COVID-19***Hari Krishnan Kanthimathinathan******Manu Sundaram*******Santosh Sundararajan********Padmanabhan Ramnarayan*********Barnaby R Scholefield**

Abstract: *Children tend to have relatively milder COVID-19 illness compared to adults. However, a small proportion of children may need critical care support either due to hypoxic respiratory failure or due to multi-system inflammatory syndrome (Pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2). While the principles of management are consistent with any other severe acute respiratory illness, there are numerous challenges to ensure that the healthcare workers are adequately protected. Significant planning and prior preparation are required to overcome these challenges. Even in the rare circumstances of severe illness*

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in children, good outcomes are possible. The role of specific therapies is unclear and a brief review of medication is presented.

Keywords: *COVID-19, Pediatric inflammatory multisystem syndrome, Temporally associated with SARS-CoV-2.*

Children have been relatively less affected than adults in both frequency and severity of COVID-19 caused by the SARS-CoV-2 virus.¹ Given the rarity of severe disease in children, international critical care community response, including in the USA and UK, has largely been focused on expansion of adult critical care units and redeployment of personnel and equipment from pediatric critical care into adult critical care units to cope with the surge in numbers of critically ill adults with COVID-19. While children needing critical care with COVID-19 is a relatively rare occurrence, severe disease and COVID-19 related deaths in children have also been reported.² More recently, a possibly SARS-CoV-2 related, multi-system inflammatory syndrome with overlapping features of Kawasaki disease and toxic shock syndrome affecting children has been reported.³ While debate about appropriate nomenclature for this condition is still ongoing, it is currently referred to as 'pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2' (PIMS-TS).⁴ It is therefore of utmost importance that the pediatric critical care community is well versed with strategies and considerations for managing children with confirmed or suspected COVID-19.

PICU admission- Indications

Assessment of children should follow established institutional policies. However, given the high infectivity of SARS-CoV-2 virus, risk-assessment to identify appropriate level of personal protective equipment (PPE) to protect the health care workers (HCW) should be performed. This may include obtaining information about symptoms and signs, travel, contact history and the results of any recent tests for SARS-CoV-2 virus before reviewing the children. Where this is not practical or feasible in situations when urgent assessment is required, high level of personal protective equipment (PPE) including that used for aerosol generating procedures (AGP) may be the safest option. This 'full PPE' includes water-repellent protective

body suit or long-sleeved gown, double gloves, wipeable shoes or shoe covers, N95 mask or filtering face piece 3 (FFP3) or FFP2 mask fit-tested for each staff member and visor/goggles \pm head cap. There is no clear evidence to suggest a different threshold for PICU admission related to COVID-19 infection compared to other childhood pneumonias or severe acute respiratory infections (SARI). In general, the following clinical scenarios may necessitate a PICU admission.

- Requirement for significant respiratory support that cannot be provided elsewhere such as non-invasive or invasive ventilation. This may be due to hypoxia, hypercarbia or increased work of breathing.
- Requirement for cardiovascular support including multiple fluid boluses or inotropes. This may be because of hyperinflammatory syndrome, myocarditis or significant co-infections.
- Deterioration of neurological status. This may be due to direct COVID-19 related neurological complications (e.g. seizures, encephalopathy) or related to respiratory complications such as hypoxia.
- Any child considered to be at risk of further deterioration requiring continuous or close monitoring requiring higher nurse: patient ratios.

PICU management - General principles

Hypoxic respiratory failure has been widely reported in adults with SARS-CoV-2 infection and is the most common indication for ICU admission. Respiratory illness related to COVID-19 in children may resemble other causes of SARI including other bacterial or viral pneumonias. While characteristic radiological and laboratory features have been described in adults, non-specific changes are the norm in children with COVID-19. A high-index of suspicion and low threshold for testing for SARS-CoV-2 antigen by PCR is required. Due to sub-optimal sensitivity of the SARS-CoV-2 PCR test, a single negative test is not sufficient to exclude COVID-19 with high-level of certainty in patients with a high pre-test probability. The pre-test probability also depends on the population prevalence of COVID-19 and therefore will need to be interpreted in context of wider picture of the stage of the pandemic within the local area. Therefore repeat testing with nasal, throat or nasopharyngeal swabs in patients who are not invasively ventilated or lower airway specimen such as endotracheal aspirates in invasively ventilated patients may be required. Two or more tests may be required before full PPE precautions are stepped down to droplet PPE precautions (aprons, gloves, fluid-repellent surgical mask \pm visor/goggles), especially in those admitted with a SARI without an alternative diagnosis.

Where possible, children with suspected COVID-19 should be treated in single-occupancy negative pressure cubicles, at least until COVID-19 is excluded with reasonable certainty. Where this is not possible, every effort should be made to minimise exposure of other patients admitted to PICU for reasons unrelated to COVID-19. Consideration of additional visiting restrictions and arrangements for isolation of parent/carers along with the children where appropriate may be required. Significant planning and re-organisation of the physical ICU footprint and staffing models may be required to ensure that this is possible. Communication between team members can be difficult while wearing PPE. Similarly the use of phones, computers and other resources may be limited inside the cubicles with COVID-19 patients. Working in full PPE for prolonged periods may cause dehydration of the health care worker (HCW). It is important to stress, however, that while significant changes may be required for infection prevention and control purposes, the clinical management principles of a child with COVID-19 are identical to any other SARI.

Respiratory failure - Management

There is no specific evidence to guide a different management strategy for respiratory failure in children with COVID-19, compared to children with other causes of SARI. However, minimising HCW exposure to aerosols by reducing AGP and where this is unavoidable, using appropriate PPE precautions is the key.⁵ Having minimal number of personnel, reducing equipment in close proximity, decontamination of exposed equipment, use of disposable equipment where possible are all important. Significant uncertainties related to procedures which are associated with aerosol generation exists. While there is a school of thought that early invasive ventilation, avoiding non-invasive ventilation and/or high flow nasal cannula (HFNC) oxygen therapy minimises HCW exposure to aerosols, it may not be practicable or safe in all circumstances. Therefore, step-wise escalation of respiratory support as with other causes of SARI may be the best course of action in children with COVID-19 also.⁶ Management principles for ARDS in adults with COVID-19 may largely apply to pediatric critical care management also. An informative summary of escalation of respiratory support and management of COVID-19 related acute respiratory distress syndrome (ARDS) can be found in website of 'The Society of critical Care Medicine'.⁷

High flow nasal cannula (HFNC) oxygen therapy

Children with hypoxia (oxygen saturation $<92\%$) should receive supplemental oxygen. In children who

require higher concentration of supplemental oxygen, heated and humidified oxygen with HFNC may be well tolerated and may reduce the need for invasive ventilation. There is limited evidence behind the concerns about aerosol generation due to HFNC. In fact a recent study showed that the aerosol production from HFNC was no worse than spontaneous respiration regardless of presence or absence of cough and regardless of higher or lower flows used in HFNC.⁸ Some North American centres do not consider HFNC as an AGP. It is probably safe to use HFNC for children with mild-moderate disease severity, especially if the HCW uses full PPE and children are nursed in cubicles. Routine monitoring of heart rate, respiratory rate, fractional inspired oxygen (FiO_2), work of breathing and comfort levels are essential to assess the effectiveness of HFNC therapy. In fact, nearly a quarter of the children in the North American cohort of COVID-19 were managed with HFNC only.² HFNC therapy therefore is a useful immediate respiratory support. However, treatment failure needs to be promptly recognised and respiratory support rapidly escalated to either non-invasive ventilation (NIV) or invasive mechanical ventilation.

Non-invasive ventilation

NIV using a full face or oro nasal mask interface can be tried in selected patients based on local experience. Bubble CPAP may especially be a useful mode of support in young infants. As with HFNC, effectiveness and response to therapy should be carefully evaluated. Escalation to invasive ventilation should not be delayed especially in those children with a rapidly deteriorating disease trajectory. Intubation must be recommended if there is no improvement in oxygenation (target SpO_2 92 - 97% and $\text{FiO}_2 < 0.6$) within 60-90 minutes of initiating NIV.⁹ As with HFNC, the risk associated with aerosol generation and exposure to HCW should be carefully considered and appropriate PPE worn.

Invasive ventilation

Strategies to minimise HCW protection from aerosols during invasive mechanical ventilation of suspected or confirmed COVID-19, may include the use of appropriate full PPE, inline suction, minimise circuit disconnection, temporary clamping of endotracheal tube (ETT) when disconnection is essential, passive humidification with a heat moisture exchanger (HME) filter rather than active humidification, viral filter in the expiratory limb of the ventilator circuit and pre-attached viral filters in bagging circuits for use in emergencies.

In children requiring mechanical ventilation, established strategies for lung protective ventilation should

be followed. Initial setting should aim to achieve tidal volumes between 4 to 8 mL/kg of ideal body weight, with a PEEP between 6 to 10 cm H_2O and plateau pressure under 28 cm H_2O .^{10,11} Permissive hypoxia (SpO_2 88-92% if PEEP >10, or else 92-97% if PEEP <10cm H_2O) and permissive hypercapnia (if $\text{pH} > 7.15$) are acceptable to achieve optimal lung protection.^{10,11} Deep sedation with or without muscle relaxation may be needed to facilitate this.

Prone position has been thought to provide survival advantage in adults with severe hypoxemia ($\text{PaO}_2/\text{FiO}_2$ ratio < 150). Prone ventilation can improve oxygenation and lung homogeneity in children, although a survival advantage has not been demonstrated.¹² Proning is recommended for 12-16 hours/day in adults and due precaution needs to be taken to avoid complications like pressure sores and ET tube obstruction/displacement. It is likely that pediatric critical care units have had already experience with proning and have set policies and procedure which would help them to adapt to it. For e.g., adaptation would need to ensure that disconnection of ventilator circuit does not occur.

Trial of inhaled Nitric Oxide is warranted in children with persistent hypoxemia. High frequency oscillatory ventilation (HFOV) has been used in neonates and children with severe hypoxemia as a rescue therapy. However, the disadvantage with HFOV is that it is an open circuit with potentially significant aerosol generation. HFOV circuits with viral filters are available and are strongly recommended if that is considered.

Extra-corporeal oxygenation

Extra-corporeal oxygenation (ECMO) has been used in adults with SARS-CoV-2 in established and adequately resourced ECMO centres with variable outcome. This has usually been necessitated for refractory hypoxemia despite conventional ventilator management strategies including the use of prone positioning and inhaled nitric oxide. Very few children with COVID-19 have required ECMO.¹³ Children have also been placed on ECMO for PIMS-TS (rather than acute COVID-19) for cardiovascular support if significant myocardial impairment exists.³ Given the rarity, it is unlikely that clearly defined indications for ECMO support in children with COVID-19 can be agreed upon. Individualised decision making with adaptations of existing ECMO guidelines and wider consultation with various team-members will therefore be required. Key components of planning for ECMO use during a pandemic include: resource planning, personnel assignment, training, infection control on ECMO, planning for ECMO transfers etc.¹⁴ The use of ECMO should be

restricted to experienced centres and the effect on resource utilisation in the midst of a pandemic should be carefully considered.

Other supportive care

Judicious fluid management is the key to the care of any critically ill child. Fluid overload is associated with increase in morbidity and mortality in critically ill children. Following restoration of intravascular volume, a restriction of daily allowance to 70-80% of calculated fluid requirement using Holliday-Segar formula is a good starting point. Fluid balance should be assessed clinically and using input/output chart daily, allowance made for ongoing fever and associated insensible losses and with measured body weight when feasible and safe to do so. Enteral feeding should be commenced at the earliest possible opportunity, if safe to do so. Empirical antibiotics are justified until a diagnosis is established and/or co-infections are excluded even if the SARS-CoV-2 PCR is positive. Choice of antibiotics depends on local prevalence of the various bacteria.

Other considerations

Intubation and extubation

Intubation is probably the pediatric critical care procedure associated with the most amount of aerosol production. Therefore it is done with utmost care with PPE including careful donning and doffing and use of a donning/doffing buddy. Medical literature, especially the social media, is flooded with various improvisations of the procedure to minimise HCW exposure to aerosols. Examples include perspex boxes, plastic cling film covering the patient etc. However, the unproven but potential additional protection offered by these devices should be carefully weighed against difficult ergonomics, human factors, operator difficulty related to unfamiliar equipment, spreading the infection while removing the additional device and consequences of intubation failure. Regardless of any new equipment used, team simulation for intubating a COVID-19 patient is essential to fine tune the procedure and adapt it to the local environment and personnel. The challenges of performing pediatric critical care procedures while wearing full PPE cannot be underestimated. The use of a checklist, such as the one produced in conjunction with the UK Pediatric Intensive Care Society can be invaluable.¹⁵ It is recommended that the most experienced airway operator intubates the child and where possible cuffed endotracheal tubes should be used to minimise leak around the tube. The use of video laryngoscopes has been recommended in several

guidelines. However, familiarity is the key. Routine induction medications used by pediatric critical care physicians to provide optimal intubating conditions in other critically ill children can also be used for children with COVID-19. This often includes a combination of ketamine, and/or an opioid and/or a benzodiazepine. Bag and mask ventilation is avoided to limit aerosol generation, if clinical situation permits. If required, as low a tidal volume as possible with a low respiratory rate may be prudent. A heat moisture exchange (HME) filter can be placed between the mask and the bagging circuit. Prior to connecting to ventilator, the ETT can be temporarily clamped while attaching to the ventilator circuit. Viral filters are recommended in the expiratory limb (between the circuit and machine), but significant variations in compatibility based on the make and model of the ventilators may exist.

Extubation may also produce significant aerosols and therefore similar appropriate precautions apply.

Intra-and inter-hospital transport considerations

The key principles relevant to the transport of a child with COVID-19, whether within the hospital (e.g. for a CT scan) or between hospitals (e.g. for enhanced care), are similar. The primary consideration is always to maintain patient safety; however, the additional consideration of staff safety is important when dealing with COVID-19 due to its highly infectious nature.

Preparation for transport: It is important to identify early, the COVID-19 status of the patient, either suspected (based on the case definition) or confirmed by laboratory testing. COVID-19 status will affect several aspects of the transport: the type of PPE needed, the seniority of staff involved (most senior personnel), logistics of moving the patient (ground ambulance, air ambulance, trolley push within the hospital), the choice of respiratory support provided (non-invasive versus invasive ventilation) and appropriate decontamination of transport equipment. All staff involved in the transport of children with COVID-19 should be in full PPE to protect against AGP.¹⁶ Common AGP performed during transport include HFNC, NIV, endotracheal intubation and open endotracheal suction. If patients are self-ventilating, a surgical face mask can be considered to minimise aerosol spread.

Airway and respiratory management: Inter-hospital transfers of children on HFNC or NIV are challenging due to aerosolisation risk - staff must be in full PPE throughout and the ambulance must not re-circulate air (instead, should be set to exhaust). Where possible, NIV should be delivered using dual-limb circuits and unvented face masks.

Alternatively, a high-efficiency viral filter should be attached proximal to the expiratory leak.⁹ Emergency intubation is a high-risk procedure even without the challenges of full PPE and therefore the need for intubation during patient transport should be avoided wherever possible by early identification of NIV failure and early intubation.¹⁰ Use of a standardised checklist for intubation, as highlighted earlier, is recommended.¹⁵ Transport ventilators are often turbine-driven and use ambient air rather than compressed medical air from cylinders, therefore viral filters are recommended on the inspiratory limb of the circuit (to prevent the patient being infected) as well as expiratory limb of the circuit (to prevent the ventilator being contaminated by the patient).

Patient handover: To avoid contamination of clean areas of the receiving hospital, a secure and dedicated pathway for accessing the relevant areas (e.g. ICU, CT scanner) should be identified and followed during intra and inter-hospital transfer. Following verbal handover, transfer documentation may be transmitted by electronic means, where possible, due to the risk of contamination of paper notes during transport.

Equipment and decontamination: To avoid equipment wastage due to contamination, they should be in wipeable, closed, small pouches (e.g. airway equipment, resuscitation drugs) that should be opened only if required. Decontamination of equipment such as the patient trolley, transport ventilator, infusion pumps and patient monitor should be performed using universal detergent wipes followed by a 1:1000 chlorine-based solution/wipes. The exposed surfaces of the ambulance will require similar decontamination, especially if an AGP was performed during transport.

Cardiopulmonary resuscitation (CPR)

Cardiac arrest due to COVID-19 in children is an extremely unlikely event. However, in children who unfortunately have an in-hospital cardiac arrest, the COVID-19 status may be unclear either because of unclear history, awaiting test results, or because of a concern that a repeat test is warranted due to the sequence of events leading to the cardiac arrest. In any case, HCW protection is an important consideration in CPR as with the other pediatric critical care aspects mentioned here. There is limited evidence base related to status of CPR as an AGP.¹⁷ However, it has been helpful that various life support organisations have produced consistent consensus statements recommending that the HCW donning PPE before commencing CPR in patients with suspected or confirmed COVID-19 because of concerns related to aerosol generation with CPR.^{18,19}

In essence, therefore the adaptation required for patients with suspected or confirmed COVID-19 are two-fold, i) Donning full PPE prior to any contact with patients to commence CPR and ii) Early intubation, as soon as it is practical, following initial bag and mask ventilation. Potential delays in initiating CPR can be minimised by close monitoring, anticipation of deterioration, preparedness and simulation of donning PPE.

Specific therapies for SARS-CoV-2 infection

The vast majority of children with COVID-19 only require routine supportive treatment as described above. However, a number of specific therapies to treat COVID-19 have been proposed, especially in adults given that the severity of disease and case-fatality rate are significantly worse than in children. Many of these are repurposed medications used in COVID-19 because of in-vitro evidence or hypotheses only. None have been convincingly shown to be of benefit yet, in either adults or children. Adults have been recruited to several large scale clinical trials.²⁰ Therefore, literature related to this is rapidly evolving and multiple trials are due to publish their findings within the next few weeks to months. A summary of mechanism of action, dose ranges and recommendations for some of the COVID-19 specific medications is listed in Table I.²¹⁻²³ Additional details related to a few of the proposed specific therapies are provided below.

Remdesivir: In the United States, the Food and Drug Administration (FDA) authorized the emergency use of remdesivir to treat hospitalized adult and pediatric patients with suspected or laboratory confirmed SARS-CoV-2 infection and severe COVID-19.²⁴ Although, the double-blind placebo controlled Adaptive COVID-19 Treatment Trial showed a significantly faster time to recovery in hospitalized adults, the differences in mortality rate was minimal and did not reach significance.²⁵ Children were excluded from this study. Therefore caution is warranted.

Chloroquine/Hydroxychloroquine: The repurposed anti-malarial/immune-modulator medications, used sometimes in combination with a macrolide such as Azithromycin attracted significant media attention during the early stages of the pandemic due to a much publicised study with significant limitations.²⁶ 239 clinical trials of either chloroquine or hydroxychloroquine are currently ongoing.²⁰ Therefore it is likely that a definitive answer about effectiveness of these medications will be obtained soon. Recently, data from a large-scale multi-national registry analysing drug regimens that used either hydroxychloroquine or chloroquine, with or without a macrolide for COVID-19 revealed an association with more

Table I. Specific therapies in children with COVID-19 ^{21- 23}

Drug	Mechanism of action	Pediatric recommendations Comments	Dosing guidance*
Remdesivir	Inhibits viral RNA - dependent RNA polymerase	May be considered on a case-by-case basis in children with severe disease unresponsive to standard management without specific COVID-19 therapy	<40 kg: 5 mg/kg IV loading dose on day 1; then 2.5 mg/kg IV OD. ≥40 kg: 200 mg IV loading dose on day 1; then 100 mg IV OD. 5-10 days
Chloroquine(CQ) Hydroxychloroquine (HCQ)	Inhibits viral entry and endocytosis. Inhibition of glycosylation of ACE-2 receptor. Additionally, host immune-modulatory effects postulated to be beneficial	May be considered on a case-by-case basis in children with severe disease without access to Remdesivir. No evidence related to prophylaxis. Co-administration with Azithromycin not recommended Monitor QTc	CQ: 10mg/kg base stat followed by 5mg/kg base BD HCQ: 8mg/kg stat, followed by 4mg/kg BD for 5 days.
Lopinavir-Ritonavir	Inhibits proteolysis	Recommendation unclear. Do not co-administer with Ribavirin Major p450 interactions	14 day-12 months: 16 mg/kg/dose [Lopinavir dose] 15-25kg: 200/50mg 26-35kg: 300/75mg >35kg: 400/100mg 12 hourly PO, BD, 5-14days
Tocilizumab	Binds IL6 receptor and prevents IL6 activation	Has been used in COVID-19 cytokine storm in adults. Limited pediatric data. Recommendation unclear. May be considered in PIMS-TS patients who are unresponsive to standard management, as part of clinical trial.	<30 kg-12 mg/kg/dose >30 kg-8 mg/kg/dose IV infusion. Further single dose after 12h, if required.

* Other drug dosing suggestions exist. Please consult local formulary prior to prescribing.

frequent ventricular arrhythmias and decreased survival which was retracted later.²⁷ This stresses the importance of balancing hypothetical benefits of treating children with COVID-19 with specific therapies, against the real treatment related risks.

Steroids: The role of steroids is unclear. There are concerns that steroids may be associated with prolonged viral shedding and therefore not routinely recommended. However, there is a weak consensus for the use of steroids in select circumstances such as refractory shock (low, replacement dose of steroids) or in patients who fail to improve with conventional management for severe ARDS.⁷

Convalescent plasma: A systematic review and meta-analysis of convalescent plasma for treatment of SARI of viral aetiologies suggested a significant reduction in mortality.²⁸ Indeed, various reports of improved outcomes with the use of convalescent plasma from donors with sufficient titres of neutralizing antibody to SARS-CoV-2 exist. However, the Surviving Sepsis campaign COVID-19 panel recommended against the routine use of convalescent plasma on the basis of limited trial evidence.⁷ Important knowledge gaps regarding optimal titres of neutralizing antibodies to SARS-CoV-2 and availability of a sufficiently large enough donor pool with optimal antibody titres exist. However further trials are ongoing, including at least two in India.²⁰

Pediatric Inflammatory Multisystem Syndrome, Temporally associated with SARS-CoV-2 (PIMS-TS)

In April 2020, pediatric critical care clinicians in the UK and elsewhere witnessed clusters of children requiring PICU admission for an inflammatory syndrome which appeared to have overlapping features of Kawasaki disease (KD), toxic shock syndrome and potentially macrophage

activation syndrome or hemophagocytic lymphohistiocytosis. This syndrome is commonly being referred to as PIMS-TS or Multisystem Inflammatory Syndrome in Children (MIS-C).^{4, 29}

Case definition: The UK Royal College of Paediatrics and Child Health (RCPCH), Centers for Disease control (CDC) and prevention in the US and the World Health Organization (WHO) have all put forward case definitions

Table II. Case definition and additional features of PIMS-TS, adapted from the UK Royal College of Pediatrics and Child Health guidelines

RCPCH Case Definition		
<ol style="list-style-type: none"> 1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features listed below. This may include children fulfilling full or partial criteria for Kawasaki disease. 2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice). 3. SARS-CoV-2 PCR testing may be positive or negative 		
Additional Features		
Clinical: All: <ul style="list-style-type: none"> • Persistent fever >38.5°C Most: <ul style="list-style-type: none"> • Oxygen requirement • Hypotension Some: <ul style="list-style-type: none"> • Abdominal pain • Confusion • Conjunctivitis • Cough • Diarrhoea • Headache • Lymphadenopathy • Mucus membrane changes • Neck swelling • Rash • Respiratory symptoms • Sore throat • Swollen hands and feet • Syncope • Vomiting 	Imaging and ECG: <ul style="list-style-type: none"> • Echocardiogram & ECG - myocarditis, valvulitis, pericardial effusion, coronary artery dilatation • CXR - patchy symmetrical infiltrates, pleural effusion • US abdomen - colitis, ileitis, lymphadenopathy, ascites, hepatosplenomegaly • CT chest – patchy symmetrical infiltrates, pleural effusion, may demonstrate coronary artery abnormalities if with contrast 	Laboratory: All: <ul style="list-style-type: none"> • Abnormal fibrinogen • Absence of potential causative organisms (other than SARS-CoV-2) • High CRP • High D-Dimers Some: <ul style="list-style-type: none"> • High ferritin • Hypoalbuminemia • Lymphopenia • Neutrophilia in most - normal neutrophils in some Some: <ul style="list-style-type: none"> • Acute kidney injury • Anemia • Coagulopathy • High IL-10 • High IL-6 • Neutrophilia • Proteinuria • Raised CK • Raised LDH • Raised triglycerides • Raised troponin • Thrombocytopenia • Transaminitis

for this condition.³⁰⁻³² While subtle variations exist, they refer to a combination of fever, evidence of hyper-inflammation, multiple organ involvement, a link to SARS-CoV-2 infection and exclusion of other underlying etiologies. The exact nature of this illness and its association with COVID-19 is far from clear at this moment. While the RCPCH case definition (Table II) merely mentions that the SARS-CoV-2 PCR may be positive or negative, the CDC and WHO criteria go further in suggesting an aetiological link with SARS-CoV-2 serology testing or contact with COVID-19. Indeed, several patients with PIMS-TS were found to have either SARS-CoV-2 RNA by PCR or more commonly IgG and IgM antibodies to SARS-CoV-2.^{3,33} This raises the possibility of this being an immune-mediated disease process in children who had either asymptomatic or mildly symptomatic recent COVID-19 illness.

Clinical features and investigations: While some variability within individual patients existed, they were generally older (6-15 years of age) than the usual age-group affected by KD (<5 years of age). Patients often presented with fever

for several days. While the CDC case definition suggested fever for longer than 24 hours, the WHO case definition requires presence of persistent fever of at least 3 days. Gastro-intestinal manifestations such as abdominal pain, diarrhea and vomiting were common. The abdominal signs and symptoms may be severe enough to mimic an acute abdomen such as appendicitis in some patients. Rash and mucositis were also common, however, they were less consistent than GI symptoms. Patients were noted to have high inflammatory markers (C-reactive protein, procalcitonin, ferritin). Various interleukins, especially IL-6 levels may be elevated. CRP has good correlation to IL-6 levels and may be used as a proxy marker. Warm shock with significant vasoplegia requiring vasopressors is common. Myocarditis and development of coronary artery aneurysms are the potentially life-threatening short and long-term consequences respectively. Myocarditis and reduced cardiac function have been severe enough in some patients to necessitate ECMO support.³ Serial troponins, brain natriuretic peptides (BNP) or N-terminal-pro hormone brain natriuretic peptides (NT-proBNP), ECG and echocardiography may be useful to track the cardiac

Table III. Suggested investigations in children suspected to have PIMS-TS. Adapted from the UK RCPCH guidelines

<p>Blood Tests:</p> <ul style="list-style-type: none"> • Full blood count, blood film • Urea, creatinine, electrolytes • Liver function tests • CRP • ESR • Glucose • Blood gas with lactate • Prothrombin time, partial thromboplastin time, fibrinogen • D-Dimer • LDH • Triglycerides • Ferritin • Troponin I • BNP or NT-proBNP • Creatine kinase • Vitamin D • Amylase • Save blood, serum sample (pre IVIG) for any other investigations that may be required later 	<p>Microbiology:</p> <ul style="list-style-type: none"> • Blood culture • Urine and stool culture • Throat swab culture • Nasopharyngeal aspirate or throat swab for respiratory virus /bacterial panel • Mycoplasma antibody titres • Pneumococcal, Meningococcal, Group A Streptococci, Staph aureus Blood PCR [include locally prevalent pathogens] • ASO Titre • EBV, CMV, Adenovirus, Parvovirus, Enterovirus PCR on Blood • Consider blood for enterotoxin/staph toxins • Stool for virology
<p>Cardiac investigations:</p> <ul style="list-style-type: none"> • ECG • Echocardiogram 	<p>SARS-CoV-2 Investigations:</p> <ul style="list-style-type: none"> • SARS-CoV-2 Respiratory PCR • Consider SARS-CoV-2 PCR on stool and blood, if available • SARS-CoV-2 serology

involvement and help prognosticate. Coagulation abnormalities such as elevated fibrinogen, elevated D-dimers, thrombocytopenia or thrombocytosis were also frequently observed. The implications of these are not yet well understood. Heightened anxiety related to potential for new thrombosis or embolism to occur exists. However, this has not been well characterised in the literature as yet. Surveillance for thrombosis and precautions to prevent thrombosis from occurring are essential. A suggested list of investigations as per the UK RCPCH is provided in Table III. This needs adaptation to include investigations for ruling out common causes of sepsis as per the local situation.

Management: Given that this is a relatively new condition, knowledge and understanding related to this disease is evolving. Mainstay of treatment is supportive care. All patients should receive supportive therapies such as empirical antibiotics tailored to the local prevalence of bacteria, judicious fluid resuscitation and if required inotropes and/or vasopressors. Many centres used intravenous immunoglobulin (IVIG), aspirin (commonly 12.5mg/kg QDS, if no contra-indications exist) and steroids in line with existing guidelines for the apparently related Kawasaki disease with shock.³⁴

If hyper-inflammation persisted, various other immunomodulators have also been tried on a case-by-case basis such as anakinra, tocilizumab and infliximab; although it is unclear whether they improve longer term outcomes. Clear definitions of failure to respond to treatment and indications to consider these immunomodulators are lacking. Tocilizumab has been considered for its inhibitory effects on IL-6. Anakinra has been used for blocking IL-1 receptor signalling which then acts on other pro-inflammatory cytokines.³⁵ Recovery of myocardial function after intravenous immunoglobulin has been reported.²⁹ However, there is limited evidence base to provide precise indications or to support one therapy over the other. In fact, coronary artery aneurysms have been reported to occur even in patients who had received tocilizumab for Kawasaki disease prior to this pandemic.³⁶ Concerns about re-activation of latent diseases such as tuberculosis must be borne in mind when immunomodulators are considered.

The role of anti-coagulation in management of PIMS-TS is unclear. However, several centres have used prophylactic low-molecular weight heparin after a case-by-case consideration weighing up the risks and benefits.

The key principle underpinning management of such patients is individualised management with a multi-

disciplinary team approach with members of pediatric rheumatology, immunology, infectious diseases, hematology and cardiology. Serial blood tests, ECG and echocardiography may be indicated for surveillance. Frequency of monitoring and investigations has to be tailored to the individual depending on clinical, laboratory, ECG, echocardiographic response. Longer term follow-up of such patients may be essential, especially focusing on recovery of myocardial function and progression to coronary artery aneurysms. Information from global registries such as the recently established WHO Global COVID-19 Clinical Data Platform may help reduce some of the many uncertainties related to monitoring and management of this new entity.³²

Conclusion

While children are relatively spared from the severity of COVID-19 infection, it is prudent for pediatric critical care physicians to get prepared. The challenges related to managing children with COVID-19 span every level of an organisation from procurement, estates to physicians and nurses. Simulation of a patient journey through the hospital including the critical care environment, with considerations including parents, families and other non-COVID-19 patients, can be invaluable in highlighting the lessons that need to be learnt and adaptations that must be performed. The challenges of communication and performing procedures while wearing full PPE cannot be underestimated. By following good critical care practice in airway, breathing and circulatory management with very careful attention to personal protection of staff with PPE practices and infection control for other patients, good outcome for children with COVID-19 can be achieved. Additional research into pharmacological treatments for adults and children with COVID-19 and PIMS-TS are needed to demonstrate their benefits and recommend use.

Points to Remember

- *Though COVID-19 infection in children is less frequent and need for critical care is a relatively rare occurrence, severe disease and COVID-19 related deaths have been reported.*
- *Indications for PICU admissions are similar to other emergencies.*
- *In COVID-19, step-wise escalation in respiratory support is considered as best practice. Compared to the early days of pandemic, NIV and HFNC use is increasing since it is believed that HFNC does not produce much aerosolisation.*

- ***Supportive management with repurposed or unproven medications is practised widely and more evidence for or against will be available in the next weeks or months from the ongoing studies.***
- ***A new clinical presentation reported recently is the PIMS-TS, a possibly SARS-CoV-2 related, multi-system inflammatory syndrome with overlapping features of Kawasaki disease and toxic shock syndrome.***
- ***While managing PIMS-TS, concerns about re-activation of latent diseases such as tuberculosis must be borne in mind when immunomodulators are considered.***

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COVID - 19

NEONATAL COVID-19

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Abstract: *Novel coronavirus infection is a disease caused by severe acute respiratory syndrome coronavirus 2 and named as coronavirus disease 2019. First confirmed case in adult was reported in December 2019 in China. Since then, research is being conducted in multiple sites in order to better define the epidemiology, clinical characteristics, prevention and treatment of severe acute respiratory syndrome-coronavirus-2 infection in adults. Few cases have been observed in children and newborn infants who seem to have a milder form of clinical disease than other age groups. The purpose of this review is to summarize the available evidence on severe acute respiratory syndrome-coronavirus-2 transmission, the associated clinical presentation, outcomes and treatment in newborn infants with the aim to provide adequate information to neonatologists, pediatricians and obstetricians for managing such patients.*

Keywords: COVID-19, Perinatal COVID, Neonatal COVID, Corona virus, Vertical transmission.

Since the first case in December 2019, the coronavirus disease 2019 (COVID-19) has spread rapidly across the world. As of May 20, 2020, the World Health Organization (WHO) had reported just over 5 million people infected with COVID-19 worldwide.¹ At the same time, 1.1 Lakh people were infected in India according to Ministry of Health and Family Welfare Department (MOHFW).² During the earlier stage of the pandemic, older adults were reported to be more likely infected.^{3,4} However, with the sharp increase in the number of infections, the number of pregnant women, newborn infants and children with COVID-19 is also on the rise.

The general information from the literature so far indicates that neonatal COVID-19 infection may be uncommon. Besides, it is generally acquired through postnatal transmission rather than vertical transmission. Newborn infants with COVID-19 infection exhibit either no symptoms or mild respiratory illness.⁵ Some researchers postulate that milder disease in newborn infants and young children is due to the relative immaturity of angiotensin-converting enzyme 2 (ACE2) protein, which usually acts as a receptor for SARS-CoV-2 in adults.⁶ Furthermore, the higher percentage of fetal hemoglobin in newborn infants may be protective over SARS-CoV-2.⁷

With the current pandemic, there is an urgent need to address certain pertinent issues- whether pregnant women who have confirmed COVID-19 infection are more likely to spread the virus vertically to endanger the fetus, clinical features and management of newborns born to those affected mothers. A comprehensive review of the available evidence regarding all such issues is presented.

Vertical transmission

Initial reports suggested that while severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection could result in adverse pregnancy outcomes, newborn infants did not show any clinical signs of illness and had negative viral testing.^{8,9} However, new evidence for this is being published often that contest the information from the earlier reports. A recent review found 27 publications describing 217 newborns born to mothers with COVID-19.¹⁰ They showed that 7 out of 217 newborns (3%) had evidence of SARS-CoV-2 infection. Three had positive serum levels of IgG and IgM antibodies with negative PCR tests, and four had positive PCR tests. All positive infants had favorable neonatal outcomes with no major morbidities. Thirty (14%) newborns were born through vaginal delivery and all were negative for SARS CoV- 2 PCR. Vertical transmission during pregnancy is thought to be unlikely in these cases as PCR testing on placenta, umbilical cord, amniotic fluid, vaginal secretions and breast milk samples has been uniformly negative. Likely explanation for this is the postnatal infection through horizontal transmission. Another systematic review by Elshafeey et al., also presented similar findings from their

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review of 33 studies and 385 pregnant women with COVID-19 infection.¹¹

More recently, there are case reports indicating the possibility of vertical transmission.^{12, 13} Sinelli et al., reported that the mother and newborn tested positive for PCR from nasopharyngeal swab on day 2 of age.¹² The newborn required non-invasive ventilation with 30 % FiO₂ for few days, but recovered well. In the second report, the nasopharyngeal swab of the newborn, taken at 16 hours after delivery, was positive for SARS-CoV-2 PCR, and immunoglobulin IgM and IgG were negative.¹³ This newborn was ventilated for 12 hours in the beginning, but recovered well soon. Both authors discussed the possibility of vertical transmission in these babies.

Among the small number of pregnancies described until now, there is no strong evidence of vertical transmission to the neonate; however, women were infected in the third trimester. The effects of the virus earlier in pregnancy (first and second trimester) are yet to be known.

Clinical features

The extent of the disease severity in newborn infants is difficult to describe with available limited data. The incubation period may vary from 2-14 days with a median of 5 days. Newborn infants tend to get diseases that are milder and associated with better outcomes compared to adults.⁵ They can be asymptomatic most of the times or can present with mild symptoms like minimal respiratory distress. The review by Elshafeey et al, discussed the clinical outcomes of newborn infants who were born to 252 COVID positive mothers.¹¹ Among the 256 newborns (248 singleton and eight babies as four twins), the reported outcomes were, respiratory distress syndrome (4.7%), neonatal pneumonia (1.2%) and disseminated intravascular coagulation (1.2%). Majority of newborns were asymptomatic. Three newborns died. Two stillbirths were reported for two critical women

(one maternal mortality and one woman on ECMO). One early neonatal death occurred due to complications of prematurity following cesarean delivery at 34 weeks for antepartum hemorrhage. All these three infants who died were PCR negative. Four (1.6%) newborns, delivered by cesarean, had a positive RT-PCR test result and were classified as mild. They recovered well and were discharged. Another three (1.4%) were positive for IgM antibodies and were asymptomatic or mildly symptomatic. All three infants again recovered well and were discharged. Two recent reports indicated that one newborn required ventilatory support for brief period, but recovered well and another newborn with mild febrile illness with hypoxia who required non-invasive ventilation, also recovered well.^{12, 13}

Laboratory features in the newborn infants may include lymphopenia, elevated liver enzymes, coagulation abnormalities and X-ray chest showing bilateral infiltrates in the lungs suggestive of pneumonia.⁷ All clinical features and laboratory features of newborns with PCR positive for SARS-CoV-2 are summarized in Table I.

Diagnosis

Diagnosis of a newborn infant born to a suspected or COVID positive mother is imperative, but can be challenging at times as the sensitivity of the test depends on the timing and sample. RT-PCR testing of nose and throat swab for detection of SARS-CoV-2 nucleic acid has been recommended as the confirmatory test for COVID-19. Other alternative sample could be endotracheal aspirate. FOGSI, NNF and IAP, have teamed up together recently and published the criteria for testing newborns as follows.¹⁴

Whom to test: All newborn infants who have any one of the following:

- 1) History of exposure to COVID-19 positive adult (irrespective of symptoms), mother had COVID-19 infection within 14 days before birth, history of contact

Table I. Clinical and laboratory features of all neonates who tested positive for COVID-19, reported so far in the literature.

Clinical characteristics	Laboratory characteristics
Asymptomatic	Lymphopenia
Respiratory distress - mild to moderate	Leukocytosis
Cough – sporadic	Elevated transaminases
Mild fever	Elevated cytokine levels (IL-6 and IL -10)
Cyanosis (without respiratory distress)	X-ray Chest – normal or bilateral infiltrates
Feed intolerance	

with COVID-19 positive persons (including mother, family members in the same household or direct healthcare provider) in the postnatal period.

- 2) Irrespective of history of exposure: Presenting with pneumonia or severe acute respiratory infection (SARI) that require hospitalization, with onset at more than 48-72 hours of age, unless there is another underlying illness that completely explains the respiratory signs and symptoms.

When to do the test

- a) At birth (if mother had COVID-19) or at detection of the history of contact with COVID-19 positive person (postnatal exposure)
- b) If a sample is not obtained at birth due to logistic reasons, it should be obtained as soon as possible.

When to do repeat test?

If the first test is negative, a repeat test should be done after 5-14 days of birth/exposure. However, the test should be done immediately, if new symptoms such as respiratory distress, lethargy, seizures, apnea, refusal to feed, diarrhoea appear.

Management

Management of newborn infants includes team work involving obstetricians, neonatologists, staff nurses and hospital management. Management flow chart is depicted in Fig.1.

Personal protective equipment (PPE)

SARS-CoV-2 is a respiratory virus transmitted from person-to-person primarily by respiratory droplets. Precautions have to be taken and personal protective equipments have to be worn while taking care of newborn infants with COVID-19 positive mother. Following definitions for precautions were given by AAP.¹⁵

Droplet and contact precautions: Gown, gloves, standard procedural mask and eye protection (either face shield or goggles) should be used for most encounters with infants born to mothers with COVID-19.

Airborne, contact and droplet precautions: Gown, gloves, N95 respiratory mask with eye protection should be used when patients require bag-mask ventilation, intubation, tracheal suctioning, nasal cannula oxygen at a flow greater than 2 liters per minute/kilogram, continuous positive airway pressure and/or positive pressure ventilation of any type, given the potential for these supports to generate aerosols.

Antenatal management

Pregnant women should follow the same recommendations as nonpregnant adults for avoiding exposure to the virus like social distancing, hand hygiene, disinfecting surfaces and wearing a mask in public. Pregnancy is a partially immunocompromised state, however despite the fact that COVID-19 is known to cause severe life-threatening respiratory complications in adults, especially the immunocompromised, there are no comparative data to determine whether pregnancy is a risk factor for severe COVID-19. Pregnant women should be monitored and clinical manifestations are similar to those in nonpregnant individuals.¹¹ Pregnant women with confirmed COVID-19 should be managed with supportive care recommended for non-pregnant adults. Currently recommended management includes: oxygen therapy/respiratory support for treatment of hypoxemic respiratory failure, fluid therapy, antibiotics and management of shock.¹⁴ All COVID-19 positive pregnant women should be referred to designated COVID care facility. In such COVID care facilities, three demarcated zones (clean, potentially contaminated, contaminated), each housing all the needed equipment and services for women and newborns are required for management of non-COVID, suspected and confirmed COVID-19 mothers. The standards and facilities required for infection control in these areas should be same as that for other adults with suspected or confirmed COVID-19. Every pregnant woman should be triaged at entry and then allotted into one of the zones. If a pregnant woman, who delivers in a non-COVID facility, turns out to be COVID-19 positive, actions should be taken as per the Ministry of Health and Family Welfare and referred to COVID facility, and take steps to disinfect the non-COVID facility.¹⁴

Antenatal steroids have proven benefits in neonatal mortality and morbidity. American College of Obstetricians and Gynecologists (ACOG) continues to recommend its use in pregnant women between 24+0 and 33+6 weeks of gestation with suspected or confirmed COVID-19.¹⁶ For pregnant women between 34+0 and 36+6 weeks of gestation, these decisions may need to be individualized, weighing the neonatal benefits with the risks of potential harm to the pregnant woman.¹⁶ The use of magnesium sulfate for maternal seizure prophylaxis and/or neonatal neuroprotection should be decided on a case-by-case basis.¹⁶

Delivery room management

The mode of delivery and anesthesia is best decided as per maternal and fetal indications by the obstetric and

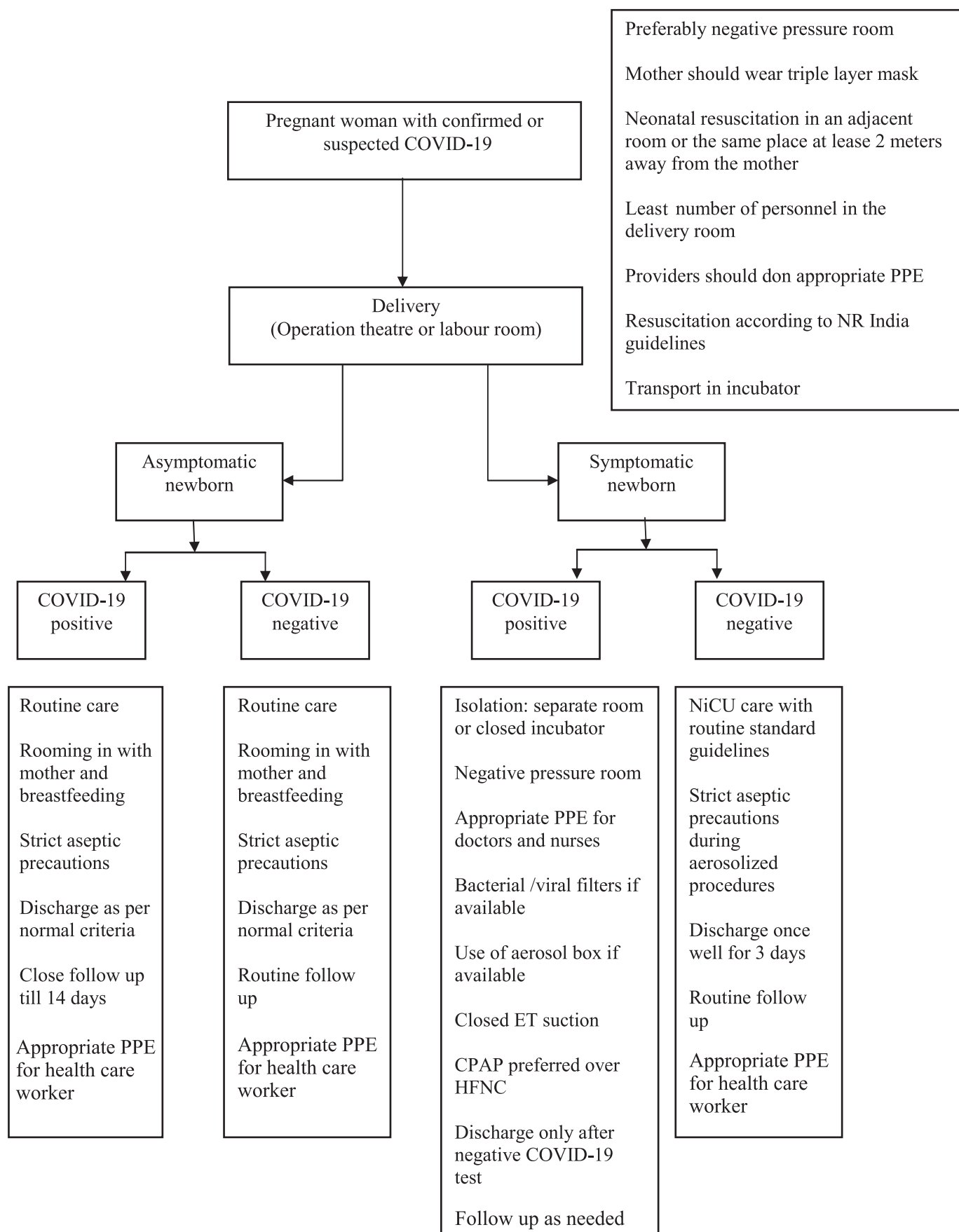


Fig.1. Management of newborn infants born to the suspected or confirmed COVID-19

anesthesia teams regardless of the COVID-19 status. There is no evidence to suggest one mode of delivery is preferred over the other.¹⁰ Delivery of a suspected or confirmed COVID-19 patient should rather take place in a center with the capacity to care for critically ill adults and newborns and in a negative pressure room if available. The optimal location for neonatal stabilization and resuscitation could be in an adjacent room or the same place at least 6 feet or 2 meters away from the mother with a physical barrier. To minimize exposure, the least number of personnel should enter the delivery room. Providers should don appropriate PPE as mentioned above. Mother should perform hand hygiene and wear triple layer mask.

Neonatal resuscitation should be performed according to the Neonatal Resuscitation India, 3rd edition, published by National Neonatology Forum, India.¹⁷ Delayed cord clamping and skin-to-skin contact can be practiced. Following key aspects must be kept in mind during resuscitation:

- During initial steps: Routine neonatal care and the initial steps of neonatal resuscitation are unlikely to be aerosol generating, however, suction of the airways is an aerosol generating procedure and should not be performed routinely for clear or meconium-stained amniotic fluid.
- During endotracheal intubation and medications (Endotracheal intubation and instillation of medications, such as surfactant or epinephrine, are aerosol generating procedures): Intravenous administration of medicines via umbilical venous catheterization is rather preferred.
- Transport to NICU: Closed incubator transfer should be used to transfer newborns to neonatal intensive care when available.

Management in NICU

In the NICU, the baby should be cared for in an incubator in a single room preferably with the potential for negative room pressure. If this is not available or not possible, newborns should be maintained in a closed incubator at least 6 feet apart. These areas should not be a part of the central air-conditioning. If room is air-conditioned, ensure 12 air changes/ hour and filtering of exhaust air.¹⁴ In NICU, doctors and nurses have to wear PPE as mentioned above.

In the NICU, following aspects must be kept in mind while providing respiratory care to newborns:

- During manual ventilation, bacterial/viral filters could

be used to reduce viral dispersion if available.¹⁸ Addition of a filter can reduce efficiency by increasing mask leaks and so it is vital to understand and provide pressure accordingly while using the filter. It is better to avoid filters in ELBW infants (birth weight <1000 grams) to avoid possible iatrogenic hypercapnia with subsequent intraventricular hemorrhage.

- Consider use of aerosol box during intubation if available.
- The area providing respiratory support should be a negative air pressure area.
- Closed ET suction circuit should be used, and a hydrophobic filter placed at the exhalation port.
- CPAP should be preferred over high flow nasal cannulas (HFNC). Limited data from adults suggest that there is possibly a significant dispersion of exhaled air with HFNC.¹⁹

Location of care and breastfeeding

There is some ambiguity around neonatal infection risk during postnatal period and care practices vary for newborns born to mothers with COVID-19. The possibility of the vertical transmission of SARS-CoV-2 through breast milk could not be categorically confirmed. Presently, only limited data on SARS-CoV-2 excretion in breast milk are available. Chen et al., reported that all breast milk samples from 9 mothers with COVID-19 pneumonia were negative.⁸

Recommendations on these areas from several national and international organizations are summarized in Table II. WHO supports skin-to-skin care, rooming-in and breastfeeding for infants born to mothers with COVID-19.²⁰ The Royal College of Paediatrics and Child Health from United Kingdom supports rooming-in and breastfeeding with appropriate infection prevention measures for these infants, unless mothers are too ill.²¹ The American Academy of Pediatrics (AAP) suggests separation of the COVID-19 positive mother and her infant when possible and use of expressed breast milk.¹⁵ The Centers for Disease Control and Prevention (CDC) suggest shared-decision making between family and clinical team with regards to location of care as well as breastfeeding.²² The Indian team (FOGSI, NNF and IAP) recommends rooming in and breastfeeding with strict precautionary measures.¹⁴

There are problems with separation approach, as separation limits opportunities for parent teaching, disrupts breastfeeding and may have negative impacts on mother-

Table II. National and international organizations guidance - Newborn care location and breastfeeding with COVID-19¹⁵

Organization	Location of newborn care	Breastfeeding
WHO ²⁰	Rooming-in with mother	Breastfeeding
AAP ¹⁵	Separation	Expressed Breast milk
CDC ²²	Case to case decision	Case to case decision
RCPCH, UK ²¹	Rooming-in with mother	Breastfeeding
FOGSI/NNF/IAP, India ¹⁴	Rooming-in with mother	Breastfeeding

newborn bonding. Rooming-in during hospitalization helps mother and family to learn infection prevention practices. Finally, with the available current evidence, benefits of breastfeeding outweigh the risks of passing infection from mother to infant. Nevertheless, specific precautions have to be taken, such as wearing a mask during breastfeeding and observing meticulous hand hygiene.

Specific treatment

Specific anti-COVID-19 treatment like antivirals or chloroquine/hydroxychloroquine is not recommended in symptomatic newborns. Use of adjunctive therapy such as systemic corticosteroids, intravenous immunoglobulin and convalescent plasma is also not recommended in symptomatic newborns with suspected or confirmed COVID-19.¹⁴ Only supportive care is needed, as per the problem identified.

Discharge

Stable newborns, tested negative for COVID-19, can be discharged based on the center's normal criteria with mother or care taker. Asymptomatic newborns tested positive for COVID-19, may also be discharged home with mother or care taker (if mother is unwell) with appropriate precautions and plans for frequent outpatient follow-up contacts till 14 days after birth. Specific guidance regarding use of masks, gloves and hand hygiene should be provided to all caretakers. In mild to moderate respiratory illness, they can be discharged as soon as they are well for 3 days, without waiting for a negative COVID-19 test. However, in severe illness, it is prudent to wait for a single negative COVID-19 test after resolution of symptoms, prior to discharge.

Conclusion

The proportion of newborns with the COVID-19 is extremely low when compared to adults. Besides, neonatal COVID-19 appears to be acquired postnatally rather than through vertical transmission and associated with good

outcomes. For well newborns, rooming in with mother and breastfeeding are advocated with adequate safety precautions. For unwell newborns, those who require intubation and ventilation, it is critical to consistently implement safe respiratory practices including proper isolation, ideal PPE and the use of viral filters to the expiratory limbs of any respiratory device if available. Finally, current recommendations on the management of COVID-19 positive mothers and their newborn infants are based on limited data, demanding continuous and comprehensive updates.

Points to Remember

- *Current evidence is inconclusive about vertical transmission of SARS-CoV-2 from mothers with COVID-19 to their newborns.*
- *Majority of newborns tested positive for SARS-CoV-2, are asymptomatic or have mild disease. However, their immature immune system makes them vulnerable to serious respiratory viral infections.*
- *Airborne, droplet and contact precautions should be followed when attending deliveries and in all aerosol-generating procedures like suction and endotracheal intubation.*
- *Mothers with COVID-19 can breastfeed their newborn baby, as SARS-CoV-2 has not been detected in breast milk to date.*
- *Infants born to mothers with COVID-19 should be tested for SARS-CoV-2 at birth or as soon as detection of contact with COVID-19 positive person:- Repeat testing may be needed, if the baby develops symptoms within 14 days of contact or after delivery.*

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COVID - 19

COVID-19 : PREVENTION AND EDUCATION

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Abstract: *The novel coronavirus 2019 pandemic has caused an unprecedented global catastrophe. At present there is no known cure, drug or treatment for this disease. Personal hygiene, social distancing, hygienic practices and care of the infected persons (asymptomatic/ mild symptomatic) are the only preventive measures we have at present. Usefulness of hydroxychloroquine as a preventor drug is yet to be proved. At the time of writing, eight vaccines have reached clinical stage of trials and are being evaluated across the world. In the most optimistic timeline that we can anticipate, it will not be less than a year before any of the vaccines will be available for public use. It is also very important that all routine immunisation practices be continued.*

Keywords: *Novel coronavirus, SARS-CoV-2, Hydroxychloroquine, Coronavirus vaccine.*

From the time this pandemic has struck across the globe, it has been a catastrophe for almost all nations. There is no definitive treatment or vaccine available at present. Hence movement restriction, general awareness, social distancing and measures to improve personal hygiene will go a long way in mitigating the spread of this disease. The preventive aspects can be considered at the level of an individual, community as a whole and institutions - be it school or hospital or a workplace.

Prevention at individual level¹

Novel Corona virus - SARS-CoV 2 spreads from person to person by means of respiratory droplets and contaminated fomites. The virus is highly infectious and current evidence suggests that it spreads more readily than influenza virus, but not as much as measles. Maintaining good physical distance, preferably more than

6 feet is one of the most important steps in preventing spread of the virus. The following steps will help an individual in preventing spread or minimizing contact with SARS CoV-2.

1. Wash your hands frequently with soap and water for 20 seconds especially after coming back from a public place or after coughing, sneezing or blowing your nose. If soap and water is not available, then using hand sanitizer with minimum 60% alcohol concentration is recommended. Avoid unnecessary touching of nose, mouth or eyes.
2. Maintain social distancing in public places and from household members who are sick.
3. Avoid crowded places and gatherings - this is of paramount importance.
4. Cover your nose and mouth with cloth cover (cloth mask or hand kerchief) when in public or going out for daily errands. Follow cough etiquette. At present, use of medical masks (also known as surgical masks) is not recommended for general public.
5. Cleaning and disinfecting frequently touched surfaces like door knobs, light switches, mobile phones, tablets, laptops, table surface etc. is recommended. Any household level disinfectant can be used. A recent article recommended the use of 70% isopropyl alcohol or Clorox wipes for disinfection of mobile phones. When such a solution is used for disinfection, it is preferable that the mobile phone is in switched off mode.²

Use of masks and gloves by public^{1,3,4,5}

It is known that the novel coronavirus can be transmitted from asymptomatic carriers as well as presymptomatic patients. In the light of this evidence, it is recommended that people should use cloth based coverings or masks when they go out in public places. The intention of cloth based covering is to protect people around the individual. However, the use of such a mask should not give a false sense of security leading one to stray away from social distancing. These masks can be washed with soap and water and reused. Due to shortage, medical masks

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and respirators are not recommended to be used by general public. In the following conditions triple layer surgical mask may be used:³

1. When a person develops respiratory symptoms
2. When visiting a healthcare facility
3. When you are caring for someone who is sick at home
4. Close contacts of suspected cases

If used properly, a surgical mask will be protective for 8 hours, unless it gets wet. The mask should be discarded after use by disinfecting with 5% bleach or 1% hypochlorite and then burnt or by deep burial.³ The routine use of gloves is also not recommended except when caring for a sick patient at home or non-healthcare based setting.

Cleaning and disinfection at home¹

Novel coronavirus is transmitted by respiratory droplets more readily as compared to fomites. So, apart from precautions against droplets, cleaning and disinfection of contaminated surfaces will also decrease the transmission of virus. Cleaning, basically means removal of the dirt impurities and germs from a surface. It does not kill the microbes. On the other hand disinfection refers to the process of killing the microbiological organisms. Usually disinfection is a process which should be followed after cleaning. Frequently touched surface in the household environment can be cleaned and disinfected by commercially available products. 1% hypochlorite solution is an excellent disinfecting agent, if the surface is compatible. Following manufacturer recommendations and the compatibility of such a procedure with the surface should be kept in mind. Use of gloves, mask if required and good ventilation is needed during the process of disinfection. Electronic devices can be disinfected by 70% isopropyl alcohol based solutions or wipes.

Clothes can be laundered as routine or as per manufacturer recommendations. Use of warm or hot water is preferable. Use of gloves is preferable when handling laundry which is dirty or from an infected person. We should also try to avoid shaking dirty laundry because that may generate aerosols. Clothes from a sick person can be washed along with routine laundry.

If there is a sick person at home, then he should be cared for in a separate room isolating from everybody else at home. It is preferable that the washroom used by the sick person should be separate. If separate washroom is not feasible, then common washroom should be cleaned and disinfected after each use. All the food, linen and other material connected to the sick person should be handled

with gloves. It is to be noted that the gloves used during any of these procedures as mentioned above should be discarded in a sterile manner as discussed before. If reusable gloves are being used, then they should be cleaned and disinfected with 1% hypochlorite after every use.

Prevention at schools⁶

Today's students are tomorrow's global citizens and hence, arming them with the right knowledge about COVID-19 is going to decrease their anxiety and fear about the disease. It will also help them to cope up with the pandemic and decrease the stigmatization of sick amongst teachers and fellow students. Students armed with the right tools of knowledge will help a society in fighting against the disease and also serve to pursue preventive measures at their own homes..

In the event of an extremely high community based transmission, schools are likely to be closed down till the situation ensures safety of students. The discussion below pertains to a situation wherein the schools are eventually going to open. The World Health Organization and UNICEF have released a joint document in March 2020 addressing issues related to prevention of spread of COVID-19 in schools.⁶ The detailed document is available on the WHO and UNICEF websites. There is a checklist in this document which the schools can implement to make sure that they are safe. Here is a brief summary of the recommendations.

1. All the personal hygiene, social distancing, cleaning and disinfecting principles mentioned above need to be followed at school very strictly.
2. Regular hand washing and sanitisation should be encouraged and implemented by students and staff alike. Cleaning and disinfection of the school campus, class rooms, cafeteria, office and other frequently touched surfaces should be done on a regular basis - at least once a day. The managements of schools should ensure that the above required facilities, equipment and supplies are adequate at all times.
3. Social distancing in school maybe practiced by staggering the start and the end of the school working hours, avoiding any activity which will involve a gathering, trying to distance the classroom seating areas by one meter and teaching students to avoid unnecessary touching.
4. Sick students and staff should not attend school. The school should have emergency contact numbers of the caretakers of children as well as the local health

authority. This will help in formulating an emergency plan in case someone falls sick at school. Monitoring the pattern of school absenteeism due to respiratory illness can help the local authorities in tracking cases.

5. In the unlikely event of difficulty in reopening the schools, online classes and e-learning should be encouraged.

Prevention at workplaces⁷

The principles of hand hygiene, social distancing, cough etiquette, regular cleaning and disinfecting of the environment have all been discussed earlier and apply in a similar manner to a workplace. Hand hygiene can be promoted by availability of hand sanitizers at all entry and exit gates in the work environment as well as at multiple other places where the likelihood of contamination is high. Posters highlighting these aspects can be obtained from WHO website and pasted across the workplace to promote such activities. Employees should be educated about the disease, recognition of early symptoms and should be instructed to stay at home if they are unwell. Gatherings and meetings should be avoided as far as possible. Use of teleconference should be encouraged to maintain social distancing. If a meeting is mandatory, then all possible precautions should be undertaken. If feasible, social distancing should be maintained even during such meetings. Hand hygiene and respiratory hygiene should be maintained during the course of a meeting. Details of all the people coming to work and especially those attending such close gatherings should be available. In the unlikely event of someone falling sick, this information would be of utmost importance to trace all contacts. Contingency plans and protocols for employees falling ill at work should be available in conjunction with local health authorities.

Precautions during home isolation⁸

As per the revised guidelines from Government of India published on 10th May 2020, it has been recommended to isolate pre symptomatic or mildly symptomatic cases at home itself. Precautions at home for the sick person as well as the caretakers involved are described. The following are the prerequisites for home isolation:

1. Diagnosis of COVID positivity in asymptomatic patients as well as categorising as mild when they have symptoms should have been done by a qualified doctor.
2. There should be a facility for home isolation for the patient and the caregivers or family members.

3. Caregiver should be available 24/7 and there should be smooth and convenient source of communication with the healthcare system at any given point of time.
4. The caregivers and close contacts will be on hydroxychloroquine prophylaxis as per recommendations of Indian Council of Medical Research (ICMR).
5. The patient will regularly monitor his health and update the status to district surveillance officer.
6. The patient will download “Arogya Setu” app which will remain active via internet and bluetooth at all given times.
7. The patient has to give an undertaking as per Annexure I in the guidelines. He is liable for legal action if he fails to follow home isolation guidelines.

In addition, ANNEXURE II is available which outlines the precautions the caregiver needs to take at home. The caregiver has to be explained the important warning signs for immediate consultation to the hospital. Home isolation is for a period of 17 days after the onset of symptoms, provided the patient is afebrile for 10 days.

The following is a summary from Annexure II

1. The patient should stay in a separate room away from all other family members. It is preferable to have a separate washroom for the patient. He should wear a triple layer surgical mask at all given times. The mask should be discarded after 6 hours or whenever it is soiled or wet. The patient should follow hand hygiene, respiratory etiquette and social distancing at all times. He should maintain nutrition, hydration, monitor temperature regularly and inform health authorities if any warning signs develop.
2. The caregiver should always wear triple layer surgical mask when entering the room of the patient. He should not unnecessarily touch his face, nose or mouth. The mask of the caregiver and the patient should be discarded only after disinfection with 1% hypochlorite solution.
3. All kinds of contact in the patient area should be done by using gloves. This includes touching of anything in the patient room like beddings, clothes, food, surfaces, etc. Frequent disinfection of the patient care area should be done at all times.
4. The caregiver will also monitor his as well as other family members' health which includes temperature monitoring and reporting to health authorities, if there is a problem. They may need to be tested for COVID when they become symptomatic

Hydroxychloroquine (HCQ) prophylaxis

The COVID-19 pandemic has put the medical community across the globe in a very precarious situation. At the time of writing this article, there is no known definitive treatment or prophylaxis available against SARS-CoV-2. This has let the scientific community to find quickly a safe and effective drug for this virus resulting in a flurry of publications on various possible therapeutic options. The antimalarials chloroquine and hydroxychloroquine have shown some promise against the virus in laboratory studies⁹. In fact, according to a recent report, there is no evidence of in vitro viral activity of HCQ.¹⁰ The published data available so far do not include any high quality studies and there is hardly any evidence based information about the efficacy of HCQ in prophylaxis. Fig.1 demonstrates the possible mechanism of HCQ in SARS-CoV-19 infection.

Data from Gautret, et al¹², with 36 patients of COVID-19 treated with HCQ and azithromycin revealed higher percentage of negative nasal swabs between day 3 to day 6 in the treatment group. This study used 600 mg of HCQ per day for 10 days in the treatment group. The shortfalls of this study were – a very small number of which only 8 cases actually had pneumonia, lack of any randomisation, extremely short observation period, inclusion of asymptomatic cases, and lack of data on clinical efficacy. A second study¹³ from the same author had a larger patient cohort (80 cases). Similar to the earlier data, rapid nasopharyngeal viral clearance was noted-83%

were negative at day 7 and 93% were negative at day 8. However, clinically relevant outcomes were not described, there was no control group and majority of the patients had early warning scores less than 4, indicating that they were not that sick, leading to a possible bias in the results. Another observational study¹⁴ from France in 11 patients with COVID-19, did not report any benefit in nasopharyngeal clearance of the virus even after 5 - 6 days of treatment. In this study, the cohort of patients were more sick as compared to the studies by Gautret et al. In a pilot trial of 30 cases from China¹⁵, Jun Chen and colleagues did not find any difference in the viral clearance in the HCQ treated group as compared to the control group. However, concomitant use of other antiviral drugs was also there in both the groups which could have confounded the results. HCQ was used in a dose of 400 mg per day in the study. Another Chinese randomised parallel group trial¹⁶ was conducted in 62 patients, out of which 31 received HCQ in addition to standard care. Time to clinical recovery, defervescence of fever and cough remission were significantly lower in the treatment arm. Most of the patients had mild to moderate disease and whether these results can be directly extrapolated in sicker patients is not clear. In another observational study¹⁷ of 1376 patients, out of which 811 received HCQ, the investigators did not find a benefit in the composite endpoint of decreased risk for intubation or death. However, in this study, the treatment arm had significantly more sick patients at baseline as compared to the control arm. So far, there is no published data on the effectiveness of HCQ as prophylaxis.

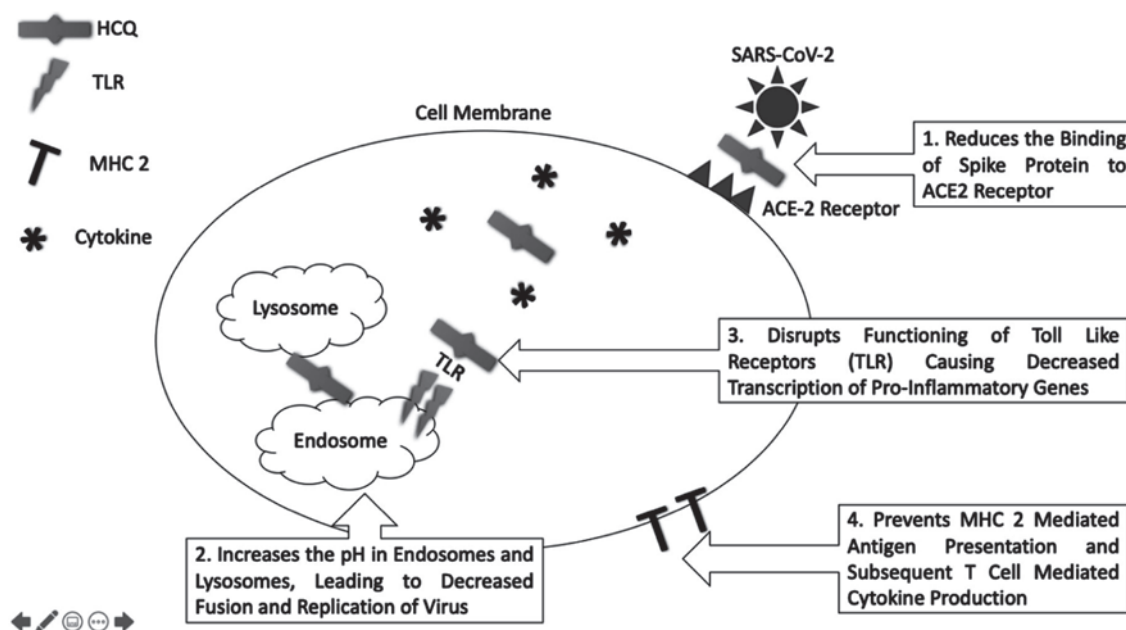


Fig. 1. Proposed mechanisms of action of HCQ in a simplified manner. (Action 1 and 2 disrupt viral infectivity and multiplication. Action 3 and 4 reduce cytokine storm.)¹¹

At the time of writing this article, 175 trials on HCQ in various combinations as well as monotherapy are going on; 50 studies out of these are evaluating the role of HCQ as prophylaxis.¹⁸ Large scale multicentre trials, such as the Discovery study (NCT04315948) and the Solidarity study (EudraCT Number 2020-000982-18), will give us answers in due course of time. There is a risk of prolongation of QT interval with HCQ, especially if combined with azithromycin. The current data, albeit very less and our historical experience with this drug tell us that the risk is very small. The National Task Force for COVID-19 constituted by the ICMR¹⁹ recommends the use of HCQ as prophylaxis against SARS-CoV-2 in high risk groups. This chemoprophylaxis is recommended for:

1. Asymptomatic healthcare workers involved in the care of suspected or confirmed COVID-19 cases.
2. Asymptomatic household contacts of lab confirmed COVID-19 cases.

A loading dose of 400 mg twice on the first day is recommended. The weekly maintenance dose is 400 mg to be given for 7 weeks in the case of healthcare workers and 3 weeks in the case of household contacts. The use of

prophylaxis should not undermine the need for personal hygiene and other mitigating measures explained above. Prophylaxis should not give one, a false sense of security and is to be taken only under prescription from an authorised medical authority/doctor. It is not recommended for children less than 15 years of age and those with retinopathy or hypersensitivity.

Vaccines for COVID-19

At the time of writing this article there are 102 vaccines in pre-clinical trials and 8 vaccines in phase 1 and phase 2 clinical trials.²⁰ Table I lists vaccines that are in clinical trials. The detailed document can be obtained from WHO website.

ChAdOx1 nCoV-19 (Vaccine 1 in Table.I): The vaccine being developed by the University of Oxford's Jenner Institute and Oxford Vaccine group in UK (ChAdOx1 nCoV-19) has taken the lead and is currently the forerunner amongst the COVID-19 vaccines. Human trials have begun as of April 2020. Human adenovirus is used in this vaccine. The genetic material for expression of the spike glycoprotein of novel coronavirus has been inserted into the weakened adenovirus to make this vaccine candidate.

Table I. Candidate vaccine in clinical trials against COVID-19²⁰

S.No.	Vaccine	Platform	Developer	Current stage of clinical trials
1	ChAdOx1 nCoV-19	Non-replicating viral vector	University of Oxford	Phase 1/2 NCT04324606
2	Adenovirus Type 5 vector recombinant vaccine	Non-replicating viral vector	CanSino Biological Inc./Beijing Institute of Bioechnology	Phase 2 ChiCRT2000031781 Phase 1 CHiCTR2000030906
3	LNP encapsulated mRNA-1273	RNA based vaccine	Moderna/NIAID	Phase 2 (IND accepted) Phase 1 NCT04283461
4	Inactivated vero cell vaccine	Inactivated vaccine	Wuhan Institute of Biological Products/Sinopharm	Phase 1/2 ChiCTR2000031809
5	Inactivated vero cell vaccine	Inactivated vaccine	Beijing Institute of Biological Products/Sinopharm	Phase 1/2 ChiCTR2000032459
6	Inactivated coronavirus vaccine + Alum	Inactivated vaccine	Sinovac	Phase 1/2 NCT04352608
7	BNT16a1, BNT162b1, BNT162b2, BNT162c2	RNA based vaccines	BioNTech/Fosun Pharma/Pfizer	Phase 1/2 2020-001038-36 NCT04368728
8	DNA plasmid vaccine with electroporation (INO-4800)	DNA based vaccine	Inovio pharmaceuticals	Phase 1 NCT04336410

As of date, 1090 participants aged 18-55 years have been planned to be enrolled in the clinical trial which will utilise quadrivalent meningococcal vaccine in the control group. The vaccine will be studied in a single as well as two dose schedules. Efficacy of the vaccine as well as occurrence of serious adverse events are the primary outcomes of this study. Serum Institute of India plans to produce 60 million doses of this vaccine. Astra Zeneca has tied up with the University for production and global distribution of the vaccine. The preliminary completion date and data collection is expected to be completed by May 2021.

Recombinant adenovirus vaccine (Vaccine 2 in Table I): This vaccine has been registered for a phase 2 trial on the Chinese clinical trials registry. It has been proposed to use two different inoculation doses of the vaccine in the trial and a placebo in control group. 250 subjects will be enrolled in medium dose group, 125 in low dose group and 125 in placebo. Trial details and completion of data collection is expected by January 2021.

LNP encapsulated mRNA-1273 vaccine (Vaccine 3 in Table.I): This is a novel lipid nanoparticle (LNP)-encapsulated mRNA vaccine that encodes for a prefusion stabilized form of the spike protein of SARS-CoV-2. It is being developed by Kaiser Permanente Washington Health Research Institute (KPWHRI) in Seattle, and is funded by the National Institute of Allergy and Infectious Diseases (NIAID). The phase 1 trial is evaluating the safety and immunogenicity of the vaccine in 105 subjects. The participants aged 18 years and older will receive 2 doses, 28 days apart; in 1 of the 3 concentrations - 25mcg, 100mcg or 250mcg. It has also received an FDA approval for phase 2 trial. Phase 2 will enrol 600 subjects with 3 groups receiving placebo or 50mcg vaccine or 250mcg vaccine in adults 18 years and older. The primary completion of phase 1 is expected to be around September 2021.

Inactivated coronavirus vero cell vaccine (Vaccine 4 and 5 in Table. I): Inactivated vero cell based novel coronavirus vaccine is being evaluated by Wuhan Institute of Biological Products and Beijing Institute of Biological Products into separate phase 1 / 2 trials. The vaccine manufactured by Sinovac Research and Development Company will be inoculated in 2 doses, 28 days apart. The Wuhan trial will enrol subjects more than 6 years of age where as the Beijing trial will enrol subjects from the age of 3 years onwards. The initial data is expected 6 months after the completion of the trial. At the time of writing, no other timelines are available from the Chinese clinical trial registry.

Inactivated coronavirus vaccine with alum (Vaccine 6 in Table. I): The parent company manufacturing the inactivated corona virus vaccine is doing its own phase 1/2 randomised double blind placebo controlled trial. Study is enrolling adults aged 18-59 years to receive 2 doses of the vaccine or a placebo. The vaccine will be studied at 2 different inoculation doses of 600 SU or 1200 SU. 144 subjects are expected to be enrolled for phase 1 and 600 subjects will be enrolled in phase 2. The estimated date of completion is expected to be December 2020.

BNT162a1, BNT162b1, BNT162b2 & BNT162c2 RNA based vaccine candidates (Vaccine 7 in Table. I): This phase 1/2 randomized, placebo controlled and observer blind trial is being conducted by Biontech and Pfizer. One of the four vaccines will be given in a 1 or 2 dose schedule. The control group will receive a placebo vaccine. The vaccine will be evaluated at 3 different doses in 7600 participants aged 18 – 85 years. It is expected to be completed by March 2023.

INO 4800 (Vaccine 8 in Table. I): This is a one of a kind DNA plasmid based vaccine presently being evaluated in a phase 1 trial in 40 subjects. The vaccine is administered intradermally on day 0 and day 28. Electroporation is a technique where permeability of cells is increased to enhance the uptake of DNA. This DNA then leads to transcription inside the cells, causing an immune reaction which will generate protective immunity against novel coronavirus. CELLECTRA is a patented hand held device made by Inovio Pharmaceuticals which helps in electroporation following vaccination. The initial trial is expected to be completed by April 2021.

Routine vaccination in COVID-19 pandemic²¹

Immunisation has been recognised as a core essential healthcare service, and needs to be continued in a safe manner even during the pandemic. A healthy child undergoing immunisation does not have any additional risk due to the pandemic. On the other hand, immunisation is going to protect the child against vaccine preventable communicable diseases. Immunisation should be done in separate or segregated OPDs at all levels, be it a private clinic, nursing home or a multi-speciality hospital. The birth dose of vaccines needs to be given before discharge from the hospital. All the vaccines in the first year of life are a priority and should not be postponed. Influenza and varicella vaccines also need to be given. Other vaccines and boosters may be postponed only if logistics do not permit. All mass immunisation activities should be postponed to maintain social distancing measures.

Points to Remember

- *Individual level prevention of COVID-19 by general public depends on social distancing, frequent hand washing, wearing of cloth masks and periodic decontamination of surfaces.*
- *Schools, when they start functioning and work places should constantly educate the students and employees respectively, on maintaining adequate distance, avoiding crowding and hand hygiene and make it possible by provision of facilities. They must also encourage to report early if any symptoms develop in them.*
- *The patient and care giver must strictly follow all the norms laid down for home isolation of pre symptomatic or mildly symptomatic cases.*
- *The role of hydroxychloroquine in prevention and treatment await robust published results. Till then, the recommendations of ICMR are to be followed for chemoprophylaxis with hydroxychloroquine by high risk contacts only under prescription from an authorised medical authority/doctor.*
- *There are eight RNA or DNA based inactivated vaccines in phase I/II stages of development.*
- *Immunization services especially the primary doses of vaccines should be administered to all the eligible children.*

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Annexure I

Undertaking on self-isolation

I S/W of, resident of being diagnosed as a confirmed/suspect case of COVID-19, do hereby voluntarily undertake to maintain strict self-isolation at all times for the prescribed period. During this period I shall monitor my health and those around me and interact with the assigned surveillance team/with the call center (1075), in case I suffer from any deteriorating symptoms or any of my close family contacts develops any symptoms consistent with COVID-19. I have been explained in detail about the precautions that I need to follow while I am under self-isolation.

I am liable to be acted on under the prescribed law for any non-adherence to self-isolation protocol.

Signature _____
Date _____
Contact Number _____

Annexure II

Instructions for care-givers

- **Mask:** The caregiver should wear a triple layer medical mask appropriately when in the same room with the ill person. Front portion of the mask should not be touched or handled during use. If the mask gets wet or dirty with secretions, it must be changed immediately. Discard the mask after use and perform hand hygiene after disposal of the mask.
- He/she should avoid touching own face, nose or mouth.
- Hand hygiene must be ensured following contact with ill person or his immediate environment.
- Hand hygiene should also be practiced before and after preparing food, before eating, after using the toilet, and whenever hands look dirty. Use soap and water for hand washing at least for 40 seconds. Alcohol-based hand rub can be used, if hands are not visibly soiled.
- After using soap and water, use of disposable paper towels to dry hands is desirable. If not available, use dedicated clean cloth towels and replace them when they become wet.
- **Exposure to patient:** Avoid direct contact with body fluids of the patient, particularly oral or respiratory secretions. Use disposable gloves while handling the patient. Perform hand hygiene before and after removing gloves.
- Avoid exposure to potentially contaminated items in his immediate environment (e.g. avoid sharing cigarettes, eating utensils, dishes, drinks, used towels or bed linen).
- Food must be provided to the patient in his room
- Utensils and dishes used by the patient should be cleaned with soap/detergent and water wearing gloves. The utensils and dishes may be re-used. Clean hands after taking off gloves or handling used items.
- **Use triple layer medical mask and disposable gloves** while cleaning or handling surfaces, clothing or linen used by the patient. Perform hand hygiene before and after removing gloves.
- The care giver will make sure that the patient follows the prescribed treatment.
- The care giver and all close contact will self-monitor their health with daily temperature monitoring and report promptly if they develop any symptom

suggestive of COVID-19 (fever/cough/difficulty in breathing).

Instructions for the patient

- Patient should at all times use triple layer medical mask. Discard mask after 8 hours of use or earlier if they become wet or visibly soiled.
- Mask should be discarded only after disinfecting it with 1% sodium hypochlorite.
- Patient must stay in the identified room and away from other people in home, especially elderlies and those with co-morbid conditions like hypertension, cardiovascular disease, renal disease etc.
- Patient must take rest and drink lot of fluids to maintain adequate hydration.
- Follow respiratory etiquettes all the time.
- Hands must be washed often with soap and water for at least 40 seconds or clean with alcohol based sanitizer.
- Don't share personal items with other people.
- Clean surfaces in the room that are touched often (tabletops, door knobs, handles, etc) with 1% hypochlorite solution.
- The patient must strictly follow the physician's instructions and medication advice.
- The patient will self-monitor his/her health with daily temperature monitoring and report promptly to the health authorities, if develops any deterioration of symptom.

CLIPPINGS

Soluble urokinase plasminogen activator receptor (suPAR) predicts who needs higher levels of respiratory support.

Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker for activation of the inflammatory and immune systems. Blood levels of suPAR are positively correlated with pro-inflammatory biomarkers, such as tumor necrosis factor- α , leukocyte counts, and C-reactive protein.

Since March 1, 2020, 57 patients with at least two signs of the systemic inflammatory response syndrome with community-acquired pneumonia and molecular documentation of SARS-CoV-2 in respiratory secretions were enrolled.

Patients were followed up daily for 14 days; the development of Severe respiratory failure (SRF) defined as PO_2/FiO_2 ratio less than 150 requiring mechanical ventilation (MV) or continuous positive airway pressure treatment (CPAP) was recorded. suPAR was measured by an enzyme immunoassay in duplicate.

The study endpoint was the prognostic performance of suPAR admission levels for the development of SRF within 14 days.

Admission levels of suPAR were significantly greater among patients who eventually developed SRF. Receiver operator characteristics curve analysis identified levels ≥ 6 ng/ml as the best predictor for SRF. At that cutoff point, the sensitivity, specificity, positive predictive value and negative predictive value for the prediction of SRF was 85.7%, 91.7%, 85.7% and 91.7%, respectively.

The time to SRF was much shorter among patients with suPAR ≥ 6 ng/ml.

An analysis of the TRIAGE III trial in 4420 patients admitted at the ED in Denmark revealed that suPAR ranged between 2.6 and 4.7 ng/ml in 30-day survivors and between 6.7 and 11.8 ng/ml in 30-day nonsurvivors.

Findings suggest that suPAR may early trace patients who need intensified management probably in need of anti-inflammatory treatment.

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COVID - 19

THE ROLE OF PEDIATRICIAN DURING THE PANDEMIC

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Abstract : *With the emergence of the corona virus disease 2019 pandemic, many containment measures were imposed including lockdowns. As the lockdown is gradually eased out, there are recommendations put in place by both the government as well as international and national professional bodies for restarting and continuing of child health care delivery in a safe manner. The pediatrician has to put in place new norms in terms of infection prevention and control practices, training and motivation of fellow healthcare workers, immunization practices, telemedicine and selfcare to render continuous quality healthcare and to mitigate risk of infection to all including oneself and to the patients.*

Keywords: *Post lockdown, Preparation, Infection prevention and control, Patient examination, Immunization.*

The emergence of corona virus disease 2019 (COVID19) pandemic has left many pediatric and general practitioners in a quandary. Many small hospitals, private clinics and consultation rooms were initially closed following government guidelines on lockdown. Patients were persuaded to contact their doctors by phone and avoid attending any health care facility for minor problems. For serious illnesses they were referred to bigger institutions, government or private. Immunization services were kept in abeyance. In April 2020, the state Governments and professional bodies like Indian Medical Association (IMA) and Indian Academy of Pediatrics (IAP) came out

with recommendations for private practitioners to resume their practice keeping in mind the 'the do's and don'ts'. Guidelines for immunization services were issued. For safe and successful patient care, pediatrician has to develop the skills of effective leadership, communication, teamwork and guidance. As the situation is dynamic and evolving, the recommendations nationally and regionally are likely to be updated and the practitioner has to keep abreast of them. Effective infection control protocols in the outpatient setting can prevent unnecessary exposures to COVID among patients, healthcare personnel and visitors at the facility. In this article, a practical approach to outpatient care of children in the post-lockdown period is summarized.

State of pandemic

As on third week of May 2020, the infection is continuing in many parts of our country with large numbers affected in many metropolitan cities like Mumbai, Delhi, Chennai, Ahmedabad and Kolkata. The important fact relevant to practicing pediatricians is that majority of the infected people are asymptomatic or mildly symptomatic and children (0-18 years) form a very small percentage of infected, ranging 1.2% (Italy) to 10% (Iceland) of total cases.¹ In Tamilnadu, as on fourth week of May, children less than 12 years constitute 6.18% (1003 out of 16,277 persons tested positive) (The Hindu newspaper, Chennai Edition, May 25, 2020).

Preparation

It has been said time and again by many experts that the virus is here to stay. Hence, the changes in our practice should stay with us and become the 'new normal'. We need to prepare ourselves and adopt new strategies. Financially, we have to make sure that there is adequate cash flow, in case of quarantine and enough securities, in case our family members get hospitalized.

The following preparations will help us to resume the services effectively.

Mental readiness

This is probably the most important preparation. The pediatrician should be willing to see his patients and help them and the parents, of course, with proper

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precautions in place. There is no halfway about it. Proper communication with parents and strict observation of 'infection prevention and control (IPC) practices will mitigate the risk of transmission.

Knowledge

Keeping abreast of the disease from reliable sources like Indian Academy of Pediatrics (IAP), Indian Council of Medical Research, Ministry of Health and Family Welfare, Government of India (MOHFW,GOI), Centre for Disease Control (CDC) and World Health Organization (WHO) is necessary. Internet based learning has become the new norm and we have to embrace it and apply to our practice judiciously. IAP website (www.iapindia.org) has provided important GOI notifications and guidelines.²

Government regulations and advisory

As the infection due to severe acute respiratory distress syndrome corona virus-2 (SARS-CoV-2) is just 5 months old and been having a significant impact in India only since March 2020, the MOHFW, GOI and respective state governments have been coming out with regulations and advisory periodically based on the available data and knowledge. As the situation is dynamic, so are the regulations. It is better for the clinician to download the government recommendations in a dedicated file and refer to them when required. There were many strict restrictive measures during the initial periods under Epidemic disease Act 1897 and the Disaster Management Act 2005, which had a bearing on the function of health care workers (HCWs) and health facilities. These have been partially relaxed taking into account the ground realities, need for accessible health care and the likely trajectory of the pandemic.

Cross-talking

Despite the guidelines and the scientific principles, maximum practical solutions are likely to come from our professional colleagues who are also in the same boat. Exchange of ideas and innovative solutions with constant revision is a way-out to overcome unique problems. No two practices or clinics are the same. Each practitioner has to adopt the good practices according to his situation.

Manpower training and support for HCWs

Private practitioners barring a few exceptions may just have one or two semi/unskilled persons to help them in patient management. Their role was confined to cleaning the premises and regulating the patient entry during consultation. These HCWs are the ones who have stood by them at all times. It is imperative to take care of their

needs and concerns during this stressful period. The financial problems faced by them are much higher than those of the doctors who also have to anticipate reduced earnings in the next few months. The HCWs also need psychological support and assurance. Besides, they need upgradation of knowledge and necessary skills related to IPC practices. HCWs are infected in much higher numbers and as per a study in Delhi in April 2020; one in every 15 COVID cases is a HCW.³ Clear instructions regarding their role and personal protection must be emphasized and periodically reinforced. Continuous supervision is needed so that they may not fault in wearing appropriate personal protective equipment (PPE) and maintaining all IPC practices. These general principles are also applicable to the out-patient settings of bigger units and teaching institutions.

Preparation of team members

- Personal protection gear: Ensure adequate availability and knowledge of use.
- Instructions to refrain from touching the eyes, nose, and mouth with potentially contaminated gloved or ungloved hands.
- Rotation of duty hours with adequate intervals.
- Instructions on interaction with parents:
 - Safe distance while questioning
 - Not to touch any documents or old records
 - Making sure that the attendant and older children above 2 years are wearing mask
 - Cashless payment or handling cash with gloves and collection in separate bags to be handled after 72 hours.
 - Avoid weighing unless absolutely necessary and cleaning surface of weighing machine after each use
 - Minimal waiting time and maximal distance between families
- Psychological: Staff can be demotivated, due to various conflicting ideas in the social media. Comforting words and clear explanations will be very helpful. Extra incentives during this season will be encouraging.

Parent and family education

Besides the economic and social impact, many parents also face great anxiety about their children's risk of getting the infection in the post-lock down period especially with

schools re-opening. An empathetic pediatrician is a great support for them. Realistic information has to be given to the family members regarding the nature of infection spread and all the possible safe practices to be followed by them and the children. Unnecessary fear or panic is to be avoided. The pediatrician should discuss with them upfront his plans and type of private practice and alternative support. Though professional charges are allowed for teleconsultations, discretion can be exercised for individual patients. The following clear instructions to parents will help in IPC practices.

- **Appointments:** Scheduled to avoid crowding and promote smooth turnover.
- **Accessibility:** Over the phone 24/7 availability of an experienced staff if possible; otherwise the pediatrician's availability over phone.
- **Briefing:** What should be brought to clinic (one change of dress, one water bottle) and what not to bring (old records, toys, etc). Attendants above 60 years to be instructed not to accompany the child.
- **Payment:** Cashless if possible and the methods to do so.

Hospital/Clinic setting^{3,4}

Flow of patients

At entry

- Hand sanitization should be universal for anybody entering the clinic and a mask if not already worn by them. Children less than 2 years of age are not expected to wear a mask.
- All parents and visitors should have Aarogya Setu app for contact tracing or their address and phone numbers have to be documented.
- Screening questionnaire for fever/ influenza like illness (ILI) should be administered and temperature checked.
- Anyone coming with fever or ILI should be directed to a separate 'Fever clinic' in all facilities where children with fever/ILI should be directed to, examined and managed as per the Government order in some states.⁵
- Proper signages should be provided for patients to go to designated areas without hassle.

Waiting area

- Schedule consultations appropriately and avoid waiting as much as possible

- Adequate distance of minimum of 1 meter on sides, front and back between waiting persons including children should be ensured. Alternate seats can be barricaded to maintain social distancing.
- Health information posters related to COVID-19 and prevention can be displayed.
- Playthings, toys, books etc., should be removed.
- Depending on the facilities available, segregate the children coming for immunization and other illnesses in terms of space and if not possible, in time by prior appointment.
- If a separate fever clinic is not possible to create, children with fever/ILI should be given separate time and not be allowed to wait with other children brought for well baby check or immunization.
- Ensure adequate ventilation in all places by keeping the doors and windows open.

Disinfection and cleaning

- Provision of sanitizing hand rub and hand wash facilities with soap and water is ensured at multiple places.
- Public areas like waiting areas and toilets have to be disinfected once in 2 hours with 1% hypochlorite (bleach) or 5% benzalkonium solution.
- Weighing machines and stethoscopes have to be disinfected after every patient use. (Table I)

Personal protection equipments (PPEs)

The PPEs are to be used based on the risk profile for HCW. Table II gives the basic PPE required.

The following points are to be remembered while using PPE:

- Standard precautions are to be followed all the time
- PPEs are not alternative to other important IPC practices such as hand hygiene, safe distancing and cough etiquette
- PPEs are to be disposed as per the IPC regulations
- In practice, N95 masks and face/ eye shields may be restricted to fever clinics, suspected and confirmed COVID wards and aerosol generating procedures such as nebulization and sample collection. Many practitioners prefer to use N95 mask also during well baby and other non-COVID consultations in view of significant number of infected asymptomatic persons.

Table I. Cleaning different areas of clinic²⁻⁴

Area/items/Frequency	Item/equipment	Process	Method
Floor of the clinic / Waiting area- 2 hourly	Dust mop/damp mop 3 buckets (Plain water, detergent solution with water, 1% sodium hypochlorite)	Sweeping, Cleaning, Daily mopping	i) Sweep with dust mop/damp mop ii) Next, mop the area with water and detergent solution - Then clean the mop in plain water and squeeze iii) Repeat this in the remaining area iv) Then, mop the whole area again with 1% hypochlorite solution starting at the far corner of the room and work towards the door
Railings, doorknobs, surfaces (reception desk, doctors table) - Every 4 hours	Damp cloth, Detergent solution with water 1% sodium hypochlorite solution	Clean and wipe	- Clean with damp mop - Wipe with hypochlorite or detergent and water
Stethoscope, thermometer (axillary) - between every patient	70% alcohol based rub/ spirit swab	Clean and wipe	Wipe with alcohol based rub/spirit swab

Table II. PPEs for different areas^{2,3,6,7,8}

Setting	Risk stratification	Recommended PPE	Other precautions
Registration/ Front desk	Mild risk	Triple layer mask, Latex examination gloves	Physical distancing at all times
Doctor	Mild risk*	Triple layer mask **, Latex examination gloves	Hand sanitization after every patient examination No aerosol generating procedures such as nebulization
Nurses	Mild risk*	Triple layer mask** Gloves	Minimum distance of one meter needs to be maintained.
Pharmacist	Mild risk	Triple layer mask, Latex examination gloves	Frequent use of hand sanitizer over gloves

* Categorised as moderate risk by IAP; **IAP- N95 mask

MoHFW,GOI⁸ and others - For non COVID setting, mild risk

Video/tele consultations

This is promoted as much as possible. The recent notification by Government of India clearly spells out the type, charging of professional fees and the drugs which can be prescribed.⁹

Consultation planning¹⁰

- Provide as many tele consultations as possible. Clear instructions are provided regarding the charges for follow-up consultations and new consultations.

- When scheduling appointments by phone, provide instructions to persons with or without signs or symptoms of COVID-19 on how to arrive at the clinic, including which entrance to use and the precautions to take (e.g., how to notify clinic staff and follow triage procedures)
- Make them wait in their vehicle and inform them through phone when their appointment is due.
- If possible, schedule appointment for any child with illness at the end of day and complete the well child consultations earlier.

- Do not have people waiting at OPD or diagnostic areas; minimize the waiting time by providing spaced appointments.
- Discourage walk-in patients.
- Keep the doors of consulting room open so that nobody needs to touch them while opening or closing.
- Keep a separator or rope to avoid people touching the registration counter.
- Patients with respiratory symptoms can directly go to a separate room spacious and airy and sit in the centre of the room where they cannot touch anything in the surrounding and they can be quickly examined and sent.
- Inform all patients, that if they or any close contact have cough or fever, they should call first and not visit the clinic/hospital without tele consultation.

Patient examination

- Keep a distance of three feet while taking history
- Avoid throat examination unless absolutely necessary.
- Avoid auscultation as much as possible, auscultate from back if needed; Blue tooth stethoscope is gaining more attention during this COVID era. It is a simple cost effective device to auscultate children safely during the pandemic period. All it requires is an old stethoscope with a workable diaphragm, and a blue tooth device, costing approximately Rs.3000. Commercial variants are available which are manufactured indigenously, some with artificial intelligence that filter surrounding noise and can be shared across iOS and android platforms. A simpler variant can be designed by the following procedure. Cut the tubing of the stethoscope about 2 inches from the chest piece. From the blue tooth device, the mike can be removed and soldered to the chest piece. Connecting wires are threaded through the tube and then connected with the speaker, Fix the blue tooth speaker securely to the tubing and make sure the diaphragm of the stethoscope is screwed tight. This blue tooth device is then paired to a mobile which is kept in the examining room. The blue tooth stethoscope is ready for use. (Figs.1,2,3,4).
- Either the mother or fully protected HCW, can switch on the blue tooth speaker and keep the stethoscope over the chest of the child, at various places as indicated by the doctor. The pediatrician can ring up the paired mobile from any place and use either headphones or loudspeaker to hear the auscultated sounds.



Fig.1. Assembling blue tooth stethoscope



Fig.2. Cut steth with blue tooth device



Fig.3. Steth opened up to show tip of receiver at the central hole



Fig.4. Bluetooth device

- Viewing old records: Preferably digital, e.g., IAP approved software.
- Prescription: Preferably digital, like IAP approved software.
- Maintain supply of masks, disinfectant/sanitizer and other personal protective equipment.

- Disinfect all things that one touch us during work: including computers, keyboards, scanners, door handles, BP instrument, stethoscope, SpO₂ monitor with alcohol swab (Table I).
- Infant weighing scales can be washed with soap and water. Separate clean paper (news paper) should be used for every baby to prevent risk of hypothermia and cross infection.
- While the Pediatrician returns back home from clinic, he should wash feet first, then hands, face, change clothes (keep them in separate box for washing), decontaminate all surfaces he may have touched including car and finally wash hands again with soap and water. Mobile can be cleaned with a soft cloth and 70% alcohol after switching off.
- Doctors with cough and fever should opt for self-quarantine and COVID assessment.

Immunization¹¹⁻¹³

General instructions for vaccination clinics

1. It is strongly recommended to have exclusive vaccination sessions and exclusive vaccination rooms. A polyclinic/ nursing home/ hospital should have segregated vaccination areas with separate entrance and exit.
2. Give vaccinations by appointment only.
3. Well-baby visits may be combined with immunizations.
4. Utilize every healthcare visit for immunization, provided there are no contraindications and the interval between vaccines are maintained as per published guidelines.
5. It is essential that the doctor and supporting staff utilize adequate PPE. In a vaccination clinic, surgical masks and gloves are necessary along with scrupulous hand hygiene.
6. All other IPC practices outlined above are to be followed stringently in vaccination sessions too

Prioritizing vaccines in routine immunization

- Vaccinate newborns in maternity set up, before discharge with BCG, OPV and Hepatitis B vaccines.
- Prioritize primary vaccination series: DPT, Hep B, Hib, OPV/IPV, rotavirus vaccines, PCV, influenza, varicella and MR/MMR. Avoid postponing these vaccines.

- Prioritize pneumococcal and influenza vaccines to vulnerable groups. Healthcare personnel should be upto date in their age appropriate vaccinations.
- Typhoid conjugate vaccines may be clubbed with the influenza vaccine at 6 months or MR/MMR at 9 months.
- Hepatitis A vaccines and HPV vaccines may be postponed to a later date if logistic issues of transport, etc., exist.
- Multiple vaccines can be administered in the same session without fear of any increased adverse effects.
- Boosters may be postponed to a later date, if logistic issues of transport, etc. exist.

Preparing one's own family to handle COVID pandemic

- Explanation: The pediatrician has to explain about the disease to all his family members. Even young children can understand a few aspects of the disease.
- Protection: Hand washing, disinfection, distancing from elders as needed, physical activity, healthy diet, regular food habits and sleep.
- Sharing: Information regarding financial situation with spouse, location of important documents like house deeds, cheque books, aadhar card, etc. Telephone numbers of important contacts like lawyer, auditor, close family members, as well important passwords to be accessible to spouse.
- Contingency plan: If one of the spouses falls ill or has to be quarantined (a distinct possibility), what should the other members of the family be doing, and who should be responsible. Hospitalization options and insurance to be utilized may be planned.

Points to Remember

- *Be prepared, mentally, physically and financially, to handle this pandemic.*
- *Safety guidelines, personal and personnel protection, can never be taken too lightly, even if the rest of the society are not compliant.*
- *Give priority to catch up vaccination in the initial days of resuming practice and designate separate times and space for handling healthy children.*
- *Telemedicine, phone consultation, use of social media to communicate our plans, judicious use of our instruments of practice, planned consultation, and meticulous screening of patients are the new normal.*

- ***Parent and family education goes a long way in the smooth handling of our practice.***

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CLIPPINGS

CDC guidance on antibody testing.

- Do not use antibody tests to determine a person's immune status until evidence confirms that antibodies provide protection, how much antibody is protective and how long protection lasts.
- Antibody testing can help establish a clinical picture when patients have late complications of COVID-19 illness, such as multisystem inflammatory syndrome in children.
- Antibody test results should not be used to diagnose someone with an active infection with symptoms.
- Antibody tests can support the clinical assessment of COVID-19 illness for people who are being tested 9 to 14 days after illness onset, in addition to recommended virus detection methods such as PCR. This will maximize sensitivity, as the sensitivity of nucleic acid detection is decreasing and serologic testing is increasing during this time period.
- People who receive positive results on an antibody test but don't have symptoms of COVID-19 or have not been around someone who may have COVID-19 are not likely to have a current infection. They can continue with normal activities, including work, but still take steps to protect themselves and others.
- People who receive positive results on an antibody test and who are currently or recently sick or have been around someone with COVID-19 should consult health authorities and get advice as its significance is not clear.

Content source: www.cdc.gov. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases Page last reviewed: May 28, 2020. Accessed on 10th June 2020.

COVID - 19

USE OF PERSONAL PROTECTIVE EQUIPMENTS DURING COVID-19 PANDEMIC IN RESOURCE LIMITED SETTINGS - THE BAREST MINIMUM NEEDED***Dhiren Gupta******Simalti AK*******Arun Bansal********Neeraj Gupta****#Vinayak Patki****##Ashwani Kumar Sood****###Anil Sachdev****\$Bakul Jayant Parekh**

Abstract: *Personal Protective Equipment are protective gear designed to safeguard the health care workers by minimizing exposure to a biological agent. Personal protective equipment includes mask, gloves, face and eye protection (face shield, goggles), gowns and full body suits. Different types of masks are available for specific purposes. Masks are intended for protecting others from respiratory emissions of the wearer while respirator protects wearer from small particles like aerosols besides*

large droplets. Face shields provide a barrier for suddenly expelled aerosol of body fluids and are commonly used as an alternative to goggles. Isolation gowns may be adequate for medium risk while coveralls provide full protection. It is important to know and appropriately choose the gowns based on the fabric and reliability of manufacturer. All health care workers need to be taught the correct sequence of donning and doffing=PPE in order to avoid contamination. Though not ideal, the most effective methods of sterilizing and reusing N95 masks during scarcity may have to be adopted.

Essential protective measures depend heavily on the location of patient contact, the role of the particular health care facility and the hazard vulnerability analysis. Hazards for the health care worker can be through air, surface, equipment and body secretions. Personal Protective Equipment reduces the risk of acquiring infection through any of these routes. This article deals with the selection of appropriate personal protective equipment for the health care workers managing suspected or proven COVID-19 infected persons.

Keywords: *Personal protective equipments, N 95, Masks.*

Personal protective equipments PPE is important not only to protect Health Care Worker (HCW) but also prevent patient to patient transmission of infection. Examples of PPE include items such as mask, gloves, face and eye protection (faceshield, goggles), gowns, shoe covers and full body suits. Picture of a health care worker wearing full PPE is shown in (Fig.1).¹

Need for Personal Protective Equipment (PPE) considering transmission in hospital setting

In hospitals especially in areas where aerosols are generated, like intensive care units where droplet nuclei spread quite far.² Therefore wherever intubation and procedures like manual ventilation, suctioning, nebulization, cardiopulmonary resuscitation, bronchoscopy, throat examination, endoscopy and autopsy are done, special precautions meant for airborne spread are required.³ A very important fact or that prevents extensive dissemination in hospitals is the presence of an adequate air exchange. Ideally a negative pressure room

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Fig.1. A health care worker in full PPE and coverall

with at least six air changes per hour (minimum air changes recommended by WHO is 12 per hour) or natural ventilation (with airflow of at least 160 L/second is recommended as ideal air exchange). Another important variable to consider is the exhaled air dispersion distance during oxygen administration and ventilator support.

Masks

Various types of masks

Wearing a mask helps in preventing the aerosol spread of COVID-19. Droplet transmission begins two and half days before patients show any symptoms in COVID infection. Asymptomatic individuals were responsible for 66% of transmission.⁴ In one interesting case report, an asymptomatic individual infected 5 out of 39 individuals when he was not wearing a mask but did not infect anyone when he wore a mask under the same circumstances.⁵ Importance of wearing a mask by everyone in prevention of transmission was seen during the influenza epidemic.⁶ Wearing a mask helps in preventing the aerosol spread of COVID-19. Health workers should not share the same room such as during meal time when masks cannot be worn.

Common (nonmedical) masks available to general population

- a) **Dust mask** is a disposable, molded face mask made of paper pad. It does not offer any protection against airborne pathogen such as corona virus. It is worn for protection against non-toxic dust (Fig.2).
- b) **Single layer face mask** which consists of a single layer of wood pulp tissue paper or non-woven fabric. It is also not recommended for protection against corona



Fig.2. Dust mask

virus transmission. It is used commonly in the food processing industry. It should not be reused as it is a single use item and cannot be washed.

- c) **Cloth mask** seems a practical option for usage by general public.⁷ Cotton masks are available in the market and can even be made at home. A manual for making home made cloth masks has been released by Government of India recently.⁸ This manual advises using 100% cotton like old T shirt, cotton vest, etc. Two to three layers of cloth is optimal as increasing layers can improve efficacy but makes breathing difficult.

Masks used in the health care settings

a) Three layered surgical mask

Surgical mask is the one which is most commonly worn in healthcare settings. It consists of three layers (Fig.3). The inner layer has absorbent property to absorb moisture from exhaled air. The middle layer acts as a filter and is made up of nonwoven mat of thin fiber or melt blown (The melt blown process is a nonwoven manufacturing system) material. The outer most layer repels liquid. These masks have pleats to increase the surface area in order to cover the chin and nose. These masks are disposable and they do not fit tightly around face and nose. Surgical mask prevents the release of respiratory emissions from the user into their immediate environment.⁹ The main purpose of wearing these masks is to protect patients or people nearby from the person wearing it and not the other way around. Although not protective to wearer against airborne infection because of their loose fit, they do protect the wearer from direct spray or splashes of infectious body fluids or blood.¹⁰ Surgical masks do not have safety rating but USFDA requires them to conform to certain quality standards. They should have bacterial filtration efficiency more than 98%.¹¹

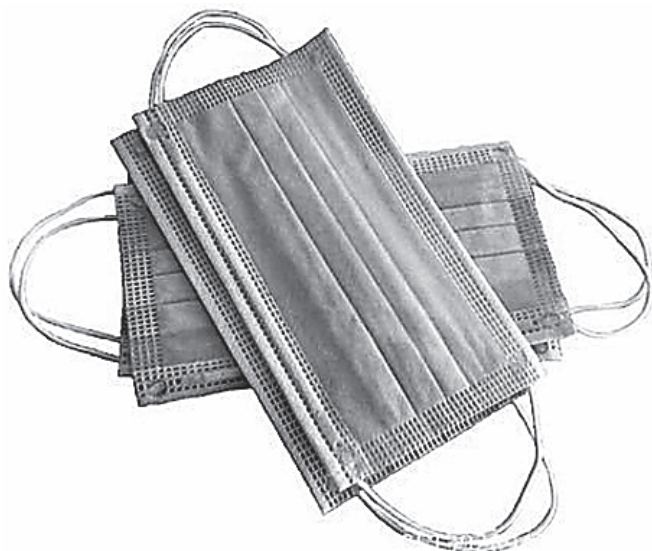


Fig.3. Triple layer surgical mask

Usefulness of surgical mask in preventing respiratory infection: Surgical masks are the most commonly used protective device but there is not much evidence in protective efficacy against airborne infection. Previously WHO recommended face masks for people with respiratory symptoms or care givers of symptomatic individuals¹² but in the present scenario where a high level of SARS-CoV2 shedding even in asymptomatic patients, some type of barrier or mask is recommended for everyone during interaction with people. Guidelines from China recommend wearing of surgical masks based on the risk of acquiring infection.¹³

Surgical mask for personal protection: Since main purpose of wearing a surgical mask is patient safety, most studies have focused on chances of wound contamination and not on protection for the person wearing it. During the influenza epidemic of 2008-9, this question was raised and at least two studies have documented that surgical masks were as effective as respirators for prevention of influenza among nurses providing care.¹⁴⁻¹⁶

b) Respirator mask

Respirators differ from surgical masks in their fit. Unlike loosely fitting surgical masks these are tight fitting. Respirators are designed to create a facial seal in order to protect the wearer from airborne particles. They provide two way protection by filtering both outflow as well as inflow of air. They are available as disposable device and also as full face or half face respirator device. These respirators are given ratings based on percentage of aerosol they can prevent from going through. Table I compares the surgical mask and respirator mask.

Working of respirators: Filters used in both surgical masks as well as respirators are fibrous in consistency. These filters are made from flat and nonwoven mats of thin fibers made of material like wool felt, fiberglass paper or polypropylene. Most important layer is melt blown layer for filtration. This layer is 100-1000 microns in thickness and composed of polypropylene microfiber with diameter in the range of 1-10 micron, the quality of mask depends on the quality of this layer and electro static charge over heat. Efficiency of the filter depends on the diameter of individual fibers, the ratio of open space to fibers termed porosity and overall thickness of the filter. In all these fibrous filters, there are four functional mechanisms which enable them to capture aerosol particles. These are interception, inertial impaction, diffusion and electrostatic attraction. First two mechanisms namely inertial impaction interception and electrostatic attraction are responsible for obstructing and filtering larger particles. Diffusion mechanism is responsible for collecting particles measuring 0.1 mm and smaller which have constant brownian motion leading them to collide with the filter fiber. Fourth one is electrostatic attraction which relies on attraction between the charged fibers and particles with opposite charge. This is very important for filter efficiency as it improves efficiency in particle collection without increasing resistance of breathing.¹⁷

Filtering efficacy of respirators: There are many types of respirators available in market which differ from each other in terms of their filtering capacity. Based on rating by different institutions such as CDC and European Committee for Standardization, masks are labelled. The mask with CDC 95 rating can collect at least 95% of the aerosol particles and doesn't allow them to pass through. Similarly CDC 99 rating means at least 99% aerosol particles get filtered out and there are even respirators with CDC100 rating which can filter almost 100% (practically up to 99.7%) of aerosol particles. Oil can impact the efficacy of the filter used in these masks as electrostatic charges in the filter media can change on contact with oil. Thus in industries where exposure to oil is common, respirators need to be made resistant to oil too. This gives rise to another rating based on permeability of oil. These are 'N' meaning not resistant, 'R' meaning resistant but not absolute while 'P' meaning oil proof or strongly resistant. With these two properties-level of resistance to oil and percentage of particles filtered, these respirators can be divided into 9 categories in CDC standard. These CDC categories are N-95, N-99, N-100, R-95, R-99, R-100, P-95, P-99, and P-100. CDC has advised that N95 respirator should be considered as standard part of the PPE against Covid-19. European Committee for Standardization (CEN)

Table I. Comparison between respirator and mask

	Surgical mask	Respirator
Testing and approval	Cleared by the U.S. Food and Drug Administration (FDA)	Evaluated, tested and approved by National Institute of Occupational Safety and Health (NIOSH)
Intended use and purpose	Fluid resistant. Protects the wearer against splashes, large droplets or sprays of hazardous fluids. Protects others from respiratory emissions of the wearer	Protects wearer from small particles like aerosols besides large droplets Not resistant to oil (considered in industrial use)
Face seal fit	Loose-fit Air enters around the edge of mask with inspiration	Tight-fit Minimal leakage around edges when fitted properly
User seal check requirement	No	Yes Every time it is donned
Fit testing requirement	No	Yes
Filtration	Does NOT protect the wearer from inhaling smaller airborne particles	Provides respiratory protection by filtering out at least 95% of large as well as small airborne particles
When to discard	Disposable Ideally should be discarded after each patient encounter.	Ideally should be discarded after each patient encounter Even during shortage should be discarded if: after aerosol-generating procedures/becomes damaged or deformed/Ineffective seal around the face/gets wet or soiled/if breathing through respirator becomes difficult.

National Institute of Occupational Safety and Health - the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.

uses another system namely filtering face piece (FFP), with ratings of P1, P2 and P3 which depend on filtering capacity of 80%, 94% and 99.95% particles respectively. So the standard N95 of US FDA is equivalent to FFP2 of CEN.¹⁸ Fig.4 shows some of the USFDA and CEN certified respirator masks.

c) Respirators with expiratory valve

There are many modifications done in the respirator to increase comfort. As the filtering capacity increases, passage of air through filter also becomes difficult. This makes it uncomfortable for the wearer to breathe through these respirators especially with N100 or FFP3 masks. In order to make them convenient to use, some respirators have expiratory valve included (Fig.5). This makes it easier to exhale and also less moisture build up inside the mask which can be very uncomfortable to

N95 (95%) = FFP2 / P2 (94%)



N99 (99%) = FFP3 (99%)

N100 (99.97%) = P3 (99.95%)



Fig.4. Comparison of N95, N99, and N100 with FFP2 and FFP3 respirator masks

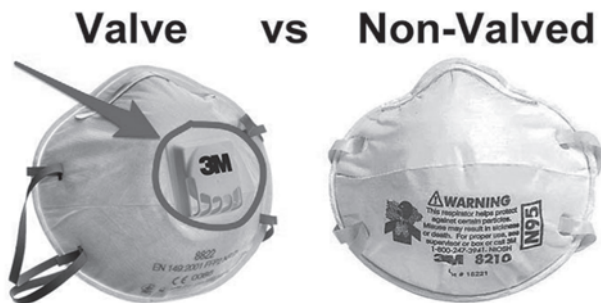


Fig.5. Valved vs non valved respirator

wearer after long duration.¹⁹ However, as the exhaled air is not passing through the filter but getting out through the valve, it doesn't protect the environment if the person wearing this mask is already infected by a respiratory pathogen. When used, wearer should be instructed to wear surgical mask over respirator with expiratory valve.¹⁹

d) Powered air-purifying respirator (PAPR) is supposed to be more comfortable for the person wearing it as it reduces heat related stress.²⁰ A battery-powered fan is used in these respirators to make air flow through a filter and facilitate easier breathing. These respirators appear to be more protective than disposable N95 respirators but there is no clear evidence for this.²¹ PAPRs are expensive, thus may not be an option in the current pandemic. Other limitations are difficulty in communication because of noise of the fan and risk of contamination during doffing. It is recommended that an expert staff should assist HCWs in the doffing process (Fig.6).²¹

Ensuring the safety of surgical masks and respirators available in the market

Surgical mask is expected to meet certain standards before it can be used. Because of sudden surge in demand, many fake surgical masks have come to the market all over the world. These counterfeit devices look like the real product and even use emblems, logos, and registration numbers of the real product. Unfortunately they do not



Fig.6. Example of a powered air purifying respirator (PAPR)

offer adequate protection.²² More than 12,000 fake N95 respirator masks were seized in Bengaluru recently.²³ To avoid this, dissect up one mask (cut open). One should be able to view three layers as mentioned above. Sometimes these similar looking masks contain only single ply or two ply instead of three ply which is recommended.

Identification of NIOSH certified respirator

National Institute for Occupational Safety and Health (NIOSH) approves all respirators used in healthcare settings to ensure standards of quality and performance. Only NIOSH authorized manufacturer can use the NIOSH logo or NIOSH name in block letters or on respirator. An established quality program to ensure respirator meeting the NIOSH requirements is expected from manufacturer. Markings of NIOSH logo or name may be on the front or on the straps. Counterfeit respirators with NIOSH name or logo are often sold in market and they may be available at lower prices. NIOSH website has a list of approved respirators and if NIOSH level is on the respirator but the name of manufacturer is not on the list, it may be a counterfeit product. There is also a TC number given by NIOSH and with the help of TC number, buyer can verify this at the website: - <http://www.cdc.gov/niosh/npptl/topics/respirators/disp>. TC number should be clearly marked on the packaging, on the respirator and also on the user instructions. Fig.7 shows markings on a N95 respirator.²⁴ If there is no TC number on any of these items, the respirator is not NIOSH-approved. NIOSH advises that even when the appropriate markings are present, any modification like how a strap is attached to main body, can compromise safety and should not be considered as NIOSH approved.²⁵ Before purchasing, mask should be verified physically.

Seal check of the respirator mask by wearer

The user must perform a seal check after wearing the respirator. This test can either be a positive or negative pressure check. To perform positive pressure seal check, person exhales gently after wearing the respirator and the face piece should become prominent and tense before elevated pressure causes leakage of the exhaled air. Similarly for a negative pressure check, face piece should collapse slightly when person inhales sharply. This procedure is called seal check and is different from a fit test. Fit test is performed by manufacturer before releasing respirator in market while seal check is performed by the user. Most of the wearers have a tendency to pull the respirator down to the chin intermittently especially during meal time. Every time the respirator is pulled down it is an episode of doffing. More than 5 doffings can lead

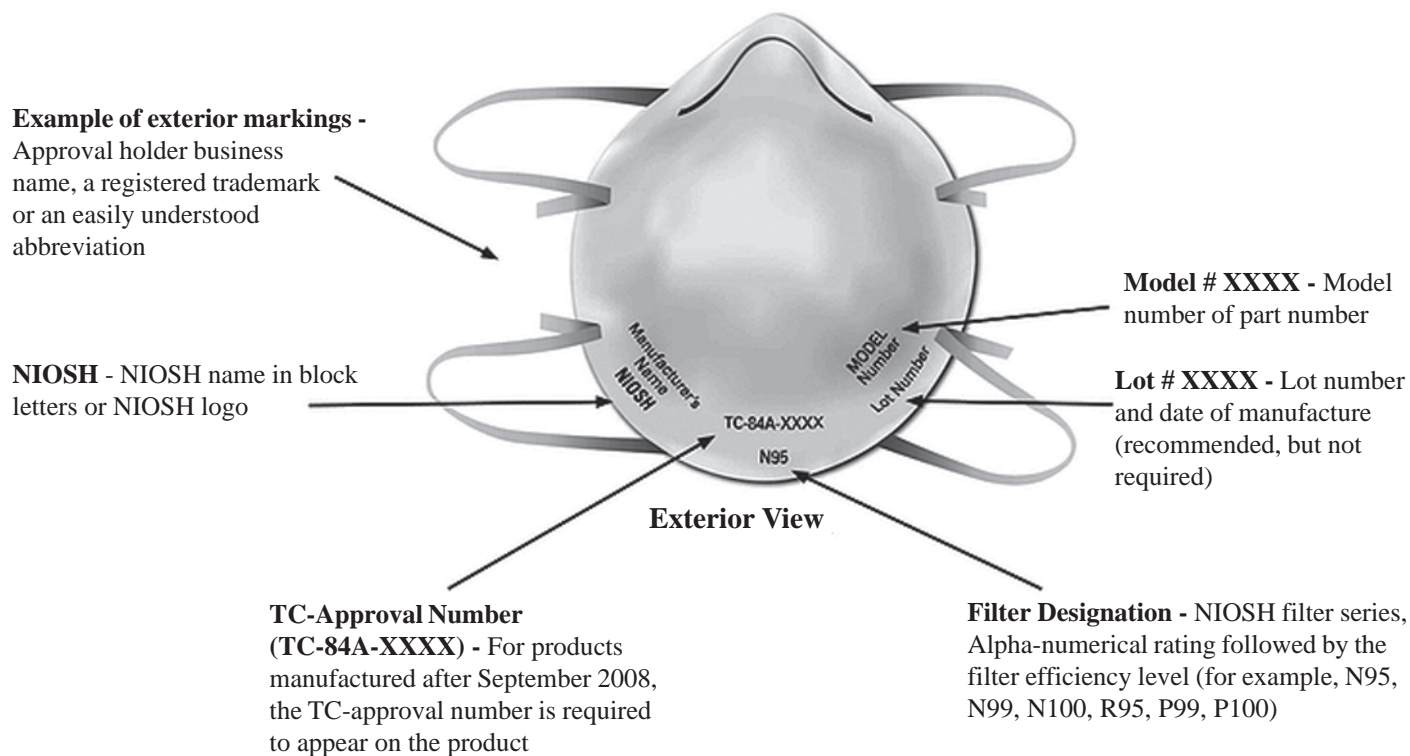


Fig.7. Example of exterior markings on NIOSH approved respirator

For more information about NIOSH-Approved respirators, to to: <http://knowits.NIOSH.gov>

to poor seal. If user ensures proper seal then respirator can be used till it is hard to breathe. After touching front of the respirator, hand hygiene should be performed.

Facial hair interfering with respirator seal

Ensuring proper seal is a vital part of effective respiratory protection. Facial hair such as sideburns, mustaches and beards, can interfere with the sealing area of a respirator. This may lead to failure of creating a tight seal to achieve maximum protection. Small particles in the air take the path of least resistance and through facial hair can bypass the filter of respirator. Hair is much larger in size and not dense enough to act as an effective filter.²⁶ Facial hair under the sealing area causes significant leakage when compared to a clean-shaven person. Even 2 days stubble can reduce protection. Generally, as per CDC, hair should not cross under the respirator sealing surface.

Alternatives to N95 NIOSH approved / FFP2 / FFP3 masks

These include other classes of filtering face piece respirators, elastomeric half-mask and full face piece air purifying respirators, powered air purifying respirators (PAPRs). All these alternatives will provide equivalent or higher protection than N95 respirators when properly worn.

e) Elastomeric respirators are half-facepiece, tight-fitting respirators that are made of synthetic or rubber material permitting them to be repeatedly disinfected, cleaned, and reused. They are equipped with replace able filter cartridges. Similar to N95 respirators, elastomeric respirators require annual fit testing. Elastomeric respirators should not be used without surgical mask over it due to concerns that air coming out of the exhalation valve may contaminate surrounding area.

Face Shield and goggles

Role of face shield as part of PPE

A face shield provides barrier protection to the facial area and the related mucous membranes (eyes, nose and lips). It provides a barrier to a bout of suddenly-expelled aerosol of body fluids and are commonly used as an alternative to goggles as they confer protection to a larger area of the face.²⁷ Combination of this face shield and an N95 filtering facepiece respirator (N95 FFR), protects the eyes, nares and mouth from contamination better than N95 combined with goggles.

Effectiveness of face shield for protection against droplets: For droplet size more than 5 micron, the efficacy is 96%

(for aerosol spread from distance of 45 cm). If the droplet size is reduced to less than $3.4\text{ }\mu\text{m}$, the efficacy goes down to 23% upto 30 min following cough (during which time the larger aerosol particles settle out, droplet nuclei form and remain airborne so that flow occurs more easily around the edges of the face shield).²⁸

Situations to wear face shield: Face shield should be worn during patient care activities where splashes and sprays are anticipated, typically aerosol generating procedures and during activities where prolonged face-to-face or close contact with a potentially infectious patient is unavoidable. Face shields should not be used while intubating because aerosols can flow behind the visor hence goggles should be worn. Face shield and goggles should not be used together as it does not offer additional protection and causes more discomfort and fogging affecting vision.²⁷

Precautions while using face shield: Health care worker should take care not to touch their face shield. If they touch or adjust their face shield, they must immediately perform hand hygiene. If they need to remove their eye protection, they should leave patient care area. Face shield should be taken off as late as possible, preferably at the end of the procedure to prevent inadvertent exposure of the mucous membranes when other potentially contaminated PPE components are being removed.²⁷ Face shields with single Velcro or elastic straps tend to be easiest to don and doff. Doffing can be accomplished with a single hand. It should be discarded if damaged.

Components of a face shield: The major structural components of a face shield include a visor which is the transparent part of face shield. Ideally width should be sufficient to reach at least the point of the ear on both sides (Fig.8). The purpose is to lessen the chances of the splash reaching the eyes and oral cavity. In addition, visors should have crown and chin protection for improved infection control purposes. It is made of either polycarbonate propionate, acetate, polyvinyl chloride, and polyethylene terephthalate glycol. Visor is available in disposable, reusable, and replaceable models. Visors can be treated with advanced coatings to impart anti-glare, anti-static, and anti-fogging properties, ultraviolet light (UV) protection, and scratch resistance features to extend the life.

Choice and regulatory standards for face shields: Face shield should be made of clear plastic and it should provide good visibility to both the wearer and the patient. There should be an adjustable band to allow good fit around the head and snug fit against the forehead also to prevent slippage of the device. Visor should ideally be fog-resistant and should cover the sides and length of the face

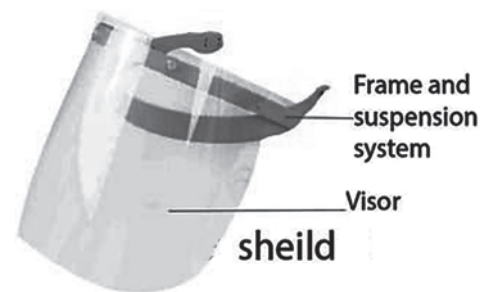


Fig.8. Face shield with visor, frame and suspension system

completely. Visors manufactured from acetate, propionate, and polycarbonate offer improved visual clarity and optical quality with the potential for less eye strain. Brow caps or forehead cushions should be of sufficient dimensions to ensure that there is adequate space between the wearer's face and the inner surface of the visor to allow for the use of ancillary equipment (medical/surgical mask, respirator, eyewear, etc.). There is currently no universal standards for face/eye protection from biological hazards. Face shields are marketed as class 1 medical devices exempt from FDA pre market notification.²⁷

Selection of appropriate goggles: Goggles should have a good seal with the skin of the face. Frame should be flexible to easily fit all face contours without much pressure on the skin. It should cover the eyes and the surrounding areas (through the silicon rim) and accommodate the prescription glasses underneath. It should have a fog and scratch-resistant adjustable band that can be firmly secured and does not become loose during clinical activity. Goggles should have an indirect venting mechanism to reduce fogging. Goggles can be reusable (provided appropriate arrangements for decontamination are in place) or disposable.

Reuse of face shields and goggles: Face shields should be reused only if they are made of robust material like polycarbonate propionate or acetate. Though propionate has the best clarity acetate is most commonly used. Face shield should be dedicated to one HCP only. WHO recommends cleaning with soap/ detergent and water and disinfection with 70% alcohol or sodium hypochlorite 0.1%; finally rinsing with clean water. Isopropanol (IPA) 75%, 95% or 99% for 5 mins, ethanol 70% for 5 mins, sodium hypochlorite 1% for > 5mins or UV-C for 15 mins are the methods recommended for sterilising face shields and goggles. Autoclave, steam or ethanol > 80% are not recommended.

Medical gowns

Types of gowns

Several types of protective gowns are available as part

of PPE. These include a) aprons b) surgical gowns c) isolation gowns d) coveralls. Aprons cover only torso and they are used occasionally where limited contamination is anticipated. A surgical gown protects both the patient and health care worker from contamination. Front of the body from top of shoulder to knees and the arms from above elbow to the wrist cuff are the critical zones most prone for receiving splashes during procedures. These parts of surgical gown are provided with extra protection while other area is made of normal material. Isolation gown differs in that all areas of the gown except bindings, cuffs, and hems are considered critical zones and must meet the highest liquid barrier protection level. All seams must have the same liquid barrier protection as the rest of the gown (Fig.9). Isolation gowns are used when there is a medium to high risk of contamination. These gowns do not provide extended whole-body protection due to possible openings in the back or neck and coverage upto the mid- calf only as compared to cover all suits or Hazmat suits which provide 360 degree protection (Fig.2). Coveralls and gowns are deemed equally acceptable.

Quality check when ordering gown or coverall for PPE: Gowns should be made of light weight fabric and it should fully cover the torso, It should comfortably cover the body and should have long sleeves that fit snugly at the wrist. It is important to have sufficient overlap of the fabric so that it wraps around the body to cover the back ensuring that if the wearer squats or sits down, the gown still protects the back area of the body. Light colours are preferable over dark ones to better detect possible contamination. Coverall should be designed to have universal fit. It should have inbuilt hood cap. Zipper of the coverall should be covered with a flap to avoid accumulation of microbes. It should be ensured that the gown or coverall being procured meets or exceeds ISO 16603 class 3 exposure pressure.

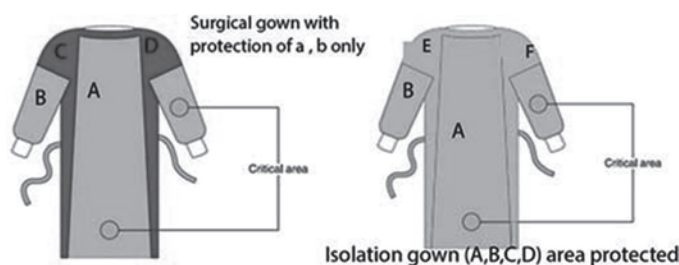


Fig.9. Surgical gown (left) gives extra protection to front and sleeves only whereas isolation gown (right) gives 100 percent protection (Unprotected area C, D; protected A,B,E,F)

Clothing material for gowns: Isolation gowns are made either of cotton or a spun synthetic material that decide whether they can be laundered and reused or must be disposed off. The clothing material should be impermeable to blood, body fluid and to COVID virus sized 0.11 microns. Reusable gowns made of cotton are not impermeable to blood or fluid so they do not provide protection against transmission of pathogen.²⁹ Recently gowns made up of microfibers have been introduced in medical field as replacement for cotton gowns since they can be reused.

Of the materials used for making gowns, non woven fabric is criss cross and functions as filter against fluid, blood, bacteria and viruses and also impermeable. The three most commonly used non woven fabrics for surgical gowns and drapes are - i) Spunlace, ii) Spunbond-meltblown-spunbond (SMS) and iii) Wet-laid

Most popular amongst these is spunbond meltblown spunbond, known as SMS.

Recommendations on gowns

Government of India requires that all gowns should have following information printed by manufacturer.³⁰

- Name of manufacturer
- South India Textile Research Association (SITRA)/ Defence Research and Development Establishment (DRDE) /Institute of Nuclear Medicine and Allied Sciences. (INMAS) Unique Certification Code (UCC)
- Test standard
- Date of manufacturing / batch number

The same UCC seal should be found on each gown. Manufacturer can be verified on sitra.org.in or DRDE website ISO/FDIS 16603 class 3 is the minimum requirement for COVID 19 isolation ward.

Another very important factor is the breathability which should be checked. This is very important for comfort of wearer. The breathability is tested by air permeability (AP) and water/moisture vapor transmission rate (WVTR/MVTR) of fabric. These tests should be done as per ambient temperature where the PPE will be used. Gown fabric must have the following range of AP and WVTR/MVTR:

- a. Air permeability ($L/M^2/\text{minute}$):100-150
- b. Water/moisture vapor transmissionrate-WVTR/ MVTR ($g/M^2/\text{day}$): 400–500

Shortage of gowns during the pandemic: Extended use, reprocessing, or use of alternative gown can be considered temporary and should be avoided as much as possible when

caring for severe or critically ill COVID-19 patients. These alternatives should also be avoided when performing aerosol-generating procedures and constant contact for more than 30 minutes in same environment or close contact (within 1 meter) for more than 15 minutes.³¹ If someone has an old gown without UCC stamp and wants to check for permeability, there is a crude method (not evidence based) to check gown fabric and seam. Pour 2 glasses of water over gown including seam. If no leak is found after 2 minutes especially over the seam, then it can be used for desired purpose. Same test can be used to assess the gowns which do not have this certificate (pushed in market as laminated products and are cheap). Clinician should always remember that these low cost, unapproved gowns may be used for low risk areas like outdoor patient services but should be avoided in isolation areas especially ICU or any aerosol generating areas. Many of these products are uncomfortable to wear as they are either too heavy (laminated cotton based) or non-breathable. Therefore before purchasing in bulk, user should try and test PPE for at least 3 hours in actual condition or run on treadmill for 15 minutes (2.5 miles/ hour). Look for the comfort, sweat and heat generated beneath fabric. Another weak point is the cuff. Ideally Gloves should overlap the cuff of gown so that no portion should be left exposed.

Precautions while wearing gowns for extended duration: Extended use means using the same gown, when providing care to a cohort of patients with COVID-19. This may increase risk of contamination with COVID-19 virus and may increase the risk of transmission of other pathogens between patients. Gown should be removed whenever it becomes wet, soiled, or damaged or exposed to splash of chemicals, infectious substances, or body fluids.³²

Cotton reusable gowns for PPE: Cotton reusable gown is not impermeable to fluid hence, does not provide adequate protection. If due to circumstances cotton reusable gown is used, it should be combined with barrier polyester sheeting which is worn above gown, with a property of water-repellent chemical finish. Main problems are thermal discomfort as these are nonbreathable and lack of protection of arms and the back of the torso, which can be exposed to splashes.³³

Washing and disinfection of cotton gowns: Washing by machine with warm water (60-90°C) and laundry detergent is recommended for reprocessing of the gown. If machine washing is not possible, linen can be soaked in hot water and soap in a large drum, using a stick to stir, avoiding splashing. It is then soaked in 0.05% chlorine (hypochlorite solution) for approximately 30 minutes. Finally, it is rinsed with clean water and sundried.

Donning and doffing PPE

Employers are required to train every employee who must use PPE about how to properly put on (Donning), take off (Doffing), adjust and wear the PPE. Everyone working in a health care facility must be trained to know about situations where PPE is necessary and also what kind of PPE to choose, its limitations and proper disposal after use.

Individuals are instructed first to perform hand hygiene and then the sequence of first gown followed by surgical mask, eye protection and gloves in the end. The order of doffing is gloves first followed by gown, eye protection and surgical mask in the end (Table II).

N95 is a tight-fitting respirator, it is not effective when it is not properly fitted. It needs to create a tight seal. Seal test is performed by inhaling after respirator is worn.³⁴ If seal is good it should get puckered in slightly. It should be done every time a respirator is worn.³⁵ Practical tips to remember while donning and doffing PPE are shown in Table III.

Tips to remember when donning a mask or respirator ties of mask/respirator should be tied up at middle of head and neck

Tackling the scarcity of PPE

Reuse of PPE

Conventionally disposable items are one time use only after which they need to be disposed. Reuse should be done by single person only and should never be shared between different persons. Recommendations have been issued for limited reuse or extended use of disposable respirators and masks. Reuse is not recommended if used for any procedure which may result in aerosol generation like suction, intubation, bronchoscopy etc.³⁶ Respirators should be discarded if seal is not adequate around mouth and nose or become moist from exhaled air or sweat or soiled or damaged (Table I).³⁷

Practical methods of sterilizing and reusing N95 masks

Air drying: Drying for at least 72 hours kills the coronavirus. Drying the used respirator in a clean, dry place for 3 days is one practical way for reusing the mask.

AIIMS, Delhi protocol: Health care workers are issued 5 masks and 5 marked paper bags. They are supposed to use one mask a day and then keep it in the paper bag and use next mask for day 2 and so on for next 4 days till by

Correct sequence of wearing PPE (Fig.10)

SEQUENCE FOR PUTTING ON PERSONAL PROTECTIVE EQUIPMENT (PPE)

The type of PPE used will vary based on the level of precautions required, such as standard and contact, droplet or airborne infection isolation precautions. The procedure for putting on and removing PPE should be tailored to the specific type of PPE.

- 1. GOWN**
 - Fully cover torso from neck to knees, arms to end of wrists, and wrap around the back
 - Fasten in back of neck and waist
- 2. MASK OR RESPIRATOR**
 - Secure ties or elastic bands at middle of head and neck
 - Fit flexible band to nose bridge
 - Fit snug to face and below chin
 - Fit-check respirator
- 3. GOGGLES OR FACE SHIELD**
 - Place over face and eyes and adjust to fit
- 4. GLOVES**
 - Extend to cover wrist of isolation gown

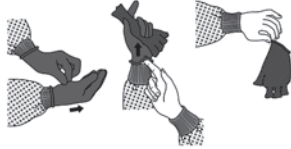



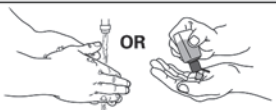
USE SAFE WORK PRACTICES TO PROTECT YOURSELF AND LIMIT THE SPREAD OF CONTAMINATION

- Keep hands away from face
- Limit surfaces touched
- Change gloves when torn or heavily contaminated
- Perform hand hygiene



HOW TO SAFELY REMOVE PERSONAL PROTECTIVE EQUIPMENT (PPE) EXAMPLE 1

There are a variety of ways to safely remove PPE without contaminating your clothing, skin, or mucous membranes with potentially infectious materials. Here is one example. **Remove all PPE before exiting the patient room** except a respirator, if worn. Remove the respirator **after** leaving the patient room and closing the door. Remove PPE in the following sequence:

- 1. GLOVES**
 - Outside of gloves are contaminated!
 - If your hands get contaminated during glove removal, immediately wash your hands or use an alcohol-based hand sanitizer
 - Using a gloved hand, grasp the palm area of the other gloved hand and peel off first glove
 - Hold removed glove in gloved hand
 - Slide fingers of ungloved hand under remaining glove at wrist and peel off second glove over first glove
 - Discard gloves in a waste container
- 2. GOGGLES OR FACE SHIELD**
 - Outside of goggles or face shield are contaminated!
 - If your hands get contaminated during goggle or face shield removal, immediately wash your hands or use an alcohol-based hand sanitizer
 - Remove goggles or face shield from the back by lifting head band or ear pieces
 - If the item is reusable, place in designated receptacle for reprocessing. Otherwise, discard in a waste container
- 3. GOWN**
 - Gown front and sleeves are contaminated!
 - If your hands get contaminated during gown removal, immediately wash your hands or use an alcohol-based hand sanitizer
 - Unfasten gown ties, taking care that sleeves don't contact your body when reaching for ties
 - Pull gown away from neck and shoulders, touching inside of gown only
 - Turn gown inside out
 - Fold or roll into a bundle and discard in a waste container
- 4. MASK OR RESPIRATOR**
 - Front of mask/respirator is contaminated — **DO NOT TOUCH!**
 - If your hands get contaminated during mask/respirator removal, immediately wash your hands or use an alcohol-based hand sanitizer
 - Grasp bottom ties or elastics of the mask/respirator, then the ones at the top, and remove without touching the front
 - Discard in a waste container
- 5. WASH HANDS OR USE AN ALCOHOL-BASED HAND SANITIZER IMMEDIATELY AFTER REMOVING ALL PPE**


PERFORM HAND HYGIENE BETWEEN STEPS IF HANDS BECOME CONTAMINATED AND IMMEDIATELY AFTER REMOVING ALL PPE




Fig.10. Sequence for putting on and safely removing PPE Source: CDC

All health care workers need to be taught the correct sequence of wearing (Donning) and taking off (Doffing) the PPE in order to avoid contamination.

rotation first worn respirator comes again. Maximum reuse of N 95 mask by a single user is 5 times.³⁸ Paper bag should be kept away from direct sunlight and ultraviolet rays. If the respirator becomes damaged, soiled or breathing becomes difficult, it is no longer fit to be used. Person wearing it should be familiar with method of removing and wearing it properly.

Heat in an oven

- Heat the respirator at 70°C for 30minutes after confirming that it is not inflammable and does not have a metal clip. Respirator can be hung in the oven using a wooden clip.³⁹
- Microwave (one minute each side) can also be used.

Chemical sterilization

Vapor of hydrogen peroxide is used for sterilising used respirators.^{40,41} During 2009 influenza epidemic, NIOSH had compared 5 methods of disinfection namely microwave

Table II. Suggested sequence of donning and Doffing PPE

Donning sequence	Doffing sequence
Hand hygiene	Outer gloves
Cap	Gown/ cover all
Shoe cover	Shoe cover
Hand hygiene	Goggles / face shield
Inner glove	Mask
Gown/ cover all	Cap
Mask (Surgical mask or N95 Respirator)	Inner glove
Goggles / face shield	Hand hygiene
Outer gloves	

Table III. Practical tips to remember when donning and doffing off mask, respirator and face shields

<p>Tips to remember when donning a mask or respirator</p> <p>Ties of mask/respirator should be tied up at middle of head and neck</p> <p>Flexible band should be at the nose bridge.</p> <p>It should fit snugly to face and below chin</p> <p>Respirator should be tested every time it is worn by inhaling deeply after wearing and it should pucker in slightly.</p>
<p>Tips to remember when doffing a mask or respirator</p> <p>Front of mask/respirator is contaminated and it should never be touched</p> <p>If hands get contaminated during removal of mask/respirator, immediate hand hygiene should be performed.</p> <p>Mask should be removed by grasping bottom ties or elastics and then the ones at the top.</p> <p>Mask/ respirator should be removed without touching the front</p> <p>Disposable item should be discarded in a designated container</p>
<p>Tips to remember when doffing a face shield</p> <p>Outside of face shield is contaminated and it should never be touched.</p> <p>If hands get contaminated during removal of face shield, immediate hand hygiene should be performed.</p> <p>Face shield should be removed by lifting ear pieces or head band from the back.</p> <p>Disposable face shields should be discarded in a designated receptacle</p> <p>If reusable, face shield should be placed in designated container.</p>

oven irradiation, bleach decontamination, ultraviolet germicidal irradiation (UVGI), ethylene oxide (EtO) and vaporized hydrogen peroxide (VHP). Out of these UVGI, EtO and VHP methods were found to be promising decontamination methods.^{40,42} Cleaning the mask with soap, alcohol, bleach or isopropanol have not been successful as they caused damage to the electrostatic charge thus significantly reducing the filtration capacity.⁴² Successful regeneration is confirmed by sprinkling the mask with small

scraps of paper-if the paper sticks, the electrostatic charge has been restored.

Storing the respirator or face mask during reuse

All respirators or facemask should be stored in a container made of material that allows breathing like paper bag. Name of user should be placed on the respirator or face mask as well as storing container in order to prevent reuse by another person. Name on mask can be written on the straps of respirators. Date and time should be written on the container bag to track duration of use.⁴³

Choice of mask to be worn

With the ongoing pandemic it is now clear that if everyone wears a mask, chances of virus transmission significantly goes down. Triple layer surgical mask seems an ideal choice but it has to be disposed after getting soiled and may need frequent replacement even within a day. A washable three layered cotton cloth mask can be a more practical option for the general public. Irrespective of the type of mask worn, the person wearing it needs to know the proper way of wearing it and general precautions - hand hygiene before wearing and after removing, not to touch the mask while it is on the face of the user. Dust mask and single layer mask should not be used and surgical mask should not be washed or reused. The N95 respirator mask should not be used in the community as it is a precious commodity. Mask should be worn even inside the house if some one is having a respiratory infection. During this pandemic all HCWs should wear a respirator when sitting in the outpatient department (OPD), irrespective of nature of OPD. All patients and accompanying attendants must be made to wear a mask before entering OPD. During aerosol generating procedure N95 mask is mandatory. Doctors and nurses are at maximum risk of acquiring infection hence no compromise should be made with respect to wearing adequate PPE.⁴⁴

Issues faced by HCW while using PPE

Danger of hypoxia and carbondioxide retention after extended use of respirator

Many clinicians feel claustrophobic after wearing tight fitting respirators, but significant hypoxemia or carbon dioxide retention of clinical significance has not been proven.

Common injuries on wearing respirators

Long hours of wearing the N-95 respirators or surgical masks and goggles can compress nose-bridge and cheeks, the mask strap can compress the ears, and face shield and

Table IV. Summary of quality standard for various components of PPE.

No	Equipment	Specifications	Quality Standard
1	Coverall suit / Surgical gowns	S-spunbound, M-meltdown • SMS (GSM >70) • SMMS (GSM >70) • SMMMS (GSM >70) • Single use only • Light colors GSM alone should not be the criterion to select cloth but all these fabrics and seams should be approved by SITRA or DRDO / INMAS. Each and every gown should have stamp on individual product.	1. Meets or exceeds ISO 16603 class 3 exposure pressure 2. UCC stamp from SITRA or DRDO
2	Gloves	• Nitrile • Non-sterile • Powder free	1. EU standard directive 93/42/EEC Class I, EN455 2. EU standard directive 89/686/EEC Category III, EN 374 3. ANSI/SEA 105-2011 4. ASTM D6319-10
3	Goggles	• Accommodates prescription glasses • Adjustable band • Indirect venting to reduce fogging • Disposable	1. EU standard directive 86/686/EEC 2. EN 166/2002 3. ANSI/SEA Z87.1-2010
4	Shoe cover	Made up of the same fabric as of coverall/gown	
5	N-95 Masks	1. NIOSH - approved N95 or 2. EN 149 & FFP2 or FFP3 3. Fluid Resistance - ASTM F1862, ISO22609, or equivalent”	Made in India masks either should be certified by NIOSH (CDC web site) or approved by SIRA or DRDO
6	Face Shield	• Made of clearplastic • Adjustable band • Fog resistant (preferable) • Disposable	1. EU standard directive 86/686/EEC, EN 166/2002 2. ANSI/SEA Z87.1-2010

surgical cap can compress the forehead, which might be the main cause of pressure injuries on multiple parts of the head and face. Following are the strategies to prevent and treat them.

1. Apply hydrogel and hydrocolloid dressings beneath N95 mask as a preventive measure
2. Adequate cleansing and applying moisturizers (coconut oil, over the counter moisturizers like Vaseline lotion or moisturizing cream) over pressure areas frequently will help.
3. If injury has occurred - for small sterile blisters, where the epidermis is intact, the blister fluid will be absorbed

without intervention; for blisters with a large area or high tension, a sterile syringe is used to suction out the fluid from the bottom of the blister, topical antibiotic ointment is applied and epidermal loss should be avoided.

Precautions during aerosol-generating procedures

Aerosol-generating procedures are nebulization, HFNC, endotracheal intubation, airway suction, tracheostomy procedures and UGI endoscopy, tracheostomy, bronchoscopy and cardiopulmonary resuscitation. Non invasive ventilation is also an aerosol

Table V. Strategies to optimize PPE and Equipment during pandemic

	N95 Respirators	Facemasks	Eye Protection
Conventional Capacity	Recommended only for use by HCW for protection from airborne as well as fluid hazards.	Use based on local guidelines	Based on local guidelines
Contingency Capacity	Use beyond the manufacturer-designated shelf life for training and fit testing. Extended use and Limited re-use for tuberculosis and non Covid cases	Restriction on use of facemasks only by HCP. Do not keep facemasks in public areas for visitors extended use.	goggles and reusable face shields to be preferred over disposable ones Implement extended
Crisis Capacity	Use beyond the manufacturer - designated shelf life also for health care limited re-use COVID-19 patients. Prioritize the use of respirators based on type activity. Use of respirators other than standard N95 (should be considered equivalent in standards prevalent in other countries)	Use beyond the manufacturer-designated shelf life limited re-use. Prioritization for selected activities.	Use beyond the manufacturer - designated shelf life limited re-use Prioritization for selected activities.
No PPE available	Non-NIOSH approved masks or even home made masks.	A face shield that covers the entire face extending to the chin or below and sides of the face with no face mask.	

generating procedure.⁴⁶ Ideally these procedures should be done in rooms with negative pressure and atleast 12 air changes per hour or room with natural ventilation with airflow 160 L per second per patient.⁴⁷ PPE for HCW performing any of the procedures discussed above should include double gloves, impervious gown with long-sleeves, eye protection with goggles and face shield and a N95 respirator mask.

Behavior and compliance issues related to PPE

Since wearing the PPE for long time can be uncomfortable with difficulty in breathing, compliance may not be optimal. Compliance for wearing gloves is high while compliance for wearing eye protection was lowest in one questionnaire based survey.⁴⁸ In another survey, availability of PPE, safety culture of unit and training of HCWs were found to be determinants of improving compliance among HCWs.⁴⁹ Everyone working in a health care facility must be trained to know about situations and type of PPE necessary. They should be taught about how to properly put on, take off, adjust and wear the PPE. They should be aware of limitations of the PPE and about proper disposal of PPE. Quality standards acceptable for PPE have been shown in Table IV.

Checklist for PPE kits required for HCWs is available as guidelines issued by MOHFW, GOI and WHO (Table V).

In view of constantly changing epidemiology (especially increase in asymptomatic spread) guidelines can be modified as per resources available.

Selection of PPE in specific situations

In non COVID /suspect COVID cases (Awaiting report)

In ICU / Emergency - Above full set of PPE is essential (preferably single use)

In ICU / Emergency (limited resources) - Above PPE (Reprocessed)

Non critical areas (wards with Covid negative cases, areas without aerosol generating procedure) - head cap, reusable gown, face shield, goggles, gloves. Three ply surgical mask or N95 mask.

If suspected case turns positive - Full set of PPE is essential to the health care workers handling (Single use).

If resource limited reprocessed full set of PPE can be used.

In ICU and Emergency ward - Health care workers to be in the full PPE with all elements (based on availability) considering all cases to be as suspected COVID.

Aerosol generating areas - Fluid resistant isolation gown, face shield and goggles / Gloves / N95 mask should be used.

Points to Remember

- *Health Care Workers should wear appropriate Personal Protective Equipment - not only to protect himself from suspected COVID patient but also to prevent patient to patient infection.*
- *Mask helps in preventing the aerosol spread and N95 respirators are recommended to be used by healthcare workers when caring for COVID-19 positive or suspect.*
- *Face shields provide a barrier to a bout of suddenly-expelled aerosol of body fluids and are commonly used as an alternative to goggles.*
- *Isolation gowns including coveralls provide higher level of protection as they cover larger critical zones than traditional surgical gown.*

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Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset.

This prospective case-ascertained study in Taiwan included laboratory-confirmed cases of COVID-19 and their contacts, from January 15 to March 18, 2020. All close contacts were quarantined at home for 14 days after their last exposure to the index case. During the quarantine period, any relevant symptoms (fever, cough or other respiratory symptoms) of contacts triggered a COVID-19 test. Secondary clinical attack rate (considering symptomatic cases only) for different exposure time windows of the index cases and for different exposure settings (such as household, family and health care) were analysed. Here 100 confirmed patients were enrolled, with a median age of 44 years. Among their 2761 close contacts, there were 22 paired index-secondary cases. The overall secondary clinical attack rate was 0.7% (95% CI, 0.4%-1.0%). The attack rate was higher among the 1818 contacts whose exposure to index cases started within 5 days of symptom onset [1.0% (95% CI, 0.6%-1.6%)] compared with those who were exposed later (0 cases from 852 contacts; 95% CI, 0%-0.4%). The 299 contacts with exclusive presymptomatic exposures were also at risk (attack rate, 0.7% [95% CI, 0.2%-2.4%]). The attack rate was higher among household (4.6% [95% CI, 2.3%-9.3%]) and non household (5.3% [95% CI, 2.1%-12.8%]) family contacts than that in health care or other settings. The attack rates were higher among those aged 40 to 59 years (1.1% [95% CI, 0.6%-2.1%]) and those aged 60 years and older [0.9% (95% CI, 0.3%-2.6%)].

Conclusions: High transmissibility of COVID-19 before and immediately after symptom onset suggests that finding and isolating symptomatic patients alone may not suffice to contain the epidemic and more generalized measures may be required, such as social distancing.

Cheng HY, Jian WS, Liu DP, Ng TC, Lin HH. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Internal Medicine / Original Investigation. JAMA Intern Med. doi:10.1001/jamainternmed.2020.2020. Published online May 1, 2020.*

Reactive lymphocytes in patients with COVID-19.

The peripheral blood films of 32 patients out of 96 COVID-19 cases confirmed in Singapore by RTPCR were examined and reactive lymphocytes were found in 23 cases (72%). The most common subtype seen in this cohort displayed a distinctive abundant pale blue cytoplasm that often abuts adjacent red blood cells. This type of reactive lymphocytes were not seen in 185 SARS cases in Singapore during the 2003 outbreak and were seen in only 15.2% of 138 cases in Hong Kong. Lymphoplasmacytoid lymphocytes were present in 16 out of 23 patients. These are small mature lymphocytes with condensed chromatin and an eccentric nucleus. Both types of cells can coexist. The latter cells are also seen in dengue and B-NHL. This is an observation seen in the peripheral smears of COVID-19 patients, significance is not known at present.

Vanessa CL Chong, Kian Guan Eric Lim, Bingwen Eugene Fan, Stephrene SW Chan, Kiat H Ong, Ponnudurai Kuperan. Reactive lymphocytes in patients with COVID-19. *British Journal of Haematology* 2020;189(5) 844.

COVID - 19

MENTAL HEALTH SUPPORT FOR PATIENTS AND PROFESSIONALS

***Jayanthini V**

****Kannan Kallapiran**

Abstract : Covid-19 has created an unprecedented health and economic crisis worldwide. Issues compounding the crises are - ongoing uncertainty about duration of the pandemic, challenges for health care workers in handling patients and personal lives and the enormous economic and social costs for the public at large. All these have led to enormous impact on the mental health of the community, patients and health care professionals. This article aims to highlight the extent of the impact of COVID on mental health and the support required for patients and professionals.

Keywords: Covid induced stress, Mental health, Emotional, Stress, Medical resilience, COVID -19.

A survey conducted in India indicated that more than 80% of Indian adults surveyed online, were preoccupied with COVID-19 with higher levels of anxiety, sleep disturbances, paranoia about getting infected with COVID-19 and distress about social media.¹ Similarly in China, over 75% were worried about family members contracting COVID-19, 53.8 % had moderate to severe psychological impact, 28.8% and 16.5% had moderate and severe levels of anxiety and depression respectively.²

The reasons for the above mentioned psychological disturbances include

- Fear of contracting the virus and being quarantined.
- Anxiety about the wellbeing of family members, especially for the frontline workers or those living in severely affected areas and countries.

- Concern over economic slowdown and fear of losing livelihood including losing jobs, pay cuts, lockouts, financial stress and possible life style changes.
- Increase in domestic violence and marital discord.
- Living alone with no social support or inability to go back to their native places/not being allowed to enter their villages resulting in social stigma.
- Non-availability of liquor and other addictive drugs.
- Extreme work pressure and burnout in the case of frontline workers.

Elderly: These people have enormous health anxiety due to their chronic medical illness, fear of death or becoming a burden to the family, needing the help of paid caregivers who are unavailable due to COVID and being alone with or without the spouse as the family members live elsewhere.³ They also worry about the well-being of their stranded/locked out quarantined family members. In addition, many of them develop a fear of being neglected due to financial crunch or worry that their children may not be able to come for their last rites in case of death. Contact with family, relevant information, phone counselling, general medical and psychological needs, personal space and respect of dignity were important components in enhancing mental care in elderly during SARS epidemic.⁴

Victims of domestic violence: A recent report from WHO says that there is a 60% rise in domestic violence calls in Europe. UN WOMEN also has reported increased violence against women and children including physical, emotional or sexual abuse. Special helplines in India reavailable for women in distress and they can get free counselling and help (Ph: 1091).WHO has released a fact sheet about domestic violence and what women can do protect themselves.⁵

Home and institutionally quarantined: Those quarantined go through anxiety, depression, low mood, fear, nervousness, irritability, boredom, frustration and sleep disturbances which can lead on to acute stress reaction or exacerbation of preexisting psychiatric conditions.⁶ Providing them with necessary information to allay their fears, adequate supplies to meet their needs, options to

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occupy themselves and communication have been recommended. We need to reinforce that quarantining is helping their family to remain safe. They should be provided a free helpline or point of contact to address their concerns.

Children and adolescents: Managing children across all ages within the confines of the home without access to school, outdoor play, peer group and extracurricular activities can be very challenging. Some parents are unsure how to discuss the COVID situation to their children in a way they can understand. Centre for the study of traumatic stress (CSTS) has provided a fact sheet with different strategies to discuss this across different age groups and can be accessed in the link provided below.⁷ Their energy needs to be channelized by continuing their extracurricular classes like dance, or music online and free remote learning of activities like using www.Pschool.in. Those who cannot afford these should be told/read stories, entertained with board games or our traditional, indoor play activities. Each family needs to devise their own practical and simple ways. NalandaWay an NGO has created 'Art for Wellbeing - A Parent's Guide' which has age-specific art activities for children to manage emotions during this time. It can be accessed via <https://www.nalandaway.org/covid.php>.

The plight of children who are quarantined away from parents because either the parent tested positive and was taken away or the child is hospitalized. Those who were separated from parents in such situations were more likely to suffer from acute stress disorder, adjustment disorder and grief. Nearly 30% fulfilled criteria for post traumatic Stress disorder.⁸ As far as possible it is important not to separate children from their parents. In the unlikely eventuality, other forms of support such as relatives, known family friends, nurses and counselling psychological supports have been recommended.⁹

Those with developmental disorders like autism spectrum disorders, cannot get accustomed to a change of routine and staying within the confinement of their homes for weeks together, resulting in acute behavioral changes including assaultive and destructive behavior, in which case family should contact their mental health provider.

Healthcare professionals: They witness extreme suffering, deaths and do not have time to mourn. Hence, they can have disturbed sleep, nightmares, frustration but have to maintain an outward calmness and empathetic outlook, and some of them develop post-traumatic stress disorder (PTSD) later.¹⁰ Professionals and health care workers' problems are further enhanced because of continuous and direct exposure, extended hours of work

with little or no incentives, non-availability of expensive personal protective equipment (PPE), inability to eat/ sleep properly, not visit toilets for 8 hours or more, disheartening social ostracism, harassment and at times assaults. In addition, they are unable to complain or quit as it is politically and ethically incorrect. The workers also face burn outs and are unable to visit their families. Hence their physical, psychological wellbeing is of utmost importance during this time. While the COVID patients and those quarantined get counselling, it is important that we provide this to the frontline professionals as well.

Simple and practical interventional strategies

The professional's duty at this juncture is to cure sometimes, to relieve often and to comfort always to quote the 16th Century aphorism. Hence, empathetic listening and skilled counselling are to be practiced to address the emotional, social and spiritual needs which include the teaching of practical skills to cope with the situation which differs from person to person

1. Accept their emotional stress non judgmentally and ensure confidentiality.
2. Create an environment of acceptance and taking positive action - encourage them to ventilate their feelings and ask for help as necessary.
3. Learn to break bad news and handle grief reaction.
4. Help sort out problems by effective communication with significant others.
5. Give simple reliable information from neutral sources such as WHO, ICMR, Indian Academy of Pediatrics and reputed journals.
6. Check for overestimating the problem and avoid negative contagion - reduce the infodemic through rumors and fake news - social media distancing.
7. Maintain a routine of daily activities (adequate sleep, healthy eating, exercise, meditation, yoga, time for hobbies) and regular social contacts.
8. Ensure adequate family time for interactions, discussions and to prepare the children for life style changes as normalcy will be redefined.
9. Never hesitate to ask them to get in touch with mental health professionals, especially if they have suicidal ideation, worsening of symptoms inspite of adequate intervention and when they are aggressive, sleepless, experience severe health anxiety or indulge in self injurious behavior.

10. Provide contact details for free online counselling offered by NGOs, Indian Psychiatric Society and other helplines like Therapists Collective.

Those who are interested in practical strategies to enhance their resilience can access the 3 session video course on resilience training for health workers by Massachusetts General Hospital by clicking on this link <https://www.resilienceandprevention.com/healthcare-providers>.

Conclusion

COVID-19 like other pandemics causes enormous strain on the mental health of people in the community, patients and health workers. It is important to organise adequate support to mitigate the severity of its impact. Early identification of worsening mental health and prompt response to address the same can prevent things from worsening. Let's remember not to be consumed by negative contagion, provide accurate information where required and maintain focus on what is within our influence.

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CLIPPINGS

Aerosol emission and super emission during human speech increase with voice loudness.

It is well known that coughing and sneezing are dramatic expiratory events that yield both easily visible droplets and invisible aerosols. Nonetheless, it has long been known that normal speech also yields large quantities of particles that are too small to see by eye, but are large enough to carry a variety of communicable respiratory pathogens. Here, the authors show that the rate of particle emission during normal human speech is positively correlated with the loudness (amplitude) of vocalization, ranging from approximately 1 to 50 particles per second (0.06 to 3 particles per cm³) for low to high amplitudes, regardless of the language spoken (English, Spanish, Mandarin or Arabic). Furthermore, a small fraction of individuals behave as "speech super emitters," consistently releasing an order of magnitude more particles than their peers. Our data demonstrate that the phenomenon of speech super emission cannot be fully explained either by the phonic structures or the amplitude of the speech. These results suggest that other unknown physiological factors, varying dramatically among individuals, could affect the probability of respiratory infectious disease transmission and also help explain the existence of super spreaders who are disproportionately responsible for outbreaks of airborne infectious disease.

Asadi S, Wexler AS, Cappa CD, Barreda S, Bouvier NM, Ristenpart WD. Aerosol emission and super emission during human speech increase with voice loudness. Sci Rep 9, 2348 (2019). <https://doi.org/10.1038/s41598-019-38808-z>. Accessed on 11th June, 2020.

COVID - 19

SOCIAL EFFECTS OF COVID-19 PANDEMIC ON CHILDREN IN INDIA

***Jeesson C Unni**

Abstract: *India as a country is completing more than two months of a nation wide lockdown, of course with different intensity. Impact of COVID-19 on child population is manifold. In addition to the disease related health issues, it has caused damage in various sectors of life - economic, social, cultural and behavioural aspects. Children have equally faced the impact caused by the corona virus and subsequent lock down. COVID-19 has put both lives and livelihood at stake. Though children are affected considerably less than the adults both in number and severity, they are very vulnerable to the non-health related impacts of this pandemic. From delay or missing of routine immunizations to more graver issues like child abuse and food insecurity, children from vulnerable sections of the society face a hoard of problems. This article deals with the social impact of the pandemic in children.*

Keywords: *COVID-19, Social impacts, Children.*

Effects of defaulting on routine immunizations

The Ebola epidemic has some lessons for us regarding the effect on routine immunization services and its impact. Immunization coverage decreased more than 25 % during the epidemic of Ebola in West Africa during 2016 as health system was disrupted during the measures to contain the epidemic.¹ According to the UNICEF report, while about 2000 people died of Ebola outbreak in the Democratic Republic of Congo, double of that number died of measles in 2019 as immunization services were affected.² The Ministry of home affairs, Government of India guidelines dated April 15, 2020 stated that essential medical services had to be maintained during the lockdown and it included immunization as an essential medical service.³ There is a definite reduction in the delivery of the universal

immunization program in India, even though the clear data is not yet available

COVID-19 and children with special needs in India

The department of empowerment of persons with disability (under the Ministry of Social Justice and Welfare) has recently released comprehensive disability inclusive guidelines for protection and safety of persons with disabilities during COVID-19.⁴ There is a lack of support mentioned for educational services - distance, open or home based. The Ministry of Human Resources Development (MHRD), through its department of school literacy and education is proactive in ensuring access to education through various online platforms and initiatives like e-Pathshala, National Repository of Open Educational Resources (NROER), Digital Infrastructure for Knowledge Sharing (DIKSHA), SWAYAM platforms (including DTH channels), etc. to enable online learning for children. It does not mention the number of special children those would benefit or how effective these programmes would be in catering to their precise needs.⁵ A pandemic which mandates social distancing and quarantine has increased complexities for parents of children with disabilities. These children, used to structured schedule and learning environments have to cope up with the change.

Effect of COVID-19 on routine non-COVID emergencies

In the anxiety and fear of pandemics, many parents are reluctant to bring their children to hospital. Common emergencies like typhoid fever, dengue, status epilepticus, surgical emergencies like torsion testis get delayed treatment. Considering the risk of transmission of infection, many hospitalized children underwent RT PCR for COVID. Surgeons are also conscious about the fact that intussusception and acute abdomen are one of the presentation of COVID in children.

Effects of the pandemic on child and adolescent psyche

Children are being exposed to an information overload and often horrifying news of the effects of the pandemic.⁶ They are witnessing high levels of stress and anxiety among

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the adults around them. Experiences of the new routine of staying cooped up at home; unable to frequent places they have enjoyed, meet friends, play and engage in activities that they enjoyed, have created a sense of insecurity in children even as young as 2 years of age.⁷ Therefore, listening to what children believe about COVID-19 is essential; providing children with an accurate explanation that is meaningful to them will ensure that they do not feel unnecessarily frightened, overanxious or guilty.

Families of children with child sexual abuse

A recent study by the Aarambh India Initiative of NGO, Prerana and ADM Capital Foundation, has found that the lockdown due to the novel coronavirus outbreak has greatly added to the woes of families of child sexual abuse survivors in Mumbai.⁸ The NGO interviewed 127 families with whom it is presently associated, most of them being from the underprivileged sections of society. The researchers feel that for many families, the challenges of dealing with the aftermath of child sexual abuse have been compounded by a sudden loss of income and a lack of social support.

A pandemic within a pandemic - the silent pandemic of child sexual abuse is a reality. Vikas Puthran of Childline India Foundation (CIF) reported that in 10 days of the lockdown - between 20 and 31 March, there was a 50% increase in the number calls to 3 lakh as compared to 2 lakh.⁹ It was noted that since a significant number of abusers, especially in cases of incest, the sexual involvement with children is situational and occurs as a result of life stresses - lockdown was perfect environment for an increase in sexual abuse. Additionally, self-quarantining at home means being in continuous and close proximity with one's abuser; which can be extremely emotionally taxing.¹⁰

Street children in India

Tens of thousands are calling help lines daily while thousands are going to bed hungry as the country shuts down to battle the pandemic. India has a large number of children who work as rag-pickers in cities or sell balloons, pens and other knick-knacks at traffic lights - these millions live in cities - on streets, under flyovers, or in narrow lanes and bylanes. During the lockdown everyone has been told to stay home. But what about the street children? Where do they go? According to one estimate, Delhi has more than 70,000 street children - may be much higher. Taking note of the plight of street children during the coronavirus lockdown, the National Commission for Protection of Child Rights (NCPCR) has suggested

measures to formulate a database of these children, so as to link them to various government social schemes and prevent them from coming out on the streets again.¹¹

Children of migrant labourers

The exodus of migrants from our cities has raised serious concerns. Children of migrant families are an invisible vulnerable population and may include the following groups. The first group consists of children left behind in the villages by parents who undertake employment elsewhere. They are dependent on remittances sent back home. The reduction or elimination of parent's wages due to the lockdown will have immediate effects on food intake and health outcomes of these children. The second group are those children who migrate with their parents who are often engaged in the construction sector, brick kilns and agricultural sectors. A study on informal worksites in seven Indian cities, revealed that 80% of the accompanying migrant children did not have access to education, 30% never enrolled in schools and 90% did not access ICDS services.¹² Almost all children were found to be living in hazardous and unhygienic conditions. The job losses encountered by the migrant workers in the current pandemic will only worsen the plight of these children. Thousands of these families left to their native places with infants and toddlers in tow, either by foot or transport arranged by state governments, exposing these children to unforeseen problems of hunger and illnesses. The third group is children who migrate for employment. Child rights activists have noted a range of issues ranging from loss of wages and physical abuse. Relief and transit camps in state borders as well as quarantine facilities should arrange safe and child friendly shelters that provide nutritious food, water and sanitation for families.

Telemedicine during the COVID-19 pandemic

There is an immense role for tele-consultation in out-patient, in-patient and ICU care.¹³ The Ministry of Health and Family Welfare (MoHFW), in collaboration with NITI Aayog and Board of Governors (BoG), Medical Council of India (MCI) have approved guidelines involving all channels of communication with the patient that leverage information technology platforms, including voice, audio, text and digital data exchange and most importantly allowed doctors to prescribe medicines.¹⁴ The government has also listed out certain drugs that cannot be prescribed through telemedicine. This includes drugs listed under Schedule X of Drugs and Cosmetics Act and Rules and any Narcotics and psychotropic substance listed in the Narcotics Drugs and Psychotropic Substances Act of 1985.

Conclusion

Some of the issues that India is facing are highlighted. Many more will surface as we live through this pandemic. We need to be better prepared for a grim future ahead - health budgets, health infrastructure, improving telemedicine facility, disaster management drills and drastic change in lifestyle and travel behavior need to be inculcated.

Points to Remember

- *The social impact of the corona pandemic on children and young people in particular may be significant.*
- *Defaulting on routine immunization due to lockdown can lead to outbreaks of vaccine preventable diseases.*
- *Government has introduced several e - platforms for making education accessible to children, but these may not be uniformly available to children with special needs.*
- *Access to management of chronic and acute medical/ surgical non COVID conditions is also hampered.*
- *Psychological impact of the pandemic on child and adolescent psyche cannot be undermined.*
- *Significant increase in child abuse has been reported.*
- *Street children and children of migrant labourers are exposed to significant challenges in food security and health.*
- *Telemedicine should be more efficiently utilized during pandemics.*

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COVID - 19

PREPAREDNESS FOR REOPENING AND CONDUCT OF SCHOOLS DURING AND POST COVID-19 PERIOD***Narmada S******Somasundaram A**

Abstract: *COVID-19 has thrown the educational system of India into turmoil. India with its vast and diverse educational scenario has to prepare itself for reopening and conducting schools, taking into account the disparity in the economic strata among its institutions. Schools serve as nodal centres for distribution of nutritious food, for physical fitness and also take care of psychosocial wellbeing of the children. Hence, closure of schools causes multidimensional effects. Lack of space, resource constraints, disparity in accessing technological advancements are huge challenges in implementing uniform policies while reopening. The introduction of new online and offline platforms of education by the efforts of government has paved the way for a new learning methodology. This combined with additional efforts to take care of the nutritional and physical needs of the children will usher in a different era in Indian educational system. This article discusses policies that can be implemented by schools with the support and willingness of all stake holders from the students to the society at large. The methods and need to implement principles of social distancing, respiratory hygiene and etiquette, minimising large gatherings, restructuring of seating arrangements, self-discipline in reporting and treatment of illnesses are discussed.*

Keywords: *Educational system, India, COVID-19 impact, Reopening schools.*

Nobody would have expected a scenario where a tiny virus would shake the entire world. As of 27th April 2020, approximately 1.725 billion learners are affected due to

school closure worldwide. One hundred and eighty six countries have implemented nationwide closures with another eight countries implementing local closures.¹ The Indian system of education was left perplexed when the much awaited public exams and other competitive examinations had to be postponed or cancelled. Given the uncertain trajectory of this pandemic, there is confusion among students and school authorities of how the upcoming academic year will be. In addition to this, it is difficult to predict the impact on children of the extended absence from regular school. India with its 15 lakh schools and 50,000 higher educational institutions is home to one of the most diverse and largest educational system in the world.^{2,3} The system here is unique, in that we have government schools with minimal infrastructure and international schools with the best possible infrastructure, existing under the same boards. The following article focuses on the issues faced by the schools in India and the measures to be implemented during and post COVID period.

Impact of COVID-19 on schools - the Indian scenario

India ordered closure of the schools and colleges on 16th March 2020. This is a crucial time for our education sector as board examinations, entrance to various universities, competitive examinations were all set to happen during this period. The new academic year also starts by June. Around 32 crore young learners in India have been impacted and the most severe among them, are approximately 13 crore students in classes 9 to 12. The resultant impact on the students are :

1. Interrupted learning
2. Poor nutrition - mid day noon meal scheme providing significant proteins and calories is unavailable
3. Confusion and stress for parents and teachers
4. Challenges of e-learning and home schooling
5. Gaps in child care and high economic burden for parents
6. Rising exposure to child pornography, sexual exploitation and domestic violence
7. Social isolation⁴

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Unique challenges of Indian educational system

Indian education system has 70% of students in government institutions with minimal access to online system of education.⁵ The considerable gap in the infrastructure between government and private schools and the domestic environments of students is a huge challenge.

The main issue is the space constraint in schools. The average work area a student gets in India is only 2 feet. With an average student's shoulder width of 2 feet, even in the most elite of schools, children are made to sit very close to each other. Some classes cater to around 150 students which means they are in close proximity to each other. Almost 45% of schools lack playgrounds.⁶

With schools shut down, remote learning is the only way available. However, the major challenge in India is the access to electricity and internet connections. A nationwide survey of villages done in 2017-18 showed that though 99.9% of homes had access to power connection, 53% of the houses did not have electricity for upto 12 hours in a day. Only 24% of Indians had access to smart phones and hardly 11% of households had access to any form of smart devices like net books, palmtops, desktops or tablets. Besides, there are interstate variations in the availability of the electricity and internet.⁷

The other issue is the nutritional needs of the children. There is now a logistic challenge in providing food for nearly 12 crore children who are dependent on the midday meal, which is probably the only nutritious meal they get. On the other hand, there is a growing incidence of obesity from 3.6 to 11.7% among affluent school students.^{8,9} We are at the crossroads where the double challenge of obesity and undernutrition have to be addressed.

In the following sections, we would discuss the measures to be adopted by various stakeholders, keeping in mind the unique challenges of the Indian education system.

Measures to be adopted by the school administration

When schools are fully or partially open, COVID-19 prevention and control strategies should be maintained. The recommended actions and requirements outlined in the following section are simple and can be adopted in all schools irrespective of the economic discrepancies.¹⁰

1. Hygiene and environmental cleaning to limit exposure
2. Physical distancing at school

3. Regular screening and management of symptomatic students, teachers and other school staff
4. Communication with parents and students
5. Additional school-related measures
6. Regulations to be followed in Residential schools¹¹

1. Hygiene and environmental cleaning to limit exposure

a) Educate everyone in the school about COVID-19 with emphasis on its prevention; this includes appropriate and frequent hand hygiene, respiratory hygiene, mask use, symptoms of COVID-19 and what to do if one gets sick. Non-contact greetings should also be advised. Weekly updates must be provided as the pandemic evolves.

b) Create a schedule for frequent hand hygiene, especially for young children, and provide sufficient alcohol-based rub or soap and clean water at school entrances and throughout the school. Hand washing strategies include washing with soap and water for at least 20 seconds, especially after using the toilet, before eating, after blowing their nose, coughing or sneezing. Where feasible, using an alcohol-based hand sanitizer that contains at least 60% alcohol can be encouraged where water is scarce.¹²

c) Schedule regular cleaning of the school environment, including toilets, with water and soap/detergent and disinfectant. Clean and disinfect frequently touched surfaces such as door handles, desks, toys, supplies, light switches, doorframes, play equipment, teaching aids used by children and covers of books.

d) Limiting the timing of exposure or direct physical contact is mandatory like in physical education classes, sports or other physical activities and play in playgrounds, wet areas and changing rooms. Can avoid contact sports/swimming classes and encourage alternate methods of individual sport activities.

e) Increase frequency of cleaning in gym, sports facilities and in changing rooms, provide hand hygiene stations at entrances and exits, establish one-way circulation of students through the facilities and limit the number of persons allowed in the locker room at one time.

f) Put in place respiratory and hand hygiene and physical distancing measures in transportation such as school buses and tips for students on safe commute to and from school, including those using public transport. Allow only 1 child per seat and at least 1 metre apart in school buses, if possible. This may lead to a need to increase the number of school buses per school. If possible, windows of the bus should be kept open.

g) Develop a school policy on wearing a mask or a face covering in line with national or local guidance. If a child or school staff is sick, she/he should not come to school. Provide sufficient medical masks for those who need it, such as school nurses and children with symptoms.

2. Physical distancing at school: Measures given here also addresses the issues of spacing in schools especially staggering the opening hours and modification of timetable.

a) Maintain a distance of at least 1 metre between everyone present at school.

b) Increase desk spacing (at least 1 metre between desks), putting dividers in between desks, altering the arrangements like a circular class room, staggering recesses/breaks and lunch breaks (if difficult, an alternative is to have lunch at the desk).

c) Modify the timetable, with some students and teachers attending in the morning session and others in the afternoon session. Another alternative is to have half the students attending on 3 days of a week and the other half on the other 3 days {odd-even plan}.¹³

d) Consider increasing the number of teachers, if possible, to allow for fewer students per classroom (if space is available).

e) Advise against crowding during school pick-up or day care and if possible, avoid pick up by older family or community members (e.g. grandparents) and stagger arrival and/or dismissal times.

f) Move lessons outdoors or ventilate rooms as much as possible (and try to avoid use of air conditioners, especially central type).

g) Create awareness to ensure the students do not gather and socialize when leaving the school and in their free time.

h) Cancel field trips, assemblies and other large gatherings.

i) Limit nonessential visitors and reduce congestion in the office.

j) Limit bringing in students from other schools for special programs (e.g., music, robotics, academic clubs)

k) Parent teacher meetings can be restructured via phone rather than face-to-face, - enabling easier communication both ways.

l) Discourage staff, students and their families from gathering or socializing anywhere at places like a friend's

house, a favourite restaurant, a birthday party or the local shopping mall.¹⁴

3. Screening and management of sick students, teachers and other school staff

a) Enforce the policy of “staying at home if unwell” for students, teachers or school staff with symptoms.

b) Create a checklist for parents/students /staff to decide whether students /staff can go to school taking into consideration the local epidemiology of COVID-19. The checklist could include:

- underlying medical conditions and vulnerabilities, to protect the student/staff
- recent illness or symptoms suggestive of COVID-19, to prevent spread to others
- special circumstances in the home environment, to tailor support as needed
- special considerations regarding school transport as needed.

c) Consider daily screening for body temperature, and history of fever or ‘feeling feverish’ in the previous 24 hours, on entry into the building for all staff, students and visitors to identify persons who are sick. Ensure that enough personnel are available for this screening.

d) Ensure students who have been in contact with a COVID-19 case stay at home for 14 days. The school officials should notify public health authorities in case of a positive COVID-19 case.

e) Establish procedures for students or staff who have symptoms of COVID-19 or are feeling unwell in any way to be sent home or isolated from others.

4. Communication with parents and students

a) Inform parents about the measures the school is putting in place and ask for cooperation to report any cases of COVID-19 that occur in the household. If someone in the household is suspected to have COVID-19, keep the child at home and inform the school.

b) Explain to the students the reason for school-related measures, including discussing the scientific considerations and highlighting the help they can get through schools (e.g. psychosocial support).

5. Additional school-related measures

Ensure that during school entry, all age appropriate vaccinations especially those against vaccine preventable diseases are completed.

6. Regulations to be followed in residential schools

Most of the policies discussed above will also be applicable for boarding schools. The following are some of the policies specific for Residential school

- a. It is imperative that the students are screened on arrival to the hostel
- b. There is a need to have an inhouse nurse and if students are more to have an inhouse doctor on call
- c. Students to be encouraged to report even if there are minor health related complaints
- d. Seperate facilities or local guest houses to isolate children or staffs who turn out to be positive with minor symptoms need to be prepared in advance.
- e. Cleaning of the exposed areas according to government protocols should be followed - Close and Clean response.¹⁵

Measures to be adopted by the students

1. Learning the steps for hand washing

It is mandatory that every student learns the techniques of hand washing which should be done on school entry, before and after food and snacks and after using the rest rooms. Remember not to touch the face.

2. Maintaining social distance in the school

They need to maintain their designated places with 1 metre distance between friends, avoid touching each other during free time and avoid sharing cups, eating utensils, food or water bottles.

3. Training the children to be leaders in keeping themselves, their school, family and community healthy

They need to learn about preventing disease spread and model good practices such as sneezing and coughing into elbows.

4. Learn to accept other children who return after recovering from illness

Children should be taught to accept others and not tease anyone since everybody is prone to the infection.

5. Should learn to immediately contact the caregiver if they feel slightly sick

Children should be encouraged to seek the help of the caregiver if they feel sick and should be supported psychologically so that they are not frightened by their sickness.

6. Age appropriate technique to be adopted - For e.g. The kindergarten schools can be close. If open, pre-schoolers can be taught all these etiquettes with simple rhymes and manoeuvres like flapping their wings or extending their arms to instill the concept of safe distance.

7. E- learning - Children should be encouraged to adapt to this new method of learning, to have their doubts clarified and supported.¹²

Role of parents and care givers

Parents and caregivers have seldom spent so much time with children as during this pandemic, therefore this is a unique opportunity to mould their children's behaviour. With no other diversions or people to distract them and with so much uncertainties around, parents' presence and their psychological support is essential to all children from pre-schoolers to adolescents.

1. It is of utmost importance for parents to update themselves on the latest facts from reliable sources about COVID-19. They should take care not to share inaccurate information or videos regarding the negative aspects of illness.

2. They need to recognise symptoms of COVID-19 like fever, cough, sore throat or shortness of breath and seek immediate medical attention. They need to notify the school and also reassure their child in simple language. Unnecessary panic by the parents will further frighten the children.

3. Encourage the children to attend school when they are healthy.

4. It is their responsibility to reinforce basics of hand washing, cough etiquette and social distancing.¹²

5. Parents should be supportive to their children in their efforts to attend classes online. Make provisions at home to install gadgets and monitor their use by their children. Many NGOs are ready to help with distance learning. Pooling of resources in the community to help less fortunate students in the area can also be initiated by parents.

6. It is the duty of the parents to ensure a child friendly and calm environment to facilitate learning at home as school timings may change allowing the children to do their work predominantly through e-learning.

7. Domestic violence to be strictly condemned as it is the right of every child to have a safe environment at school or home.

Future of education

This pandemic will change the course of education as we know it. We need to teach the guardians of tomorrow, resilience, adaptability, communication, empathy, creativity, emotional intelligence and other life skills for the future. Theory based learning should give way to experiential learning, taking greater recourse to technology. Schools need to keep these challenges in mind while designing the curriculum. Government schools have commenced smart classes and Montessori system of learning and in due course will learn to keep pace with these changes.¹⁶

New systems of learning

We need content and delivery systems that harness and utilize technology to its fullest. Looking at these challenges of colleges and schools, various initiatives have come up from the Ministry of Human Resources, Department of Technical Education, National council of educational research and training (NCERT) and NGOs.

Some of the new initiatives are Swayam - online courses for teachers, UG/PG teachers for non technology courses, e-modules on various subjects. National digital library, google classroom and e-Yantra are other resources. Swayam portal integrates NCERT textbooks, engineering and non-engineering courses and e-books for students. It is a viable alternative and easy learning to grasp the course. The portal was set up by Government of India nearly two and a half years ago and it definitely endorses the fact that e-learning may not be a distant dream.¹⁷

Government has created National Knowledge Network, National Project on Technology Enhanced Learning (NPTEL), National Mission on Education Through Information and Communication Technology (NMEICT). These connect easily with institutions and provide the high speed band network for education institutes.

Efforts need to be made by all of us to make sure PC/ Desktop/ Mobile for end delivery are available to every student irrespective of the strata of society. Giving away laptops to all students studying in 11th standard and above in Tamilnadu is an example which shows us that this is feasible.² Future of education is going to be global teachers, global university, degrees obtainable from reputed universities offering interesting distant learning content and a global outlook. Faculty will also need to stand up to this challenge of integrating technology in their teaching. Accreditation criteria need reconsideration.

New laws to maintain online privacy of children

While online platforms are being developed, commitment to protect the privacy of children should be a top priority and all stake holders especially vendors need to be covered by the law.¹¹ Children's Online Privacy Protection Act (COPPA) adopted now in USA may have to be integrated in India too.

New system of arrangements of classes

With greater space constraint, effective and efficient ways of conducting classes have to be devised. We need to do away with traditional bench system of seating and use alternative type of seating like a circle, or running school in shift systems.

Future modalities to maintain physical fitness

Opening up of other avenues for physical fitness becomes essential. Starting of online yoga instructions and short physical education videos for students of all ages may be a viable alternative. The portal needs to integrate social/ club virtual hangouts and online school counselling.¹¹

Adopting new ways to deliver and maintain nutrition of children

Unfortunately India would be one of the 88 countries to miss its nutrition related target of reducing stunting in children. India is identified as among the three worst countries, along with Nigeria and Indonesia, for wide, within-country disparities on stunting, where the levels varied four-fold across communities. It is imperative that alternate system to maintain nutrition is facilitated even if children stay at home due to new modes of learning. This can include delivery of foods to their homes using public distribution system, making available nutritious powders for collection at the school and provision of cash or vouchers.^{18,19}

Conclusion

In conclusion, a joint effort by all stake holders from the management of schools, parents, students, government and NGOs have a great part in preparing the schools to handle the post COVID situation. Future of our younger generation will be protected by our willingness to bring in changes in the system that not only raises them to be responsible individuals, but also fosters a responsible community that appreciates and protects nature and nurtures posterity.

Points to Remember

- *COVID-19 has disrupted India's educational system which is vast and varied with wide disparity in resources amongst the schools in the public and private sector.*
- *Schools are not only centres of education in India but take care of nutritional and physical needs of children through various schemes.*
- *Schools need to implement uniform policy to maintain social distancing, respiratory etiquette as well as usher in new modalities of education for the coming years.*
- *The future of the education system will involve more of e-learning platforms with policies to maintain the privacy of children and newer modalities to take care of nutrition and fitness with significant changes in infrastructure.*

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COVID - 19

GUIDELINES FOR HANDLING DEAD BODY OF A COVID-19 PATIENT

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Abstract: *As the number of positive cases for the novel Coronavirus continues to increase, so do the deaths associated with it. There exists a theoretical risk of infection during handling of the dead bodies and standard infection control practices should be followed when handling such bodies. The government has allowed both the burial and cremation as per the faith. However there is a standard procedure that all health workers and family members need to adhere to. This article highlights some of the guidelines recommended for managing dead bodies of COVID-19 patients.*

Keywords: *Handling dead body, COVID-19, Children.*

There is likely to be a continuing risk of infection from the body fluids and tissues of patients who have died of severe acute respiratory syndrome-Corona virus2 (SARS-CoV-2) infection. After death, their bodies should be treated with sensitivity, dignity and respect, at the same time taking due precautions to protect persons in proximity from infection. Unzipping the body bag by mortuary staff using standard precautions may be allowed for the relatives to see the deceased for one last time.

In actuality, there is little residual hazard of transmission of SARS-CoV-2 from the deceased apart from potential droplet generation from artificial air movement during the initial care of the deceased and post-mortem examination where power tools are used, posing a risk for aerosol generation.

It is estimated that viable virus could be present for up to 48 to 72 hours on environmental surfaces in 'room air' conditioners. In dead bodies, particularly those retained at refrigeration conditions, infectious virus may persist for

Box 1. Handling dead bodies of COVID-19 Standard precautions

- i. Hand hygiene.
- ii. Use of personal protective equipment (e.g. water resistant apron, gloves, masks, eyewear, shoe covers).
- iii. Safe handling of sharps.
- iv. Disinfect the instruments and devices used on the patient, after disposing the dead body.
- v. Disinfect linen, clean and disinfect environmental surfaces

longer. Due to the congealing of respiratory secretions and rapid destruction of the virus when not sustained by live tissues, residual hazard from body fluid spillage will not present a risk. However WHO recommends transporting a body with acute respiratory infection by applying a face mask and sealing in an impermeable body bag before being removed from the isolation area to avoid leakage of body fluid.

Standard precautions are to be followed by health care workers while handling dead bodies of COVID-19 (Box 1).

Removal of the body from the isolation room or area

- The health worker attending to the dead body should perform hand hygiene, ensure proper use of PPE (water resistant apron, goggles, N95 mask, gloves).
- All tubes, drains and catheters on the dead body should be removed. After use, the disposable items such as gloves and protective clothing should be disposed of in a plastic bag.
- Any puncture holes or wounds (resulting from removal of catheter, drains, tubes, or otherwise) should be disinfected with 1% hypochlorite and dressed with impermeable material.
- Caution recommended while handling sharps such as intravenous catheters and other sharp devices. They should be disposed into a sharps container.
- Plug oral, nasal orifices of the dead body to prevent leakage of body fluids.

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- If the family of the patient wishes to view the body at the time of removal from the isolation room or area, they may be allowed to do so following the standard precautions.
- Place the dead body in leak-proof plastic body bag. The exterior of the body bag can be decontaminated with 1% hypochlorite. The body bag can be wrapped with a mortuary sheet or sheet provided by the family members.
- The body may be taken to mortuary.
- All used/ soiled linen should be handled with standard precautions, put in a bio-hazard bag and the outer surface of the bag disinfected with hypochlorite solution.
- Used equipment should be autoclaved or decontaminated with disinfectant solutions in accordance with established infection prevention control practices.
- All medical waste must be handled and disposed of in accordance with bio-medical waste management rules.
- The health care worker who handled the body should remove personal protective equipment and perform hand hygiene.
- Provide counselling to the family members and respect their sentiments.

Autopsies on COVID-19 dead bodies

Autopsies should be avoided. If autopsy is to be performed for special reasons, the following infection control practices should be adopted:

- The team should be ther heavy duty blades with blunt points to be used to reduce needle stick injuries.
- Only one body cavity at a time should be dissected
- Unfixed organs must be held firm on the table and sliced with a sponge – care should be taken to protect the hand
- Autopsies should be performed in an adequately ventilated room, i.e. natural ventilation with at least 160 L/s/patient air flow or negative pressure rooms with at least 12 air changes per hour.
- An oscillator saw with suction extraction of the bone aerosol into a removable chamber should be used for sawing skull, otherwise a hand saw with a chain-mail glove may be used
- Needles should not be re-sheathed after fluid sampling - needles and syringes should be placed in a sharps bucket.

- Reduce aerosol generation during autopsy using appropriate techniques especially while handling lung tissue.
- Autopsy table to be disinfected as per standard protocol.

Transportation

- The body, secured in a body bag, exterior of which has been decontaminated, poses no additional risk to the staff transporting the dead body.
- The personnel handling the body may follow standard precautions (surgical mask, gloves).
- The vehicle, after the transfer of the body to cremation/ burial staff, should be decontaminated with 1% sodium hypochlorite.

Disinfection of isolation room / Mortuary

All surfaces of the isolation area (floors, bed, railings, side tables, IV stand, etc.,) should be wiped with 1% sodium hypochlorite solution and allowed to air dry allowing a contact time of 30 minutes.

Mortuary staff handling the dead body of COVID-19 patients must observe standard precautions like storing them in cold chambers maintained at approximately 4°C, disinfecting environmental surfaces, instruments and transport trolleys with 1% hypochlorite solution and cleaning the chamber door, handles and floor with 1% sodium hypochlorite solution after removing the body.

Embalming: Embalming of the dead body should not be allowed.

Burial

People who have died from COVID-19 may be buried or cremated but always conform to national and local requirements that may dictate the handling and disposal of the remains. Family and friends may view the body after it has been prepared for burial, in accordance with customs. They should not touch or kiss the body and should wash hands thoroughly with soap and water after the viewing. Mourners should not take part in any rituals or practices that bring them into close contact with the body of the deceased.

Those tasked with placing the body in the grave, on the funeral pyre etc., should wear gloves and wash hands with soap and water after removal of the gloves once the process is complete.

Funeral rites

Religious rituals such as reading from religious scripts, sprinkling holy water and any other last rites that do not require touching of the body can be allowed. Large gathering at the crematorium/ burial ground should be avoided. A maximum of 20 people with masks may be allowed to attend the funeral rites (may vary according to local guidelines). The ash does not pose any risk and can be collected to perform the last rites.

Conclusion

There remains a theoretical risk of infection from spread of virus from the body of the deceased. Nevertheless, the usual precautions and principles of standard infection control apply for bodies that are suspected or confirmed to be infected with coronavirus. Precautions should be taken at every level, starting from health care workers, mortuary staff, body handlers and mourners alike.

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CLIPPINGS

COVID-19 plasma therapy safe, without adverse side effects: Study done in Houston, USA in March 2020.

The clinical administration of the blood component plasma from recovered COVID-19 patients to those severely affected by the disease could be a safe option without adverse side effects, according to a study which may lead to better treatment protocols against novel coronavirus infection.

On March 28, researchers from the Houston Methodist Hospital in the US, began clinical trials to transfuse plasma from recovered COVID-19 patients into critically ill patients, they noted in a statement. In the study, published in The American Journal of Pathology, the scientists described the clinical outcomes of the convalescent plasma transfusion trial, showing 19 out of 25 patients improving with the treatment and 11 discharged from the hospital.

However, the study noted that a randomised clinical trial, with a large control group, is needed to validate the findings. According to the researchers, this is the largest cohort worldwide assessed for outcomes pertaining to convalescent plasma transfusion for COVID-19 and is the first peer-reviewed publication on convalescent plasma use in the US.

While physician scientists around the world scrambled to test new drugs and treatments against the COVID-19 virus, convalescent serum therapy has emerged as potentially one of the most promising strategies. The scientists noted that the century-old therapeutic approach dates back to at least as early as 1918 to fight the Spanish Flu.

Convalescent plasma therapy was used with some success during the 2003 SARS pandemic, the 2009 influenza H1N1 pandemic and the 2015 Ebola outbreak in Africa. According to the study, the observed complications were consistent with findings reported for COVID-19 disease progression, and did not result from the plasma transfusions. The researchers said the study's findings were consistent with several other small case studies of convalescent plasma use for severe COVID-19 that have been recently reported. The limitations of the research as a small case series and no control group was included. It is not clear if the 25 patients given convalescent plasma would have improved without the treatment, as all patients were treated with multiple other medications, including antiviral and anti-inflammatory agents.

Salazara E, Perezza KK, Ashraf M, Chena J, Castilloa B, Christensena PA, et al. Treatment of COVID-19 patients with convalescent plasma. Am J Pathol. Epub ahead of print. DOI:<https://doi.org/10.1016/j.ajpath.2020.05.014>.

GENERAL ARTICLE

TELEMEDICINE - GUIDANCE FOR PEDIATRIC PRACTICE

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Abstract: *Advancement in technology is a boon in disguise for mankind especially during this COVID-19 pandemic. Telemedicine provides a platform whereby patients are able to receive treatment even without an in-person hospital visit. With proper care, consent and guidelines, telemedicine paves the way for a better tomorrow. At this time, it also serves to prevent spread of infection by minimizing hospital visits which is of due importance in the vulnerable pediatric group. This article is presented as a guidance for the practicing pediatrician embarking on teleconsultation for the first time - issues to be aware of while prescribing and the legal aspects.*

Keywords: *Telemedicine, Pediatrics, Technological infrastructure, Optimum healthcare.*

Epidemics and pandemics are challenges in providing optimum healthcare for the needy. Access to health care delivery may be hampered in such a scenario due to distance, lack of sufficient manpower, need for social distancing and time. Telemedicine is a useful tool in such situations to provide specialized care, in responding to emergencies and providing access to pediatric care in remote and underserved populations.¹ Exposure to microbes during epidemics can be minimized by telemedicine. With advancement in technological infrastructure on a national scale it is possible to maintain the health of children around the country without unnecessary exposure to the infection.

Telemedicine may be defined as “The delivery of health care services using telecommunication technologies for exchange of information for diagnosis, treatment and

prevention of disease and injuries.” It can also be used for research, evaluation and continuing medical education for improving the health of individuals and their community.² In March 2020, Medical Council of India came out with telemedicine practice guidelines, in partnership with National Institution for Transforming India Commission (NITI Ayog).³ Though telemedicine has been in use for the last 30 years its increasing use in the last 3-4 years especially now during the COVID-19 pandemic has the potential to transform pediatric practice. Any pediatrician is entitled to provide telemedicine consultation to patients in any part of India upholding professional and ethical norms and standards. They would be required to undergo a mandatory online course by the Medical Council of India (within 3 years of start of telemedicine) which is in the pipeline.

Implementation

There are more than 50 platforms which provide telemedicine facility. One must have very good internet connectivity and a computer/ laptop/ smart phone with preferably high resolution camera. Telemedicine has applications in Government, NGO and Private sector. For pediatricians in the private sector, a payment gateway can be integrated into the platform for online payments.

Irrespective of the tool of communication used, the core principles of telemedicine is the same.⁴ Telemedicine applications can be classified in to 4 basic types.

1. Video: This gives the nearest experience to an inpatient consultation and real time interaction. It is also the most preferred tool of communication in telemedicine and is expected to replace other tools in the days to come. Patient can be seen and certain signs may be identified. Visual cues can be perceived. Success depends on the quality of internet connectivity at both ends and we have to ensure privacy of the patients. The possibility of abuse or misuse should be kept in mind. Patient records and other documentation can be stored in the cloud and or in hospital servers and accessed as and when required. Confidentiality pertaining to patient treatment should be ensured.

2. Audio: Audio can be carried out through mobile or land phone. It is convenient, fast and privacy ensured.

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Real-time interaction is possible. Nonverbal cues will be missed. Visuals and patient identification is not possible.

3. **Text** (chat platforms and messages): It is convenient and documentation is integrated and can be real-time too. May miss verbal cues, difficult to establish rapport and identity is questionable.

4. **Asynchronous** (e- mail or fax): This method is more convenient and provides additional benefit of documentation. Laboratory reports, data and images can be easily shared, and is more useful when accompanied with follow-ups and second opinion. This is not a real time interaction as doctor may not see the mail immediately.^{5,6}

A few elements have to be considered carefully before tele-consultation. Prescribing medicine, without an appropriate diagnosis or provisional diagnosis will amount to professional misconduct. Not all medications can be prescribed via telemedicine. The following list classifies the medications and the safety with which it may be prescribed.

List 0: Very safe drugs like paracetamol, ORS solutions and over the counter (OTC) products.

List A: Can be prescribed during first consultation which is a video consultation. Can be prescribed again to refill during follow up. These are relatively safe drugs with low potential for abuse like i) Ointments/Lotion for skin ailments: Clotrimazole, Mupirocin, Calamine Lotion, Benzyl Benzoate Lotion etc, ii) Local Ophthalmological drops such as: Ciprofloxacin for Conjunctivitis, etc, iii) Local Ear Drops such as: Clotrimazole ear drops, drops for ear wax etc. and iv) Refill medications for diabetes mellitus, hypertension and asthma.

List B: Can prescribe add-on medications in a patient in a follow up consult for the same illness e.g., patient is already on atenolol for hypertension and the blood pressure is not controlled, an ACE inhibitor can be added such as enalapril.

Prohibited list: These medicines have high potential for abuse. Medicines listed in schedule X or any narcotics or psychotropic substances.

Pros and cons of telemedicine

Pros

1. Increases timely access to appropriate interventions. Faster access to otherwise unavailable services.
2. Reduces the cost associated with travel.
3. More prompt documentation and maintenance of records.

4. Availability of laboratory parameters and investigation results online helps the treating pediatricians.
5. Telemedicine prevents the transmission of infection (especially hospital acquired infection) to the healthcare providers and to the patients especially during epidemics and pandemics.
6. Even if the consultant is not immediately available in a tertiary institution, patient can have rapid access to other consultants.
7. Pediatricians can offer counselling about lactation, nutritional counselling and chronic care management through telemedicine.⁷
8. Pain and palliative clinics of children can utilize telemedicine to replace home visits. Health care providers / volunteers can visit their home with laptops and provide them access to the doctor and assist them by providing vital signs of the patient and patient will be happy to see and communicate with his doctor. A palliative medicine doctor can visit only 3 or 4 patients in a day. But through telemedicine he/she can take care of up to 10 to 20 bedridden patients in addition to their routine OPD related work.

Cons

1. Patient cannot be physically examined and hence more chance for bias and errors.
2. Regulatory and industry barriers like which drugs can be prescribed and which are prohibited .
3. Technical glitches may lead to interruption of communication.
4. Awareness and attitude towards telemedicine have been found to be less satisfactory. Further awareness programmes are also required for patients.
5. Acceptance among healthcare professionals has not been studied in depth.
6. Widespread implementation of telemedicine has been a slow process due to poor organization in healthcare institutions.
7. Only very basic care, counselling and advice can be provided.
8. Cannot replace situation which require physical presence such as immunization , growth monitoring , clinical examination, surgery and procedures like dialysis.

Reimbursement for services provided

For pediatricians in the private sector, a payment gateway can be integrated into the platform for online payments. Telemedicine consultations should be treated the same as in-person consultations from a fee perspective. A doctor may charge an appropriate fee for the Telemedicine consultation and also provide a receipt/invoice for the same.

Most platforms for teleconsultation charge an upfront fee to register the doctor services cover managing the appointment, storing patient data, sending an invoice and mailing the prescription. Some platforms deduct 10-20% from the fees charged by the doctor.

A practical way is for the doctor to complete the consultation via a video or audio call following which a photo of the prescription on his/her letterhead may be sent to the patient. This ensures documentation and security of patient data. Fee payment can be made through NEFT / Google pay which circumvents service fee to the platforms and benefits doctor and patient alike.

IAP has also suggested a simple solution using some of the most widely used and secure platforms in the world - WhatsApp Business for consultation or Paytm (for Business) to manage payments. A doctor can start his / her telemedicine practice within 30 mins in 2 simple steps:

1. Download and setup WhatsApp Business and Paytm for Business Apps on the mobile.
2. Activate special Paytm features by registering his/ her account on <https://diapindia.org/telemedpaytm.php>.

Thus, instead of subscribing to an expensive telemedicine software charging Rs. 15-20,000/- per annum, with the ever present 'Damocle's sword' of data misuse, IAP's solution is very simple and employs time tested platforms. And this is completely free for IAP members.

Benefits for IAP members from Paytm

- All IAP doctors will get upgraded as 'Unlimited Merchants' and get payment link enabled. These are enterprise level features and not available to individual Paytm merchants.
- Special deal on physical POS/ EDC machine once the lockdown is over – Paytm field team will be in touch directly. An EDC (electronic data capture) works to make use of POS (point of sale) terminals for credit card processing in addition to its submission to the e-commerce providers of merchant accounts or other types of credit card processors.

- Moreover, there are special offers from Paytm from time to time.

Guidelines pertaining to hardware and software to be used for telemedicine

The Guidelines are silent and do not deal with issues pertaining to hardware, software, technology, data management and other IT related issues. However they mandate that it is the doctors' responsibility to be aware of data protection and privacy laws. The pediatrician has to maintain logs of all teleconsultations, records, prescriptions and has to maintain reasonable degree of confidentiality.

During a telemedicine consult, identification of the patient and the pediatrician is important.⁸

A detailed consent with mention regarding mode of communication and type of consultation is necessary. Besides, we have to keep the following points in mind:

1. Legal aspect
2. Consent
3. Privacy and security of patient data and identity
4. Pharmacy rules
5. Insurance coverage to the patient
6. Indemnity coverage of the consultant
7. Issues of liability and negligence
8. Referral for emergency⁹
9. Misuse and abuse of data
10. Rules pertaining to the place of residence of the patient

Conclusion

During the COVID-19 pandemic, there has been a significant decrease in the number of patients visiting the pediatric outpatient department. While in person consultation is the preferred mode, telemedicine can be used for health supervision visits and acute and chronic care visits. It is useful for essential newborn screening, initial assessment of children with minor illness and follow up visits after discharge from hospital, infection control and immunization advice. Well baby clinics can be encouraged to use telemedicine with the rider that general examination cannot be done during teleconsultation.⁹ Laboratory tests, hearing, vision and oral health screening should be completed in person when circumstances improve. Chronic care can easily be carried out through telemedicine. It is important to remember that telemedicine cannot replace physical examination. With the advent of newer technologies, even some of the requirements for

physical examination can be addressed. Telemedicine despite its limitations, will continue to grow and be adopted by more and more pediatricians and patients in future.

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CLIPPINGS

COVID-2019 infection among health care workers.

Data were collected from January 1 to February 9, 2020. Exposure, epidemiological and demographic information was collected by a structured questionnaire. Clinical, laboratory and radiologic information was collected from electronic medical records. A total of 335 medical staff were randomly sampled to estimate the prevalence of subclinical infection among a high-risk, asymptomatic population. Samples from surfaces in health care settings were also collected. Overall, 110 of 9684 HCWs in Tongji Hospital tested positive for COVID-19, with an infection rate of 1.1%. Seventeen (15.5%) worked in fever clinics or wards, indicating an infection rate of 0.5% (17 of 3110) among first-line HCWs. A total of 93 of 6574 non-first-line HCWs (1.4%) were infected. Non-first-line nurses younger than 45 years were more likely to be infected compared with first-line physicians aged 45 years or older (incident rate ratio, 16.1; 95% CI, 7.1-36.3; $P < .001$). The prevalence of subclinical infection was 0.74% (1 of 135) among asymptomatic first-line HCWs and 1.0% (2 of 200) among non-first-line HCWs. No environmental surfaces tested positive. Overall, 93 of 110 HCWs (84.5%) with COVID-19 had nonsevere disease, while 1 (0.9%) died. The 5 most common symptoms were fever (67 [60.9%]), myalgia or fatigue (66 [60.0%]), cough (62 [56.4%]), sore throat (55 [50.0%]), and muscle ache (50 [45.5%]). Contact with indexed patients (65 [59.1%]) and colleagues with infection (12 [10.9%]) as well as community-acquired infection (14 [12.7%]) were the main routes of exposure for HCWs.

Conclusions: That non-first-line HCWs had a higher infection rate than first line HCWs differed from observation of previous viral disease epidemics. Rapid identification of staff with potential infection and routine screening among asymptomatic staff could help protect HCWs.

Lai X, Wang M, Qin C, Tan L, Ran L, Chen D, et al. COVID-2019 infection among HCWs and implications for prevention measures in a tertiary hospital in Wuhan. *JAMA Network Open* 2020; 3(5):e209666. May 21st 2020 P. 1-12 doi:10.1001/jamanetworkopen.2020.9666.

RADIOLOGY

IMAGING IN URINARY TRACT INFECTION

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Urinary tract infection (UTI) is a clinical diagnosis and confirmation is done with urine analysis and culture. The role of radiology, as we have seen in earlier issues, is to rule out obstructive and congenital anomalies that predispose to urinary tract infection. This is why all children less than 2 years with UTI are advised ultrasound abdomen for study of the urinary tract, which is a very simple investigation. Another important radiological investigation is the micturating cystourethrogram for ruling out vesico-ureteric reflux. Though it is the gold standard for diagnosis and grading of vesico ureteric reflux (VUR), it carries the risk of inducing UTI and also means much discomfort for the patient. Therefore it is reserved for recurrent UTI, atypical UTI, family history of VUR and when there is ureteric dilation in the ultrasound in the absence of obstructive abnormalities. Sometimes the indications may be expanded to male children and all children with UTI who are less than 5 years.

Dimercapto succinic acid (DMSA) is another investigation, role of which in UTI is not clear. In acute pyelonephritis inflamed areas are seen as cold areas or photopenic areas. False negative scans may occur if infection is confined to the medulla and has not yet reached the cortex or due to immature renal tubular function in infants less than 3 months. The cold areas may resolve, usually in 3 months, or persist if irreversible scarring has occurred. Consequently the timing of the scan is 3 to 6 months after infection. The MCU is done 4 weeks after UTI has subsided as transient VUR may sometimes be seen during infection and because it is an invasive test.

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Ultrasound is best done 2 weeks after an attack of UTI as toxin from E.coli, which is the commonest organism, can cause dilatation of the collecting system.

However, ultrasound is urgently required in the presence of continued spiking of temperature, loin mass or tenderness or rising creatinine to assess the status of the kidneys and development of complications. In acute pyelonephritis, the kidneys can appear normal or maybe mildly enlarged with or without a mild increase in parenchymal echogenicity and loss of corticomedullary differentiation. These findings are due to tissue edema. Movement with respiration may be reduced. Sometimes focal inflammation and vasospasm can cause a hypoechoic lesion that can be mistaken for a mass. But, unlike a mass there is reduced vascularity which is more easily appreciated with power Doppler. Abscess formation can also be a complication of pyelonephritis (Fig.1) shows multiple small abscesses in an enlarged kidney. (Fig.2) shows an abscess in the mid segment of the kidney which has perforated the capsule to collect in the perinephric space that has to be drained. A cyst in the upper pole (Fig.3) is a common finding. If infected, they develop



Fig. 1. Multiple small pyemic abscesses in the kidney

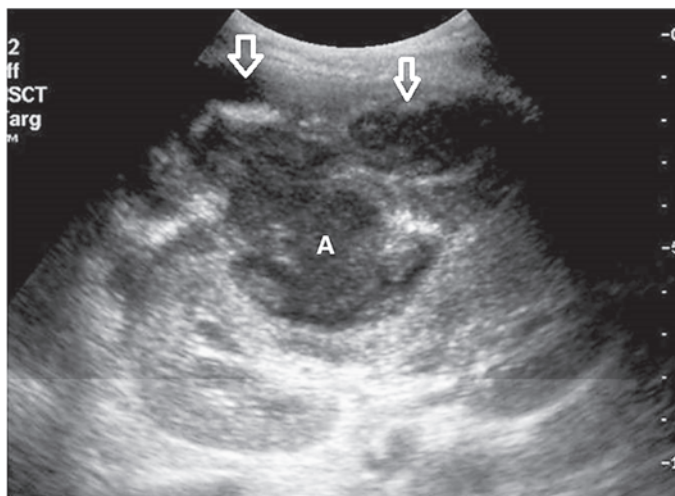


Fig.2. Abscess (A) in the kidney with perinephric collection (arrows)

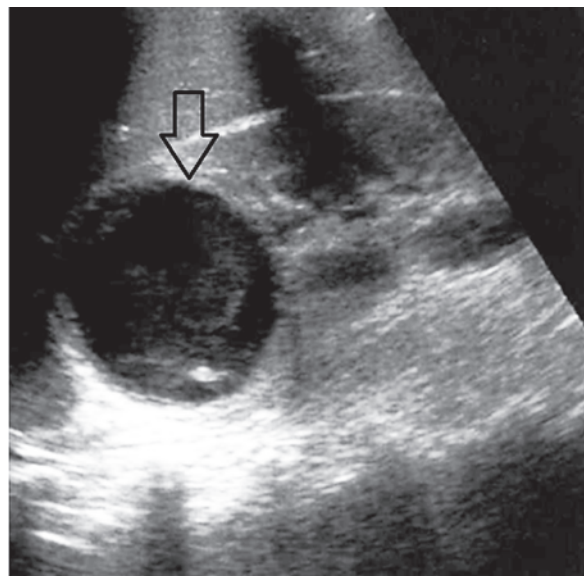


Fig.3. Infected cyst in the upper pole of the kidney

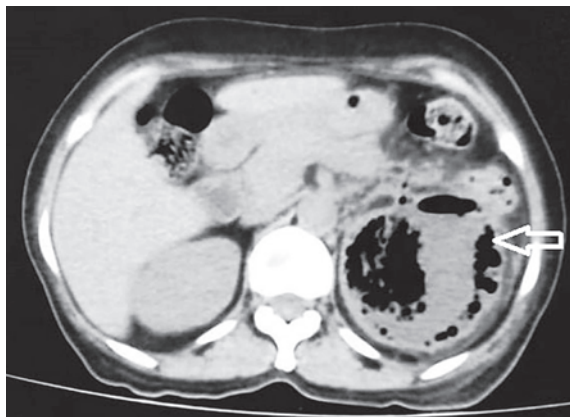


Fig.4. CT Abdomen-Air in the kidney (arrow) - emphysematous pyelonephritis

a thick wall, plenty of septations and turbid content. Turbidity of content in the bladder or in a dilated collecting system could be due to infective debris, but they are also seen in nephritis and nephrotic syndrome due to cell debris and with the use of certain drugs that induce crystalluria. Thickening of the urothelium may be seen in pyelonephritis. In CT, abscesses are seen as low attenuation foci that show an enhancing rim on contrast.

There are some special types of pyelonephritis. Emphysematous pyelonephritis is a necrotizing infection of the kidneys characterised by gas formation in the kidneys usually due to *E.coli*, *Klebsiella* and *Proteus mirabilis*. It is seen more often in adults with diabetes mellitus. Ultrasound shows an enlarged kidney with bright echoes that are different from calculi in that the after shadows are not dark and sharp as in calculi but irregular with less bright echoes due to reverberation. CT is the modality of choice as air is seen more clearly as black streaks or collections (Fig.4) or as air-fluid levels in abscesses.

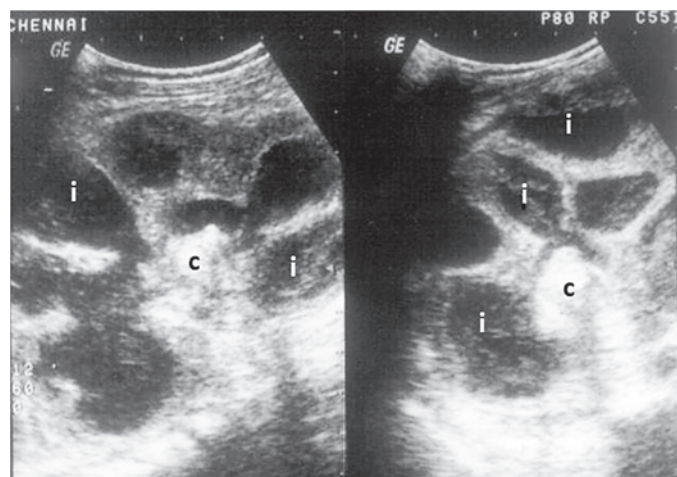


Fig.5.Xanthogranulomatous pyelonephritis. Note calculus(c) and collections of exudate(i)

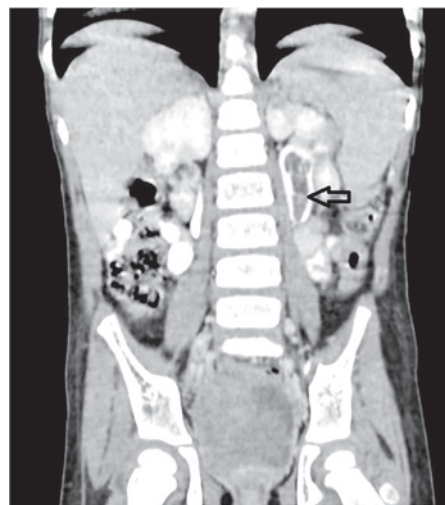


Fig.6. CT abdomen - Aspergillus cast in renal pelvis (arrow)

Xanthogranulomatous pyelonephritis is actually an abnormal immune response to subacute bacterial infection. This is also more often seen in diabetics. Though rare it can be seen in children. Classically the kidney is enlarged, there is a large pelvic calculus in a contracted pelvis and there is no excretion on contrast administration. What looks like dilated calyces are actually inflammatory exudates (Fig.5). Rarely it can be focal, or not associated with calculus or seen with renal atrophy.

Tuberculous pyelonephritis occurs with hematogenous seedling. Initially there is papillary necrosis which manifests as an enlarged calyx. The calyx can further dilate

due to the propensity for fibrosis causing infundibular stricture. Calcification is seen very often in tuberculosis.

Fig.6 is that of a child whose left renal pelvis shows an aspergillus cast seen as a filling defect. This can occur in the immunocompetent also. They usually follow instrumentation and need to be removed surgically. Invasive aspergillosis is seen in grossly immunosuppressed patients.

Though it is generally agreed upon that radiological evaluation in urinary infection does not always have an impact on treatment, targeted imaging in specific clinical situations is necessary.

CLIPPINGS

Classification of the cutaneous manifestations of COVID 19.

Dermatologists carried out a nationwide case collection survey of images and clinical data of 375 patients during peak of the COVID-19 pandemic in Spain. Patients with most severe disease were excluded. Using a consensus they described clinical patterns and the association of these patterns with patient demographics, the timing in relation to symptoms of the disease, the severity and the prognosis. The strength of the study is that the description of clinical patterns has been done by experts based only on morphology. The 5 clinical patterns included pseudo-chilblain (19%), other vesicular eruptions (9%), urticarial lesions (19%), other maculopapules (47%) and livedo or necrosis (6%). There were also reports of increased numbers of herpes zoster cases in patients with COVID-19. While Pseudo-chilblain lesions tended to affect younger patients with less severe disease, vesicular lesions appeared more in middle-aged patients with intermediate severity of disease. Urticarial, maculopapular and livedoid/necrotic lesions were all associated with more severe disease. A mortality rate of 10% was noted in the livedoid/necrotic group. They suggest that further research could be improved by having more tests to confirm COVID-19 and to exclude other infections, and utility of this classification should be confirmed in clinical use.

Casas CG, Català AG, Carretero, Hernández GC, Rodríguez Jiménez P, Fernández Nieto D, et al. Classification of the cutaneous manifestations of COVID 19. Br J Dermatol 2020 Apr 29 doi: 10.1111/bjd.19163 [Epub ahead of print].

Gastrointestinal features in children with COVID-19: an observation of varied presentation in eight children.

Eight children were referred for pediatric surgical review over an 8-day period (April 25-May 2, 2020). They presented with fever, abdominal pain, diarrhea and vomiting presenting at a single centre in the UK. The working diagnosis was of systemic sepsis based on raised blood inflammatory markers thought to be secondary to suspected appendicitis. All patients apart from one presented with markedly elevated CRP. USG/CT was done and the findings were lymphadenopathy and presence of inflammatory fat throughout the mesentery, with thickening of the terminal ileum and non-inflamed appendix. One child had a severe inflammatory response and myocarditis. Three other developed systemic inflammatory response and haemodynamic instability requiring inotropes. Two among eight were SARS-CoV-2 PCR was negative, but strongly suspected because of the similarity of their clinical presentation and imaging. They were treated with immunoglobulin and steroid treatment for atypical Kawasaki disease.

No patients have died. Given the convincing nature of clinical findings for appendicitis in children with COVID-19, we stress the importance of abdominal imaging and a swab for SARS-CoV-2 PCR in all children with clinically suspected appendicitis, before surgical intervention. It is important to stress the need to visualise the appendix through ultrasound, CT or both.

Tullie L, Ford K, Bisharat M, Watson T, Thakkar H, Mullassery D. Gastrointestinal features in children with COVID-19: an observation of varied presentation in eight children. Lancet Child Adolesc Health 2020 Published Online May 19, 2020 [https://doi.org/10.1016/S2352-4642\(20\)30165-6](https://doi.org/10.1016/S2352-4642(20)30165-6).

CASE REPORT

CHALLENGES ENCOUNTERED IN MANAGING NON COVID-19 ILLNESS DURING A PANDEMIC

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Abstract: *The SARS-CoV-2 pandemic has impacted health care delivery in an unprecedented manner. The uprising COVID-19 trend in India, combined with the information explosion and resource constraints have contributed to uncertainty in managing otherwise straight forward emergencies. Here, we report challenges faced whilst managing a child with a common illness in the COVID-19 period. Modification of current practices and developing universal precautions against COVID-19 is needed to overcome challenges in managing non COVID-19 patients during this pandemic.*

Keywords: SARS-CoV-2, Foreign body aspiration, Respiratory distress, Bronchoscopy.

The SARS-CoV-2 pandemic has impacted the world especially clinicians in unprecedented ways.¹ India sees a rising trend, with over 130,000 positive cases as on May 2020.² Compelling data on high infectivity especially to health care workers (HCW), asymptomatic carriage and limitations of testing, coupled with constraints of resource such as personal protective equipment (PPE) have led to fear amongst Indian HCWs affecting health care delivery.¹ Here, we report challenges faced whilst managing a child with a common illness in the COVID era.

Case report

A 2 year-old boy from rural Karnataka presented with two-week history of cough, preceded by transient fever. His cough worsened 2 days prior to presentation with breathlessness and recurring fever. He was referred as

severe acute respiratory infection (SARI) suspicious of COVID-19. On arrival, child was febrile, severely distressed and hypoxic with poor air entry on left side. He required emergency intubation using full personal protective equipment (PPE). Chest radiograph (CXR) showed mediastinal shift to left side with reduced volume of left hemithorax with collapse/consolidation of entire left lung (Fig.1). Ventilator settings were PEEP-6, PIP-20, rate-30 with 100% FiO₂. High total counts 28,820 cells/mm³ and CRP 5.6 mg/dL were noted. Piperacillin tazobactam and vancomycin were started. Computerized tomography (CT) chest showed collapse of left lung with obstruction due to suspected mucus plugging of left main bronchus (LMB) and patchy consolidation on the right lower zone (Fig.2). Parents denied any history of choking suggestive of foreign body (FB) aspiration. RT PCR for COVID-19 was done and it took 36 hours to get the result which was negative. Positioning, suctioning, mucolytics and ventilatory strategies failed to show improvement and hence rigid bronchoscopy was planned.

Initially the surgeon and anesthetist were reluctant to intervene, as he was COVID-19 suspect and high risk of aerosol generation during the procedure. However, as child was severely hypoxic, emergency flexible bronchoscopy was performed in the pediatric intensive care unit, confirming mucoid obstruction in left main bronchus which could not be extracted. Emergency rigid bronchoscopy was then performed in the operating theatre.

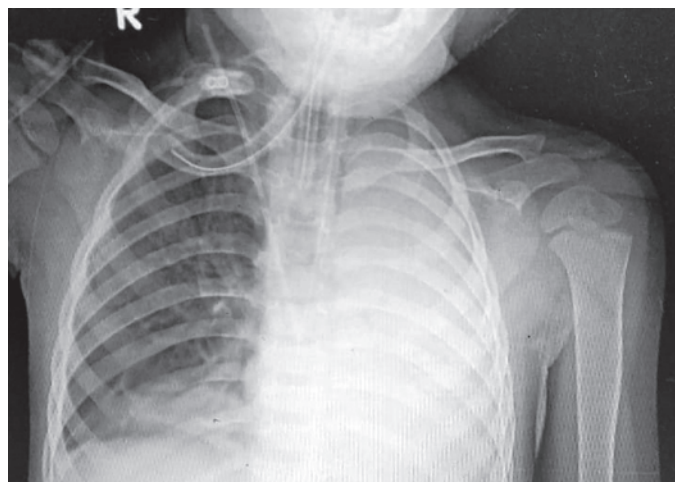


Fig.1. Left lung collapse on chest radiograph

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Fig.2. CT showing obstruction at LMB with lung collapse

Three pieces of areca nut were removed from the left main stem bronchus and saturations dramatically improved (Fig.3). Child was extubated the next day and was discharged in 3 days.

Discussion

Foreign body (FB) aspiration is a life-threatening emergency that peaks in toddlers with male preponderance.³ Vegetable FBs notably peanut, lodged in right main bronchus is typical.^{3,4,5} Cough, respiratory distress, wheezing and hypoxia are common presentations. Unilateral decreased air entry, wheeze, stridor and distress are seen.^{3,4,6} Fever is associated with late presentation and leading history is absent in 40% cases both of which were observed in our case.⁴ During this pandemic era as shown in the Chinese series, cough and fever were commonest symptoms of COVID-19.⁷ Coupled with hypoxia and respiratory distress, they qualify as SARI and a COVID-19 suspect according to Indian guidelines. Hence a clinical presentation which in other times would have straightaway led us to suspect FB, masqueraded as COVID-19. However, unilateral lung collapse with obstruction of LMB pointed to a different diagnosis. Typically in FB aspiration, CXR may show obstructive emphysema or unilateral collapse, mediastinal-shift, an opaque FB or even normal study.^{3,4,5,6} CT has better sensitivity and specificity than the CXR in the evaluation of collapse and may even delineate the exact location



Fig.3. Extracted foreign body areca nut

of FB.⁵ Flexible bronchoscopy is diagnostic and sometimes therapeutic for distal FBs.³ Rigid bronchoscopy remains the gold standard which shouldn't be delayed when FB is suspected.^{3,5} However, in clinical COVID-19 suspects, knowing limitations of RT PCR testing, bronchoscopies may be avoided due to high aerosolization and viral transmission, especially in OT with risk of exposure to multiple personnel.⁸ Recent pediatric guidelines on modified/ newer approaches to these procedures with simulation training allow for safer practices.^{1,9,10}

Conclusion

Children with non COVID health issues suffer more than the COVID-19 positive patients during this pandemic. Even the number of children who suffer from non COVID problems are more than that with COVID-19. Diagnosis and management of even common conditions like FB aspiration may get delayed or totally missed because of fear or mislabeling as COVID-19. This is an avoidable impact of current pandemic. One should have an open mind to consider non COVID causes during the evaluation of COVID-19 suspects. Following universal precautions, modified approach and simulation preparedness can overcome the risks faced by HCW during anesthesia and high aerosol generating procedures. Lesson learnt is that one should consider non COVID treatable illnesses, amongst COVID-19 suspects and evaluate and treat them skillfully.

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CLIPPINGS

Convalescent plasma for patients suffering from COVID-19 Study done in Wuhan, China.

A multicenter, open-labelled randomized controlled trial on patients with severe or life-threatening COVID-19 was performed in Wuhan, China, enrolling 103 adult participants (Study aimed to enroll 200 but terminated early for lack of patients). The objective was to evaluate the efficacy and adverse effects of convalescent plasma therapy in severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation) disease.

Convalescent plasma was obtained from persons who had recovered from COVID-19 and were more than 2 weeks out from hospital discharge. Only plasma with an IgG titer against the S protein-receptor binding domain of at least 1:640 was used, at a dose of 4 to 13 mL/kg (median infusion, 200 mL). The primary endpoint was time to clinical improvement within 28 days, defined as discharge or a reduction of 2 points on a 6-point disease severity scale. 52 patients (23 with severe and 29 with life-threatening disease) were enrolled. Clinical improvement occurred in 27 convalescent-plasma recipients (51.9%) and 22 control patients (43.1%), a nonsignificant difference. Among those with severe disease, the primary outcome occurred in 91.3% versus 68.2%, suggesting a possible benefit, but the test for interaction by disease severity was not significant. The early termination could have underpowered the study, the authors note.

This well-conducted randomized clinical trial of convalescent plasma in patients with COVID-19 suggests that this treatment is not of benefit in all patients but may have a role in some patients with severe disease. Further studies are needed to study the utility of convalescent sera.

Li L et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. *JAMA* 2020 Jun 3; [e-pub]. (<https://doi.org/10.1001/jama.2020.10044>).

CASE REPORT

UNUSUAL PRESENTATION OF COVID-19 AS INTUSSUSCEPTION

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******Ezhilarasi S**

Abstract: *COVID-19, caused by novel coronavirus SARS-CoV-2, presents with varied clinical manifestations in pediatric age group. Gastrointestinal (GI) symptoms with/without respiratory manifestations are increasingly reported in children. This infant presented with features of intussusception and fever. Further evaluation showed RT-PCR positivity for COVID-19 in the nasopharyngeal swab. Child did not develop any other respiratory manifestations or features of hyperinflammatory syndrome. It is extremely difficult to distinguish if this a manifestation of COVID-19 or an associated illness.*

Keywords: *Intussusception, COVID-19, SARS-CoV-2, Children.*

Intussusception is one of the commonest surgical emergencies encountered in infants between 6-12 months of age, usually following gastrointestinal infections or introduction of complementary feeds. Here, we report an unusual presentation of COVID-19 as intussusception.

Case Report

An 8 months old male infant, presented with low-grade fever for 2 days, 6-7 episodes of non-bilious, non-projectile vomiting and 2 episodes of blood-stained stools for 1 day. He was a well thriving and developmentally normal child. He has been on breast feeds and complementary feeding was started at 6 months of age. There was a history of

introduction of new weaning food in the past week. There was no irritability or crying spells suggestive of abdominal pain. He had no respiratory symptoms, rashes or ear discharge. There was no history of contact with COVID-19 patients or any history of recent travel or new visitor in the home. It was decided to send a nasopharyngeal swab for RT-PCR for SARS-CoV-2, on third day of illness considering the fact that gastrointestinal manifestations are one of the presentations in children with COVID-19, as seen in studies published from Wuhan Province, China.

On examination, he was lethargic, febrile (99.4°F), with HR of 120/min, RR of 45/min, and SpO₂-98%. Signs of some dehydration such as sunken eyes and listlessness were present. Examination of the abdomen revealed an ill-defined mass palpable in the abdomen, with normal bowel sounds and no distension. The stools were of red currant jelly type. Cardiovascular, respiratory and nervous system examination showed no significant abnormality.

Intussusception was suspected and the child was started on intravenous fluid and other supportive management. Emergency ultrasound was done which confirmed the ileocolic intussusception in the subxiphoid region (Fig.1). Investigations revealed a Hb of 10.5 g/dL, and hematocrit of 32.7%, total count was 7590 cells/mm³ with polymorphic predominance of 72% and lymphocytes of 23%, platelet count was 3.04 lakhs/mm.³ Renal function, electrolytes and coagulation profile were within normal limits. Pediatric surgeon's opinion was obtained and emergency pneumatic reduction was planned.

Child underwent pneumatic reduction (Fig.2) of ileocolic intussusception at the level of transverse colon and the same was reduced in a single attempt. Child tolerated the procedure well. Dehydration was corrected, follow up screening ultrasound showed no recurrence, fever and vomiting settled, slowly feeds were initiated. However, surprisingly, the nasopharyngeal RT-PCR sample sent for SARS-CoV-2 came as positive, suggesting that intussusception could be a manifestation of COVID-19 in young infants. There were no recurrence of symptoms, fever or respiratory manifestations, hence no other treatment was initiated. Parents were tested for COVID-19 by nasopharyngeal swab RT-PCR on day 5 of

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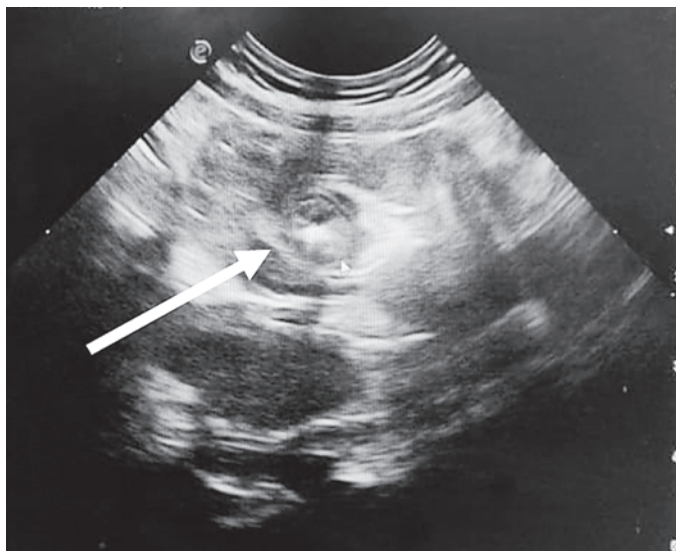


Fig.1. Ultrasound showing intussusception

exposure and were negative. Child was stable with no deterioration during 5 days of hospital stay and was discharged and advised home isolation. Further procedures of isolation, notification, quarantining and screening of contacts were initiated as per government protocol. Follow up telephonic consultation was done, child remained well and repeat RT-PCR was done and found to be negative.

Discussion

Evidence regarding pediatric COVID-19 is still evolving. During the ongoing pandemic, COVID-19 must be considered in patients with increased inflammatory variables and abdominal symptoms.¹ The most common GI manifestations include diarrhea, vomiting and acute abdominal pain. A positive contact history is elicitable in majority of the cases.²

Both respiratory (cough, rhinorrhea, sore throat, tachypnea) and GI (diarrhea, vomiting) manifestations along with fever have been described in children with COVID-19.^{3,4,5} However, Cai, et al., in their report on 10 pediatric patients, observed respiratory manifestations (cough, sore throat, stuffy nose, sneezing, rhinorrhea), while none had diarrhea or dyspnea.⁶ In a meta-analysis of 266 pediatric and 6064 adult COVID-19 patients, GI symptoms including diarrhea, nausea or vomiting were observed similarly in both groups. It was observed that 10% of pediatric patients (95% CI 4-19; range 3-23; $I^2=97\%$) presented with gastrointestinal symptoms alone without respiratory features.⁷

Genome sequences showed that SARS-CoV-2 expresses the spike (S) glycoproteins that could bind with high affinity to the entry receptor angiotensin converting

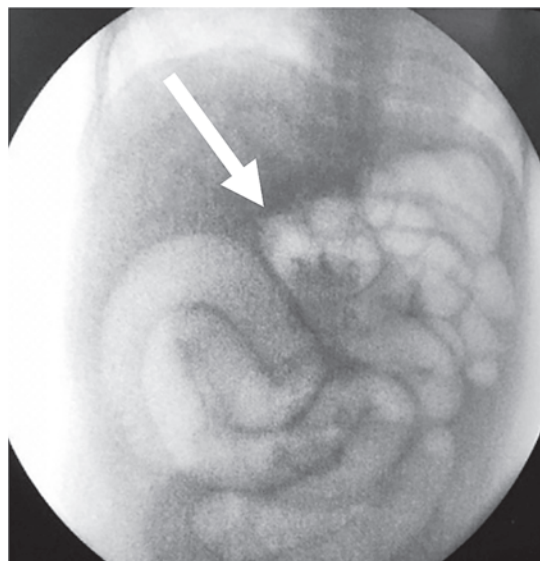


Fig.2. Pneumatic reduction under C-Arm

enzyme 2 (ACE2) to enter human cell. ACE2 is highly expressed in type II alveolar cells in the lungs and in gastrointestinal tract, especially in the small and large intestines. Staining of viral nucleocapsid protein has been visualized in cytoplasm of gastric, duodenal, and rectal epithelium. The presence of SARS-CoV-2 RNA in anal/rectal swabs and stool specimens even after the clearance of the virus in the upper respiratory tract and expression of the viral receptor ACE2 in gastrointestinal epithelial cells substantiates the GI involvement in COVID-19.⁸ In fact, the first ever severe case reported in pediatrics presented with GI manifestations progressing to acute respiratory distress syndrome.⁹

It has been observed that there is an increased GI wall permeability to foreign pathogens once infected by the SARS-CoV-2 virus. The radiologic manifestation of these findings are distended fluid filled small and large bowel loops with mural post-contrast enhancement with surrounding stranding on CT and ileus pattern on abdominal radiographs.¹⁰ It is well known that GI infection leading to swollen Peyer's patches in terminal ileum is the cause for mucosal prolapse of ileum into colon resulting in intussusception. Thus, the demonstrated GI inflammation and infection by SARS-CoV-2 makes us consider intussusception as a possible manifestation of COVID-19.

Literature on COVID-19 presenting as intussusception are scarce. Lu, et al have reported 10 months old infant with intussusception, who progressed to multiorgan dysfunction and succumbed in 4 weeks.¹¹ However, mortality in COVID-19 children is relatively lower than adults. Most routine blood examinations were normal, and C reactive protein levels were normal or transiently

increased, except in cytokine storm syndrome.^{9,12} These lab findings were consistent with the present case.

Our index child presented here did not progress to respiratory involvement or cytokine storm syndrome or multiorgan dysfunction and hence we did not proceed to do transaminases, ferritin, D-dimer assay and other inflammatory markers. Rectal swab was not done as well, as the child recovered clinically. None of the other family members/contacts developed any symptoms and their screening for SARS CoV-2 was negative, at the time of hospitalization of the child and up to two weeks after discharge. There are not many standardized studies regarding data on the sensitivity and specificity of RT-PCR for COVID-19. However, in a study providing invitro data with minimal clinical information have shown high specificity and moderate sensitivity (63-78%)¹³. As per American Society for Microbiology COVID-19 International Summit report, a negative test does not exclude the possibility of infection. A positive test is most likely correct, although stray viral RNA that cross contaminates from an infected laboratory worker (while the specimen is being collected or tested) could result in a falsely positive result.¹⁴

In conclusion, this case report shows the variability in the clinical presentation of COVID-19. Gastrointestinal manifestations should raise the suspicion of SARS-CoV-2 and authors would like to emphasize the need for increased testing to identify the causal association in children. In this index child, intussusception may be a GI manifestation of COVID -19, due mucosal inflammatory changes or may be an unrelated problem. Though clinical syndrome is still in an evolving stage, it is worthwhile to evaluate all children with acute abdomen for COVID-19 and it is equally important that surgery and radiology team should take proper preventive measures including hand hygiene and wearing PPE.

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