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REVIEW ARTICLE

Severe acute respiratory syndrome-coronavirus-2 infection: A review of the clinical-pathological correlations of coronavirus disease-19 in children

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Abstract

The coronavirus disease-19 (COVID-19) has become a global pandemic of acute respiratory disease in just less than a year by the middle of 2020. This disease caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has resulted in significant mortality especially among the older age population and those with health co-morbidities. In contrast, children are relatively spared of this potentially ravaging disease that culminates in the acute respiratory distress syndrome, multi-organ failure and death. SARS-CoV-2 infection induces exuberant release of pro-inflammatory mediators, causing a "cytokine storm" and hypercoagulable states that underlie these complications. The SARS-CoV-2 infection median incubation is 5.1 days, with most developing symptoms by 11.5 days. It is highly infectious, spreading via the horizontal mode of transmission, but there is yet very limited evidence of vertical transmission to the newborn infant occurring either transplacentally or through breastfeeding. This said, various immune factors during childhood may modulate the expression of COVID-19, with the multisystem inflammatory syndrome in children (MIS-C) at the severe end of the disease spectrum. This article gives an overview of the SARS-CoV-2 infection, clinical presentation and laboratory tests of COVID-19 and correlating with the current understanding of the pathological basis of this disease in the paediatric population.

Keywords: Angiotensin converting enzyme 2 (ACE 2), Coronavirus disease-19 (COVID-19), Cytokine storm, Innate immunity, Multisystem Inflammatory Syndrome in Children (MIS-C), Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2),

INTRODUCTION

In December 2019, a novel coronavirus virus was first reported in Wuhan, China. Although the origin was unknown, the outbreak was initially associated with one seafood market in Wuhan. In January 2020, a group of Chinese scientists isolated the genetic sequence of the virus. They identified the virus as a new type of coronavirus (2019 novel coronavirus, 2019-nCoV). This virus was named as the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the disease labelled as coronavirus disease-19 (COVID-19).[1] As of November 2020, the COVID-19 cases were at more than 55 million, with more than 1.3 million deaths worldwide.[2]

Malaysia first reported a case of COVID-19 on 25th January 2020. The first three cases were Chinese nationals who were in close contact with a patient from Singapore. On 29th January 2020, the first paediatric case in Malaysia was a 4-year-old Chinese-national girl. In May 2020, there were 317 children under the age of 12 years who tested positive for COVID-19. This accounted for 6% of the total cases in Malaysia. Among these children about half were six years old and younger.[3] Later on in the year, in October 2020, it was reported that more than 1,000 positive cases were among school-age children during the third wave of this disease.[4] From November 2020 onwards, Malaysia has a total of more than 50,000 cases with an average daily reported of 800-1,000 cases.[5] In this review, the authors focus on the clinical presentation correlating with disease pathophysiology of COVID-19 in the paediatric population.

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SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-CoV-2)

Coronaviruses are enveloped, single-stranded RNA viruses that are ~30kb.[6] They are divided into four types; α, β, γ, and δ. Only α and β could infect mammals.[7] The first coronavirus that caused severe acute respiratory syndrome (SARS) was SARS-CoV, which led to the 2002 pandemic. Following that was the Middle-East respiratory syndrome (MERS) which originated from the middle-eastern region in 2012. Both of these viruses as well as the SARS-CoV-2 belong to the β-type coronavirus.[8] Comparatively, SARS-CoV-2 is more infectious than SARS and MERS. The SARS-CoV-2 basic reproduction number, R0, which reflects infectivity, is estimated to be 2.0 to 2.5, as compared to 1.70 to 1.79 for SARS and below 1 for MERS. This translates to every one patient can potentially spread SARS-CoV-2 to another 2 or 2.5 people.[9]

SARS-CoV-2 is a large virus, with a diameter of 50 - 200 nm. It has characteristic spikes of 9 -12 nm.[10] Genetic components of SARS-CoV-2 has 88% similarity with the two bat-derived SARS-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21. This suggests that bat may be a reservoir for SARS-CoV-2. In relation to both SARS-CoV and MERS-CoV, although bats are also the natural reservoir, there are intermediate hosts (masked palm civet for SARS-CoV; dromedary camel for MERS-CoV) that are involved in the transmission chain to human. During the outbreak in late December 2019, bats were hibernating, and no bats were found in the epicentre of the outbreak, Huanan seafood market. Current available data shows that there might be an intermediate host between bats and human, and further studies are needed to identify this host.[11] Malayan pangolins (*Manis javanica*) were also investigated in relation to SARS-CoV-2 transmission. It was found that five genomic sequences of pangolins; GX/P1E, GX/P2V, GX/P3B, GX/P4L, GX/P5E, and GX/P5L, have very high genomic similarities to the virus isolate (99.83-99.92%). This suggests that pangolins might be possible hosts of SARS-CoV-2.[12] This association was highly suspect with the illegal trafficking of pangolins in the exotic food market particularly in the Asian region.

TRANSMISSION OF COVID-19

Horizontal transmission

Data suggest that the most common mode of transmission is through water droplets expelled during talking, coughing or sneezing. Exposure within 1 meter for at least 15 minutes to a symptomatic person increases the risk of transmission. Usage of face mask particularly N95, and eye shield could reduce the risk of transmission of the virus.[13] Exhalation, sneeze, and cough could produce a cloud of gas that carries droplets of various sizes. These droplets need more time to evaporate due to the warm and humid surrounding of the gas cloud, thus could potentially carry pathogens further up to 7 meters away and settle on various surfaces.[14] While studying the room environment of a symptomatic patient, several sites were found to be positive for SARS-CoV-2, including air exhaust outlets, toilet bowls, sinks and door handles.[15] SARS-CoV-2 was found to remain viable in aerosol for 3 hours, and was more stable on impenetrable surfaces. This virus could be detected up to 72 hours after exposure on plastic and stainless steel, while on cardboard, the virus was no longer viable after 24 hours.[16] Therefore, there is a serious need to maintain strict environmental and hand hygiene to reduce the risk of transmission.

Vertical transmission

At the present moment there are negligible conclusive reports of vertical transmission from COVID-19 infected pregnant women to the foetus during follow-up of the newborn infants.[17] A possible reason may be that the placenta serves as a protective barrier against this virus transmission. Several studies found that the expression of both angiotensin converting enzyme 2 (ACE2) and serine protease transmembrane protease serine 2 (TMPRSS2) are low in the maternal decidua and placenta. There are only a few placental cells and chorioamniotic membrane that has ACE2 and TMPRSS2 expression throughout pregnancy.[18-20] Since both of these are essential in facilitating entry of SARS-CoV-2 into the host cells, the low expression might contribute to a negligible risk of transplacental transmission.

The structure of placenta itself provides an intrinsic defence against pathogens. The outermost syncytiotrophoblast layer is intermittently regenerated and enclosed by a compact network of microvilli. This layer does not contain intercellular cell gap junctions, thus preventing exploitation for entry or invasion by pathogens.[21] The syncytiotrophoblast also has remarkably dense actin cytoskeletal network,

forming a brush border at the apical surface of the layer.[22] Besides that, the syncytiotrophoblast layer has limited expression of toll-like receptors (TLR) which could recognise pathogens or mediate their entry into the cells. In the first trimester, TLR-2 and TLR-4 are expressed in extravillous trophoblast and villous cytotrophoblast. Later at term, they are expressed only in syncytiotrophoblast and extravillous trophoblast.[23] Furthermore, syncytiotrophoblasts have little to no expression of caveolins, which are needed to assist in endocytosis or transcytosis to allow invasion of pathogens to enter host cells. The lack of expression of caveolins protects syncytiotrophoblast from virus-related damages.[24] Lastly, the basement membrane beneath the villous cytotrophoblast creates further a physical barrier against pathogens.[25]

The placenta also has an immunological barrier against invasion of pathogens. The maternal-foetal interface has a potent immunomodulatory property, consisting of stromal cells and maternal leukocytes. In the first trimester, decidua natural killer (NK) cells, decidual macrophages, and T cells are present in the decidua basalis.[26] Other than that, the core of the placental villi has high concentrations of mesenchymal stem cells (MSCs) contributing to the villous integrity as well as homeostasis of foetal blood vasculature.[27] Moreover, at the placenta level, the type III interferon (IFN) provides a powerful antiviral response. The IFN initiates a signalling cascade that activates transcription of IFN-regulated genes. An animal study found that type III IFN protects the foetus against Zika virus infection.[28] Given that SARS-CoV-2 induces the release of type III IFN, this could be one of the mechanisms protecting the foetus against SARS-CoV-2 infection.[29]

Breastfeeding infants by mothers with COVID-19

Breastfeeding provides numerous benefits to the infants. Breast milk is considered the ideal nourishment to the infant as it supplies a perfect balance of nutrients, cellular components, and a host of bioactive molecules, that delivers passive immunity and protection to the newborn infant.[30]

Currently there is limited evidence that suggests SARS-CoV-2 could be transmitted through breast milk. A series of case studies analysed breast milk samples of 68 mothers and found that nine samples were positive for SARS-CoV-2 RNA. Out of the nine samples, three neonates and one infant were positive for SARS-CoV-2 infection, confirmed by real-time PCR. However, the description of the feeding practices of the babies were incomplete, and the studies were observational in nature with lack of controls.[31] Therefore, there is a need for a more thorough study to determine more conclusively whether breast milk could transmit SARS-CoV-2.

In a pragmatic approach to promote breastfeeding safely in COVID-19 positive mothers, several steps are needed to be taken to avoid transmission from mother to the baby, as recommended by the American Academy of Pediatrics. Mothers who are asymptomatic or with mild symptoms should wear a surgical mask, wash hands and the breast with soap before breastfeeding. The infant's crib should be placed two meters apart from the mother's bed and behind a curtain. These steps should be taken until there is an improvement to the mother's symptoms, and the mother has tested negative twice for SARS-CoV-2. Similar precautions should be taken for mothers with moderate to severe symptoms, except that the breast milk should be expressed with a dedicated breast pump, and given to the baby in a separate room.[30]

CLINICAL PRESENTATION OF COVID-19 IN CHILDREN

A large proportion of children may be asymptomatic. Otherwise, the symptoms of COVID-19 in children of all age groups are rather similar, only that the frequency of symptoms may vary as shown in FIG. 1. The United States of America (USA) case surveillance from January to May 2020 segregates paediatrics into two large groups, children age less than 9 years (n=20,458) and children age between 10 to 19 years (n=49,245). In the younger group, the more commonly reported symptoms were fever (46.3%), followed by cough (36.9%), headache (15.1%), diarrhoea (13.6%), sore throat (12.8%), myalgia (10.4%), nausea/vomiting (9.8%), runny nose (6.8%), abdominal pain (6.7%), shortness of breath (6.5%) and loss of smell or taste (1.3%). On the other hand, the symptoms more frequently complained by the older group are headache (41.9%), followed by cough (41.4%), fever (35.0%), myalgia (29.5%), sore throat (28.6%), shortness of breath (16.3%), diarrhoea (13.5%), nausea/vomiting (10.4%), loss of smell or taste (9.9%), runny nose (8.1%) and abdominal pain (7.7%). Across these two groups, the majority of children presented with fever and cough or shortness of breath (69.0%

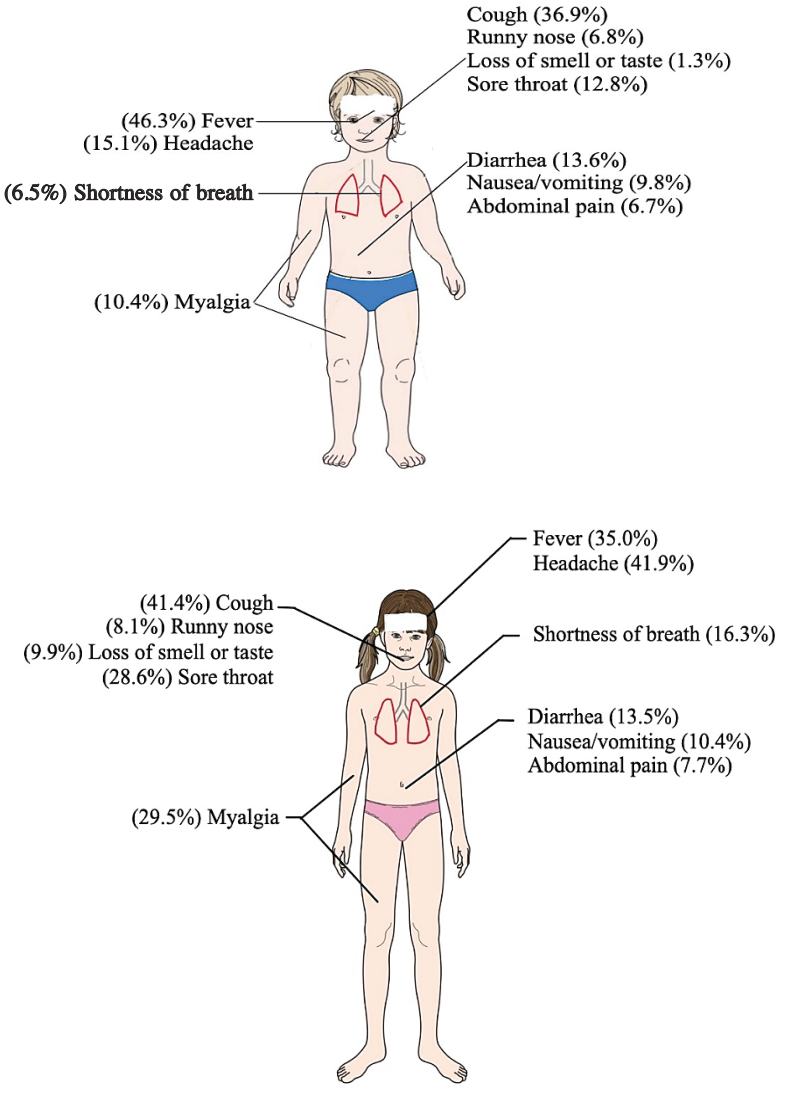

FIG. 1: Clinical presentation of children with COVID-19.[32]
The boy figure represents younger children of less than 9 years old. The more commonly presenting symptoms are fever, cough, headache and diarrhoea. The girl figure representing the older children group, between 10 and 19 years old, shows that headache, cough, fever and shortness of breath are more common symptoms, similar to adults. Very young children appear to report less on the loss of smell and taste. This could be due to the younger age group not expressing these concerns as accurately as older children and adults.

in the younger group and 63.2% in the older group).[32] Limited data were available for infants with COVID-19. The largest number of infants with COVID-19 was published in China, with a total of 46 infants under the age of 1 year. The most frequently reported symptoms were cough (58.7%) and fever (34.8%), while other less frequent symptoms included vomiting (10.9%), runny nose (6.5%), dyspnoea (2.2%), tachypnoea (2.2%), diarrhoea (2.2%) and sneezing (2.2%).[33] The data from the USA with systematic review of 7780 paediatric patients (21-year-old as the upper age limit) showed that most in the infant group presented with fever (59.1%), cough (55.9%), rhinorrhoea and/or nasal congestion (20%), while 19.3% were asymptomatic. The rate of admission to the intensive care unit was 3.3% and seven deaths (0.09%) were reported.[34] By far, the available data consistently showed that children generally experienced mild symptoms

and the small percentage who had adverse outcomes, usually had underlying co-morbidities.

LABORATORY INVESTIGATIONS FOR COVID-19

Laboratory findings are generally nonspecific, with complete blood counts showing marginal lymphocytosis and neutropenia. Inflammatory markers, such as procalcitonin and interleukin-6 (IL-6), D-dimer, and creatinine kinase results are abnormal. These should be interpreted with the clinical signs and symptoms if they meet the criteria for admission into the paediatric intensive care unit (PICU).[35] Renal and liver profile are largely normal at presentation.[34]

Many of the children may have normal chest X-rays.[34] Another meta-analysis showed that diffuse bilateral ground-glass opacities is the most common reported abnormality at all stages of COVID-19.[36] However, such abnormality is a common finding for other diseases, and secondary infection should be sought and treated. One important lesson from the past pandemic, the 1918 influenza outbreak, is that most fatalities were due to secondary bacterial infection. While managing COVID-19, the potential lethality from co-infections should always be considered, otherwise these may easily be overlooked.[37] More data is needed to establish the role of co-infections contributing to COVID-19 mortality.

The diagnosis of COVID-19 is established when a child has laboratory confirmation of infection, irrespective of the signs and symptoms.[38] The two widely used laboratory tests are the nucleic acid detection and antigen testing. Nucleic acid test involves determining the reverse transcription polymerase chain reaction (RT-PCR) of the virus genomic sequence present from the nasal sample. The result shows the status of a current infection and is highly sensitive and specific. The reported rate of false-negative ranges from fewer than five percent to forty percent.[39] On the other hand, the antigen rapid test kit (RTK) has the advantage of detecting a large number of COVID-19 samples in a relatively shorter time. The result also shows the status of current infection with the sensitivity of 90% and specificity of 100%.[40] Another less commonly used test is serology to detect the antibodies against COVID-19. This provides information of exposure and past infection with variable sensitivity and specificity.[39]

IMMUNOPATHOGENESIS OF SARS-CoV-2 INFECTION

Generally, the life cycle of a virus consists of five main stages. The first stage is attachment, which occurs when the virus attaches to the host cell surface, followed by penetration, when the virus enters the host cell either by endocytosis or membrane fusion. The third stage is biosynthesis when the contents of the virus are released in to the host cells, and the virus RNA enters the nucleus to produce viral proteins. The fourth stage, which is the last stage, is maturation when new viral particles are produced and finally released.[8]

The protein structures of coronavirus consist of spike protein (S), membrane protein (M), envelop protein (E), and nucleocapsid protein (N) as shown in FIG. 2. The spike is made up of S1 subunit, responsible for the binding to the host cell receptor, and S2 subunit for fusion of viral and cellular membranes. The spikes are glycoproteins extended from the viral surface and they determine the unique characteristic of the virus and its infectivity to a particular host.[41]

ACE2 was found to be a functional receptor for both SARS-CoV and SARS-CoV-2 and molecular simulation reveals highly similar ternary structures. However, SARS-CoV-2 has a distinct loop with flexible glycyl residues replacing rigid prolyl residues in SARS-CoV. Molecular modelling revealed that SARS-CoV-2 receptor binding domain has a stronger interaction with ACE2.[42, 43] The ACE2 expression was found higher in the lungs, heart, kidney, bladder and ileum. In the lungs, ACE2 is highly expressed on the lung epithelial cells through which SARS-CoV-2 invades human cells after the host TMPRSS2 cleaves the viral S1/S2 subunit.[44] Following that, the virus enters the cytoplasm through endocytosis and replicates inside the host cells (FIG. 3).[45] The incubation period between exposure of a person to the virus and the onset of the symptoms is estimated to be from 5 to 11.5 days, hence the basis for a 14-day quarantine period.[46] After the virus enters the cell, the viral peptides are exposed to $CD8^+$ cytotoxic T cells via class I major histocompatibility complex (MHC)[47], activating the $CD8^+$ T cells to develop virus specific effector and memory T cells. At the same time, the virus is recognised by antigen-presenting cells such as dendritic cells and macrophages and presented to $CD4^+$ T cells through Class II MHC.[47] B cell then recognises the virus, is activated, and interacts

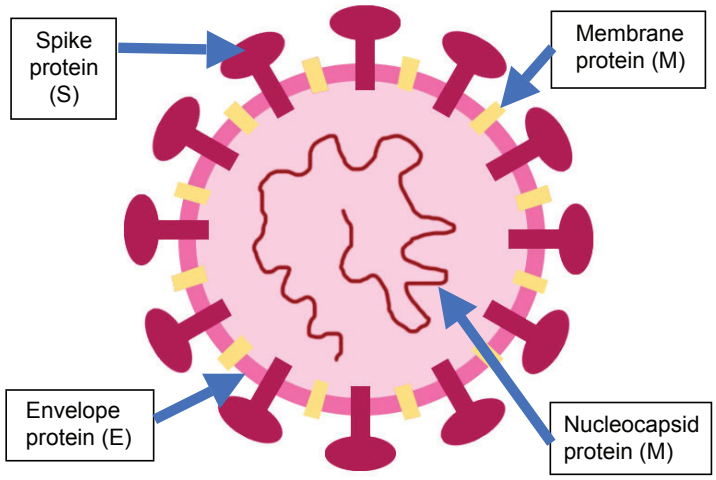

FIG. 2: Basic protein structures of coronavirus.[41]
The diameter of SARS-CoV-2 is 50-200 nm, and the size of the spikes are 9-12 nm.[10] It is similar to the size of influenza virus but smaller than the respiratory syncytial virus and bacteria such as streptococcus.[89–91] The virus is encased in an envelope protein which breaks down readily upon contact with soap.[92]

with $CD4^+$ T cells producing antibodies. IgM is observed during the first week of the symptoms. Within 19 days of the onset of symptoms, IgG is observed.[48]

Lymphopenia is found to be an important pathological finding that is considered as one of the criteria for severe COVID-19 infection.[49] Patients with severe COVID-19 also showed a decrease count of memory T cells, cytotoxic $CD8^+$ T cells and regulatory T cells, but increase in naive $CD4^+$ T cells in peripheral blood. T cell counts were found to be nearly half the lower reference limit and tend to be lower in severely ill patients.[50] As the disease progresses, the

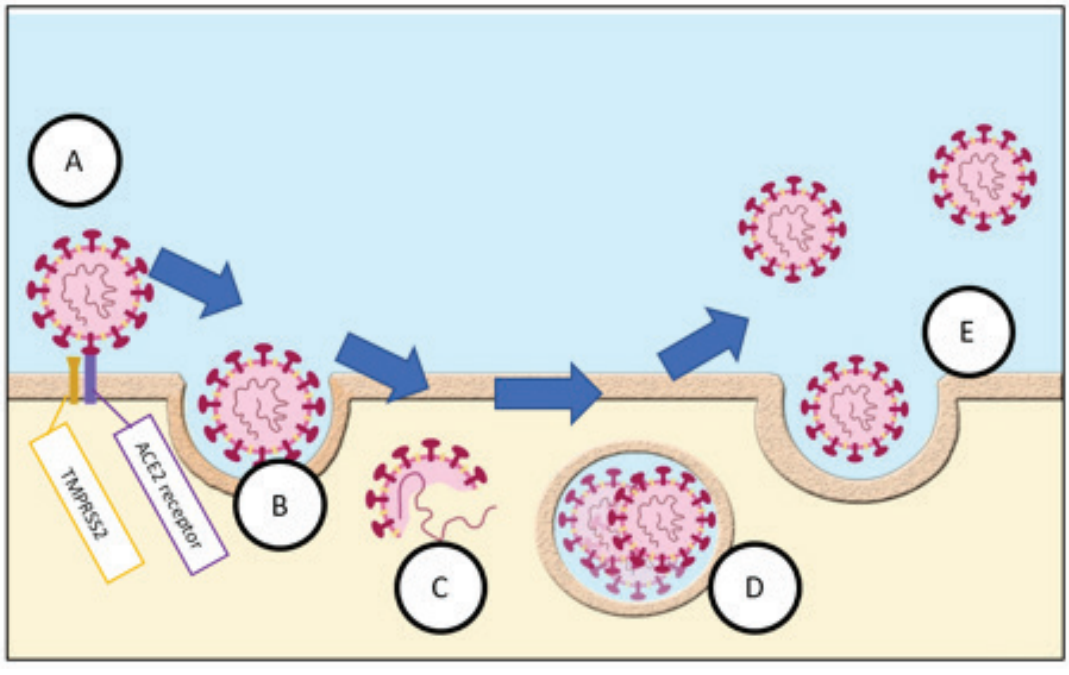

FIG. 3: The basic mechanism of SARS-CoV-2 entering host cells and the replication process.[45,48] (A) TMPRSS2 activates viral S protein, which later binds to ACE2 receptor. (B) Virus enters the host cell through endocytosis and (C) releases the viral RNA. (D) The virus replicates inside the host cell, matures, and (E) is released to infect surrounding cells.

lymphocyte count gradually reduces, and among older patients with lower lymphocyte counts, they make up those with a higher risk of severe disease.[51] This mechanism for the significant reduction of lymphocyte remains unclear. In a post mortem done in a patient who passed away on day 14 of illness, it was found that while the counts of T-helper (Th) and cytotoxic $CD8^+$ T cells were low, the cells were hyperactivated, evidenced by elevated concentration of pro-inflammatory $CCR6^+$ Th17 in $CD4^+$ T cells and cytotoxic granules in CD8 T cells. This implied that the overexcitation could account for severe immune injury sustained.[52]

Consequently, a "cytokine storm" phenomenon appears whereby there is an increase in circulating levels of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), TNF-α and interferon.[53] Cytokines are manufactured by immune cells such as innate macrophages, dendritic cells, natural killer cells, and adaptive T and B cells. The cytokines induce more immune cells aggregating at the site of infection. The "cytokine storm" fulfils the following criteria; increase in circulating cytokines levels, acute systemic inflammatory symptoms and secondary organ dysfunction due to excessive inflammatory response.[54] This leads to damage of the vascular barrier causing capillary leakage, destabilisation of cell-to-cell interactions, and diffuse alveolar injury. One of the grave consequences is lung injury, which could progress to acute respiratory distress syndrome (ARDS). ARDS causes failure in lung oxygenation and gas exchange, which is one of the main causes of mortality in COVID-19.[53]

Presence of elevated levels of pro-inflammatory cytokines, such as IL-2, IL-6 and interferon-γ (IFN-γ), contributes to activation of the coagulation cascade by favouring thrombus formation. IL-2 stimulates endothelial plasminogen activator inhibitor-1 in an in-vitro study, therefore has the potential to inhibit fibrinolysis.[55] A clinical study showed that IL-2 has the ability to activate coagulation.[56] IL-2 could further stimulate the release of IFN-γ, which is associated with pro-coagulant effect.[57] IFN-γ acts by increasing platelet activity, and mediating monocyte activation and recruitment, promoting vascular inflammation, producing reactive oxygen species, and causing dysfunction to vascular endothelial cells and vascular smooth muscle.[58] Damage to the vascular endothelial cells exposes sub-endothelial surface to circulating platelets, resulting in platelet adhesion, activation and aggregation.[59] Furthermore, IL-6 plays a role in promoting hypercoagulable state by enhancing platelet production and activation, accelerating blood clot formation.[60] IL-6 also upregulates thrombopoietin production, and increases tissue factor expression to activate the extrinsic pathway of coagulation.[61] Additionally, IL-6 induces endothelial dysfunction by increasing expression of chemokines and cell adhesions, elevating the risk of vascular thrombotic events.[62]

The exaggerated release of pro-inflammatory cytokines in COVID-19 could be due to the infection from SARS-CoV-2 itself, a secondary bacterial infection in immunocompromised patients, or excessive innate immune response to molecules produced as a result of SARS-CoV-2 invasion. Hence, preventing the entry and replication of the virus in the early infection phase is vital to avoid excessive release of pro-inflammatory cytokines which could cause aggravated injury.[60]

PATHOLOGICAL BASIS OF WHY CHILDREN WITH COVID-19 FARE BETTER THAN ADULTS

Early and cumulative data seemed to indicate that the mortality rate of COVID-19 may be age dependent. Overall, children mortality rate averages 0 to 0.2%, while adult mortality rates are more variable between 0.1% and 20%.[63]

Angiotensin Converting Enzyme 2 (ACE2)

One of the plausible explanations on why children fare better than adults in COVID-19 is in relation to ACE2 level of expression. Currently, there is still inconclusive evidence on ACE2 levels in children. One group believes ACE2 receptor level is lower in children, hence fewer children exhibit respiratory symptoms.[64] Another group found that children have higher expression of ACE2 as compared to adults, which theoretically make them more susceptible to COVID-19.[65,66] Adults with increased age and co-morbidities such as diabetes mellitus and hypertension are found to have lower ACE2 and this population is associated with greater risk of severe COVID-19. To explain such a paradox, the role of ACE2 physiologically is to maintain homeostasis by cleaving angiotensin II into angiotensin 1-7. While angiotensin II induces vasoconstriction, inflammation, fibrosis and proliferation, angiotensin 1-7 has the exact opposite function of antiproliferation,

antiapoptotic and vasodilation.[67,68] Once SARS-CoV-2 successfully enter human cells, ACE2 expression may be downregulated, thereby increasing the level of angiotensin II and promoting a pro-inflammatory state. A linear relationship is observed where a higher level of angiotensin II is associated with greater COVID-19 infectivity and worse lung injury.[69] During mid to late pregnancy, maternal level of ACE2 is increased, and ACE2 can cross the placenta to the foetus, offering certain level of protection against COVID-19.[65] With higher level of ACE2 comes with lower angiotensin II level, it may explain why children experience mild or no symptoms from COVID-19. More research is needed to shed light on whether ACE2 could be a therapeutic target for COVID-19.

Innate Immunity

Immunosenescence, as characterized with lower T cells is commonly observed in adults and it is thought to be one of the reasons why adults have worse COVID-19 compared to children.[70] However, a recent study compares the T cell responses between adults with poor outcomes and children has shown otherwise. Adults have overall higher neutralizing antibody titres, antibody-dependent cellular phagocytosis and more vigorous T cell responses compared to the paediatric population.[71] This is supported by another study which focuses on the type of antibody and the neutralizing activity after recovery from COVID-19. Adults are found to have more antibodies with higher levels of neutralizing activity after recovery from COVID-19, while children generated only IgG antibodies with low levels of neutralizing activity.[72] The main difference between these two groups was the inverse relationship of serum concentrations of interleukin-17A (IL-17A) with age. The linear relationship between IL-17A and the innate immune response suggests that children have a stronger innate immune response, perhaps to compensate for their weaker adaptive immune response.[71] Interestingly, it is this robust innate immune response that confers protection against COVID-19 in children. More studies would need to focus on boosting the innate immune response in combating COVID-19.

Trained Immunity

Closely related to the innate immune system, is trained immunity, which is thought to be another reason in explaining why children experience milder COVID-19. Simply put, trained immunity is the activation of the innate immune system to subsequent triggers in an enhanced manner, similar to what adaptive immune system does. There have been numerous reports of live vaccines, such as the Bacillus Calmette-Guerin (BCG), measles and smallpox that have beneficial protective effects against other infections.[73] For instance, BCG can produce "heterologous" or non-specific immune effects via enhancing pattern recognition against non-mycobacterial pathogens in myocytes and upregulating interleukin-1β (IL-1β). Increase viral load clearance is associated with the upregulation of IL-1β.[74] This may be speculative of SARS-CoV-2 in countries without universal BCG vaccination such as Italy and USA, that are more severely affected by COVID-19 in general as compared to countries implementing such a policy.[75] Based on this observation, we may further extrapolate this speculation to why children, especially in countries where BCG vaccination is compulsory, may have milder COVID-19. It is also recognised that BCG vaccination does not provide long-lasting protective immunity into adulthood.[73]

Immune Cross-Reactivity

Immune cross-reactivity among the coronavirus family is hypothesized to provide certain protection against SARS-CoV-2. Sera analysis from adults that have never contracted COVID-19 but recovered from previous seasonal human coronavirus infections (HCoV), revealed SARS-CoV-2 S-reactive IgG, an antibody that cross-reacts with the spike glycoprotein of SARS-CoV-2. In comparison, children with a similar clinical profile had SARS-CoV-2 S-reactive IgG that was found to be significantly higher than in adults. Indeed, the production of such antibody increases with higher frequency of HCoV infections, more commonly encountered in children. This study concluded that presence of pre-existing antibodies may recognize and protect against SARS-CoV-2 in individuals that had never contracted SARS-CoV-2. Although this confers only short-term protection, such defence may be stronger in children than in adults.[76] Other explanations on why children fare better include more of adults having significant co-morbidities, the deteriorating functional and decreased regenerative capacity of the lung with aging.[68]

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

Even though most children experience mild to no

symptoms with COVID-19, they can be severely affected with the clinical manifestation peculiar to this population. First observed in weeks after the initial COVID-19 outbreak, an increasing rate of Kawasaki disease-like illnesses was reported among children. This emergence was initially noticed in Italy, United Kingdom (UK) and the USA, countries that have been severely affected by COVID-19. Preliminary data and laboratory testing showed positive COVID-19 serology in these children suggest the link to SARS-CoV-2.[77] Some features of this disease share similarities to those of Kawasaki disease and toxic shock syndrome. However, as compared to classical Kawasaki disease, affected children are generally older, have more respiratory, gastrointestinal, neurological and cardiovascular manifestations with laboratory evidence of lymphopenia, thrombocytopenia and myocarditis.[78] By May 2020, WHO has named this as the multisystem inflammatory syndrome in children (MIS-C) and developed a preliminary case definition (Table 1).[79] The WHO and CDC named this as MIS-C, while the Royal College of paediatric and Child Health, UK defined this as paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS).[80] The affected children appeared to develop a significant systemic inflammatory response. These children may require paediatric intensive care and input from paediatric infectious diseases, cardiology, and rheumatology experts. This rare syndrome shares common features with other paediatric inflammatory conditions that include Kawasaki disease, staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndromes. It can also present with unusual abdominal symptoms with significantly elevated inflammatory markers. Early recognition by paediatricians and specialist referral including to critical care is essential as healthcare professionals need to be vigilant of MIS-C presenting as a wide spectrum of disease and to initiate prompt early treatment.[81]

All children diagnosed with MIS-C have fever, with other organ involvement that includes the gastrointestinal (abdominal pain, nausea/vomiting, diarrhoea), dermatological (rash, swollen hands/feet), mucocutaneous (conjunctivitis, mucosal changes) and cardiovascular (chest pain) systems. Laboratory findings are consistent with a clinical picture of hyperinflammation, with highly elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, and ferritin. There is also elevated cardiac markers of troponin and N-terminal pro b-type natriuretic peptide (NT-proBNP). The reported haematologic abnormalities include those described earlier, such as elevated D-dimer and low fibrinogen.[77,82-86]

The pathophysiology of MIS-C remains elusive to researchers. What has been ascertained is that MIS-C is probably not due directly to the

TABLE 1: WHO Preliminary Case Definition of MIS-C.[79]

Children and adolescents 0 – 19 years of age with fever > 3 days
PLUS two of the following:
1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet)
2. Hypotension or shock
3. Features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP)
4. Evidence of coagulopathy (by PT, PTT, elevated D-dimers)
5. Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain)

PLUS
Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin
PLUS
No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndrome
PLUS
Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19

Expected laboratory abnormalities in MIS-C are additionally, lymphopenia and thrombocytopenia, which are not in the definition.

viral factor of SARS-CoV-2, as viral sequencing from children with MISC-C and those without, are relatively similar.[87] Comparing children with MIS-C and those without, both groups have similar antibody profiles, suggesting that the adaptive immune system may not play a major role in the pathogenesis. The low neutralizing activity of antibodies may actually predispose children to a persistent infection, leading to the development of MIS-C.[72] Many children who were diagnosed with MIS-C had negative RT-PCR but positive serology test. These are suggestive that MIS-C is related to host immune dysregulation that can occur after an acute phase of COVID-19 has passed, but the exact underlying mechanism is still an area actively studied.[77,82,84]

Children diagnosed with MIS-C requires careful cardiovascular examination as most series reported 35 – 100% of cardiac involvement.[86] Although most children have complete recovery, there has been one study that reported residual mild to moderate left ventricular dysfunction.[88] The mechanism of cardiac injury is unclear, but purportedly to be acute myocarditis, hypoxic injury, ischemic injury from microvascular damage or coronary artery disease, cardiomyopathy and systemic inflammatory response syndrome.[86]

CONCLUSION

The COVID-19 pandemic has caused disruption to our normal lifestyles, creating a new norm with the way we communicate and affecting children in their education, especially those disadvantaged with limited access to digital technology. Devastating outcomes around the globe affect all age groups, although children may be less affected by the disease directly, impact from long term effects on their social and neuro-behavioural development will only be obvious years later. Only time will tell. Strict hand and personal hygiene, wearing a mask in public and physical distancing remains the norm to curtail this pandemic until hopefully, effective vaccines are available to protect the world from the scourge of SARS-CoV-2 infection.

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Disclaimer: Information correct at press time. This may change as new evidence emerges as we continue to learn about this virus.

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