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REVIEW ARTICLE

COVID-19 in children. II: Pathogenesis, disease spectrum and management

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The global disruption of the COVID-19 pandemic has impacted the life of every child either directly or indirectly. This review explores the pathophysiology, immune response, clinical presentation and treatment of COVID-19 in children, summarising the most up-to-date data including recent developments regarding variants of concern. The acute infection with SARS-CoV-2 is generally mild in children, whilst the post-infectious manifestations, including paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) and 'long COVID' in children, are more complex. Given that most research on COVID-19 has focused on adult cohorts and that clinical manifestations, treatment availability and impacts differ markedly in children, research that specifically examines COVID-19 in children needs to be prioritised.

Key words: COVID-19; management; PIMS-TS; SARS-CoV-2; virology.

Key Points

1 The mild nature of COVID-19 in most children points to important age-related factors in the pathogenesis of disease. Emerging evidence suggests differences in innate and adaptive immunity.
2 COVID-19 in children consists of acute COVID-19 - both complicated and uncomplicated -, post-infectious multi-system inflammatory syndromes and post-acute sequelae of COVID-19 (PASC) also known as 'Long COVID'. 'Long COVID' in children is poorly characterised, but likely less frequent than in adults.
3 The management of acute COVID-19 in children is based at present on data from adult trials, and management of multisystem inflammatory syndromes on observational data. In both cases, anti-inflammatory treatments appear to show greatest benefit.

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The World Health Organisation (WHO) declared coronavirus disease 2019 (COVID-19) a global pandemic on 11 March 2020, and spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has brought unprecedented health, social and economic disruption world-wide.[1] World-wide, the research community has mobilised to generate an astounding volume of data regarding disease pathogenesis as well as approaches to diagnosis and management of COVID-19. This review (Part II of II) aims to summarise the current understanding of COVID-19 disease in children. The authorship group have together been active across research, clinical care, treatment guidelines, policy development and advocacy with respect to COVID-19 in children.

Pathogenesis of COVID-19

Viral cell entry and replication

SARS-CoV-2 is from the *Coronaviridae* family of enveloped, positive sense, single-stranded ribonucleic acid (RNA) viruses, with relatedness to SARS-CoV (the virus that caused the SARS pandemic of 2002) and other bat-origin betacoronaviruses.[2] The virus spike (S) protein is both key to human infection and the major antigen for humoral immunity and as such is the antigen used in licenced vaccines employed in most jurisdictions.[3] The

primary human cell receptor for the S protein receptor binding domain (RBD) is Angiotensin-Converting Enzyme 2 (ACE2), with a binding affinity much higher in SARS-CoV-2 compared to SARS-CoV.[4] Mutations in the SARS-CoV-2 RBD are associated with enhanced ACE2 affinity and are considered to underpin key characteristics of variants such as Delta (B.1.617.2), which show increased transmissibility and immune evasion.[5]

The ACE2 protein is present on multiple human epithelial surfaces including the upper and lower respiratory tract, gastrointestinal tract and endovascular epithelia. Limited evidence suggests ACE2 expression in the upper respiratory epithelium increases across the age-spectrum.[6] SARS-CoV-2 downregulates ACE2 expression following infection and this may contribute in the lung pathology, and more widely to dysregulation of angiotensin-related physiology in particular with respect to endothelial function and inflammation. Paradoxically, children show increased ACE2 protein density on pneumocytes, which may confer protection against dysregulation of the angiotensin system during acute COVID-19.[7]

Immunological response in children

The immune response in children to SARS-CoV-2 is of particular interest for two reasons[1]: the apparent mild acute spectrum of disease may yield important lessons for management of severe disease in adults, and[2] the phenomenon of post-infectious systemic inflammation – namely paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) – which occurs mostly in children may reveal new insights into aberrant adaptive immune responses.

Recent efforts have begun to differentiate the SARS-CoV-2 immune response between adults and children. One Australian study of a family with SARS-CoV-2 infection showed that both adults and children mounted similar cellular, antibody and mucosal adaptive immune responses to SARS-CoV-2.[8] However, some of the children did not have detectable SARS-CoV-2 nucleic acid by polymerase chain reaction (PCR) testing and had minimal or mild symptoms, in contrast to the parents who were symptomatic and PCR positive.[8] The authors suggested that mucosal immunity in children may prevent the establishment of SARS-CoV-2 infection. This finding is now supported by detailed research showing an increased innate anti-viral response in the upper airways of children compared to adults.[9]

Interestingly, there appear to be differences in circulating innate immune cells in children compared to adults during SARS-CoV-2 infection.[10] Additionally, children with SARS-CoV-2 infection have a more targeted antibody response compared to adults. Furthermore, anti-spike antibodies from children appear to have less neutralising activity.[11] Whilst this does not explain the milder infections in children, the authors argue that the more restricted and less functional antibody response may be secondary to better control of the virus by innate or T cell immune responses in children.[11] Somewhat paradoxically healthy elderly individuals have higher titres of cross-reactive SARS-CoV-2 immunoglobulins (active against a range of human coronaviruses) compared to children,[12] and severe COVID-19 in adults is associated with cross-reactive low avidity SARS-CoV-2-specific CD4+ T cells.[13]

Taken together, it appears likely that innate immune responses in the upper respiratory tract may be more effective in children and that prior and more frequent common coronavirus infections in adults may result in immunological memory that hampers, rather than enhances, the antigen-specific immune response to a neoantigen such as SARS-CoV-2.[12] Furthermore, senescence of the immune system with impaired thymic output and T-cell receptor repertoire in the elderly,[14] and possible impacts on innate immune function of obesity and the metabolic syndrome,[15] may further impair immune responses to SARS-CoV-2.

Studies of human leukocyte antigen (HLA) genotype associations with disease severity are few.[16] Limited evidence suggests particular HLA genotypes may confer vulnerability to (or protection from) severe disease, and differences may underly variability in disease spectrum among ethnic groups,[17] but further validation is required in larger patient groups. A full understanding of the immunology in adults versus children is still evolving with many aspects not yet fully elucidated.

Clinical Presentation of COVID-19 Disease in Children

Mild disease not requiring hospitalisation

The majority of children with COVID-19 have mild disease, with asymptomatic infection reported in 15–42% of children (Fig. 1).[18,22] However, accuracy of prevalence estimates in countries with widespread and high daily case numbers of COVID-19 is limited by low case ascertainment of paucisymptomatic children.[23]

Children with symptomatic COVID-19 infection usually present with one or more respiratory symptoms, which are indistinguishable from seasonal respiratory viral infections, most frequently fever and cough (Table 1).[22] Non-specific presentations are common and it is possible that these have been under-recognised and under-reported in many studies.[24] Illness duration increases with age in children with a median duration of 6 days in school-aged cohorts.[24]

Children with mild or asymptomatic COVID-19, representing the majority of paediatric cases, can be managed safely without hospitalisation. Adequate hydration and supportive care are the primary management priorities in these children, in common with other respiratory viruses. In well-resourced settings, hospital in the home services provides additional support, including a medical escalation pathway, often operating predominantly via telehealth.

Pulmonary disease in hospitalised children

Hospitalisation and critical care support are required in only a small proportion of SARS-CoV-2 positive children (Fig. 1).[25] Risk factors for severe disease in children include young age[26] and pre-existing medical conditions such as obesity, asthma, diabetes mellitus and cancer[25]; infection in the neonatal period is a particular risk factor.[27] Children who develop severe disease requiring intensive care level support are more likely to have had lower respiratory tract signs and symptoms at time of presentation.[25]

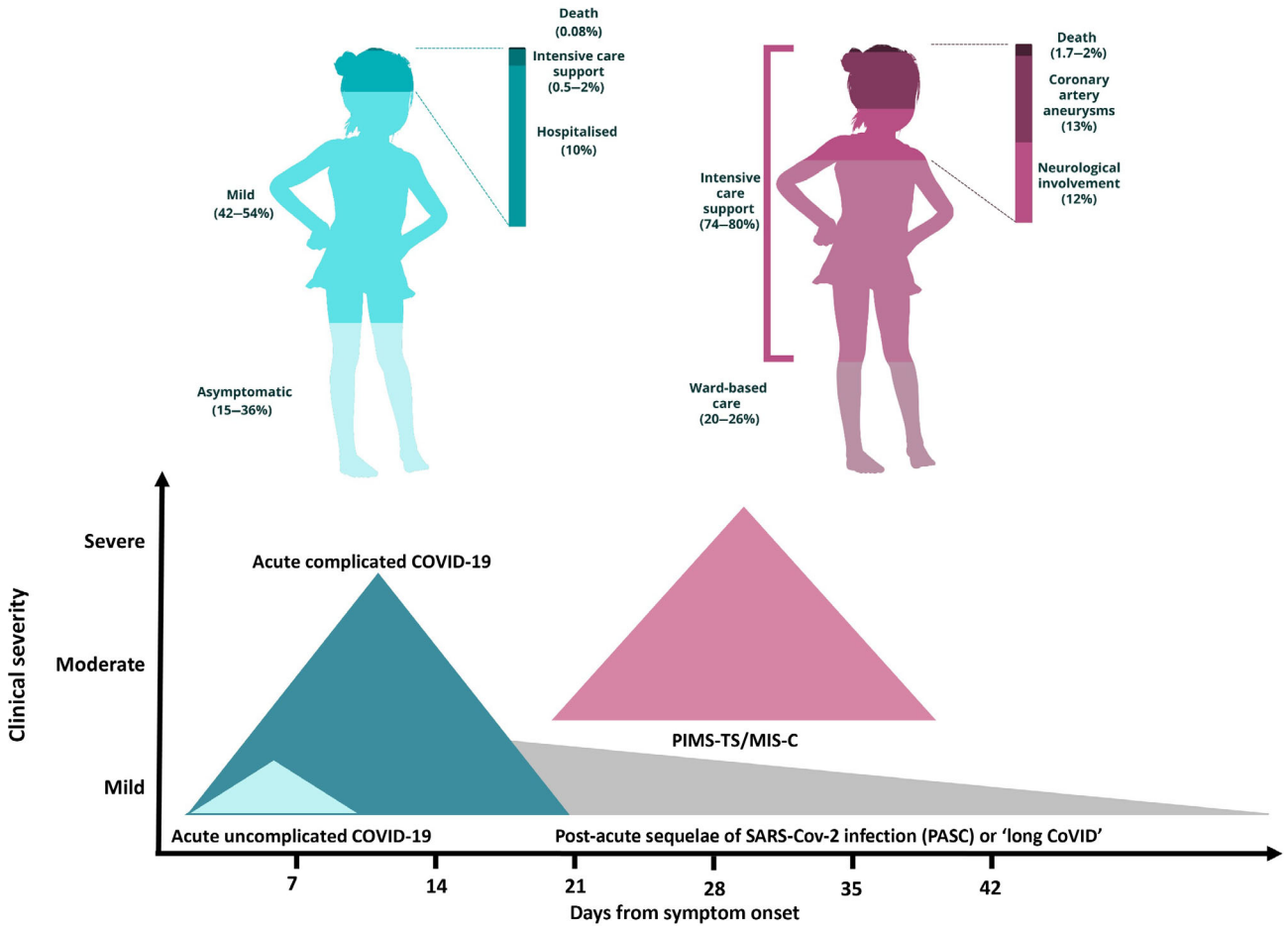

Fig 1 Overall severity of COVID-19 disease in children.[18–21] The left-hand panel depicts outcomes from acute COVID-19 infection; the right-hand panel represents outcomes from PIMS-TS in children. Estimates of the proportion hospitalised and those requiring intensive care shown here are higher than are being observed in Australia in 2021 (Hospitalised ~1% for medical reasons and ICU admitted ~0.1% of symptomatic cases; unpublished data, PN Britton).

The timing of respiration deterioration is not well characterised in children with severe disease due to low case numbers. Case series suggest that the natural history is similar to that in adult cohorts[28] with hospitalisation occurring approximately 1 week after symptom onset and acute lung injury, if it evolves, manifesting in the second week.

Radiological investigations in hospitalised children have shown patchy opacities on plain radiographs and ground-glass opacities on chest computed tomography (CT).[23] Given the radiation load of CT imaging, this modality is not justified in a paucisymptomatic child. Laboratory features include elevated inflammatory markers such as C-reactive protein in approximately 50%.[23] Serum ferritin and lactate dehydrogenase may also be raised, less frequently procalcitonin, erythrocyte sedimentation rate and interleukin-6.[23] Most children with COVID-19 have a normal blood count,[19] with lymphopenia (16%) and leukocytosis (10%) in a minority,[29] in contrast to adults in whom lymphopenia is common. Coagulopathy markers such as D-dimer may be elevated, and less frequently biomarkers for organ injury such as troponin, liver function tests, pro B-type natriuretic peptide (proBNP) and creatinine kinase-MB.[23]

Extrapulmonary manifestations in hospitalised children

In children, extrapulmonary involvement is rare but can be severe. Such non-pulmonary findings, including neurological manifestations and cardiac dysfunction of varying severity, are seen in under 5% of hospitalised children and often coexist with pulmonary disease.[23] In contrast to adult infection with SARS-CoV-2, clinically significant acute hepatitis is rare in children with COVID-19 though occasional case reports exist.[30]

Neurological findings in acute COVID-19 include status epilepticus, encephalopathy, encephalitis, Guillain-Barré syndrome and acute demyelinating syndromes.[31] These occur rarely, in approximately 4% of hospitalised children, and are most commonly seen in children with pre-existing neurological conditions.[31] A significant proportion (37%) may have ongoing neurological deficits at the time of discharge from hospital.[31]

Acute COVID-19 can rarely cause cardiac dysfunction, manifesting as acute myocardial injury, myocarditis, arrhythmias and cardiomyopathy. The proposed pathophysiology[32] is comparable to our understanding of myocardial injury in adult populations with COVID-19.

Table 1 Frequency of symptoms in children diagnosed with COVID-19 infection

Symptom	Frequency in children with COVID-19 infection	Reference
Fever	46–64%	22
Cough	32–56%	22
Rhinorrhoea	<10–20%	23
Sore throat	<10–20%	23
Dyspnoea	<10–20%	23
Headache and malaise	Up to 60%†	24
Gastrointestinal symptoms (diarrhoea, nausea, vomiting and/or abdominal pain)	10–20%	22,23
Other: fatigue, myalgia, arthralgia, rash, conjunctivitis, disturbances of smell or taste	Up to 20%	22

† Most common in adolescents.

Post-infectious inflammatory syndrome (PIMS-TS/MIS-C)

PIMS-TS is a hyper-inflammatory syndrome related to COVID-19, variously referred to as PIMS-TS in the UK and multi-system inflammatory syndrome in children (MIS-C) in the USA and by the WHO. Initially reported in April 2020, PIMS-TS occurs approximately 4–6 weeks following infection with SARS-CoV-2.[33] This condition has caused as much if not greater morbidity and mortality in children as the direct impact of the acute infection itself.[34]

The peak age for PIMS-TS is 9–10 years and may follow a clinically insignificant acute infection as paediatric COVID-19 is usually mild.[35] It is estimated that PIMS-TS occurs in approximately one in 3000 children infected with SARS-CoV-2,[36] a figure supported by Australian registry data (case notification rate <1 per 1000 cases of COVID-19 in children and adolescents).[37] PIMS-TS has also been described in younger children and in adults. It is more common in Black, Hispanic and South Asian populations.[20] The reasons for these racial differences are unclear and may partly reflect socio-economic differences, such as health-care access and populations with higher transmission of SARS-CoV-2.

PIMS-TS shares some features with Kawasaki disease (KD), but it is a distinct syndrome in terms of epidemiology, clinical symptoms, signs and laboratory features.[21] It is most commonly characterised by fever, rash, conjunctival injection, gastrointestinal symptoms (particularly pain) and shock due to myocardial dysfunction. Laboratory features include lymphopenia, marked inflammation (neutrophilia, increased C-reactive protein, procalcitonin and ferritin), coagulopathy (increased D-dimer) and myocardial dysfunction (elevated troponin and proBNP).[35] In more severe cases, echocardiography may demonstrate myocardial dysfunction leading to shock; extracorporeal membrane oxygenation (ECMO) may be required (in 4%).[38] As in KD, coronary artery dilatation or aneurysms occurs in 15–25% of cases.[20,21] Anecdotally, the coronary artery lesions appear less severe than in KD and resolve more quickly.[39] Milder cases are increasingly being recognised in settings with high COVID-19 incidence.

Considerations in immunocompromised children

The highest relative risk of severe COVID-19 disease undoubtedly occurs in patients with defects of innate immunity, many of whom were undiagnosed before the pandemic.[40,41] In older adults, this is most commonly associated with autoantibodies against type I interferons, which block the immune response to the virus.[42] These autoantibodies are rare in children, other than those who have autoimmune polyendocrine syndrome type I (APS1).[43] Genetic defects in the antiviral type I interferon response[40] and X-linked Toll-like receptor-7 deficiency[41] also confer a more than 50-fold increased relative risk for COVID-19. By contrast, adaptive primary immunodeficiency or immunosuppression that impacts T cells, B cells, and antibodies may be less important than expected in terms of COVID-19 disease severity. Primary immunodeficiency patients[44] and patients with combined immunodeficiency or HIV,[45] who might have been expected to have difficulties with viral control, are not clearly defined as carrying additional risk from SARS-CoV-2 infection. The assessment of iatrogenic immunocompromise is harder to quantify, though outcomes appear similar to immunocompetent children.[46] Children with cancer have similar disease severity,[47] though all-cause mortality appears to be higher than the general population.[48]

Considerations in neonates and pregnancy

Newborn babies can be affected by COVID-19 either indirectly or directly. SARS-CoV-2 infection may be severe during pregnancy and is associated with increased risk of preterm delivery,[49] often initiated for maternal indications such as hypoxia or pre-eclampsia.[50] Perinatal acquisition of SARS-CoV-2 has been demonstrated in 1.8–10% of tested neonates born to mothers with COVID-19,[50] with antepartum (12%), intrapartum (17%) and postpartum (71%) transmission well recognised.[51] Detection of SARS-CoV-2 RNA in placental samples and amniotic fluid is uncommon.[50] SARS-CoV-2 RNA is rarely found in breastmilk; however, SARS-CoV-2 antibodies are detectable in breastmilk from 83% of COVID-19 positive mothers; hence, breastfeeding is encouraged for women with COVID-19.[52] Contact with the infected mother increases the risk of late onset SARS-CoV-2 infection (>72 h of age), presumably via respiratory droplets as breast feeding is not a risk factor.[51]

Disease severity data in neonatal COVID-19 are variable. Active surveillance in a hospitalised UK cohort revealed 42% of neonates with COVID-19 had severe disease.[27] A quarter of these babies were born prematurely and one-third received one or more forms of respiratory support. Other studies report mostly mild illness, with asymptomatic infections in 11–48%.[27,50] In symptomatic neonates, fever, poor feeding or vomiting are common, as well as coryza, cough, respiratory distress, diarrhoea and lethargy.[27,50] Apnoea and cardiovascular features such as tachycardia and hypotension, as well as rash and conjunctivitis, have been reported.[51] Investigations

typically reveal elevated lactate, with C-reactive protein and procalcitonin raised in only the minority.

Published guidance for management of newborn infants at risk of SARS-CoV-2 infection has been varied. Australian guidelines have largely promoted rooming-in and breastfeeding unless separation is necessitated by the degree of maternal or neonatal illness.[53]

Management of COVID-19 in Children

Recommendations on therapy for COVID-19 in children are predominantly extrapolated from adult data, reflecting exclusion of children from these therapeutic clinical trials. At time of writing, over 300 randomised controlled COVID-19 trials have been published and over 3000 registered, but almost none included persons <18 years for therapy of acute COVID-19 among trial participants (as opposed to trials of vaccines).[54] Consideration of repurposed or novel therapeutic agents in children must take into account regulatory requirements, extrapolation of efficacy data from adult studies and paediatric-specific safety and dosing information, which may be limited.

Clinician confidence is strong in recommending supportive care only for the vast majority of children with mild disease and those not requiring supplemental oxygen. There is insufficient evidence for definitive recommendations on use of other agents in children with more severe disease (Fig. 2). Several guidelines for treatment of children with acute COVID-19 suggest consideration of antiviral therapy with remdesivir and/or immunomodulatory therapy with corticosteroids (dexamethasone) or biologic agents (tocilizumab) based on efficacy data from adult studies (Fig. 2).[55] Dexamethasone and other steroids are widely used in children for other conditions and have a well-established safety and toxicity profile, whilst fewer data are available for remdesivir and tocilizumab. The Therapeutic Goods Administration has approved the monoclonal antibody therapy Sotrovimab for use in children aged 12 years and above with risk factors for progression to severe COVID-19 disease.[56] Given the absence of safety data for this agent in children and the mild course of COVID-19 infection in most children, use of Sotrovimab should be considered on a case-by-case basis. The use of other emerging therapies, for which safety and efficacy data are lacking in children, should be carefully considered and preferably administered in a clinical trial only.

A number of other agents have proven ineffective in the treatment of COVID-19 infection and hence should not be used. These include hydroxychloroquine, azithromycin, colchichine, aspirin and convalescent plasma.[55]

The RECOVERY trial in the UK is currently recruiting children and adolescents with COVID-19 to some of these interventions.[57] We await these results to inform future treatment approaches and recommend the inclusion of children in future planned clinical trials on the prevention and treatment of COVID-19. Evidence is rapidly evolving and clinicians are advised to consult the paediatric-specific aspects of their local guidelines in real time (e.g. https://covid19evidence.net.au/). Consultation with an infectious diseases specialist is recommended to consider optimal treatment on a case-by-case basis.

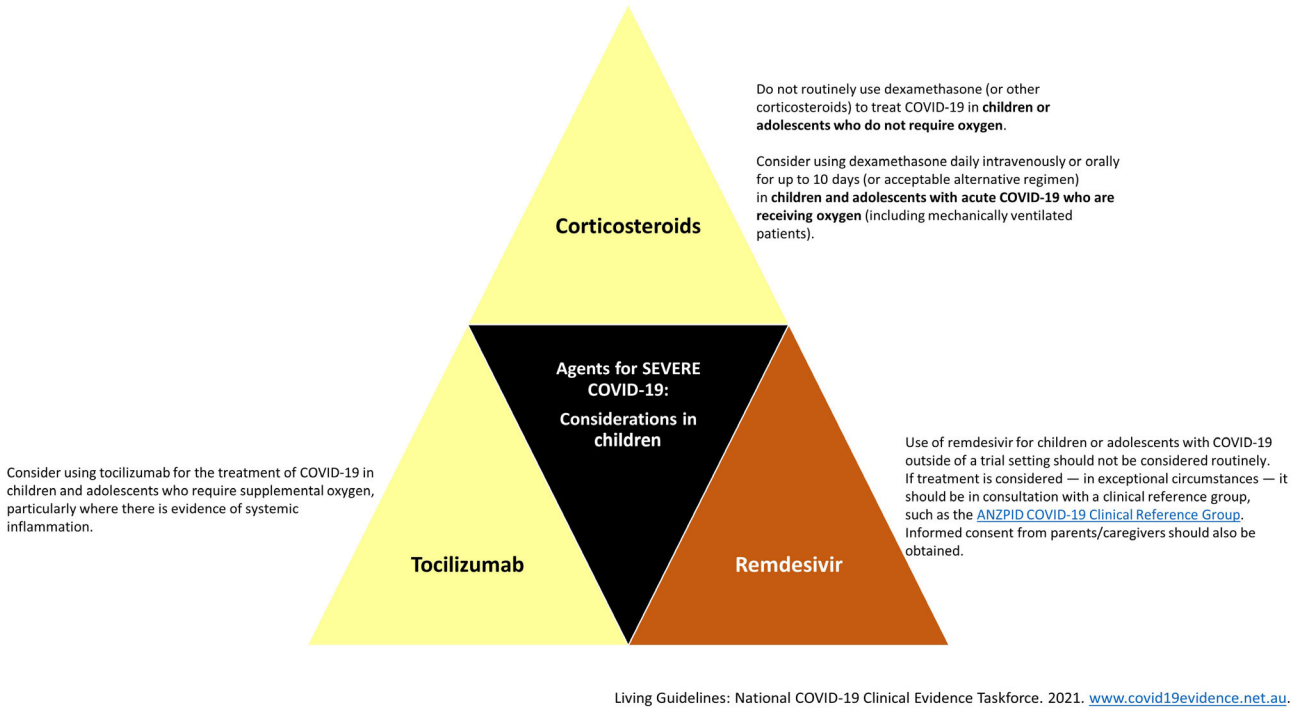

Fig 2 Pharmaceutical agents available for use in severe COVID-19 disease and important considerations for use in children,[55] based on the principles of Grading of Recommendations, Assessment, Development and Evaluations (GRADE). These considerations are reflective of advice current on 5 October 2021, which is updated regularly. The reader is directed to the most up-to-date recommendations at (■), Recommended; (■), conditional recommendation; (■), conditional recommendation *against*; (■), not recommended.

Treatment approaches for PIMS-TS are based on similarity to KD, a condition with which paediatricians are familiar.[58] In addition to supportive care, both intravenous immunoglobulin and corticosteroids – alone or in combination – are effective in reducing myocardial dysfunction and inflammation.[59]

Outcomes of COVID-19 in Children Including 'Long COVID'

Mortality from COVID-19 in children is extremely low, reportedly between 0.005% and 0.01%.[60] Whilst children with obesity or pre-existing conditions carry a relatively higher risk of death compared to those without co-morbidities, the additional absolute risk is very small. In neonates, data on COVID-19 outcomes are still emerging. All-cause mortality rates of 1.7–2.0% are described; however, most deaths were deemed not related to COVID-19 so should be interpreted with caution.[27,50]

Mortality rates vary widely between countries, likely contributed to by factors such as malnutrition, health-care access, delayed diagnosis and reduced ascertainment of paucisymptomatic patients.[61] Such factors are key determinants of COVID-19 disease outcome in low income countries. Specific groups subject to adverse social determinants of health in Australia, including those in remote settings and Aboriginal and Torres Strait Islander communities, need targeted risk mitigation to prevent worse outcomes.

'Long COVID', characterised by persistence of symptoms for over 3 months,[62] occurs mostly in those 12 years or over.[24] This condition, with a wide constellation of symptoms including fatigue, breathlessness, 'brain fog' and depression, hinders the patient's ability to re-engage with normal activities, and hence carries significant long-term morbidity.[63] There is marked heterogeneity in existing data, leading to variability in prevalence estimates (between 0% and 27% of children diagnosed with COVID-19). Reassuringly, a recent systematic review suggests that symptoms of 'long COVID' in children rarely persist beyond 8 weeks following the acute diagnosis.[64] Establishing a clear definition for 'long COVID' in children and identifying objective methods for surveillance are urgent priorities, alongside further research on associated risk factors, prevalence and natural history.[65] The inclusion of control groups in such studies will be important to account for the confounding impacts of the pandemic.

Outcomes from PIMS-TS appear promising in the short to medium term with low rates of coronary artery aneurysms and even lower mortality.[58] There have been approximately 37 reported deaths from PIMS-TS (MIS-C) across the USA during a period of high COVID-19 case numbers, and these occurred mostly early in the pandemic.[66] Studies of longer-term outcomes are ongoing.

Outstanding Questions Regarding Emerging Variants of Concern, Including the Delta Variant

Much of the early data on COVID-19 clinical phenotypes, diagnosis and management were based on the ancestral SARS-CoV-2 lineage. Emergence of novel variants of concern, including the Delta variant, is forcing re-evaluation of the applicability of this earlier information to the evolving features of newer SARS-CoV-2 variants. In one study, the emergent Delta variant has shown a viral load in the upper respiratory tract of adults three orders of magnitude higher than the ancestral strain.[67] For Delta as well as future variants of concern, ongoing validation of current diagnostic and treatment frameworks is warranted, including in children. Reassuringly, severity of COVID-19 disease in children due to the Delta variant appears largely unchanged with low hospitalisation and case fatality rates.[68]

Conclusions

The COVID-19 pandemic has brought monumental disruption spanning from global economic alliances to the lives of each individual child. Current understanding of immune response, diagnosis and treatment of COVID-19 is heavily skewed towards adult data. Whilst the acute pneumonitis of COVID-19 is typically mild in children, the complexities of its downstream manifestations, including PIMS-TS and 'long COVID', are incompletely elucidated. Children need to be prioritised in future research efforts given the clinical manifestations and impacts are so distinct in the paediatric setting compared to adult populations. The additional indirect impacts of the pandemic on the mental health, wellbeing and educational attainment of children are marked and must be considered alongside the clinical aspects discussed in this review.

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Madagascan toucan by Tyson Butt (age 9) from Operation Art 2021