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Clinical care of children and adolescents with COVID-19: recommendations from the National COVID-19 Clinical Evidence Taskforce

Abstract

Introduction: The epidemiology and clinical manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are different in children and adolescents compared with adults. Although coronavirus disease 2019 (COVID-19) appears to be less common in children, with milder disease overall, severe complications may occur, including paediatric multisystem inflammatory syndrome (PIMS-TS). Recognising the distinct needs of this population, the National COVID-19 Clinical Evidence Taskforce formed a Paediatric and Adolescent Care Panel to provide living guidelines for Australian clinicians to manage children and adolescents with COVID-19 and COVID-19 complications. Living guidelines mean that these evidence-based recommendations are updated in near real time to give reliable, contemporaneous advice to Australian clinicians providing paediatric care.

Main recommendations: To date, the Taskforce has made 20 specific recommendations for children and adolescents, including definitions of disease severity, recommendations for therapy, respiratory support, and venous thromboembolism prophylaxis for COVID-19 and for management of PIMS-TS.

Changes in management as a result of the guidelines: The Taskforce currently recommends corticosteroids as first-line treatment for acute COVID-19 in children and adolescents who require oxygen. Tocilizumab could be considered, and remdesivir should not be administered routinely in this population. Non-invasive ventilation or high flow nasal cannulae should be considered in children and adolescents with hypoxaemia or respiratory distress unresponsive to low flow oxygen if appropriate infection control measures can be used. Children and adolescents with PIMS-TS should be managed by a multidisciplinary team. Intravenous immunoglobulin and corticosteroids, with concomitant aspirin and thromboprophylaxis, should be considered for the treatment of PIMS-TS.

The latest updates and full recommendations are available at

Since December 2019, the world has faced the most significant pandemic for over a century. As of September 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 230 million people worldwide, resulting in more than 4.7 million deaths.[1] In Australia, strict isolation and quarantine measures have resulted in a comparatively low incidence of infections by global standards. Nonetheless, subsequent waves are requiring substantial additional lockdown measures to control viral spread. To date, there have been more than 100 000 confirmed SARS-CoV-2 infections and more than 1200 related deaths in Australia.[2] There have been over 25 000 children and adolescents aged less than 19 years infected with SARS-CoV-2 in Australia (a quarter of all cases of SARS-CoV-2 infection). The infection rate in 0–19-year-old children was 434 per 100 000, with one death reported in this age group in Australia, compared with 420 per 100 000 in adults.[2]

Although the recent deployment of vaccines internationally provides grounds for optimism, SARS-CoV-2 and its variants appear likely to remain threats to human health for years to come.[3] Researchers, clinicians and governments have quickly realised that establishing evidence for treatment and prevention is key to guiding patient care, not only in the coronavirus disease 2019 (COVID-19) pandemic but also in future pandemics. Clinical guidelines in the context of rapidly emerging evidence must be continually updated and tailored to specific populations, including children and adolescents.

COVID-19 in children and adolescents

Initial reports on the incidence of COVID-19 in China noted a limited number of severe cases and hospitalisations in children.[4] Larger international cohorts have confirmed that, in general, children have a much less severe acute form of the disease compared with adults, especially older adults.[5,6] However, SARS-CoV-2 infection can cause severe respiratory complications in children, especially in neonates and infants.[5,6] Other groups who appear disproportionately affected include children from minority ethnic groups in the United Kingdom and the United States[5,7] and children with comorbidities.[5] A review of COVID-19 mortality in children (> 8700 deaths worldwide as of May 2021)[8] showed larger fatality rates in lower and middle-income countries compared with higher income countries. The prevalence and severity of the disease for children and adolescents is likely to increase with the emergence of SARS-CoV-2 variants that affect younger people, such as the Delta strain.[9]

In early 2020, in addition to descriptions of acute COVID-19 in children, researchers in France[10] and the UK[11] reported a sudden increase in cases of apparent Kawasaki disease, including atypical presentations. This increase in paediatric inflammatory syndromes, later reported in the US and elsewhere, has now been recognised as temporally and causally associated with SARS-CoV-2 infection.[12] It has been termed paediatric

multisystem inflammatory syndrome (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C).[13,14] Although it has certain similarities with Kawasaki disease, differences in epidemiology and clinical features have cemented its current status as a distinct syndrome.[15,16]

The Australian response: the formation of a national taskforce

The Australian Living Evidence Consortium is a world leader in the development of living guidelines.[17] In March 2020, during the first wave of infection in Australia, the National COVID-19 Clinical Evidence Taskforce was established to produce living recommendations on the clinical care of people with COVID-19 in Australia, bringing together representatives from the peak health professional bodies whose members are providing clinical care to people with COVID-19. The Taskforce employs over 20 dedicated staff and involves more than 250 experts across all spheres of health care (average 360 volunteer hours per week). To develop recommendations specific to paediatric COVID-19 care, the Taskforce established a Paediatric and Adolescent Care (PAC) Panel. This Panel currently comprises 15 paediatric experts (53% women) from New South Wales, Victoria, Queensland, South Australia, Western Australia and the Northern Territory, including an Indigenous representative supported by the National Aboriginal Community Controlled Health Organisation, and representation from urban, rural and remote areas.

Methods

The living guidelines have been developed according to the Australian National Health and Medical Research Council (NHMRC) standards, including the use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The Taskforce uses the MAGICapp platform (https://magicevidence.org/) and its Evidence to Decision framework.[18] The guidelines were first approved by the NHMRC on 23 November 2020. Complete guideline methods are available online.[19,20] No primary data from human subjects were collected and, therefore, formal ethics approval was not sought.

Methodology issues specific to children and adolescents

Specific challenges to the provision of reliable guidance for the management of children and adolescents arise from the fact that this population is not routinely included in clinical trials.[21] Given the paucity of paediatric data, it was decided to include trial evidence from the adult population when considering paediatric recommendations. The PAC Panel noted that clinicians providing care for children and adolescents are familiar with this approach, including reviewing literature for safety and pharmacokinetic data in children, and extrapolating efficacy data from adult populations. Importantly, the resultant recommendations emphasise that rigorous clinical trials in paediatric populations are needed to establish strong evidence for interventions.[22]

As the guidelines used GRADE[23] methods, the Panel downgraded the certainty of the evidence for the outcomes of interest by one step (due to serious indirectness) if the studies being considered did not include children or adolescents. When no trial evidence in adults was available, the Panel decided to produce consensus recommendations based on best practice, data from similar conditions or treatments, and expert consensus.

As living guidelines, these recommendations are updated as new evidence, either from adults or children and adolescents, becomes available. The Taskforce's evidence team conducts daily searches for relevant population, intervention, comparison and outcomes (PICO) questions, constructed by and reviewed with the relevant panels meeting regularly to consider their findings.

For the development of PIMS-TS-specific recommendations, the Taskforce convened an expert advisory group to provide additional expertise to the PAC Panel. Experts in Kawasaki disease and related conditions advised the panel on this novel syndrome. As there was no evidence from clinical trials available for this condition, the Panel considered additional sources, including international, peer-reviewed guidelines and large, multicentre cohort studies reporting on PIMS-TS or MIS-C. The Panel then formulated consensus recommendations pending new, higher quality evidence, which will be reviewed as it becomes available.

Consumer input

The Taskforce, in collaboration with the Consumers Health Forum of Australia, convened a consumer panel beginning in June 2020, including members who were parents (including of children with health care needs) and/or involved in child advocacy, but no children or adolescents. This panel reviewed all PAC Panel recommendations, provided feedback and advised on the preferences and values of children, adolescents and their families and carers when formulating recommendations for the care of children and adolescents.

Pregnancy and perinatal care

For those recommendations involving newborn care and pregnancy and perinatal health care, collaborative discussions were held between the PAC Panel and the Pregnancy and Perinatal Care Panel to reach consensus. Recommendations for pregnancy and perinatal care have been recently published.[24]

Governance and review

Draft recommendations from the PAC Panel are reviewed and approved sequentially by the National Guidelines Leadership Group and the Steering Committee, which include representatives from the 32 Australian stakeholder organisations endorsing the guidelines.[25] The structure of the National COVID-19 Clinical Evidence Taskforce is shown in the online Supporting Information (figure 1).

Recommendations

Overarching principles

The overarching principles are detailed in the online Supporting Information (table 1). In general, our recommendations are aimed towards children under 16 years of age. The decision to apply paediatric or adult recommendations should be guided by consideration of the physical and developmental maturity of individual patients The term "child" also includes infants and neonates unless otherwise specified. The following recommendations are current as of 20 August 2021; any updates since publication are available at https://covid19evidence.net.au/.

Definition of disease severity

Box 1 provides the definitions of COVID-19 severity in children and adolescents (consensus recommendation). Cardiorespiratory and vital parameters must be considered within the normal age-appropriate ranges for neonates and children, and/or any pre-existing illness.

Disease-modifying treatments for COVID-19

Disease-modifying treatment recommendations for children and adolescents are shown in Box 2 and in the online Supporting Information (table 2), and the supporting evidence is summarised below.

Corticosteroids

Evidence informing these recommendations comes from a recent meta-analysis[28] of seven randomised controlled trials of patients with critical COVID-19;[29-36] one study of patients with moderate, severe and critical COVID-19;[26] and one study of patients with severe COVID-19.[36]

Evidence indicates that corticosteroids reduce deaths in adult patients with critical or severe COVID-19, but may increase deaths in adult patients with moderate COVID-19. Although these trials did not include children, due to a reduction in death along with no important resource implications and the likely acceptability of these drugs, we recommend considering using corticosteroids in children and adolescents with COVID-19 who are receiving oxygen, including mechanically ventilated children.

Remdesivir

Evidence supporting this recommendation comes from four randomised controlled trials that compared remdesivir with standard care in over 7300 adults hospitalised with COVID-19.[37-40]

Given the absence of children or adolescents in any of these trials, as well as concerns about how applicable this evidence is for the paediatric population (low certainty of the evidence due to serious indirectness), the PAC Panel considered that the potential benefits of remdesivir may not outweigh the harms, and that more research is needed in children and adolescents.

Tocilizumab

The evidence supporting the use of tocilizumab comes from ten randomised trials that compared cilizumab with standard care in 6570 adults hospitalised with COVID-19. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate to critical COVID-19.[35]

Evidence indicates that tocilizumab probably reduces the risk of death in hospitalised adults who require supplemental oxygen, as well as reducing the need for invasive mechanical ventilation and admission to the intensive care unit. Given this evidence, the previous experience on using tocilizumab in children plus the absence of trials in children and adolescents, the PAC Panel formulated a conditional recommendation supporting the use of tocilizumab in children and adolescents.

Treatments not recommended (strong recommendations against) and/or only recommended in trials

The Taskforce has issued a further 45 recommendations on a wide range of disease-modifying treatments (Box 2 and online Supporting Information, table 2). Full evidence summaries are available at https://app.magicapp.org/#/guideline/L4Q5An/section/L0OPkj.

Other treatments recommendations: venous thromboembolism prophylaxis

In the adult population, there has been concern of an increased risk for venous thromboembolism.[41] Paediatric guidelines published in the US in 2020 recommended a modified approach to thromboprophylaxis in children.[42] The PAC Panel currently considers that the evidence is insufficient to modify well established protocols of thromboprophylaxis in children and adolescents (Box 2 and online Supporting Information, table 2).

Respiratory support in neonates, children and adolescents

The paediatric population is particularly vulnerable to respiratory failure due to viral infection.[43] At the commencement of the COVID-19 pandemic, the roles of many established and evidence-based critical care respiratory support approaches were questioned due to the risk of infection of staff, patients and carers from aerosol generation. The Taskforce evaluated a diverse range of respiratory therapies, including non-invasive ventilation, management of the deteriorating child (including intubation and approaches to intubation), prone positioning, mechanical ventilation strategies and the use of high frequency oscillatory ventilation and extracorporeal membrane oxygenation.

The Taskforce has formulated ten recommendations on the management of respiratory support in children and adolescents (Box 3). There is currently no primary evidence on the benefits and harms of any of the respiratory support approaches in children and adolescents with COVID-19. Therefore, the PAC Panel relied on consensus and previous experience to issue these recommendations, noting that many of these therapies have established evidence, or are considered best practice, in other conditions with similar

pathophysiology to COVID-19, or are designed for disease processes that are known complications of COVID-19 (such as acute respiratory distress syndrome). Recommendations for the use of neuromuscular blockers and videolaryngoscopy were adapted from the evidence used in recommendations for adults, with specific commentary to reflect the equity, access and training limitations for these therapies in children.

Paediatric multisystem inflammatory syndrome

The panel reviewed all available definitions and reached consensus on endorsing the provisional case definition for PIMS-TS from the UK Royal College of Paediatrics and Child Health,[13] but also reviewed published articles using other common definitions, including MIS-C in the US.[12,44] This approach was considered suitable for reviewing global evidence and translating it to an Australian context. The panel also noted the initial definition and advice produced in the Australian context by the Paediatric Active Enhanced Disease Surveillance (PAEDS) network and the Royal Australasian College of Physicians.[45] The defining features of PIMS-TS are summarised in the online Supporting Information (table 3).[13] The recommendations for PIMS-TS management are informed by an ongoing living systematic review and evidence surveillance that includes observational studies, systematic reviews and meta-analyses as well as international guidance. Box 4 provides specific recommendations for the management and treatment of PIMS-TS.

Discussion

Developing paediatric evidence-based recommendations during a global pandemic has proven difficult and has produced unique challenges compared with other population groups. Traditionally, children have been excluded from clinical trials and this has remained the case for many COVID-19 therapies.[54] The Taskforce needed to rely on trial data from adults to formulate recommendations for children, with the well known limitations and risks of extrapolation this brings.[55] The need to consider certain paediatric subpopulations separately, such as neonates and adolescents, amplified this problem. Pragmatic adaptive trials such as RECOVERY[35] and WHO Solidarity[38] have proven to be successful methods of providing timely evidence; these trial designs could be applied to children and adolescents. Where high quality trial data do not exist, robust observational data are needed. Several established, and newly formed, prospective, multinational collaborations focusing on paediatric populations are providing rapid and useful information, especially when managing less frequent conditions such as PIMS-TS. In the Australian context, this includes initiatives such as the PAEDS network and the Australian and New Zealand Paediatric Infectious Diseases Group of the Australasian Society of Infectious Diseases.

Balancing the importance of providing the best therapy to a patient against the risks that it may pose to health care workers has been problematic during the COVID-19 pandemic. This was particularly relevant for the development of respiratory recommendations for children and adolescents. Non-invasive therapies were well

established before the COVID-19 pandemic and were based on a sound evidence base in paediatric critical care. Due to the high aerosol-generating potential of non-invasive therapies, this was questioned at the start of the pandemic, despite the higher morbidity profile associated with invasive therapies. These considerations, together with the lower total oxygen flow rates delivered to children compared with adults, were important in the recommendation to use non-invasive ventilation and high flow cannulae when appropriate infection control measures could be applied. Another important consideration is that dedicated paediatric critical care, especially invasive respiratory support, is highly centralised in Australia. This creates greater inequity in resource allocation (equipment and airway expertise) in rural and remote areas compared with adult populations.

Although it is not the primary objective of the Taskforce, concerns were raised by the PAC Panel regarding the impact that COVID-19 measures could have on wellbeing and psychosocial and developmental factors in children and adolescents, such as closures of schools and childcare services.[56] The potential impact of emerging aspects of the COVID-19 pandemic, such as "long COVID-19" and SARS-CoV-2-specific vaccinations, also need to be considered in children and adolescents. Development and psychosocial wellbeing of children affected by COVID-19 should be included as outcome measures in future research.

Conclusion

The Taskforce has successfully produced timely, evidence-based living guidelines for Australian clinicians (and beyond) managing COVID-19 in children and adolescents. The strength of diverse representative voices with the inclusion of different Australian health care and consumer stakeholders has enabled a values-driven and evidence-based approach. The evidence landscape is changing rapidly, and the guidelines will continue to adapt to this change. We encourage those who care for infants, children and adolescents affected by COVID-19 to keep up-to-date at https://covid19evidence.net.au/.

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[Insert boxes]

[Box 1]

1 Definitions of disease severity for children and adolescents with acute coronavirus disease 2019 (COVID-19)*

Disease severity	Feeding, hydration, conscious state	Respiratory and vital signs	Oxygen requirement†
Mild	▪ Normal or mildly reduced feeding	▪ No or mild upper respiratory tract symptoms, OR ▪ No or mild work of breathing	▪ No supplemental oxygen required to maintain Spo_2 > 92%
Moderate	▪ Poor feeding, unable to maintain hydration without nasogastric or intravenous fluids, AND ▪ Normal conscious state	▪ Moderate work of breathing, OR ▪ Abnormal vital signs for age (tachycardia, tachypnoea) but does not persistently breach early warning (eg, MET) criteria,‡ OR ▪ Brief self-resolving apnoea (infants)	▪ Requires low flow oxygen (nasal prongs or mask) to maintain SpO_2 > 92%
Severe	▪ Poor feeding, unable to maintain hydration without nasogastric or intravenous fluids, OR ▪ Drowsy or tired but easily rousable	▪ Moderate to severe work of breathing, OR ▪ Abnormal vital signs for age (tachycardia, tachypnoea) with breaches of early warning (eg, MET) criteria, OR ▪ Apnoea needing support or stimulation (infants)	▪ Requires high flow oxygen at 2 L/kg/min§ to maintain Spo_2 > 92%
Critical	▪ Poor feeding, unable to maintain hydration without nasogastric or intravenous fluids, OR ▪ Altered conscious state or unconscious	▪ Unable to maintain breathing or prevent apnoea without advanced modes of support, OR ▪ Abnormal vital signs for age with persistent breaches of early warning (eg, MET) criteria, OR ▪ Haemodynamically unstable without inotropic or vasopressor support, OR	▪ Requires advanced modes of support to maintain oxygenation: ‣ high flow nasal oxygen at > 2 L/kg/min,§ OR ‣ non-invasive ventilation, OR ‣ intubation and mechanical ventilation, OR ‣ extracorporeal membrane oxygenation

- Other organ failure

MET = medical emergency team; SpO_2 = peripheral oxygen saturation. * Depending on the physical size and/or developmental status of the patient, either the paediatric or adult severity grading can be applied. † Oxygen saturation targets should be modified for patients with cyanotic heart disease. ‡ Temperature instability should be considered an abnormal vital sign in infants. Fever is common in children and does not contribute to determination of illness severity in isolation. § Infants and neonates < 4 kg may be managed on high flow nasal cannula oxygen at 2–8 L/min irrespective of weight. Comorbidities (eg, preterm infants, oncology, immunosuppressed etc) may increase the risk of more severe disease.

[Box 2]

2 Disease-modifying treatment recommendations for children and adolescents

Treatment	Recommendations
Corticosteroids	Consider using dexamethasone daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in children and adolescents with acute COVID-19 who are receiving oxygen (including mechanically ventilated patients) (GRADE: low certainty; conditional recommendation) A dose of 6 mg daily is recommended in adults. The RECOVERY trial protocol recommended a dose of 0.15 mg/kg/day to a maximum of 6 mg/day for children, but it is not stated whether any children were included in the trial. If dexamethasone is not available, an acceptable alternative regimen would be: ▪ hydrocortisone: intravenous or intramuscular 1 mg/kg dose every 6 hours for up to 10 days (to a maximum dose of 50 mg every 6 hours); ▪ methylprednisolone may also be an acceptable alternative, but the most appropriate dosage is uncertain Do not routinely use dexamethasone (or other corticosteroids) to treat COVID-19 in children or adolescents who do not require oxygen (GRADE: low certainty; conditional recommendation against) Dexamethasone and other corticosteroids should still be used for other evidence-based indications in children or adolescents who have COVID-19 Specific recommendations on the use of corticosteroids for PIMS-TS available at https://app.magicapp.org/#/guideline/L4Q5An/section/nVp73j
Tocilizumab	Consider using tocilizumab for the treatment of COVID-19 in children and adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation (GRADE: low certainty; conditional recommendation) There is no established dose for tocilizumab for the treatment of acute COVID-19 in children and adolescents (the Taskforce notes that RECOVERY is recruiting children and adolescents with PIMS-TS for their trial of tocilizumab[26]). Tocilizumab should be administered as a single intravenous infusion over 60 minutes, with the potential for a second dose to be administered either 12 or 24 hours later if the patient's condition has not improved Following protocol information in the RECOVERY trial, as well as previous literature on the use of tocilizumab for other indications, the suggested dose is dependent on body weight: ▪ infants aged < 1 year (excluded from RECOVERY trial): dosing from other uses 12 mg/kg ▪ children weighing < 30 kg: 12 mg/kg ▪ children weighing > 30 kg: 8 mg/kg (maximum 800 mg) In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration the availability of tocilizumab In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab in adults. Use of

	combined tocilizumab and corticosteroids should be considered in children and adolescents hospitalised with COVID-19 who require oxygen; however, the optimal sequencing of tocilizumab and corticosteroid use is unclear in all populations As tocilizumab inhibits the production of CRP, a reduction in CRP should not be used as a marker of clinical improvement
Remdesivir	Use of remdesivir for children or adolescents with COVID-19 outside a trial setting should not be routinely considered (GRADE: low certainty; conditional recommendation against) ▪ If treatment is considered — in exceptional circumstances — it should be in consultation with a clinical reference group, such as the ANZPID COVID-19 Clinical Reference Group (https://www.asid.net.au/groups/anzpid). Informed consent from parents or caregivers should also be obtained. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the "practical info tab" at https://app.magicapp.org/#/guideline/L4Q5An/rec/jz9PeE. Trials of remdesivir in children and adolescents are currently being conducted, this recommendation will be updated once new evidence is available ▪ Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended in vitro[27]
Other treatments not recommended	Do not use aspirin, azithromycin, colchicine, convalescent plasma, hydroxychloroquine, hydroxychloroquine plus azithromycin, interferon-β-1a, lopinavir-ritonavir or interferon-β-1a plus lopinavir-ritonavir, for the treatment of COVID-19 (GRADE: high certainty; strong recommendation)* ▪ This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty, and those receiving palliative care. Use of these drugs may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include these drugs ▪ Rationale: the panel considered that, although none of these trials included children, given the absence of benefit in the adult population, there is no evidence that will point to a dissimilar effect in children. Hence, although indirect evidence, it was decided to recommend against these treatments, consistent with adult recommendations
Venous thromboembolism prophylaxis for children and adolescents	For children and adolescents admitted to hospital with COVID-19, refer to local thromboprophylaxis protocols and seek expert advice (Consensus recommendation) ▪ Trials of thromboprophylaxis in children and adolescents are recruiting and this recommendation will be updated once new evidence is available ▪ There is insufficient evidence in children and adolescents to recommend a modified thromboprophylaxis regimen ▪ Consider known risk factors for initiating thromboprophylaxis in children and adolescents

ANZPID = Australia and New Zealand Paediatric Infectious Diseases Group; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; GRADE = Grading of Recommendations Assessment Development and Evaluation; PIMS-TS = paediatric inflammatory multisystem syndrome;

RECOVERY = Randomised Evaluation of COVID-19 Therapy; REMAP-CAP = Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia study. * Text adapted from current recommendations.

[Box 3]

3 Respiratory support in neonates, children and adolescents

	Type of respiratory support
Non-invasive respiratory support	▪ High flow nasal oxygen and other modes of non-invasive ventilation ‣ Consider using high flow nasal oxygen or non-invasive ventilation* therapy for neonates, children and adolescents with hypoxaemia or respiratory distress associated with COVID-19 and not responding to low flow oxygen. Due to the potential for aerosol generation, use non-invasive ventilation with caution and pay strict attention to staff safety, including the use of appropriate personal protective equipment (Consensus recommendation) ▪ Prone positioning (non-invasive ventilation) ‣ For neonates, children and adolescents with COVID-19 and respiratory symptoms who are receiving non-invasive respiratory support, consider prone positioning if patient cooperation is possible. When placing a patient in the prone position, ensure close monitoring of the patient (Consensus recommendation) ▪ Respiratory management of the deteriorating child ‣ Consider endotracheal intubation and mechanical ventilation in neonates, children and adolescents with COVID-19 who are deteriorating despite optimised, non-invasive respiratory support (Consensus recommendation)
Patients requiring invasive mechanical ventilation	▪ Prone positioning (mechanical ventilation via an endotracheal tube or tracheostomy) ‣ For mechanically ventilated neonates, children and adolescents with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning if there are no contraindications. Ensure close monitoring of the patient (Consensus recommendation) ▪ Positive end-expiratory pressure (PEEP) ‣ For mechanically ventilated neonates, children and adolescents with COVID-19 and moderate to severe ARDS with atelectasis, consider using a higher PEEP strategy over a lower PEEP strategy. The absolute PEEP values that constitute a high and low PEEP strategy will depend on age and patient size (Consensus recommendation)

- Recruitment manoeuvres
  - For mechanically ventilated neonates, children and adolescents with COVID-19 and hypoxic respiratory failure characterised by severe atelectasis unresponsive to other ventilation strategies, consider using applied airway pressure recruitment manoeuvres (Consensus recommendation)
- Neuromuscular blockers
  - For intubated neonates, children and adolescents with COVID-19, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs). However, if effective lung-protective ventilation cannot be achieved, consider targeted intermittent use of NMBAs. If indicated, the choice of NMBA should be guided by the age group and regional practice (GRADE: very low certainty; conditional recommendation against)
- High frequency oscillatory ventilation (HFOV)
  - Do not routinely use HFOV as a first line mode of mechanical ventilation in neonates, children and adolescents with severe COVID-19. HFOV should be limited to a rescue therapy in neonates and children not responding to conventional mechanical ventilation in a specialist centre with experience with HFOV. HFOV delivers gas at very high flow rates. This may increase the aerosol-generating potential compared with other forms of respiratory support used in intensive care. This may limit the suitability of HFOV in patients with COVID-19 unless strict attention to staff safety and infection control measures can be applied (Consensus recommendation)
- Videolaryngoscopy
  - In neonates, children and adolescents with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy, if available, and the operator is trained in its use (GRADE: very low certainty; conditional recommendation)
- Extracorporeal membrane oxygenation (ECMO)
  - Consider early referral to an ECMO centre for venovenous or venoarterial ECMO in mechanically ventilated neonates, children and adolescents with COVID-19 with refractory respiratory or cardiovascular failure despite optimising other critical care interventions (Consensus recommendation)

ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; GRADE = Grading of Recommendations Assessment, Development and Evaluation. * Non-invasive ventilation modes include any mode of applied pressure support delivered without an endotracheal tube during spontaneous breathing, such as continuous positive applied pressure, bilevel positive applied pressure, non-invasive intermittent positive pressure ventilation via mask or nasal prongs.

[Box 4]

4 Paediatric inflammatory multisystem syndrome (PIMS-TS) recommendations

Management of children with PIMS-TS*	Recommendation	Remarks	Rationale
IVIg plus corticosteroids	Consider using IVIg (2 g/kg per dose) in combination with methylprednisolone in children and adolescents who meet PIMS-TS criteria (Conditional recommendation)	IVIg should be considered for all children with complete or incomplete Kawasaki disease, irrespective of whether it may be related to COVID-19. Depending on the age and the phenotype expression of PIMS-TS, combination therapy of IVIg and corticosteroids should be considered as a first line therapy.[46-48] This is particularly relevant for older children with myocardial dysfunction, as opposed to younger children with a more Kawasaki disease-like phenotype Note that the oncotic load from a large IVIg dose should be considered when administering this agent to children with myocardial dysfunction.[49] For selected cases of PIMS-TS with severe myocardial dysfunction, corticosteroid treatment alone and/or delayed use of IVIg may be beneficial Further details on the evidence underpinning this recommendation available at https://app.magicapp.org/#/guideline/L4Q5An/rec/jmPNAE	Three observational studies on the management of PIMS-TS have been identified:[46-48] ▪ An international observational cohort study[47] compared treatment of IVIg plus glucocorticoids to IVIg alone and glucocorticoids alone in children with multisystem inflammatory syndrome after suspected COVID-19 infection. The primary outcomes were a composite of inotropic support or mechanical ventilation (invasive or non-invasive) by day 2 or later or death, and reduction in disease severity. The study found that IVIg plus steroids compared with IVIg alone made no difference in the receipt of inotropic or ventilatory support or death (*n* = 410; OR, 0.77; 95% CI, 0.33–1.82) or compared with steroids alone (*n* = 307; OR, 0.54; 95% CI, 0.22–1.33) ▪ A cohort study[48] conducted in the United States compared IVIg plus glucocorticoids with glucocorticoids alone.[2] The primary outcome was cardiovascular dysfunction on or after day 2 through discharge or shock that resulted in the

use of vasopressors. The study found that IVIg plus steroids compared with IVIg alone was associated with lower cardiovascular dysfunction after day 2 (*n* = 212; RR, 0.56; 95% CI, 0.34–0.94)

- Data from the two studies were pooled from the previously included study[46] for the guideline. IVIg combined with steroids compared with IVIg alone were found to probably reduce the need for escalation or adjunctive immunomodulatory therapy (moderate certainty of the evidence; upgraded due to large treatment effect) and may decrease left ventricular dysfunction (low certainty of the evidence)

Corticosteroids	Consider using corticosteroids (irrespective of oxygen status) as adjuvant therapy for children and adolescents diagnosed with PIMS-TS (Consensus recommendation)	Intravenous corticosteroids (eg, methylprednisolone) may be given before, or in combination with, IVIg.[47] Corticosteroids should be considered as the next treatment option for children who remain unwell (tachycardia, need for vasoactive support) 24 hours after infusion of IVIg, particularly if they have ongoing pyrexia or have not received corticosteroids as a first line treatment For selected cases of PIMS-TS with severe myocardial dysfunction, corticosteroid treatment alone and/or delayed use of IVIg may be beneficial[50]	Corticosteroids are used for the treatment of several conditions and, in particular, in high risk refractory cases of Kawasaki disease[50]
Other immunomodulatory agents	Additional immunomodulatory agents for PIMS-TS (anti-IL-1, anti-IL-6 or anti-TNF) should be considered as a third-line option in children and adolescents with PIMS-TS who do not respond to intravenous immunoglobulin and corticosteroids (Consensus recommendation)	Before initiating additional immunomodulatory therapies, all patients with PIMS-TS need to be discussed with a multidisciplinary team and interventions carefully considered. Immunomodulatory agents previously used that have an acceptable risk–benefit ratio include: anakinra (IL-1 receptor antagonist), infliximab (TNF inhibitor), and tocilizumab (IL-6 receptor antagonist). Consider testing for infections that may be unmasked by the use of these agents	Immunomodulatory agents are routinely used to treat a range of rheumatological conditions in children and adolescents and may limit the hyperinflammatory state associated with this syndrome. Given the partial characterisation of PIMS-TS, immunomodulatory agents have occasionally been used for its treatment in international cohorts[51,52]
Aspirin and other antithrombotic agents	Children who are treated for PIMS-TS with IVIg or other agents should also be prescribed low-dose aspirin (3–5 mg/kg once	Additional measures to be considered to prevent venous thrombosis associated with PIMS-TS include anticoagulation therapy and compression stockings (in children older than 12 years of age)	Aspirin is used as an antithrombotic to prevent coronary artery thrombosis in Kawasaki disease[53]

	daily for at least 6 weeks) (Consensus recommendation)

COVID-19 = coronavirus disease 2019; IL = interleukin; IVIg = intravenous immunoglobulin; OR = odds ratio; RR = risk ratio; TNF = tumour necrosis factor. * Children and adolescents who have suspected or confirmed PIMS-TS should be managed by and discussed with a multidisciplinary team. Because of the potential for rapid deterioration, early consultation with experts and consideration of early transfer to a paediatric hospital with intensive care facilities to manage children are recommended for patients with suspected or confirmed PIMS-TS (Consensus recommendation).