Guidelines for the Prevention and Management of Children and Adolescents with COVID-19

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Abstract

Purpose: Children are the future of the world, but their health and future are facing great uncertainty because of the Coronavirus disease 2019 (COVID-19) pandemic. In order to improve the management of children with COVID-19, an international, multidisciplinary panel of experts developed a rapid advice guideline at the beginning of the outbreak of COVID-19 in 2020. After publishing the first version of the rapid advice guideline, the panel has updated the guideline by including additional stakeholders in the panel and a comprehensive search of the latest evidence.

Methods: All recommendations were supported by systematic reviews and graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Expert judgment was used to develop good practice statements supplementary to the graded evidence-based recommendations.

Results: The updated guideline comprises nine recommendations and one good practice statement. It focuses on the key recommendations pertinent to the following issues: identification of prognostic factors for death or pediatric intensive care unit admission; the use of remdesivir, systemic glucocorticoids and antipyretics, intravenous immunoglobulin (IVIG) for multisystem inflammatory syndrome in children, and high-flow oxygen by nasal cannula or non-invasive ventilation for acute hypoxemic respiratory failure; breastfeeding; vaccination; and the management of pediatric mental health.

Conclusions: This updated evidence-based guideline intends to provide clinicians, pediatricians, patients

and other stakeholders with evidence-based recommendations for the prevention and management of COVID-19 in children and adolescents. Larger studies with longer follow-up to determine the effectiveness and safety of systemic glucocorticoids, IVIG, noninvasive ventilation, and COVID-19 vaccines for COVID-19 in children and adolescents are encouraged.

Keywords: COVID-19, SARS-CoV-2, Children, Guidelines, Prevention, Management

Introduction

The worldwide spread of coronavirus disease 2019 (COVID-19) represents a serious threat to the health of children. As of June 30, 2022，nearly 13.8 million children have tested positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection since the onset of the pandemic, and children comprised 18.7% of all cases [1]. Omicron has rapidly replaced the Delta variant and become the dominant SARS-CoV-2 variant responsible for most infections, since it was first detected in November, 2021[2]. Since the emergence of the Omicron variant, the number of COVID-19 cases in children has dramatically increased [1], reigniting concerns about how to appropriately manage SARS-CoV-2 infection in children.

Since the beginning of the COVID-19 outbreak close to 100 international and national clinical practice guidelines (CPGs) for the management of adult COVID-19 patients have been developed [3]. However, there are so far only few evidence-based guidelines specifically focusing on pediatric COVID-19 [4]. The management of pediatric patients differs in many aspects from that of adults [5]. For example, COVID-19 is usually milder in children than adults [6]. Interventions used to treat adults may not be effective and safe in children. In addition, there are topics such as breastfeeding during the pandemic that are specific to children and, although mentioned in some guidelines [7,8], not necessarily covered by

most adult or general guidelines.

In response to these issues, we published the first international *Rapid Advice Guidelines for Management of Children with COVID-19* in May 2020 [9]. We provided ten recommendations addressing the most common questions in the diagnosis and management of children with COVID-19, based on the knowledge of the disease at the time of the guideline publication. Along with the emergence of new evidence related to the management of COVID-19 in children and adolescents over the last years, more information about COVID-19 related clinical syndromes has become available [10,11]. According to the World Health Organization (WHO) guideline development methodology, a standard (instead of a rapid) guideline is recommended for public health emergencies that have lasted over six months [12]. We updated the original guideline [9] following methodological handbooks [13,14], and reported the contents according to the Reporting Items for Practice Guidelines in Healthcare (RIGHT) checklist and the Checklist for the Reporting of Updated Guidelines (CheckUp) [15,16]. We registered the guideline at the International Practice Guidelines Registry Platform (http://guidelines-registry.org/, registration No. IPGRP-2020CN101) and published the guideline protocol [17].

Guideline working group

Building on the panel of the previous version of the guideline, two chairs (EL, RLS) invited and recruited more new panelists in developing this guideline, with the aim of enhancing the diversity in expertise, geographical origin and gender among the panel members. The updated panel comprised 18 specialties including pediatric respiratory medicine, pediatric infectious diseases, pediatric critical care medicine, neonatology, pediatric nephrology, pediatric immunology, general pediatrics, pulmonary and critical care

medicine, infectious diseases, nursing, radiology, epidemiology, global health, health technology assessment, health policy, health economics, law, and statistics. The newly added methodologists (GG, IDF) have rich experience in updating guidelines and using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument. The newly added pulmonary physician (BC) has experience in clinical trials on drugs for COVID-19. We also considered gender balance, nearly half of the panelists were female.

The international guideline working group comprised 69 members: 45 members of the original guideline working group and 24 new members. Members were allocated to four specific groups: 1) a steering group comprised of five members, including the chair (EL) and co-chair (RLS), a chief methodologist (YC) and two chief clinical experts (QL and ZL); 2) a consensus group comprised of 41 members; 3) an evidence synthesis and evaluation group comprised of 20 members with experience conducting systematic reviews; and 4) a patient partner group with two guardians of children and a child patient. **Appendix 1 Table 1** presents detailed information about the guideline working group.

Declaration and management of conflict of interests (COIs)

Our competing interest procedures adhered to the principles of the Guidelines International Network [18]. Before starting the updating process, all members of the guideline working group and the external reviewers declared their financial and intellectual interests. Each member completed and signed the form for declaration of interests (DOI). Two chairs (EL, RLS) and one methodologist (YC) who themselves had no COI reviewed all DOI forms and decided upon the final list of participants. **Appendix 1 Table 2** presents a summary of the DOI statements and information on how conflicts of interest were managed.

Appendix 2 includes all DOI forms filled by the group members.

Scope of the guideline

The guideline focuses on the prevention and management of COVID-19. The target population of the updated guideline is children and adolescents younger than 18 years old infected, or at risk of infection, by SARS-CoV-2. The target audience includes clinicians, pediatricians, clinical pharmacists, general practitioners, nurses and other health workers in general and children's hospitals, primary clinics and communities worldwide as well as families involved in the care of children with COVID-19.

Methodology

Formulating clinical questions

To identify a preliminary set of clinical questions, we first performed a systematic review of existing CPGs for managing COVID-19 in children[4] and noted the research gaps they identified, as well as existing clinical trials for COVID-19 in children. Second, we conducted semi-structured interviews with three experienced pediatricians. The steering group then drafted an initial list of preliminary clinical questions. All questions used the PICO format, which describes the population (P), intervention (I), comparison (C), and outcomes (O). Panelists used a seven-point Likert scale to rate whether each question should be included in the guideline [19]. The guideline included clinical questions achieving high total scores without substantial dissent and approved by all steering group members.

Evidence retrieval, evaluation, and synthesis

We performed for each question a systematic literature search of the WHO COVID-19 Database,

MEDLINE (via PubMed), The Cochrane Library, Web of Science, Embase, China Biology Medicine disc, China National Knowledge Infrastructure, and Wanfang from January 1, 2020, through July 13, 2022. Systematic reviews that met the requirements to answer our clinical questions were used directly; if such reviews were not found, we conducted new systematic reviews. We critically appraised the methodological quality of the publications using standard tools such as A Measurement Tool to Assess Systematic Reviews (AMSTAR) scale for systematic reviews [20], the Cochrane Risk of Bias tool (ROB 1.0) for randomized controlled trials (RCTs) [21], the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies [22], and the Newcastle-Ottawa Scale (NOS) for observational studies [23]. We used the GRADE approach to rate the quality of evidence and the strength of recommendations (**Table 1**) [24]. We also provided "good practice statements (GPS)" proposed by the GRADE Working Group in our guideline [25].

Formulation of the recommendations

We drafted preliminary recommendations based on the evidence for each question, balance of benefits and harms, patients' values and preferences, and cost considerations [24]. The consensus group and patient representatives participated in two rounds of Delphi survey and voted for the preliminary recommendations and gave their comments. Recommendations were taken to have reached a consensus when 70% of the voters agreed on the recommendation.

External review

Two external experts (Dr Yu-Lung Lau, Chair Professor of Pediatrics, University of Hong Kong and Dr Anthony Que, Clinical pharmacist, Lanzhou University) reviewed the final draft guideline. The two

chairs (EL, RLS) and one methodologist (YC) discussed feedback from the external reviews and revised the guideline based on their comments and suggestions.

Results

We initially identified eight clinical questions. We subsequently added a clinical question on COVID-19 vaccination for children because the issue has recently received significant attention from physicians, the public, and policymakers. All panelists agreed and approved the new question. We found two existing living systematic reviews to support clinical questions on high-flow oxygen by nasal cannula (HFNC) or non-invasive ventilation (NIV) and breastfeeding [26-28]. We conducted four systematic reviews to support the other clinical questions [29-32]. We present the summary of recommendations in **Figure 1**, including the new items and the changes to the previous guideline recommendations. **Appendix 1 Table 3** presents the process of formulating clinical questions, **Appendix 1 Table 4** presents the final list of PICO questions, and **Appendix 1 Table 5** presents a detailed overview of the new recommendations, previous recommendations, and the rationale for changes.

Recommendations

We display the final list of the recommendations along with their strength and the certainty of the supporting evidence in **Table 2**. Each recommendation is labelled as new, modified, or unchanged. The following sections describe the details of each question and the summary of the evidence and consensus process that support each recommendation.

Clinical question 1: What are the main prognostic factors for death or pediatric intensive care unit

(PICU) admission in children and adolescents with COVID-19?

Recommendation 1: We suggest that pediatricians and other guideline users should identify the presence of prognostic factors for death or PICU admission in children and adolescents with COVID-19 at an early stage. The main prognostic factors for death are multisystem inflammatory syndrome in children (MIS-C) complications and acute kidney injury (AKI); the prognostic factors for PICU admission include AKI, Acute Respiratory Distress Syndrome (ARDS), MIS-C complications, chronic pulmonary disease, and congenital heart disease *(Conditional recommendation, very low certainty of evidence) (New)*.

Evidence summary

Our systematic review included 56 observational studies (22 cohort studies, nine case-control studies and 25 case series) with 79,104 children and adolescents with COVID-19, with data collected between January, 2020 and July, 2021 [29]. MIS-C complications (OR 58.00, 95% CI: 6.39 to 526.79) and AKI (OR 3.15, 95% CI: 1.25 to 7.90) increased the odds of death. AKI (OR 55.02, 95% CI: 6.26 to 483.35), ARDS (OR 29.54, 95% CI: 12.69 to 68.78), MIS-C complications (OR 3.83, 95% CI: 1.48 to 9.87), chronic pulmonary disease (OR 3.45, 95% CI: 1.47 to 8.07), and congenital heart disease (OR 2.90, 95% CI: 1.26 to 6.67) increased the odds of PICU admission.

Explanation

Most children with COVID-19 have milder clinical symptoms and better prognosis than adults [33]. However, as the number of SARS-CoV-2 infected children and adolescents continues to rise globally, the number of children with severe forms of the disease, including complications such as respiratory failure and multiple organ failure also increases. Therefore, identifying the prognostic factors for unfavorable outcomes is crucial to identify the children at highest risk early, and to allow hierarchical

management and prevention of disease progression.

Only a few guidelines that focus on prognosis of COVID-19 in children exist. The guidelines of the Centers for Disease Control and prevention (CDC) indicate that the risk of developing severe COVID-19 for children was higher if pre-existing conditions, such as obesity, diabetes, asthma, chronic lung disease, or immunosuppression, were present [34]. One consensus statement mentioned that increased respiratory rate, poor mental response or lethargy, progressive elevation of lactate levels, bilateral or multiple lobar infiltrates, pleural effusion or rapid progression of pulmonary lesions in the short term, and age less than 3 months were predictors for developing severe or critical COVID-19 [35]. A systematic review showed that male sex, elevated inflammatory markers (including C-reactive protein [CRP], procalcitonin, ferritin, and D-dimer), and decreased lymphocyte count were associated with various indicators of poor prognosis including death, PICU admission, progression to critical disease, progression to MIS-C, need of respiratory support, organ dysfunction, and hospitalization in children with COVID-19 [36].

Clinical question 2: Should remdesivir be used to treat children and adolescents with COVID-19?

Recommendation 2: We suggest standard care without remdesivir to treat children and adolescents with COVID-19 ***(Conditional recommendation, very low certainty of evidence) (Modified)*****.**

Evidence summary

Our systematic review identified three single-arm cohort studies with 112 children and adolescents with COVID-19, with data collected between January, 2020 and August, 2021 [30]. In one of these studies, all patients had severe COVID-19 [37]; in another study, 75% of the patients were admitted to the pediatric intensive care unit (PICU) [38]; and in the third study, 22% of the patients received mechanical

ventilation [39]. The pooled results showed that among those treated with remdesivir, 5.9% (95% confidence interval [CI]: 1.5% to 10.2%) died, 37.2% (95% CI: 0.0% to 76.0%) needed extra-corporeal membrane oxygenation (ECMO) or invasive mechanical ventilation (IMV), 37.1% (95% CI: 0.0% to 74.5%) experienced adverse events, and 16.2% (95% CI: 1.8% to 30.5%) experienced serious adverse events.

One published living systematic review of four clinical trials with 3826 hospitalized adults with COVID-19 found little to no difference between patients receiving or not receiving remdesivir in the main outcomes: mortality (odds ratio [OR] 0.90, 95% CI: 0.72 to 1.11), mechanical ventilation (OR 0.75, 95% CI: 0.52 to 0.98), viral clearance at 7 days (OR 1.06, 95% CI: 0.35 to 3.20), time to symptom resolution (ratio of mean days with symptoms between remdesivir and standard care 0.82, 95% CI: 0.64 to 1.06) [40].

Explanation

Remdesivir is a broad-spectrum antiviral agent that can integrate into the ribonucleic acid (RNA) strand of SARS-CoV-2 and prematurely terminate the RNA replication process [41]. On October 22, 2020, the U.S. Food and Drug Administration (FDA) approved remdesivir for the treatment of COVID-19 in children and adolescents aged at least 12 years and weighing at least 40 kg requiring hospitalization [42]. Now, it expanded the approval of an use of remdesivir to treat pediatric patients 28 days of age and older weighing at least 3 kilograms with SARS-CoV-2 infection, who are hospitalized, or not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19 [43]. Only a few single-arm cohort studies of remdesivir for the treatment of COVID-19 in children have been published [37-39]. Its efficacy and safety for treating children and adolescents with COVID-19 is currently uncertain. The recommendations for remdesivir therapy vary greatly among different countries

and organizations [44-46]. Given the uncertainty of the effectiveness and safety of remdesivir in children, as well as the situation that the drug was not licensed for use in most countries and regions, the panelists made the final decision not to recommend its use under standard care after consulting two patient members of the panel for their preferences.

Clinical question 3: Should antipyretics (ibuprofen or paracetamol) be used to treat children and adolescents with COVID-19?

Recommendation 3: We suggest that antipyretics (ibuprofen or paracetamol) can be used to relieve fever and pain in children and adolescents with COVID-19 ***(Conditional recommendation, very low certainty of evidence) (New).***

Evidence summary

Our systematic review included 40 studies (37 retrospective cohort studies and three prospective cohort studies) with 4,881,423 adults with COVID-19, with data collected between January, 2020 and November, 2021 [31]. During the COVID-19 pandemic, the use of non-steroidal anti-inflammatory drugs (NSAIDs) was shown to potentially reduce mortality (OR 0.89, 95%CI: 0.72 to 1.11; adjusted odds ratio [aOR] 0.71, 95% CI: 0.58 to 0.87 compared with people who did not receive NSAIDs). The use of NSAIDs was not significantly associated with higher risk of SARS- CoV-2 infection (OR 0.96, 95% CI: 0.86 to 1.07; aOR 1.01, 95% CI: 0.94 to 1.09), ICU admission (OR 1.28, 95% CI: 0.94 to 1.75; aOR 0.89, 95% CI: 0.65 to 1.22), requiring mechanical ventilation (OR 1.11, 95% CI: 0.79 to 1.54; aOR 0.80, 95% CI: 0.52 to 1.24), or administration of supplemental oxygen (OR 0.80, 95% CI: 0.52 to 1.24; aOR 1.00, 95% CI: 0.89 to 1.12). The subgroup analyses revealed that, compared with not using any NSAID, the use of ibuprofen (OR 1.09, 95% CI: 0.50 to 2.39; aOR 0.95, 95% CI: 0.78 to 1.16) and Cyclooxygenase-

2 (COX-2) inhibitor (OR 0.62, 95% CI: 0.35 to 1.11; aOR 0.73, 95% CI: 0.45 to 1.18) were not associated with an increased risk of death during the COVID-19 pandemic.

Explanation

Ibuprofen and paracetamol are commonly used as antipyretic drugs in children [47]. Their effectiveness for reducing fever or pain is undisputed. However, concerns exist that the use of NSAIDs could worsen COVID-19 symptoms [48,49]. In vitro experiments confirmed that SARS-CoV-2 virus can invade human cells by binding to angiotensin-converting enzyme-2 (ACE2), and ibuprofen can increase the bioavailability of ACE2 to a certain extent, thereby enhancing the viral replication process [50,51]. Therefore, ibuprofen might exacerbate the progression of the disease [52]. However, the evidence we collected shows that the drug is safe for adults with COVID-19. Despite the indirectness of the evidence for this result for children with COVID-19, the panel remains somewhat confident that the use of ibuprofen is relatively safe for children with COVID-19. Therefore, panelists suggest that ibuprofen can still be used if necessary. Recommendations for ibuprofen in other guidelines are also consistent with ours [53,54].

Clinical question 4: Should systemic glucocorticoids be used to treat children and adolescents with severe COVID-19?

Recommendation 4: We suggest low-dose short-course dexamethasone therapy for children and adolescents with severe COVID-19 ***(Conditional recommendation, low certainty of evidence) (Modified)*****.**

Evidence summary

Our systematic review, which included one prospective cohort study and one case series with a total of

69 children and adolescents with COVID-19, with data collected between January, 2020 and August, 2021, did not find statistically significant impact of glucocorticoid therapy on the critical outcomes mortality (OR 2.79, 95% CI: 0.13 to 60.87), mechanical ventilation (OR 2.83, 95% CI: 0.78 to 10.30) or duration of PICU admission (weighted mean differences [WMD] 2.0, 95% CI: -0.95 to 4.95) when compared with no glucocorticoid therapy [30].

One published systematic review included fourteen RCTs on glucocorticoid therapy with over 2000 adult COVID-19 patients [40]. Compared with standard care, corticosteroids probably reduce mortality (risk difference [RD] 20 fewer deaths per 1000 patients, 95% CI: 36 fewer to 3 fewer) and mechanical ventilation (RD 25 fewer per 1000, 95% CI: 44 fewer to 1 fewer), and increase the number of days free from mechanical ventilation (RD 2.6 more, 95% CI: 0.3 more to 5.0 more). Another published systematic review included seven RCTs with 1703 critically ill adult COVID-19 patients [55]. The 28-day all-cause mortality was lower in patients receiving dexamethasone than in patients receiving usual care or placebo (OR 0.64, 95% CI: 0.50 to 0.82); mortality did not differ between patients receiving hydrocortisone (OR 0.69, 95% CI: 0.43 to 1.12 compared with usual care or placebo) and patients receiving methylprednisolone (OR 0.91, 95% CI: 0.29 to 2.87 compared with usual care than placebo).

Explanation

Glucocorticoids are the most widely used, effective anti-inflammatory and immunosuppressive agents in clinical practice, and they can reduce the severity of inflammatory lung injury in patients with severe COVID-19 [56-58]. Although there are so far no high-quality clinical trials confirming the efficacy of glucocorticoid therapy for COVID-19 in children and adolescents, the efficacy of dexamethasone has been demonstrated in adult patients [56]. Dexamethasone is inexpensive, easy to administer and readily available globally [58]. A short course of dexamethasone therapy is generally safe and does not increase

the risk of adverse events among critically ill patients [55]. Although our direct evidence from children, due to the small sample size, does not yet prove its effectiveness, glucocorticoid therapy is becoming routine in the treatment of adult patients with COVID-19. After balancing the potential risks and benefits of the drug in children, the panel believed that it may potentially be associated with lower mortality. The panel therefore suggested to use low-dose (0.15 to 0.3 mg/kg/dose once daily, maximum 6 mg) and short-course (generally 3-5 days, up to 10 days) dexamethasone therapy for children and adolescents with severe COVID-19 [59]. When dexamethasone is not available, equivalent dosage of alternative glucocorticoids (hydrocortisone and methylprednisolone) could be considered. Of note, direct evidence from pediatric patients is very limited and the evidence is extrapolated from adult patients. Therefore, systemic glucocorticoids are suggested to be used for pediatric COVID-19 patients with caution, preferring dexamethasone over other glococorticoids if available.

Clinical question 5: Should intravenous immunoglobulin (IVIG) be used to treat children and adolescents with MIS-C?

Recommendation 5.1: We suggest IVIG for children and adolescents with MIS-C ***(Conditional recommendation, very low certainty of evidence) (New)*****.**

Recommendation 5.2: We suggest using glucocorticoids in combination with IVIG for children and adolescents with MIS-C who have a severe clinical presentation at the time of diagnosis (acute left ventricular dysfunction, immediate admission to PICU care, or hemodynamic support requirement) ***(Conditional recommendation, very low certainty of evidence) (New)*****.**

Evidence summary

Our systematic review identified four cohort studies of children and adolescents with MIS-C with data

collected between January, 2020 and August, 2021) [30]. The review showed that 64 patients receiving IVIG (2g/kg) as the only first-line therapy had a treatment success rate of 62% (treatment failure was defined as the persistence of fever 2 days after the introduction of first-line therapy or recrudescence of fever within 7 days after the beginning of the first-line therapy treatment). One published systematic review of 27 case series with 917 MIS-C patients (mean age 9.3 years, 95% CI: 8.4 to 10.1) found that 81.0% (95% CI: 75.0% to 86.9%) of MIS-C patients received IVIG treatment; overall mortality was 1.9% (95% CI: 1.0% to 2.8%) [60].

One of the cohort studies included in our systematic review [30] found that 32 MIS-C patients with a severe initial clinical presentation at the time of diagnosis (acute left ventricular dysfunction, admission to PICU care, or need of hemodynamic support) who received a combination of IVIG and methylprednisolone (0.8-1mg/kg/12h for 5 days; or 15-30mg/kg/d for 3 days) as first-line therapy, had lower odds of treatment failure (OR 0.25, 95% CI: 0.09 to 0.70), need of second-line treatment (OR 0.19, 95% CI: 0.06 to 0.61) and hemodynamic support (OR 0.21, 95% CI: 0.06 to 0.76), and occurrence of secondary acute left ventricular dysfunction (OR 0.20, 95% CI: 0.06 to 0.66) compared with 64 MIS-C patients who received IVIG alone (2g/kg, single dose) as first-line therapy [61]. One study (n=40) showed that 22 MIS-C patients who received a combination of IVIG and methylprednisolone (0.8 mg/kg/d for 5 days) had a shorter time to recovery of left ventricle ejection fraction (2.9 vs. 5.4 days, p=0.002) than the remaining 18 patients who received IVIG alone (2g/kg, single dose) as first-line therapy [62]. Another study with larger sample size (103 patients in the IVIG plus glucocorticoids group and 103 in the IVIG group after propensity score matching) also indicated that IVIG plus glucocorticoids was associated with a lower risk of the composite outcome of cardiovascular dysfunction on or after day 2 than IVIG alone (17% vs. 31%; RR=0.56, 95%CI: 0.34 to 0.94) [63].

Explanation

MIS-C is a newly discovered clinical syndrome associated with SARS-CoV-2 infection and characterized by fever, systemic inflammation, and multiple organ dysfunction. Similar to Kawasaki disease, MIS-C patients can develop severe manifestations including coronary artery dilation, coronary aneurysms, toxic shock syndrome, sepsis, and macrophage activation syndrome [60]. IVIG produces a general anti-inflammatory effect. Direct evidence supporting the use of IVIG in MIS-C is very limited. A few case series found that the majority of MIS-C patients treated with IVIG had their condition improved and very low mortality [60]. A vast body of indirect evidence supporting IVIG use is available in patients with Kawasaki disease, where IVIG has been found to reduce abnormalities of the coronary artery and myocarditis in patients and is the recommended first-line therapy [64]. Given the similarity of the two diseases, we therefore recommend IVIG to treat MIS-C. However, due to the indirectness of the evidence, we gave a conditional recommendation. High-dose IVIG (2 g/kg, single dose) can be used if the cardiac function and fluid status are normal; otherwise, IVIG should be given as divided doses (1 g/kg/d, for 2 days). For MIS-C patients who have more severe initial clinical presentation (shock, severe cardiac dysfunction or other severe end-organ involvement, or requiring PICU care and hemodynamic support), methylprednisolone (1-2 mg/kg/d for 5 days) may be added because the combination therapy is more effective and causes only minor adverse events when used for a short period of time [30,55,58].

Clinical question 6: Should high-flow oxygen by nasal cannula (HFNC) or non-invasive ventilation (NIV) including continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) be used as the initial modality of therapy to treat acute hypoxemic respiratory failure in hospitalized children and adolescents with COVID-19?

Recommendation 6: We suggest HFNC or NIV (CPAP or BiPAP) as the initial modality of therapy for acute hypoxic respiratory failure in hospitalized children and adolescents with COVID-19 ***(Conditional recommendation, low certainty of evidence) (New)*****.**

Evidence summary

One published living systematic review on HFNC or NIV including CPAP and BiPAP identified 123 studies (45 on COVID-19, 70 on severe acute respiratory syndrome [SARS], and eight on Middle East Respiratory Syndrome [MERS]) published until May 2020, without any direct evidence in children with COVID-19 [26]. The mean ± standard deviation age of the hospitalized patients was 40.5 ± 15.6 years. Mortality was lower in hospitalized patients who received HFNC or NIV compared to those who received conventional oxygen therapy (OR 0.21, 95% CI: 0.09 to 0.47). However, health care workers (HCWs) who performed HFNC or NIV for COVID-19 patients had higher odds of being infected than those who did not perform these procedures (OR 3.10, 95% CI: 1.40 to 6.80). Thirty-five percent of HCWs exposed to COVID-19 patients treated with HFNC and NIV developed respiratory symptoms and 2.5% were tested positive for SARS-CoV-2 with polymerase chain reaction. This living systematic review has been updated three times and the search date of the last update is 21 June 2021 [27]. The new evidence from the latest update did not change the original finding that HFNC may reduce mortality compared with conventional oxygen therapy [27]. Moreover, NIV was not found to increase the risk of mortality in patients with COVID-19 compared with invasive mechanical ventilation (OR 0.74, 95% CI: 0.46 to 1.18) [27].

Explanation

Low-certainty evidence suggests that HFNC and NIV (CPAP and BiPAP) can ameliorate hypoxemia, and reduce the need of early intubation and rate of complications associated with mechanical ventilation

for patients with acute respiratory failure [26]. However, both HFNC and NIV may cause propagation of aerosol particles containing the virus, which may increase the risk of transmission of SARS-CoV-2 to HCWs [65]. Recommendations on the use of HFNC and NIV as the initial modality of therapy for treating COVID-19 patients with acute hypoxic respiratory failure are currently inconsistent across different guidelines [66-67]. Appropriate use of personal protective equipment can minimize the risk for infections to HCWs from aerosols [26,68]. Therefore, HFNC or NIV can be used to treat acute hypoxic respiratory failure in children and adolescents with COVID-19 if appropriate precautions are taken. Cooperation from the patients is crucial for successful ventilation and therefore should be a consideration when performing HFNC and NIV [69]. After providing HFNC or NIV, the condition of the patients must be monitored every one to two hours with clinical and arterial blood gas evaluation to ensure the efficacy and safety of the ventilation. If there are signs of rapid deterioration, the patients should be intubated promptly.

Clinical question 7: Should mothers with COVID-19 continue to breastfeed their babies?

Recommendation 7: We recommend that mothers with COVID-19 continue to breastfeed their babies if their health condition permits, while taking appropriate precautions *(Strong recommendation, low certainty of evidence) (Unchanged)*.

Evidence summary

One living systematic review included 427 studies with 28,952 mothers with COVID-19 and 18,237 babies, with data collected between December 2019 and August 2021 [28]. The overall rate of SARS-CoV-2 positivity in babies born to mothers with COVID-19 was 1.8% (95%CI: 1.2% to 2.5%). Of the 592 SARS-CoV-2 positive babies with test data, 14 had confirmed mother-to-child transmission (seven

in utero, two intrapartum, and five during the early postpartum period). Of the 800 SARS-CoV-2 positive babies with outcome data, 749 babies were alive at the end of follow-up. Mother with severe COVID-19 (OR 2.4, 95% CI: 1.3 to 4.4), maternal death (OR 14.1, 95% CI: 4.1 to 48.0), maternal admission to an ICU (OR 3.5, 95% CI: 1.7 to 6.9), and maternal postnatal infection (OR 5.0, 95% CI: 1.2 to 20.1) were associated with SARS-CoV-2 positivity in babies.

Explanation

Breastfeeding is recognized as the best source of nutrition for infants, benefiting their neurological and immune system development, while reducing the risk of breast cancer, ovarian cancer, and type 2 diabetes in mothers [70,71]. The WHO and the Rapid Advice Guidelines for Management of Children with COVID-19 currently recommend that mothers with suspected or confirmed COVID-19 continue breastfeeding while taking the necessary protective measures [9,72]. However, there are concerns that mothers with COVID-19 could transmit the virus to their babies while breastfeeding.

Although in utero, intrapartum, and early postpartum transmission of SARS-CoV-2 is possible, the vertical transmission rate is very low [28]. Current evidence shows the overall rate of SARS-CoV-2 positivity in babies born to mothers with COVID-19 is less than 2% [28]. In addition, the mortality of SARS-CoV-2 positive babies is very low [28]. As the benefits of breastfeeding for the infant outweigh the risk of SARS-CoV-2 infection, the panelists agreed that breastfeeding should be continued as long as the health conditions of the mother and infant permit. However, mothers need to take appropriate protective measures (e.g., washing hands before contact with the infant and wearing a mask during close contact), especially those with severe COVID-19, admitted to ICU, or having a postnatal infection, who seem to have an elevated risk of SARS-CoV-2 positivity in their babies [28].

Clinical question 8: Should children and adolescents be vaccinated against COVID-19?

Recommendation 8: We suggest COVID-19 vaccination for children and adolescents aged 3-17 years if a COVID-19 vaccine is available and approved by local health authorities for their age and health condition, while closely monitoring for potential side effects after vaccination *(Conditional recommendation, moderate certainty of evidence) (New)*.

Evidence summary

One systematic review, which is an updated version of a previous systematic review we conducted [73], included six RCTs with 9962 children aged 3-17 years, with data collected until November 2021 [32]. As for the safety of vaccines, the overall risk of unsolicited adverse reactions (RR 1.21, 95%CI: 1.07-1.36) was significantly higher in the vaccine group than in the control group within 28 to 30 days after vaccination. However, no significant difference was found in severe (RR 2.35, 95%CI: 0.78-7.03) or life-threatening (RR 1.00, 95%CI: 0.06-15.94) adverse reactions between the two groups. No significant differences were found after receiving the first and the second dose (RR 1.00, 95%CI 0.99-1.02). Compared with mRNA vaccines and adenovirus vector vaccines, inactivated vaccines have a more satisfactory safety profile, both after the first (RR 1.40, 95% CI: 1.04-1.90) and the second (RR 1.84, 95% CI: 1.20-2.81) dose. As for the immunogenicity of vaccines, seroconversion rate after the first dose injection increased significantly for receptor binding domain (RBD)-binding antibodies (RR 99.48, 95%CI: 6.31-1559.12) compared with the unvaccinated. After booster vaccination, the immunogenicity of vaccines was further enhanced; seroconversion rate for RBD-binding antibodies (RR 101.50, 95%CI: 6.44-1600.76) and pseudovirus neutralizing antibodies (RR 144.80, 95%CI: 44.97-466.24) were further increased compared with the unvaccinated, and reached optimal levels. As for the efficacy of vaccines, three RCTs with mRNA vaccine as the intervention found that the risk of diagnosing COVID-19 after

mRNA vaccination was low (RR 0.10, 95%CI: 0.05-0.21) compared with the unvaccinated. Other RCTs with inactivated vaccines or adenovirus vector vaccines as interventions did not assess vaccine efficacy..

Explanation

Some international and national guidelines recommend vaccination for children, but the recommendations vary between guidelines [74-76]. The WHO guideline recommends two doses of the COVID-19 vaccine for children aged 5 to 15 to protect against COVID-19 [74]. CDC recommends COVID-19 vaccines for children aged 6 months and older[75]. The National Institute for Health and Care Excellence recommends vaccination for children over 5 years old who meet certain conditions, such as immunosuppression [76]. The COVID-19 vaccines which have so far been validated in completed clinical trials in children include BNT162b2, mRNA-1273, CoronaVac, BBIBP‐CorV, Ad5‐nCoV, and ZyCov-D, with an overall age range of 3 to 17 years **(Table 3)**. None of the vaccines increased the risk of severe or life-threatening adverse reactions, and all generated immune response to SARS-CoV-2 [77-83]. We also observed the interim findings from two ongoing clinical trials of the BNT162b2 and mRNA-1273 that included children 6 months through 3 years of age [84,85]. The findings of these clinical trials showed that both vaccines may prevent children aged 6 months to 3 years against COVID-19 without increasing the risk of serious adverse events [84,85]. However, we have serious concern about the short duration of follow-up (median = 35 days), limiting the ability to detect severe adverse events that might occur specifically after dose 3. We also concern about the small study size. These clinical trials may be not adequately powered to detect rare adverse events and efficacy against severe disease in young children. Therefore, more studies are needed to demonstrate the efficacy and safety of COVID-19 vaccine in children aged 6 months to 3 years.

Based on the currently available evidence on COVID-19 vaccines for children and a consideration of

the patients' values and preferences, the panel believes that the benefits of administering vaccines to children aged 3-17 years would outweigh the harms. It should be noted that the overall age of vaccination has been extended to 3-17 years old in the current clinical trials, but different types of vaccines are approved for different age groups (**Table 3**). In addition, there are substantial differences across countries and regions in the types of vaccines that are available and the age at which children are eligible to be vaccinated. Therefore, decisions related to COVID-19 vaccination should be made in accordance with local regulations and local research data.

Cases of myocarditis and pericarditis were found in children and adolescencts, especially in male adolescents, after receiving mRNA (BNT162b2 or mRNA-1273) vaccines, which requires close monitoring [86]. Myocarditis and pericarditis occurred more often after the second dose, and usually within a week of vaccination[86]. The conditions of most patients with myocarditis or pericarditis improved quickly after treatment and they could return to their normal daily activities [87]. Although the short-term risks of adverse outcomes among children with myocarditis after mRNA vaccination were low, the long-term risks associated with myocarditis and pericarditis remain unknown. Besides, the evidence on the effects of COVID-19 vaccination for children below three years is very limited. Larger studies with longer follow-up are needed to inform recommendations for COVID-19 vaccination in this population.

Clinical question 9: How should the mental health of children and adolescents with COVID-19 be managed?

Good practice statement: We suggest pediatricians, parents and caregivers should explore possible mental health problems among children and adolescents with COVID-19 and provide them with

the optimal support feasible in the local setting *(New)*.

Evidence summary

Our systematic review did not identify studies that met the requirements.

Explanation

Managing mental health of patients with COVID-19 during the pandemic is important, especially in the context of a pandemic where the huge social-psychological impact brought by the COVID-19 epidemic may exceed the role of the disease itself [88]. People with COVID-19 are at increased risk for mental health problems [89]. Anxiety and depression appear to be the main symptoms among children and adolescents in the context of COVID-19 [90], especially among hospitalized COVID-19 patients [91,92]. Possible reasons include the isolation from family members and friends which can lead to helplessness and loneliness [93], and the fear of being stigmatized and discriminated because of being infected [94]. Apart from the high incidence of short-term mental disorders, some studies have indicated that survivors may develop psychological sequelae after recovering from COVID-19, such as anxiety and/or depression, post-traumatic stress disorder, and cognitive deficits [95]. Therefore, we suggest that children and adolescents with COVID-19 should be monitored for possible mental health problems.

The symptoms of mental disorders in children and adolescents are atypical and vary across different ages. Young children may experience fussiness and irritability, startling and crying more easily, and difficulties in consolation [94]. Older children and adolescents may show symptoms such as changes in mood, ongoing irritability, and feelings of hopelessness or rage [94].

Out of consideration for children's mental health, the panel proposed a statement on psychological interventions based on the concept of a Good Practice Statement according to the GRADE framework. The panel suggested that pediatricians, parents and caregivers should observe whether the children have

features of anxiety, depression or other psychological symptoms. The optimal mental health support feasible in the local setting should be provided for children and adolescents with COVID-19 [96].

Discussion

Children are the future of the world, but in the context of the pandemic, their health and future are facing great uncertainty [97,98]. The attention paid to children with COVID-19 globally is far from enough. There also exist clearly less clinical evidence and fewer practice guidelines related to children with COVID-19 than for adults. The guideline working group has been concerned about SARS-CoV-2 infections in children as early as the beginning of the outbreak in 2020 and continues to assemble evidence and conduct researchon children with COVID-19. After publishing the first version of the evidence-based rapid advice guideline for children, the panel has updated the guideline by including additional stakeholders in the panel and through a comprehensive search of the latest evidence. This guideline can assist pediatricians in clinical decision making, support policy makers in developing relevant policies, and inspire researchers in prioritizing clinical trials. In addition, the guideline will help children and their guardians access and understand up-to-date evidence-based knowledge of COVID-19.

Strengths and Limitations

Our guideline has several strengths. First, to our knowledge, this is one of the few guidelines for children with COVID-19 that is registered and has a published protocol. Second, we strictly followed methodological handbooks to update our guideline and report its contents. Third, all recommendations were supported by systematic reviews and solicited suggestions from patient representatives. The guideline has however also limitations. First, we comprehensively searched the literature and used

systematic reviews to support recommendations. However, very few clinical studies have been conducted specifically on children and the study quality was not optimal. The weakness of the evidence may cause some bias and lead to low certainty of evidence. Therefore, it was difficult for panelists to make strong recommendations. However, we still provide specific recommendations on key clinical questions, such as the application of IVIG for treating MIS-C, the use of systemic glucocorticoids in children with severe COVID-19, and the vaccination of children, based on scientific consensus. Caution is nevertheless needed when translating these recommendations into clinical practice. More reliable evidence about the management of children with COVID-19 is urgently needed. Another limitation is that while the guideline can be used at different levels of healthcare facilities, some recommendations, such as those for HFNC or NIV, may be difficult to implement in resource-limited settings. Finally, the guideline development group did not include any general practitioners, who nevertheless constitute a target audience group for our guideline.

Updating

This guideline has been last updated in July, 2022. The evidence synthesis group will systematically search for evidence on children with COVID-19 every three months. The trigger for updating or producing specific recommendations is based on the following criteria (the fulfillment of any of the three may initiate the process): (1) practice-changing evidence is identified; (2) the evidence can be incorporated in our systematic review and is sufficient to change the certainty of evidence; and (3) new clinical issues arise that may attract interest on an international level.

Suggestions for future research

There is an urgent need for clinical trials on children with COVID-19. The research gaps for future research identified by the panelists are listed in **Table 4**.

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Competing Interests: Bin Cao is one of the key investigators in the clinical trial on remdesivir for COVID-19 in China and was excluded from all discussions and voting related to remdesivir. Gordon Guyatt is a member of the Clinical Management COVID-19 Guideline Development Therapeutics Group for the WHO and co-chair of the GRADE working group. Ivan D. Florez is the current leader of the AGREE Collaboration. Jürgen Schwarze is employed by the University of Edinburgh and the Secretary General of the European Academy of Allergy and Clinical Immunology, which receives industrial sponsorship as indicated on the EAACI website (https://www.eaaci.org/organisation/founder-sponsors.html). Yasser Sami Abdel is employed as a pediatrician and CPG methodologist responsible for all CPG adaptation projects at the King Saud University Medical City, and receives a monthly salary.

Yaolong Chen is the Co-Founder and Co-Chair of RIGHT working group. The conflict of the above authors was not considered serious enough to affect guideline working group membership or participation in the updating process. All other authors declare no relevant conflicts of interest.

Declarations

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Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Enmei Liu, Zhengxiu Luo, Qinyuan Li, Qi Zhou, and Yaolong Chen. The first draft of the manuscript was written by Enmei Liu, Rosalind Louise Smyth, Qinyuan Li, Qi Zhou, and Yaolong Chen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Grading of certainty of evidence and strength of recommendations*

Certainty of evidence	**Description**
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect maybe substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	**Description**
Strong	Advantages of the intervention significantly outweigh disadvantages or disadvantages of the intervention significantly outweigh advantages
Conditional	Advantages of the intervention may outweigh disadvantages, disadvantages of the intervention may outweigh advantages, or the relationship between advantages and disadvantages is not clear

*: According to the GRADE Working Group.[23,24]

Table 2 Summary of the recommendations and good practice statements

Recommendations	Status
Recommendation 1: We suggest that pediatricians and other guideline users should identify the presence of prognostic factors for death or PICU admission in children and adolescents with COVID-19 at an early stage. The main prognostic factors for death are MIS-C complications and AKI; the prognostic factors for PICU admission include AKI, ARDS, MIS-C complications, chronic pulmonary disease, and congenital heart disease *(Conditional recommendation, very low certainty of evidence)*.	New
Recommendation 2: We suggest standard care without remdesivir to treat children and adolescents with COVID-19 *(Conditional recommendation, very low certainty of evidence)*.	Modified
Recommendation 3: We suggest that antipyretics (ibuprofen or paracetamol) can be used to relieve fever and pain in children and adolescents with COVID-19 *(Conditional recommendation, very low certainty of evidence)*.	New
Recommendation 4: We suggest low-dose, short-course of dexamethasone therapy for children and adolescents with severe COVID-19 *(Conditional recommendation, low certainty of evidence)*.	Modified
Recommendation 5.1: We suggest IVIG for children and adolescents with MIS-C *(Conditional recommendation, very low certainty of evidence)*.	New
Recommendation 5.2: We suggest using glucocorticoids in combination with IVIG for children and adolescents with MIS-C who have a severe clinical presentation at the	New

time of diagnosis (acute left ventricular dysfunction, immediate admission to PICU care, or hemodynamic support requirement) *(Conditional recommendation, very low certainty of evidence)*.	
Recommendation 6: We suggest HFNC or NIV (CPAP or BiPAP) as the initial modality of therapy for acute hypoxic respiratory failure in hospitalized children and adolescents with COVID-19 *(Conditional recommendation, low certainty of evidence)*.	New
Recommendation 7: We recommend that mothers with COVID-19 continue to breastfeed their babies if their health condition permits, while taking appropriate precautions *(Strong recommendation, low certainty of evidence)*.	Unchanged
Recommendation 8: We suggest COVID-19 vaccination for children and adolescents aged 3-17 years if a COVID-19 vaccine is available and approved by local health authorities for their age and health condition, while closely monitoring for potential side effects after vaccination *(Conditional recommendation, moderate certainty of evidence)*.	New
Good practice statements	**Status**
Good practice statement: We suggest pediatricians, parents and caregivers should explore possible mental health problems among children and adolescents with COVID-19 and provide them with the optimal support that is feasible in the local setting.	New

Note: Unchanged: the main content and the strength of recommendation remain unchanged from the original recommendation; Modified: the main content or strength of the recommendation has changed compared to the original recommendation; New: the recommendation was not included in the original version of the guideline has been added in the updated guideline. Abbreviations and acronyms: COVID-

19: coronavirus disease 2019, IVIG: intravenous immunoglobulin; MIS-C: multisystem inflammatory syndrome in children; PICU: pediatric intensive care unit; HFNC: high-flow oxygen by nasal cannula; NIV: non-invasive ventilation; CPAP: continuous positive airway pressure; BiPAP: bilevel positive airway pressure; AKI: acute kidney injury; ARDS: acute respiratory distress syndrome.

Table 3 A summary of vaccines that have been validated in clinical trials in children.

Vaccine name (developer)	**BNT162b2 (Pfizer/BioNTech)[77, 78]**	**mRNA-1273 (Moderna)[79]**	**CoronaVac (Sinovac)[80]**	**BBIBP-CorV (Sinopharm)[81]**	**Ad5-nCoV (CanSino Biologics)[82]**	**ZyCov-D (Cadila Healthcare)[83*]**
Vaccine type	mRNA vaccine	mRNA vaccine	Inactivated vaccine	Inactivated vaccine	Adenovirus vaccine	DNA vaccine
Age range	5-15	12-17	3-17	3-17	6-17	12-17
Location	USA, Spain, Finland, Poland	USA	China	China	China	India
Dose of administration	5-11 years: 10 μg/dose 12-15 years: 30 μg/dose	100 μg/dose	1.5 or 3 μg/dose	2 ug, 4 ug or 8 μg/dose	0.3 ml/dose	2 mg/dose
Number of scheduled doses	First and second dose (0, 21 days)	First and second dose (0, 28 days)	First and second dose (0, 28 days)	First, second, and third dose (0, 28, and 56 days)	First and second dose (0, 56 days)	First, second, and third dose (0, 28, and 56 days)
Vaccine efficacy	5-11 years: 90.7% (after second dose) 12-15 years: 100% (after second dose)	93.3% (after second dose)	N/A	N/A	N/A	66.6% (after first dose), 100% (after two dose)
Immune response	99.2% serologic response	98.8% serologic response	Over 96.8% serologic response	100% serologic response	98%-100% serologic response	93.33% serologic response at day 84
Adverse reaction	Injection site pain, fatigue, headache, and fever	Injection site pain, headache, and fatigue	Injection site pain, and fever	Fever, and cough	Fever, headache, fatigue, injection site pain, abdominal pain	Injection site pain, muscle pain, headache, fever, and fatigue

Note: Not applicable: N/A

* Included both children aged 12-17 years and adults.

Table 4 Priority research gaps on COVID-19 in children and adolescents

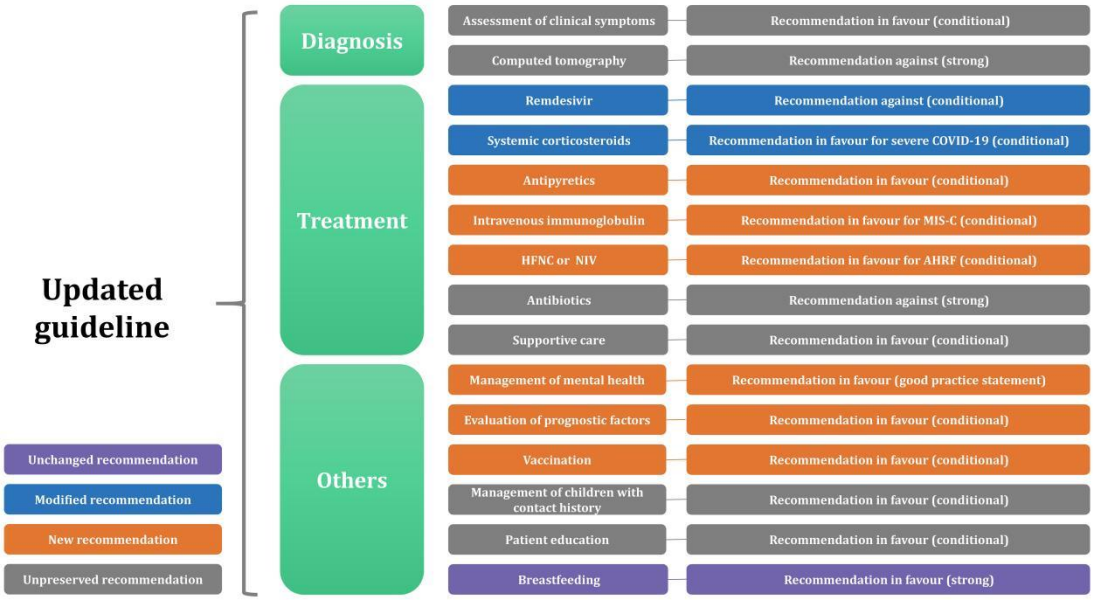
- What is the effectiveness and safety of systemic glucocorticoids for the treatment of children with COVID-19?
- What is the effectiveness and safety of IVIG and combination of IVIG and glucocorticoids in the treatment of children and adolescents with MIS-C?
- Which ventilation mode (HFNC, CPAP or BiPAP) is the most efficient and has the lowest risk of SARS-COV-2 transmission, and should be the primary intervention option for acute hypoxemic respiratory failure in children and adolescents with COVID-19?
- How can mental disorders such as obsessive-compulsive disorder in children who have been subject to lockdown measures, or in children and adolescents with COVID-19, be managed?
- Should children younger than three years old be vaccinated against COVID-19?
- What are the long-term sequelae (such as lung function and growth and development) in children who recovered from COVID-19?
- What are the impacts of new variants (e.g., Omicron variant and possible future variants) on children and adolescents?
- What is the effectiveness and safety of paxlovid for the treatment of children with COVID-19?
- What is the effectiveness and safety of sotrovimab for the treatment of children with COVID-19?
- What is the effectiveness and safety of tocilizumab and other immunomodulatory medication for the treatment of children with COVID-19?

Abbreviations and acronyms: COVID-19: coronavirus disease 2019, IVIG: intravenous immunoglobulin; MIS-C: multisystem inflammatory syndrome in children; HFNC: high-flow oxygen by nasal cannula;

CPAP: continuous positive airway pressure; BiPAP: bilevel positive airway pressure

Figure

Figure 1 Structure and modifications of recommendations in the updated guideline.



Note: Unchanged recommendation: the main content and the strength of recommendation remain unchanged relative to the original recommendation; Modified recommendation: the main content or strength of the recommendation has been changed from the original recommendation; New recommendation: the recommendation was not included in the original version of the guideline has been added during the update; Unpreserved recommendation: the recommendation in the original version of the guideline has not been preserved in the updated guideline. Abbreviations and acronyms: COVID-19: coronavirus disease 2019; MIS-C: multisystem inflammatory syndrome in children; HFNC: high-flow oxygen by nasal cannula; NIV: non-invasive ventilation; AHRF: acute hypoxemic respiratory failure.