



COVID-19 Infection in Children: Diagnosis and Management

Frank Zhu¹ · Jocelyn Y. Ang^{2,3,4}

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Abstract

Purpose of Review Due to the rapidly changing landscape of COVID-19, the purpose of this review is to provide a concise and updated summary of pediatric COVID-19 diagnosis and management.

Recent Findings The relative proportion of pediatric cases have significantly increased following the emergence of the Omicron variant (from < 2% in the early pandemic to 25% from 1/27 to 2/3/22). While children present with milder symptoms than adults, severe disease can still occur, particularly in children with comorbidities. There is a relative paucity of pediatric data in the management of COVID-19 and the majority of recommendations remain based on adult data.

Summary Fever and cough remain the most common clinical presentations, although atypical presentations such as “COVID toes,” anosmia, and croup may be present. Children are at risk for post-infectious complications such as MIS-C and long COVID. Nucleic acid amplification tests through respiratory PCR remain the mainstay of diagnosis. The mainstay of management remains supportive care and prevention through vaccination is highly recommended. In patients at increased risk of progression, interventions such as monoclonal antibody therapy, PO Paxlovid, or IV remdesivir × 3 days should be considered. In patients with severe disease, the use of remdesivir, dexamethasone, and immunomodulatory agents (tocilizumab, baricitinib) is recommended. Children can be at risk for thrombosis from COVID-19 and anticoagulation is recommended in children with markedly elevated D-dimer levels or superimposed clinical risk factors for hospital associated venous thromboembolism.

Keywords COVID-19 · SARS-CoV-2 · Pediatrics · Diagnosis · Management · Treatment

Introduction

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in Wuhan, China, in December 2019 and rapidly spread globally. It

was declared a global pandemic named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) on March 11, 2020 [1]. As of February 3, 2022, there have been a total of 12,042,870 pediatric COVID-19 cases reported in the USA, representing 18.9% of all cases with a rate of 16,000 cases per 100,000 children [2]. While the relative number of pediatric cases were small (< 2% of reported cases) during the early stages of the pandemic [3–5], the true incidence of COVID-19 pediatric infections at that time may have been underestimated due to large percentage of asymptomatic children and low rate of testing [6]. As the COVID-19 pandemic progressed, the relative proportion of pediatric cases has increased. Indeed, with the emergence of the Omicron variant in late 2021 [7], pediatric cases have significantly increased. Children represented 25% of the weekly reported US cases from 1/27/22 to 2/3/22 [2], a significant increase from the < 2% of reported cases in the early stages of the pandemic.

Despite the numerous publications dedicated to the diagnosis and management of COVID-19 disease, the quality

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✉ Frank Zhu
frzhu@mcw.edu

¹ Division of Pediatric Infectious Diseases, Department of Pediatrics, Medical College of Wisconsin, Suite 450C, 999 North 92nd Street, Wauwatosa, Milwaukee, WI 53226, USA

² Division of Pediatric Infectious Diseases, Children’s Hospital of Michigan, Detroit, MI, USA

³ Department of Pediatrics, Central Michigan University College of Medicine, Mount Pleasant, MI, USA

⁴ Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI, USA

of the guidelines can significantly vary [8]. Additionally, research involving pediatric patients remains limited and currently there are no pediatric-specific recommendations for the treatment of COVID-19. The current National Institutes of Health (NIH) guidelines for the treatment of children are based on outcome and safety data for adult disease [9]. However, the current landscape of the COVID-19 pandemic is rapidly changing. The rising rates of pediatric infections with the Omicron variant poses significant challenges to clinicians managing pediatric COVID-19 given the possible changes in clinical manifestation, post-infectious manifestations such as multisystem inflammatory syndrome (MIS-C), as well as new therapeutic options in management. Therefore, this paper aims to provide a concise review of pediatric literature on the diagnosis and management of pediatric COVID-19.

Clinical Manifestations

Pediatric cases of COVID-19 have traditionally presented with milder symptoms and lower risks of hospitalization and death when compared to adults [5]. Additionally, a large percentage of pediatric COVID-19 infections are asymptomatic. The reported total percentage of asymptomatic pediatric COVID-19 cases range from a rate of 15% [5] to 65% [10].

The clinical presentation of COVID-19 in children varies by age group. Children ≤ 9 years of age the most commonly presents with fever (46%), cough (37%), headache (15%), diarrhea (14%), and sore throat (13%). While older children 10–19 years of age are more likely to have symptoms similar to COVID-19 in adults with headache (42%), cough (41%), fever (35%), myalgia (30%), sore throat (29%), and shortness of breath (16%) [5]. Of note, the incidence of rhinorrhea is typically low in children with COVID-19 (ranging from 10 to 22%) [11]. Anosmia is a rare finding in children [12, 13], but has been reported as the strongest predictor of a positive test for COVID-19 [14]. Additionally, the Omicron variant may be significantly more associated with the development of croup in pediatric patients than prior variants of SARS-CoV-2. A recent review showed that patients who presented with croup in the Omicron surge were more likely to test positive for COVID-19 than during the Delta surge (48.2% vs 2.8%) [15].

Cutaneous findings can be associated with COVID-19. Unlike adult patients, pediatric COVID-19 patients are often asymptomatic except for these cutaneous manifestations [16•]. Indeed, >90% of patients may be asymptomatic or have mild/moderate disease in which the diagnosis of COVID-19 was overlooked [17•]. Cutaneous findings can range from rash (maculopapular, urticarial, vesicular) to painful lesions on the finger and feet that resemble chilblains (“COVID toes”). These cutaneous lesions typically present

on the feet (74–100%) but have been reported on the hands as well. The lesions usually present as multiple, round erythematous, violaceous, or purpuric patches and swellings which can evolve to become vesicubullous or present with dark-purple or black crusts. The most commonly affected regions are the plantar region and lateral aspect of the feet and heels. Additional cutaneous manifestations include erythema multiforme, urticaria, and vesicular exanthema [18•].

Severe disease manifestation of COVID-19 in pediatrics presents in a similar clinical spectrum as in adults. Children may present with respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, neurological involvement (encephalopathy, stroke, cerebral edema, Guillain-Barré syndrome), and multi-system organ failure [19, 20]. Hospitalization rate of children with COVID-19 has ranged from 0.7% (2/22) to 3.8% (5/20) in the USA from May 2020 to February 2022. Approximately 0.01% of all pediatric COVID-19 cases resulted in death [2]. Of hospitalized children, approximately 30% had severe COVID-19 and 0.5% died during hospitalization in a review of 3106 hospitalized children by Woodruff et al. Risk factors for severe disease were stratified by age group. For children < 2 years of age, risk factors were chronic lung disease (aRR 2.2), neurologic disorders (aRR 2.0), cardiovascular disease (aRR 1.7), prematurity (aRR 1.6), and airway abnormality (aRR 1.6). Among children 2–17 years, risk factors included feeding tube dependence (aRR 2.0), diabetes mellitus (aRR 1.9), and obesity (aRR 1.2). Additionally, infants < 1 year of age had the highest rates of hospitalization and severe COVID-19 compared to other age groups. Hispanic and non-Hispanic black children had higher rates of hospitalization than non-Hispanic white children. However, once hospitalized, these children were not at increased risk of severe disease when compared to white children once controlled for the presence of underlying medical conditions [21••].

Post-infectious Complications

Multisystem Inflammatory Syndrome in Children (MIS-C)

Children who were infected with SARS-CoV-2 may develop a post-infectious hyperinflammatory response, MIS-C. Initial reports in April 2020 from the UK described children who presented with clinical features similar to Kawasaki disease (KD) and toxic shock syndrome [22•]. The peak incidence typically occurs 4 weeks after the peak of COVID-19 cases [23]. There are significant epidemiological differences when compared to KD. Older children are typically affected (peak incidence 5–14 years compared to < 5 years for KD) with a slight male preponderance. Additionally, MIS-C more commonly affects those of African or Afro-Caribbean

descent and Hispanic children. KD by comparison is more prevalent in those of East Asian descent [24].

There is a broad spectrum of clinical presentations for MIS-C. However, a diagnosis of MIS-C requires the presence of fever for at least 24 h, laboratory evidence of inflammation, evidence of clinically significant illness requiring hospitalization with multisystem involvement, evidence of prior or current SARS-CoV-2 infection, and no alternative plausible diagnosis (see Table 1). In a systemic review of 35 manuscripts, the most commonly affected organ system was cardiovascular (82% patients tachycardic, 61% hypotensive). Coronary artery abnormalities, a finding characteristic of KD, can be present in children with MIS-C who present both with and without features of KD [22•]. The prevalence of coronary artery abnormalities is estimated to be 13–26% [25]. Pulmonary involvement was uncommon (9.6% of cases) [26]. Additional organ system involved included gastrointestinal (hepatitis, pancreatitis, abdominal pain, diarrhea), hematological (coagulopathy, thrombus formation), dermatological (rash), musculoskeletal (myositis, myalgia, arthritis, arthralgia), neurological (headache, confusion, altered mental status), and renal (acute kidney injury) [27•]. Younger children (< 5 years) were found to have higher rates of KD features, dermatological manifestations, and lower rates of GI symptoms, cardiomyopathy, and neurological symptoms [28]. Treatment is beyond the scope of this review, but includes IVIG, immunomodulatory agents such as steroids/anakinra, and antiplatelet agents such as aspirin [29•].

Long COVID-19

Similar to adults, children may experience persisting symptoms following COVID-19 infection affecting a variety of systems (sensory, neurologic, cardiorespiratory, and

psychiatric). Over 200 symptoms have been attributed to “long COVID,” but numerous symptoms are nonspecific (fatigue, sleep disturbance, concentration difficulties, loss of appetite, muscle/joint pain). There is limited data available on “long COVID” in pediatrics. In a review of 5 studies, Zimmerman et al. found that all studies had substantial limitations or did not show a difference in children infected by SARS-CoV-2 and those who have not. However, symptoms did not tend to persist longer than 12 weeks in most children [30•].

Vaccination

Prevention of COVID-19 disease through vaccination is highly recommended for all children. Currently, only the Pfizer-BioNTech vaccine (BNT162b2) is approved in children (EUA approval given in 5–11 years old and 12–15 years old, FDA approved for use in 16 years and older) [31]. The Pfizer vaccine is a lipid nanoparticle formulation containing nucleoside-modified mRNA encoding the SARS-CoV-2 spike protein. It is given as a 2-dose series, 21 days apart. An 8-week interval may be optimal for children ages 12 years and older, especially for males as the small risk of myocarditis associated with mRNA COVID-19 vaccines may be reduced and peak antibody responses and vaccine effectiveness may be increased with an interval longer than 4 weeks [32]. Immunocompromised children should get a 3rd dose 28 days after 2nd dose [33]. A booster is recommended 5 months after completing the primary vaccination series [34]. It has been shown to be 95–100% efficacious in preventing COVID-19 disease from 7 days to approximately 2 months after 2nd dose in 12–15 year old children and 95% in adolescents ≥ 16 years of age [35•, 36].

Table 1 MIS-C case definition

Criteria	Specifications
Age	< 21 years
AND	
Fever	> 38.0 °C for ≥ 24 h or report of subjective fever ≥ 24 h
AND	
Laboratory evidence of inflammation	≥ 1 of the following: CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, IL-6, elevated neutrophils, reduced lymphocytes, low albumin
AND	
Evidence of clinically significant illness requiring hospitalization with multisystem organ involvement	> 2 organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, neurological)
AND	
Evidence of recent or current SARS-CoV-2 infection	Positive RT-PCR, serology, antigen test, or COVID-19 exposure within the 4 weeks prior to the onset of symptoms
AND	
No alternative plausible diagnoses	

Overall vaccine efficacy from 7 days after 2nd dose to 6 months is 91% [37]. In children 5–11 years of age, vaccine efficacy was 90.7% [38]. Vaccine side effects are generally mild and most commonly consist of transient injection site pain, fever, fatigue, chills, and headache [35, 36, 38]. Rare cases of myocarditis have been reported as a post-vaccination complication. Estimates rates based on reported to Vaccine Adverse Event Reporting System (VAERS) were significantly higher in males (70.7 per million doses for 12–15 year olds, 105.9 per million doses in 16–17 year olds, 52.43 per million doses in 18 year olds) than females (6.35 per million doses for 12–15 year olds, 10.98 per million doses in 16–17 year olds, 6.87 per million doses in 18 year olds) [39]. Data for 5–11 year old patients are still not well known, but a total of 14 cases were reported to VAERS as of Dec 10, 2021, following the administration of approximately 7,141,428 total doses [40]. Post-vaccination myocarditis is typically mild with rapid resolution of symptoms. The median time to onset is 2 days after vaccination and occurs more commonly after the 2nd dose of vaccination [39, 41].

Diagnosis

Nucleic Acid Amplification Tests

Nucleic acid amplification tests (NAATs) remain the gold standard for the detection of SARS-CoV-2 virus and therefore diagnosis of COVID-19 [42]. There are several commercially available SARS-CoV-2 RT-PCR assays with a variety of genetic targets such as RdRp (RNA-255 dependent RNA polymerase of SARS-CoV-2), ORF1ab (open reading frame 1a and b of 225 of SARS-CoV-2), N (nucleocapsid protein of SARS-CoV-2), E (envelope protein of SARS-CoV-2), S (spike protein of SARS-CoV-2) [43]. The CDC currently recommends collection of nasopharyngeal (NP) or oropharyngeal (OP) specimens for initial diagnostic testing of current SARS-CoV-2 infections. Mid-turbinate swabs can also be obtained [44]. However, sensitivity of mid-turbinate specimens is significantly lower than NP (94% vs 75% in a review of 115 patients by Jamal et al.) [45]. However, in a subset of patients with concurrent saliva PCR, the sensitivities were similar (86% NP swabs vs 88% for combined mid-turbinate/saliva PCR). Therefore, if mid-turbinate samples are to be used, the sensitivity can be increased to be comparable to NP PCR with the use of a concurrent saliva PCR.

The timing of the NAAT test also significantly affects sensitivity. In a systemic review of 32 studies, Mallet et al. found that the highest percentage of virus detected was from NP sampling 0 to 4 days post-symptom onset (89%) and dropping to 54% after 10–14 days. Lower respiratory tract (LRT) sites cleared significantly slower than upper respiratory tract (median 12 days URT vs 28 days LRT) [46].

Additionally, both symptomatic and asymptomatic/pre-symptomatic samples viral loads were found to be similar in a review of 113 studies by Walsh et al. Of the 36 studies which included children, Walsh et al. found no discernible differences in viral load or duration when comparing children in adults [47].

It should be noted that prolonged detection of SARS-CoV-2 from NAATs may be present in patients who have recovered from COVID-19 infection. However, detection of viral RNA does not necessarily indicate infectivity. Sub-genomic RNA fragments can associate tightly with intracellular vesicles, thereby preventing degradation and may explain persistently positive PCR results [48]. Indeed, for most immunocompetent individuals with mild disease, replication-competent virus has not been isolated 10 days following symptom onset [49]. Immunocompromised patients may have prolonged shedding (replication-competent virus has been isolated 10–20 days after symptom onset). However, this was still a minor occurrence (88% specimens no longer yielded replication-competent virus after 10 days, 95% after 15 days) [50]. In moderately or severely immunocompromised patients, isolation of replication-competent virus or sub-genomic SARS-CoV-2 has been reported beyond 20 days [51]. Prolonged shedding may occur in severe disease. The longest duration of viable virus shedding in an immunocompetent child with severe SARS-CoV-2 is currently 54 days [52].

Antigen-based Tests

Antigen tests utilize immunoassay to detect the presence of a specific viral antigen. There is a variety of settings in which antigen-based are currently approved such as point of care, self-tests, and laboratory-based settings [53]. However, it should be noted that antigen tests can vary in sensitivity. A review of the Cochrane COVID-19 Study register of 48 studies showed significant variation in sensitivity (34.1% Coris Bioconcept to 88.1% SD Biosensor). Average sensitivity was higher in the first week of symptom onset (78.3%) and significantly higher in symptomatic patients when compared to asymptomatic (72% vs 58.1%) [54]. Due to the variance in sensitivity, the CDC currently recommends confirmatory testing with NAAT in some situations based on the algorithm in Fig. 1 [55].

Serological Testing

Infection with SARS-CoV-2 produces antibodies against the nucleocapsid (N) protein and spike (S) protein. Antibodies (IgM, IgG, IgA) are detectable within 1–3 weeks of infection. In a review of 41 patients with serial serum samples in a Chinese hospital in Shenzhen, Qu et al. found that the median conversion time was 11 days for IgG and 14 days for

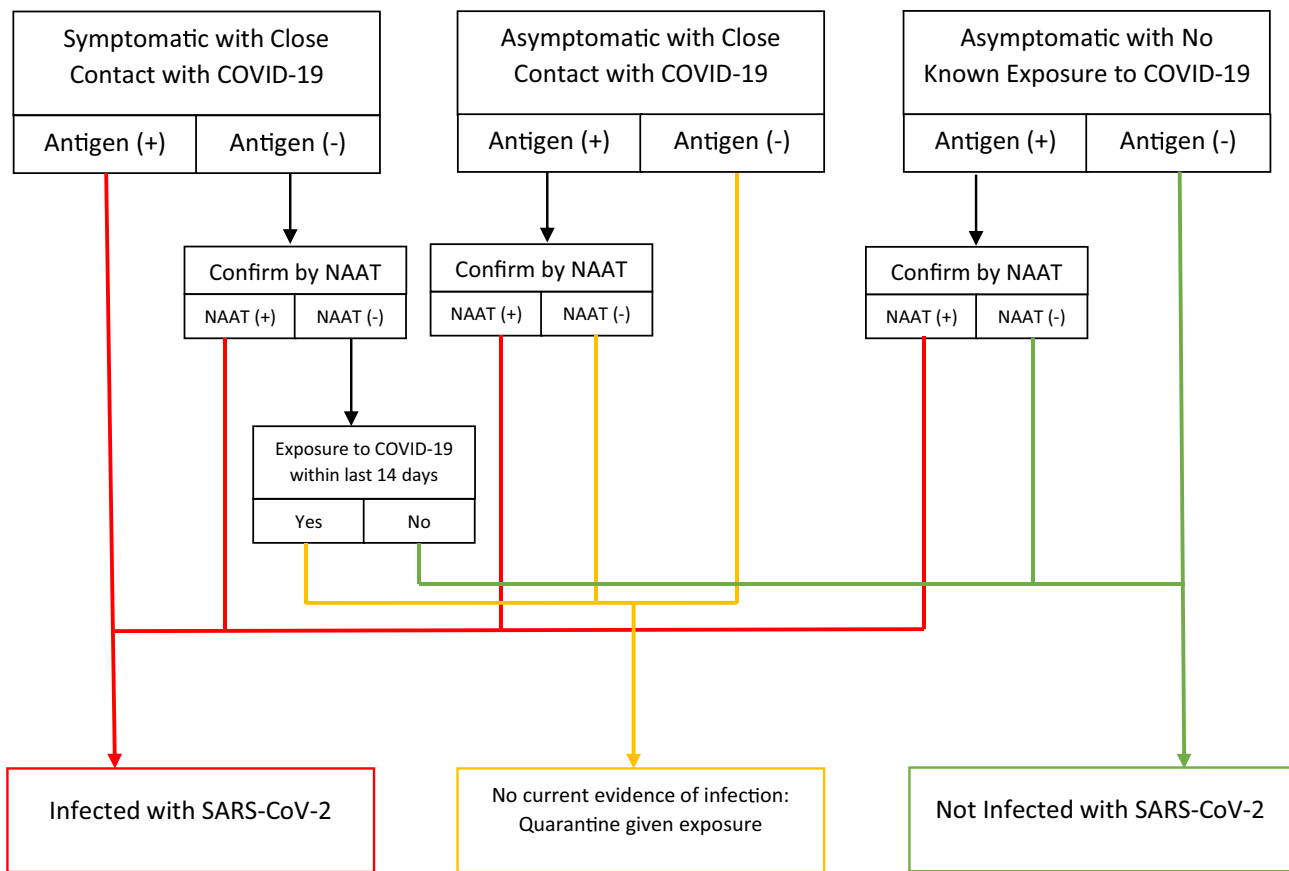


Fig. 1 CDC algorithm for antigen confirmatory testing

IgM. However, IgM serum concentrations declined earlier (day 18) while IgG concentrations continued to rise until day 30 [56]. IgG concentration typically persists for several months (6+ months) following infection [57]. Therefore, IgM antibody positivity could suggest a relatively recent infection (within a few weeks) but a positive IgG can indicate prior infection from over 6 months prior.

Serological testing should not be used as a substitute for NAAT or antigen-based tests for the diagnosis of acute disease. Current CDC guidelines recommend the use of antibody for occupation health, public health purposes (i.e., serologic surveys), and specific clinic situations [58]. The predominant clinical use of serological testing is to determine the presence of prior disease. In children, the presence of a positive serological test indicating prior disease can be used as evidence of prior SARS-CoV-2 infection for the diagnosis of MIS-C (see Table 1).

However, vaccination can cause result in a positive serological test without prior infection with SARS-CoV-2. Vaccinated individual will produce antibodies to the S protein alone. In contrast, individuals with prior infection with COVID-19 will produce antibodies to both S and N proteins [58]. Therefore, it is vital to know the vaccination status as

well as the protein target for a particular serological test in order to determine whether a positive serological test result indicates prior vaccination or infection or both.

The presence of positive SARS-CoV-2 serology has been demonstrated to provide protection against reinfection in a variety of cohort studies [59–61]. Indeed, an 80–90% reduction in infection incidence for approximately 6 months after infection for antibody positive individuals [62–64]. However, it remains uncertain what concentration of antibodies is necessary to provide immunity to SARS-CoV-2 and how long that immunity would persist. Additionally, humoral immune response can remain intact even after presence of neutralization antibodies has faded (commonly seen in mild infection) due to the persistence of memory B-cells [65]. Finally, while it is unclear the degree of protection prior infection or vaccination provides against new SARS-CoV-2 variants, the available evidence suggests a lower degree of protection. In the UK, people with primary infections > 180 days prior to reinfection were found to be more likely infected with Delta variant when compared to reinfection with the Alpha variant [66]. A review of the national database of Qatar noted that the effectiveness of prior infection in preventing reinfection with Alpha, Beta,

and Delta variants of SARS-CoV-2 was 90%, but protection against Omicron variant was significantly lower at 60% [67]. Therefore, antibody testing is not recommended to assess for immunity to SARS-CoV-2 or determine need to quarantine after close contact with a COVID-19 positive individual [58].

Laboratory Findings

Routine CBC with differential in COVID-19 infected children resembles many other viral respiratory infections. The total white blood cell count is normal or reduced. Lymphopenia may be present and progressive, particularly in severe cases. C-reactive protein (CRP) and procalcitonin (PcT) were found to be elevated in 13.6% and 10.6% of cases in a review 12 articles by Henry et al. [68]. Systemic involvement can result in more frequent elevation of inflammatory markers (CRP, PcT) as well as transaminitis, coagulopathy (elevation of D-dimer), increased creatine kinase-MB (CK-MB), and lactate dehydrogenase (LDH). In a review of 24 studies with a total of 624 patients, severe disease in children was associated with frequent elevation of CRP, PcT, and LDH. However, decreased and increased lymphocyte counts were observed at equal frequency (18.7%). Additionally, cytokines were only measured in 2 studies (9 total patients) but IL-10 was seen to be elevated in 75% of severe cases while IL-6 was elevated in 37% and interferon-gamma was elevated in 25% of cases [69].

Radiographic Findings

Radiographic findings in children, particularly in mild or moderate disease, may be normal or indicative of viral/bacterial process (ground glass opacity and consolidation, respectively). In a review of 56 pediatric patients with mild or moderate COVID-19 who underwent daily chest X-ray (CXR) and CT for 2 days, Das et al. noted that 19.6% of patients were found to have abnormal CXR findings (5/11 ground glass opacity, 54.5% combined ground glass opacity and consolidation). CT findings were significantly more sensitive, detecting abnormalities in 46.4% of total patients. CT findings included combined ground glass opacity and consolidation in 73.1% of positive cases, ground glass opacity in 23.1%, and consolidation in 3.8% of cases [70].

Currently, the American College of Radiology does not recommend routine use of CXR or CT for diagnosis of COVID-19 [71]. A review of imaging management in pediatric patients with COVID-19 by Foust et al. did not recommend CXR for most pediatric patients with mild clinical symptoms but may be appropriate if those patients have risk for deterioration or severe disease. CXR is recommended for moderate to severe clinical symptoms requiring hospitalization to establish an imaging baseline and assess

for an alternative diagnosis. Chest CT should be reserved to address specific clinical questions or worsening clinical deterioration. It is not recommended as an initial diagnostic test with pediatric patients with known or suspected COVID-19 pneumonia given the radiation sensitivity of pediatric patients [72].

Management of Mild to Moderate COVID-19

The mainstay of management of pediatric COVID-19 is supportive care. A summary of management of pediatric COVID-19 is available in Fig. 2. A panel of pediatric infectious diseases physicians and pharmacists from 20 geographically diverse North American institutions published interim guidance of pediatric management of COVID-19 in February 2021. The panel recommended management of asymptomatic, mild (URT involvement only without oxygen requirement), or moderate COVID-19 (LRT involvement with oxygen saturation $\geq 94\%$ on room air) with supportive care only [73].

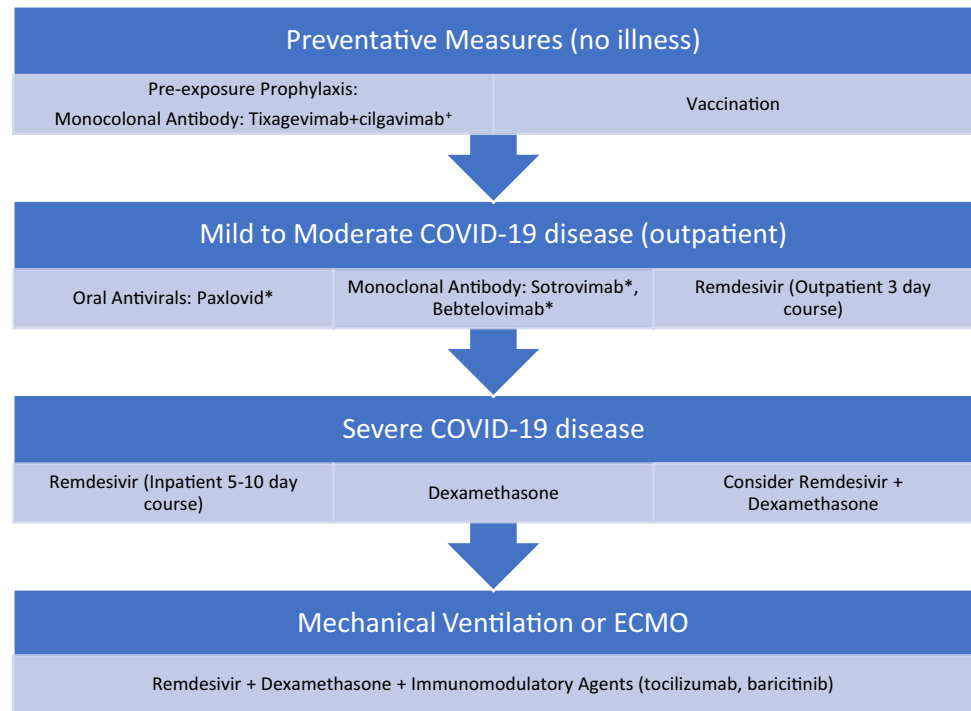
However, new therapeutic interventions are now available for mild COVID-19 disease and should be considered for high-risk pediatric populations who present with asymptomatic, mild, or moderate disease.

Monoclonal Antibody Therapy

Monoclonal antibody therapy should be considered for all eligible children with mild to moderate COVID-19 at high risk for disease progression. High risk for disease progression is defined as BMI ≥ 85 th percentile, immunosuppressive disease or receipt of immunosuppressive therapies, neurodevelopmental disorders (e.g., cerebral palsy, trisomy 21), medical-related technological dependence not related to COVID-19 (e.g., tracheostomy, gastrostomy), sickle cell disease, congenital or acquired heart disease, chronic lung disease, diabetes mellitus, chronic kidney disease, chronic liver disease, pregnancy, or age < 1 year [74•]. Currently the only approved monoclonal antibodies with neutralizing activity against the Omicron variant are sotrovimab, bebtelovimab, and tixagevimab copackaged with cilgavimab (Evusheld) [75, 76••].

Sotrovimab is indicated for children ≥ 12 years of age and weighing ≥ 40 kg with laboratory evidence of SARS-CoV-2 infection, mild to moderate COVID-19, within 10 days of symptom onset, and at high risk for progressing to severe COVID-19 and/or hospitalization [76••, 77••]. In the phase 3 COMET-ICE trial in adults (≥ 18 years of age), sotrovimab was associated with a 85% relative reduction in the risk of hospitalization or death [78].

Fig. 2 Pediatric management of COVID-19. ⁺Pre-exposure prophylaxis in children ≥ 12 years of age and weighing ≥ 40 kg and moderate or severe immunocompromised status with no known SARS-CoV-2 infection or exposure. ^{*}Among ambulatory patients ≥ 12 years and ≥ 40 kg with mild to moderate COVID-19 at high risk for progression to severe disease



Bebtelovimab was only recently given FDA authorization on February 11, 2022. It is currently authorized for the use in ≥ 12 years of age and weighing ≥ 40 kg with laboratory evidence of SARS-CoV-2 infection, at high risk for progression to severe COVID-19 disease, and for whom alternative COVID-19 treatment options are not accessible or clinically appropriate [79].

Tixagevimab copackaged with cilgavimab is currently approved for COVID-19 pre-exposure prophylaxis in children ≥ 12 years of age and weighing ≥ 40 kg with no known SARS-CoV-2 infection or exposure, and moderate or severe immunocompromised status (e.g., hematopoietic cell transplantation in the previous 2 years and lack of immune reconstitution or taking immunosuppressive medications, receipt of CAR T-cell therapy in the previous 2 years, underlying primary immunodeficiency, untreated or advanced HIV infection, receiving active chemotherapy, receipt of solid organ transplant within the last 3 months and receiving immunosuppressive medications, actively receiving treatment with immunosuppressive medications leading to moderate or severe immunocompromise) [80].

Oral Antiviral Therapy

Ritonavir-boosted nirmatrelvir (Paxlovid) combines nirmatrelvir, an orally bioavailable protease inhibitor with demonstrated activity against all coronaviruses that infect humans, with ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor and boosting agent. In adults, Paxlovid was shown to be

associated 88% absolute risk reduction in the risk of hospitalization or death in the EPIC-HR study, a multinational, randomized trial with a total of 2,246 participants [81]. It is currently authorized for children ≥ 12 years of age and weighing ≥ 40 kg with laboratory-confirmed SARS-CoV-2, within 5 days of symptom onset, at high risk for progression to severe COVID-19, and are not hospitalized for COVID-19 [81]. Paxlovid should not be used in individuals with severe hepatic or renal impairment. Providers should review medications taken by the patient closely for potential severe drug-drug interactions as Paxlovid is a strong inhibitor of CYP3A [82].

Molnupiravir is an oral prodrug of beta-D-N4-hydroxycytidine, a ribonucleoside with potent antiviral activity against SARS-CoV-2. In adults, molnupiravir was associated with a 30% relative risk reduction of hospitalization or death in the MOVE-OUT study, a phase 3 randomized trial comprising of 1433 adults [83]. Molnupiravir is currently only authorized in individuals ≥ 18 years of age with laboratory-confirmed SARS-CoV-2, within 5 days of symptom onset, at high risk for progression to severe COVID-19. Current NIH guidelines only recommend molnupiravir when no other option for the therapy of high-risk, non-hospitalized patients with mild to moderate COVID-19 is available [84••].

Remdesivir

Remdesivir is a nucleotide prodrug of an adenosine analog which binds viral dependent RNA polymerase and inhibits viral

replication via termination of RNA transcription with in vitro activity against SARS-CoV-2. Receipt of early remdesivir (once daily for 3 days, within 7 days of symptom onset) was associated with a 87% lower risk of hospitalization or death in a randomized, double-blind placebo-controlled trial of non-hospitalized patients ≥ 12 years of age testing positive for SARS-CoV-2 and with one risk factor for COVID-19 disease progression [85•]. Remdesivir is currently authorized for outpatient use for adults and children weighing at least 3.5 kg with laboratory-confirmed SARS-CoV-2, within 7 days of symptom onset, at high risk for progression to severe COVID-19, and are not hospitalized for COVID-19. IV remdesivir should be given at the following dosages for 3.5 to 40 kg children: 5 mg on day 1 (loading dose) and 2.5 mg/kg once daily on days 2 and 3. For children ≥ 12 years and ≥ 40 kg: 200 mg on day 1 and 100 mg on days 2 and 3 [77••]. Allergic reactions and transaminitis are possible side effects.

Management of Severe COVID-19

Severe COVID-19 illness is defined as individuals with a SpO₂ < 94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen < 300 mmHg, respiratory rate > 30 breaths/min or lung infiltrates of > 50%. Critical illness is defined as individuals with respiratory failure, septic shock, and/or multiple organ dysfunction [86]. Severe disease typically begins approximately 1 week after onset of symptoms and is attributed to excessive hyper-immune response. Therefore, therapeutics are aimed at both viral replication (remdesivir) as well as multiple immunomodulating agents [87].

Remdesivir

IV remdesivir is currently approved by the FDA for treatment of hospitalized adults and pediatric patients ≥ 12 years of age and weighing ≥ 40 kg. It is also available via emergency use authorization for hospitalized pediatric patients weighing 3.5 to < 40 kg or aged < 12 years and weighing ≥ 3.5 kg [88].

In the ACTT-1 trial, remdesivir was associated with improved time to recovery in 435 adults who required oxygen supplementation but not high-flow oxygen, non-invasive or mechanical ventilation (7 vs 9 days) [89]. However, the Solidarity trial reported no difference in the rate of in-hospital deaths or reduction in length of hospital stay or progression to mechanical ventilation [90]. It should be noted that given open control nature of the Solidarity trial, length of hospital stay is difficult to analyze as patient discharge may have been delayed to complete the entire 10-day course of remdesivir. The DisCoVery trial, a multi-national, open-label randomized controlled trial also failed to demonstrate

improved mortality or clinical status when comparing 10 days of remdesivir to stand of alone in hospitalized patients with moderate or severe COVID-19 [91]. In a post hoc analysis of the ACTT-1 trial, the benefit of remdesivir was greatest early in the clinical course (≤ 10 days). This is supported by data suggested the significantly lower rates of hospitalization when given to non-hospitalized outpatients [85•]. Therefore, IV remdesivir is recommended in hospitalized adults who require minimal supplemental oxygen and are early in the course of their disease [92]. Finally, Ali et al. compared remdesivir plus standard of care to standard of care alone in a randomized control trial of 1282 patients between August 14, 2020, and April 1, 2021, and demonstrated a modest benefit in both in hospital mortality (18.7% vs 22.6%) and 60-day mortality (24.8% vs 28.2%) [93].

Remdesivir is recommended for children ≥ 12 years of age who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen. Use in children < 12 years of age via EUA can be considered in consultation with a pediatric infectious disease specialist [94]. Children should have a baseline liver function tests and prothrombin tests prior to receiving remdesivir and these tests should be repeated during treatment. The typical regimen is a loading dose on day 1 (5 mg/kg for ≥ 3.5 to 40 kg, 200 mg for ≥ 40 kg), followed by daily dosing (2.5 mg/kg for ≥ 3.5 to 40 kg, 100 mg for ≥ 40 kg). The initial course is 5 days (or until hospital discharge if < 5 days), but can be extended to 10 days if the critically ill without significant improvement [92].

Dexamethasone

Dexamethasone is recommended for hospitalized children who require high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). In adults, the RECOVERY trial showed that treatment with dexamethasone was associated with improved survival in adult patients who required supplemental oxygen at enrollment (23.3% deaths dexamethasone vs 26.2% standard of care, rate ratio 0.82) [95]. The predominant benefit of corticosteroids is to treat the hyper-inflammatory state of severe COVID-19 infection [92].

The dexamethasone regimen for pediatric patients is 0.15 mg/kg/dose (maximum dose 6 mg) once daily for 10 days (or until hospital discharge if < 10 days) via IV, oral, or NG tube. Alternative steroid regimens (prednisolone, hydrocortisone, methylprednisolone) can be used if dexamethasone is unavailable.

Remdesivir Plus Dexamethasone

In adults, observational studies have suggested a possible clinical benefit of use of remdesivir plus dexamethasone when compared to dexamethasone alone [96–98]. In a prospective controlled

non-randomized study, Marrone et al. demonstrated that remdesivir plus dexamethasone was associated with faster viral clearance (median 6 vs 16 days) and improved 30-day mortality (1.3% vs 16%) when compared to dexamethasone alone [99•]. There is a theoretical benefit in the addition of an antiviral agent to inhibit viral replication in the presence of immune suppression from corticosteroids. Given the possible significant benefits in mortality, the concurrent use of remdesivir in pediatric patients in which dexamethasone is initiated is recommended.

Immunomodulatory Agents

Several adult studies have demonstrated the potential benefit of adding a second immunomodulatory drug to dexamethasone in patients requiring oxygen supplementation via high-flow device or non-invasive ventilation (NIV). Agents used in adults include baricitinib (JAK1/JAK2 inhibitor), tocilizumab (IL-6 inhibitor), and sarilumab (IL-6 inhibitor). However, sarilumab is not recommended for use in pediatric treatment of COVID-19 at this time. Additionally, immunomodulatory agents should only be used in combination with dexamethasone or another corticosteroid [92, 94].

In the REMAP-CAP trial, use of tocilizumab reduced in hospital mortality (28% tocilizumab arm vs 36% standard of care arm) in patients admitted to the ICU with severe to critical COVID-19 and rapid respiratory decompensation [100]. The RECOVERY trial suggested mortality benefit of tocilizumab plus dexamethasone in a subset of patients who required NIV or high-flow oxygen (all-cause mortality 29% in tocilizumab arm vs 33% in standard of care arm) [101].

In the COV-BARRIER trial, all-cause mortality was lower in adult patients receiving oral baricitinib when compared to local standard of care (8.1% baricitinib arm vs 13.1% placebo arm) with a more pronounced benefit in those receiving high-flow oxygen or NIV (17.5% baricitinib arm vs 29.4% placebo arm) [102].

Current adult guidelines recommend to consider the use of an immunomodulatory agent with dexamethasone in patients who require mechanical ventilation or ECMO. Tocilizumab is favored given the RECOVERY and REMAP-CAP trials both reported a mortality benefit for use of tocilizumab in patients with rapid respiratory decompensation and recent admission to the ICU [92]. Given the relative lack of pediatric data available, the use of tocilizumab or baricitinib should be considered in pediatric patients on mechanical ventilation or ECMO.

Anticoagulation

Similar to adults, children with COVID-19 are at increased risk for thrombosis and development of venous

thromboembolism. A multicenter retrospective cohort study by Whitworth et al. demonstrated a thrombotic event rate of 2.1% in children with symptomatic COVID-19 and 0.7% in asymptomatic COVID-19 [103]. Consensus-based guidelines by the Pediatric/Neonatal Scientific and Standardization Subcommittee of the International Society of Thrombosis and Haemostasis recommend low-dose low molecular weight heparin subcutaneously twice daily as anticoagulant thromboprophylaxis in children hospitalized for COVID-19 related illness who have markedly elevated D-dimer levels or superimposed clinical risk factors for hospital associated VTE. Continuous infusion of unfractionated heparin for clinically unstable patients or patients with severe renal impairment [104•].

Conclusion

Pediatric COVID-19 infection is typically milder, with lower risks of hospitalization and death when compared to adults. A large percentage of pediatric cases (up to 65%) may be asymptomatic. Fever and cough remain the most common clinical presentations, although atypical presentations such as “COVID toes,” anosmia, and croup may be present. Children are at risk for post-infectious complications including MIS-C and long COVID. Prevention through vaccination is highly recommended. Respiratory NAAT remains the mainstay of diagnosis and symptomatic management remains the mainstay of therapy. In patients at risk of progression to severe disease, interventions such as monoclonal antibody therapy, PO Paxlovid, or IV remdesivir × 3 days should be considered. In patients with severe disease, therapy recommendations are based on adult data and consist of the use of remdesivir, dexamethasone, and immunomodulatory agents (tocilizumab, baricitinib).

Compliance with Ethical Standards

Conflict of Interest Dr. Frank Zhu declares that he has no conflict of interest. Dr. Jocelyn Ang has participated as a site principal investigator for Eli Lilly and Company Study: J2W-MC PYAB/Addendum 2 (pediatric COVID-19 Study addendum), Eli Lilly and Company's Baricitinib Pediatric COVID-19 Study, from F. Hoffmann-La Roche Ltd 's Tocilizumab Pediatric COVID-19 Study, Regeneron Pharmaceuticals, Inc. 's SARS CoV2 Monoclonal Antibodies Pediatric COVID-19 Study and site co-investigator for Gilead's Remdesivir Pediatric COVID-19 study. Her employer received institutional funds associated with these research projects.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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