Review Article

Severe pediatric COVID-19 with acute respiratory distress syndrome: a narrative review

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Background and Objective: The new coronavirus has rapidly arisen to be a global pandemic since its discovery in December 19th. The prevalence of infection in children is similar to that of adults, though the symptoms are mild or even asymptomatic. However, there are also reports of admission to the Intensive care unit (ICU) or even death in children. Among them, acute respiratory distress syndrome (ARDS), as a common complication, seriously threatens children's lives and health. This review aims to offer an overview of severe pediatric coronavirus disease 19 with ARDS.

Methods: Up to December 21st, 2020, we searched the literature in English language using the online database PubMed and Web of Science with the MeSH terms of COVID-19 and ARDS, and age restricted to children.

Key Content and Findings: We summarize the epidemiology, pathogenesis, clinical manifestations, diagnosis and progress of treatment methods in severe pediatric coronavirus disease 19 with ARDS, and find that the proportion of complicated ARDS varies greatly in different studies and the actual incidence and mortality are not clear due to the lack of clinical data.

Conclusions: Children with COVID-19 are mostly mild, severe patients are few. There is no specific antiviral drug used in pediatric patients, only recommended for severe and critically ill children, and their efficacy needs to be further proved by randomized trials. This review offers a comprehensive overview of severe pediatric coronavirus disease 19 with ARDS, hoping that when the novel coronavirus continues to spread, clinicians can better understand, diagnose and treat the pediatric patients.

Keywords: COVID-19; acute respiratory distress syndrome (ARDS); children

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Introduction

The novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes COVID-19. Since the first case was reported in Wuhan, China in December 2019, it has rapidly spread to the world, then has been declared by the World Health Organization as a major global public health event, posing a huge threat to human life and health. The clinical manifestations range from asymptomatic or mild, to severe disease with acute lung injury and ultimately fatal (1). Pediatric cases are rare at the beginning of the outbreak, while recent studies suggested that children and adults may have the same chance of infection, but symptoms are usually mild or even asymptomatic (2). Nonetheless, there are also studies that reported cases of severe COVID-19 and even death in children (3). A recent study from the United States (4) showed that from March to July, the hospitalization rate of children with novel coronavirus infection showed a weekly increase, and severely ill children accounted for more than

one-third. Therefore, it is very important to pay attention to the incidence of COVID-19 in children and the diagnosis as well as treatment of critically ill children.

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of non-cardiogenic pulmonary edema and hypoxia (5), and it is most often secondary to pneumonia and is also the most common complication of COVID-19 (6). However, until now, the clinical awareness rate of ARDS is still very low. Delayed or inappropriate treatment pose serious threats to children's life and health. As the novel coronavirus continues to spread, children's ARDS caused by acute lung injury should be taken seriously by pediatricians. We present the following article in accordance with the Narrative Review checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-20-111/rc).

Methods

We searched the literature using the online database PubMed and Web of Science with the MeSH terms of COVID-19 and ARDS up to December 21st, 2020. The detailed search strategy in PubMed are as follows: (COVID-19[Title/Abstract] OR SARS-CoV-2[Title/Abstract]) AND (ARDS OR Respiratory distress syndrome* OR Respiratory distress OR lung shock) Filters: Child: birth-18 years. In addition, we also search the available online data on World Health Organization official website. We included all types of clinical studies as well as case reports in English language. Excluded criteria are as follows: (I) duplicate articles, (II) review articles, (III) articles not available electronically, (IV) articles that did not include or report data from pediatric patients that more than 28 days but under the age of 18. (V) studies on the influence of COVID-19 pandemic on health care practice and psychological aspects.

Epidemiology and mortality

As of December 21, 2020, there were a total of 75,479,471 confirmed cases worldwide and a total of 1,686,267 deaths (7), the number of confirmed and dead cases continues to rise. The COVID-19 patients are mainly elderly people, children were first reported in a family cluster in Shenzhen (8), it was a 10-year-old adolescent with asymptomatic infection. Subsequently, reports of childhood infections have increased. Reports from China and North America stated that children under 19 years old accounted for only 2% of all patients with COVID-19 (1,3), but it may be related to the milder symptoms and the lack of pathogenic testing in children. A Seattle study retrospectively tested the serological specimens of children seeking medical care during March and April, and found that 75% of the children who were seropositive were not suspected of having had COVID-19 (9).

Although most of COVID-19 are mild to moderate, the fatality rates in severe cases are high. In a study from China containing 72,314 cases, the mortality rate of critically ill patients was as high as 49% (1), while in a study in New York (10), the mortality rate of intensive care unit (ICU) patients was 24.2%, and that of ICU patients in Italy was 26% (11). ARDS is the most important complication of COVID-19 in adults, accounting for about 29% (6). While in the two subsequent studies, the proportion of ARDS was as high as 41.8% and 61.1% respectively (12,13), and the condition was severe, some studies reported that ARDS accounted for 85% in ICU patients (6) and up to 93% among dead patients (14).

Children with COVID-19 are usually mild, and severely as well as critically ill cases are rare (15). Due to the different hospital specialties and criteria for admission to the ICU, the proportion of children with severe illnesses varies greatly in different studies. The proportion of children admitted to the ICU in the United States is about 0.5–2.0% (16), the proportion of children with severe or critical illness in the Chinese study is 5.9% (17), in a European multicenter study, 8% of children enter the ICU (18), while the proportion of children in specialist hospitals in the United Kingdom is higher (18%) (19). Critically ill children often develop ARDS or respiratory failure rapidly, ranging from 10% to 70% (4,12,19,20). In pediatric reports, there are about 44 cases of ARDS (4,12,18,20-27), accounting for 1.9% to 18.4% (4,12,18,20), and the proportion of ARDS in severely ill children is 24% and 76.9% (12,18).

In most cases, more than 18% of ICU pediatrics require mechanical ventilation (4,19,21,24). Almost half of ARDS patients require mechanical ventilation, extracorporeal membrane oxygenation (ECMO) ventilation is rarely used in children in these cases (12,21-26). Despite this, the mortality rate of children is low, the deaths of a few cases result in ARDS, multiple system organ dysfunction, and neurological dysfunction (12,23,28). In several case reports describing ARDS, three children (3/20) died of severe respiratory failure (12,21,23).

However, if ARDS cannot be diagnosed and treated timely, it is likely to develop into a chronic respiratory disease, which greatly affects the quality of life of children.

Risk factors

A number of current studies have shown that patients are mostly male and older adults especially the elderly, some patients suffer from comorbidities, including hypertension, diabetes, chronic cardiovascular disease, chronic lung disease, and obesity (1,6,11,14,29). However, there is insufficient evidence to prove that these underlying diseases are risk factors for severe COVID-19 in children (30).

Studies have shown that less than 1 month is an independent risk factor for developing severe illness (18,19,31). A multi-center study in Europe indicated that men, with previous medical diseases, and manifestations of lower respiratory tract infection at visit require are significant risk factors for admission to the ICU (18). Obesity and asthma also account for significant proportions of childhood patients, but their associations with SARS-CoV-2 infection or admission to ICU in children are still unclear, further research is needed (4,12,19).

The proportion of severely ill children with ARDS is low, studies (12,21-26) have shown that ARDS mostly occurs in older children, and obesity is common.

For children and newborns with underlying diseases (congenital heart disease, bronchopulmonary dysplasia, respiratory tract malformations, abnormal hemoglobin, severe malnutrition, etc.) and immunodeficiency or immunocompromised (long-term use of immunosuppressants), though the evidence is insufficient, it is prone to developing severely or critically ill, which should be closely observed for early diagnosis and treatment (3,4,32).

The current pediatric researches have not found laboratory indicators related to the need for mechanical ventilation (20).

Qiu *et al.* (31) believe that high fever, lymphopenia, and high levels of procalcitonin, D-dimer and creatine kinase MB (CK-MB) are significantly related to severe childhood illness, however, the same conclusion has not been obtained in other studies, it needs to be further explored.

Pathogenesis

SARS-CoV-2 is classified into subgenus sarbecovirus of the genus betacoronavirus, and encodes four structural proteins, including, spike (S), envelope (E), matrix/membrane (M), and nucleocapsid (N) (33). The S protein mediates the adhesion to the host cell surface receptor and promotes the virus to enter the cytoplasm, which plays a key role in virus infection (34). The pathogenesis of acute lung injury and ARDS caused by SARS-CoV-2 has not yet been elucidated. According to current research results, ARDS may be caused by followed.

Hyperinflammation

Excessive inflammatory response to SARS-CoV-2 is considered to be the main cause of severe illness and death in patients with COVID-19 (35), and is related to the massive infiltration of monocyte-macrophage, high levels of circulating cytokines, and severe lymphopenia. Elevated levels of serum interferon gamma-induced protein 10 (IP-10) and granulocyte-macrophage colony- stimulating factor (GM-CSF) are associated with an increase in mortality in COVID-19-related ARDS, which is consistent with the role of IP-10 in recruiting T cells and monocytes and the role of GM-CSF in pro-inflammatory cytokines and leukocyte chemotaxis (36).

Macrophages play an important role in the pathogenesis of ARDS caused by SARS-CoV-2 infection. The increased production of cytokines [interleukin-6 (IL-6), interleukin-7 (IL-7) and tumor necrosis factor] and inflammatory chemokines [CC chemokine ligand (CCL) 2, CCL3, CXC-chemokine ligand (CXCL) 10, and CXCL9] in severe COVID-19 patients, promotes abnormal activation and massive infiltration of monocyte-macrophages, further aggravating the severity of the disease (35,37). SARS-CoV-2 binds to Toll-like receptors on alveolar macrophages, then activates natural immune defense (38).

As a component of innate immunity, the activation of neutrophils and the formation of neutrophil extracellular traps (Net) may further promote the release of massive cytokines in severe COVID-19 and aggravate lung damage in patients (39).

In addition, patients with COVID-19-ARDS show a phenotype of impaired adaptive immune response, which is related to severe lymphopenia (CD4+ T cells, CD8+ T cells and B cells) and delayed lymphocyte activation (40). The reduction of T lymphocytes is observed in patients with severe COVID-19, and the CD8+ T cell subset is more pronounced (41). Autopsy among patients with COVID-19 found pulmonary lymphatic infiltration (42,43), and similar observations in bronchoalveolar lavage fluid samples (44), which indicate that T lymphocytes gathers in inflammatory tissues to play a role in virus clearance. However, T cells in the secondary lymphoid organs of COVID-19 patients are significantly depleted (45,46). The high levels of tumor necrosis factor-α (TNF-α) and IL-6 in patients with

COVID-19 may be the reason for the decrease in T cell production and the acceleration of T cell apoptosis (47). In addition, studies have found that the interferon response of severe and critical patients is significantly impaired, which is conducive to the escape of the virus and aggravates the disease (48).

Endothelial and epithelial increased permeability

Diffuse alveolar damage and vascular leakage caused by SARS-CoV-2 infection are an important components of ARDS.

ACE2 is a specific receptor for SARS-CoV2 (49), the S protein can specifically bind to the ACE2 of alveolar epithelial cells, then the epithelial cells apoptosis and produce a series of pro-inflammatory cytokines and chemokines, leading to increased epithelial permeability, triggering local inflammation and recruiting immune cells to gather (50), thereby causing diffuse alveolar damage (51).

Studies have shown that SARS-CoV-2 can infect endothelial cells through ACE2 (52), leading to their dysfunction and death, and the expression of ACE2 in endothelial cells is down-regulated (53), local angiotensin can aggravate lung inflammation and promote blood coagulation. In addition, the reduction of ACE2 expression may also indirectly activate the kallikrein-kinin system (KKS), leading to increased vascular permeability, protein exudation and aggravation of pulmonary edema (54,55).

Vascular injury and thrombosis

Extensive pulmonary blood vessel thrombosis is a consistent feature of ARDS (56,57). The typical endothelial inflammation in patients with COVID-19 can lead to strong activation of the coagulation cascade, leading to microthrombosis and giant thrombosis in lung tissue (43,55,58,59), which indicates that thrombosis is involved in the development of COVID-19-related ARDS, and it is associated with the increase of D-dimer level. Vascular damage and microthrombosis cause blood perfusion disorders, then lead to hypoxemia. During extensive obstruction, due to insufficient microcirculation recruitment and increased flow rate, the gas exchange time reduced, further aggravating hypoxemia (60,61).

Recent study has concluded that, unlike typical ARDS, which mainly "hits" the alveolar cavity, patients with COVID-19-related ARDS have significantly changed the ratio of perfusion and ventilation due to vascular regulation disorders, and lung compliance and lung volume of COVID-19-related ARDS patients are higher than common ARDS, and the mechanics and dead space of COVID-19-related ARDS did not improve significantly or even worsened after positive end expiratory pressure (PEEP) increased, suggesting that recruitment potential and blood flow redistribution are low. However, this observation has not been confirmed by other studies (29,62-64). At present, there is no consensus on whether the COVID-19-related ARDS is an atypical subset in ARDS, it needs further study.

Clinical manifestation

The most common symptoms are fever and cough, followed by shortness of breath and pharyngeal erythema, some children may have nausea and vomiting, diarrhea, headache, etc. (3,19,28). There were also some patients who present simple wheezing (65). Children have a short course of illness and usually recover within 1–2 weeks (15). The most common symptoms associated with ICU admission are shortness of breath or respiratory distress, children usually present with rapidly progressive hypoxemia and has a high demand for mechanical ventilation (4,19,21,24).

The most common laboratory finding in adult is lymphopenia, some patients have elevated levels of D-dimer, CRP, lactate dehydrogenase and ferritin; severely ill patients are more likely to have abnormal laboratory examinations, lymphopenia, higher concentrations of interleukin-6, d-dimer levels, CRP, troponin, and lactate dehydrogenase are independently associated with in-hospital mortality (6,10,14,29,32,66). Laboratory findings in children are mildly abnormal, lymphocytes and white blood cells often slightly reduced (15,28), thrombocytopenia is mainly seen in critically ill children, whose inflammatory markers (lactic acid, CRP, PCT, and ferritin) are significantly increased compared with mild children (19,25,26). Among the four ARDS cases (21,22,25,26) with detailed information, three patients had increased inflammatory factors (*Table 1*).

Diagnosis

The diagnosis of COVID-19 can refer to WHO standard. The diagnostic test standard for COVID-19 is to detect unique viral sequences through Nucleic Acid Amplification Testing (NAAT), of which real-time PCR is the most commonly used technique. Currently, nasopharyngeal swabs are the first choice for detection of the novel coronavirus (67). Though positive rate of lower respiratory

Table 1 Cases of pediatric ARDS induced by COVID-19

	Patel *et al.* (25)[‡]	Lewis *et al.* (26)	Lahfaoui *et al.* (21)	Kalyanaraman *et al.* (22)
Age	12 yr	16 yr	17 mo	1 mo (corrected age)
Sex	Female	Female	Female	Male
BMI (kg/m^2)	25	31	–	–
Laboratory markers (admission)				
WBC	N	N	Elevated	N
RBC	–	N	Decreased	–
HB	N	N	Decreased	Decreased
PLT	Decreased	N	N	N
Anaemia	Macrothrombocytopenia	N	Y	Y
Lymphopenia	Y	Y	N	N
C-reactive protein	Elevated	Elevated[†]	N	Elevated
Procalcitonin	Elevated	Elevated[†]	N	Elevated
Ferritin	Elevated	Elevated[†]	N	N
PT	N	N	N	Elevated
ALT	N	Elevated	N	N
AST	N	Elevated	N	N
BUN	N	N	N	Elevated
Creatinine	N	N	N	Elevated
D-Dimer	N	Elevated[†]	N	N
Fibrinogen	N	Elevated	N	N
Outcomes				
Hospital stay				
PICU stay				
Discharge		HD21		HD27
Death			HD1	

[†], indicates an increase after the application of ECMO; [‡], the report does not record the outcome but refers the clinical condition of this patient improved. Y, Yes ; N, normal; –, no record; WBC, white blood cell; RBC, red blood cell; HB, hemoglobin; PLT, platelet; PT, prothrombin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PICU, Pediatric Intensive Care Unit.

tract specimens is very high, it is not recommended for routine use due to its safety. In addition, second-generation sequencing, virus culture, and novel coronavirus-specific antibody detection are also effective methods for diagnosing novel coronavirus (6,68-70).

When the patient with COVID-19 suffering acute onset of hypoxemia usually complains dyspnea and presents respiratory distress on physical examination, with partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2) <300 mmHg and bilateral chest radiographic opacities (71), ARDS probably occurs. As there are differences in pathophysiology between children and adults, in 2015, the International Pediatric Acute Lung Injury Consensus Conference (PALICC) defined the criteria for pediatric acute respiratory distress syndrome (PARDS) (*Table 2*) (72), which is more inclusive than the Berlin criteria for adults, and is helpful for the diagnosis of children as well as stratifying mortality better (73).

Table 2 Pediatric criteria for ARDS (PALICC) (72)

Characteristics	Definition
Age	Exclude patients with perinatal- related lung disease
Timing	Within 1 week of known insult
Origin	Respiratory failure not fully explained by cardiac function or fluid overload
Imaging	New infiltrate(s) consistent with acute pulmonary parenchymal disease
Oxygenation	
Invasive mechanical ventilation	
Mild PARDS	4≤ OI <8 or 5≤ OSI <7.5
Moderate PARDS	8≤ OI <16 or 7.5≤ OSI <12.3
Severe PARDS	OI ≥16 or OSI ≥12.3
Noninvasive mechanical ventilation	Full face-mask bi-level ventilation or CPAP ≥5 cmH_2O; PaO_2/FiO_2 ≤300 or SaO_2/FiO_2 ≤264

CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; OI, oxygenation index: airway pressure × FiO_2 × 100)/PaO_2; OSI, oxygen saturation: FiO_2 × mean airway pressure × 100)/SpO_2; PaO_2, partial pressure of arterial oxygen; SaO_2, oxygen saturation; SpO_2, peripheral capillary oxygen saturation.

Treatment

General supportive treatment

Supportive treatment is the most basic treatment for children with COVID-19, especially for children with ARDS. Early supportive treatment can greatly improve the prognosis, and removing the cause is also an important measure to control the progression of the disease. Rest in bed, take in adequate energy intake, and maintain water and electrolyte balance. During treatment, clinicians should pay close attention to disease status in children, and regularly monitor vital signs, blood oxygen saturation, etc. to detect the progress of the disease early (74). Critically ill children should be admitted to the ICU for monitoring.

Medications

The curative effect will vary in different stages or manifestations of the disease. Virus suppression is considered to be most effective in the early stages of infection, while in hospitalized patients, immunomodulators may help prevent disease progression, and anticoagulants may help prevent thromboembolic complications (75). At present, the clinical trials for the treatment of the novel coronavirus is still in progress are on-going, and there is no specific drugs that has been verified by sufficient random double-blind experiments.

Anti-viral therapy

Remdevir is currently recommended for hospitalized patients who require supplemental oxygen, while it is not recommended for patients on mechanical ventilation (76).

A randomized controlled trial showed that Remdevir can shorten the recovery time of patients, and may have a slight effect on reducing mortality and serious adverse events (77). However, another trial didn't find the association of Remdevir with statistically significant clinical benefits (78), more trail proofs are needed. A 5-day course of treatment can reduce the need for mechanical ventilation in critically ill patients, but for patients who have undergone mechanical ventilation or ECMO, there is no difference in clinical recovery time (79,80).

Currently there are no results of randomized controlled trials of Remdesivir in children.

In a multicenter study in Spain, Remdesivir used accounted for 9.3% and 25% of patients requiring mechanical ventilation (20). Sixty-nine patients were admitted to the ICU and nine received Remdesivir in the European study, but the clinical effect is unknown (4). The North American pediatric expert consensus (30) recommends that whether to use the drug can be based on need for respiratory support. For severe patients who need supplemental oxygen or who require non-invasive or invasive mechanical ventilation or ECMO, the drug is recommended. However, since the clinical effect of the drug is still uncertain, the efficacy and risk of children

must be continuously evaluated.

For critically ill children, considering the severity of extreme diseases and the lack of pediatric-specific data to evaluate the efficacy, Remdesivir should be considered on the basis of them, and the duration is suggested to be 5-10 days, for children who do not get better after 5 days of treatment, a duration of up to 10 days can be considered according to the specific condition (30).

Chloroquine or Hydroxychloroquine are also candidates of antiviral drugs for COVID-19, with 63% utilization in ICU children in Spain (20), but in several cases, the effect of hydroxychloroquine is low in pediatric patients (25,26,81). However, there are no randomized trials or observational studies to evaluate the efficacy of the two drugs in children. Published results from adult trials (82-85) show that chloroquine and hydroxychloroquine cannot improve clinical results or reduce mortality, similarly, hydroxychloroquine combined with azithromycin treatment has no obvious effect either. A multicenter observational study on COVID-19-related ARDS also proved that hydroxychloroquine does not increase the weaning and survival rate (86). A number of randomized trials are on-going, and they are yet to provide evidence as to whether to use these drugs to treat COVID-19.

Lopinavir-ritonavir has also been used for COVID-19. However, the randomized controlled trial indicates that the combination of lopinavir-ritonavir does not reduce the 28-day mortality rate (87). Further randomized trials for severe COVID-19 patients with respiratory dysfunction have shown that the combination of lopinavir-ritonavir has no obvious benefit, and cannot reduce mortality or shorten clinical improvement time (88). Researchers also found that the treatment of lopinavir-ritonavir in COVID-19-related ARDS has no obvious effect, and easily leads to acute kidney injury and requires renal replacement therapy (86). Most experts recommend against using lopinavir-ritonavir or any other HIV-1 protease inhibitors to treat novel coronavirus pneumonia outside of clinical trials.

Other antiviral drugs such as Favipiravir, Avifavir, Umifenovir, and TMPRSS2 inhibitor are also potential treatments for COVID-19. However, the roles of them are unclear in children with COVID-19-related ARDS. Clinical trials on them are being conducted around the world, which will help guide treatment.

Immunomodulation

Concerning the high inflammatory status may cause many serious symptoms of novel coronavirus pneumonia, several immunomodulatory therapies are currently being studied, recommended only for COVID-19 children who are critically ill and have inflammatory evidence (elevated ferritin, CRP and erythrocyte sedimentation rate, etc.) (89).

There is still controversy about glucocorticoid treatment of novel coronavirus pneumonia. A controlled, open-label trial showed that in patients receive invasive mechanical ventilation or only oxygen therapy, dexamethasone can reduce 28-day mortality (90). A subsequent randomized trial of COVID-19 patients with moderate to severe ARDS showed that dexamethasone plus standard care significantly increased survival days and ventilator-free days at 28 days compared with standard care alone (91). However, a multi-center studies have shown that methylprednisolone does not reduce the risk of death, and for patients treated 14 days after ARDS, the mortality rate may increase (92). An observational study on children with ARDS showed that corticosteroid exposure >24 h could reduce ventilator-free days at 28 days (93). Overall, there is insufficient evidence on the application of glucocorticoids in COVID-19 patients with ARDS, dexamethasone may be beneficial in pediatric patients with COVID-19 respiratory disease who require mechanical ventilation (76), and further research is needed.

Intravenous immunoglobulin (IVIG) plays an important role in treating critically ill patients, and has been reported in many children's cases, especially for Multi-Inflammatory Syndrome in Children (MIS-C) (94). Studies have shown that high-dose IVIG can improve the clinical symptoms of critically ill patients (95), and early use (within 48 hours after admission) can reduce 28-day mortality compared with late use (96). A randomized trial showed that IVIG can reduce the mortality of severe COVID-19, but its sample size is small, and parameters were different between two groups, which is not enough to prove the true value of IVIG (97). A subsequent randomized trial showed that IVIG could not improve the length of hospital stay, however, it is used on the basis of hydroxychloroquine and lopinavir-ritonavir, the effectiveness of IVIG alone could not be evaluated (98). Due to the lack of sufficient evidence to support the efficacy of IVIG, as well as its high price, the use of IVIG should be carefully considered according to the patient's condition.

A study of convalescent plasma (CP) therapy in children with COVID-19-related ARDS showed that CP is safe for children, but its effectiveness has not been demonstrated (23). While a randomized trial of severely ill adult patients showed that there was no statistical difference in the time

of clinical improvement within 28 days between patients receiving convalescent plasma therapy and patients receiving standard treatment alone (99). However, due to slow enrollment, the trial was stopped early, which limits the ability to find clinically important differences. More randomized trials are needed.

Interferon-α2b nebulization has shown clinical efficacy in the treatment of various viral infections and has been widely used in the treatment of patients with novel coronavirus pneumonia. However, there is little clinical evidence on the effectiveness and safety of interferon-α2b in the treatment of COVID-19. A retrospective study showed that early use of interferon-a2b (5 days after admission) in patients with severe to critically ill COVID-19 could reduce in-hospital mortality, while late interferon-a2b use (7–11 days after admission) might increase mortality (100). The clinical efficacy of interferon in the treatment of COVID-19 patients still needs to be evaluated by randomized controlled trials.

There are many kinds of monoclonal antibodies that regulate inflammation, such as interferon-γ, interleukin 1, interleukin 6, and complement factor 5a, etc. Among them, tocilizumab is more commonly used in children. Studies have confirmed that tocilizumab can immediately improve the clinical outcome of patients with severe COVID-19 and is an effective treatment to reduce mortality (101). A critically ill child with COVID-19-related ARDS was switched to Remdevir combined with tocilizumab after ineffectiveness of hydroxychloroquine and achieved significant clinical improvement (25). In Spanish pediatric ICU, the frequency of tocilizumab use reaches 32.6%, and in mechanically ventilated children up to 50% (20), but its efficacy and adverse reactions still require randomized trials to provide evidence. It is currently recommended for patients with extensive lung disease and severe disease, as well as those with elevated IL-6 levels in laboratory tests can be tried (102).

Respiratory support

As mentioned above, researchers who believe that COVID-19-related ARDS is an atypical subset in ARDS, which can be divided into two types: L type (low elastance value, lung ventilation/perfusion ratio, lung weight and recruitability) and H type (high elastance value, right--to-left shunt, lung weight and high recruitability); for patients with type L COVID-19-ARDS, [The PEEP should be reduced to 8–10 cmH_2O] to avoid the increased risk of hemodynamic failure, and if the patient is [hypercapnic, can be ventilated with volumes greater than 6 mL/kg (up to 8–9 mL/kg), as the high compliance results in tolerable strain without the risk of VILI] (103). However, there is no consistent evidence to support this conclusion. Therefore, it is still necessary to follow the recognized ARDS guidance to manage patients, including COVID-19 (104,105).

Mechanical ventilation

Tidal volume/plateau pressure limitations

With the discovery that compulsory mechanical ventilation may aggravate the degree of lung injury, low tidal volume support, has gradually been widely used in the treatment of ARDS. However, how to adjust the tidal volume to the specific needs of patients is still controversial, and further research is needed. PALICC recommends that inspiratory plateau pressure should be limited to 28 cmH_2O (72).

Lung recruitment strategy

PEEP ventilation is routinely used in clinical practice because it promotes oxygenation and maintains alveolar recruitment. The PEEP level is too low to prevent cyclic opening and collapse of distal airspaces, but too high can easily lead to tidal overdistension (106). At present, there is no consensus about the appropriate PEEP level. The slow incremental PEEP step is relatively safe and effective for improving PARDS lung oxygenation. An observational study suggest that for patients with COVID-19, the recruitment-to-inflation (R/I) ratio can be evaluated to guide the level of PPEP so as to avoid unnecessary lung damage caused by high PEEP level (107). PALICC (72) recommends that PEEP in children with severe ARDS should be set at 10–15 cmH_2O, and then increment PEEP slowly to achieve the desired effect on this basis.

Prone positioning

Prone position ventilation is mostly used as an auxiliary treatment for patients using ventilator, which can reduce the unevenness of lung inflation area, thereby improving gas exchange. Randomized trials have confirmed that in patients with severe ARDS (P/F value <150 mmHg), early application of prolonged prone position can significantly reduce 28-day and 90-day mortality (108). Recent studies have shown that prone position ventilation can increase the P/F value of

ARDS with a P/F ratio of less than 120 mmHg (109), but prolonged prone positioning can increase the risk of pressure ulcers in patients (110), and it is prone to decoupling. It is recommended for adjuvant treatment for severe ARDS not routine use.

High-frequency ventilation (HFOV)

As HFOV may increase mortality in adult patients (111), it is currently only used in children, but the evidence for the efficacy of HFOV is still scarce. In a retrospective study of 48 children with severe PARDS, compared with CMV, the use of rescue HFOV was associated with improved gas exchange, but not with reduced mortality (112). Recent studies have shown that HFOV can also increase the 28-day mortality of PARDS (113), but because it does not stratify severity, the evidence is limited. It is recommended that (72) in patients with hypoxic respiratory failure whose airway plateau pressure exceeds 28 cmH_2O and there is no evidence of chest wall compliance, HFOV can be used as an alternative ventilation mode and should be considered for use in children with moderate to severe PARDS. The efficacy of HFOV in pediatric patients still needs a lot of evidence from randomized trials.

Extracorporeal membrane oxygenation

ECMO is often used as cardiopulmonary support after the failure of conventional treatment. In the pediatric population, ECMO is used for organ support in the case of respiratory failure and heart failure (114,115). It is now recommended as an alternative treatment when lung protective ventilation is insufficient to support refractory hypoxemia in patients with COVID-19-related ARDS. However, a meta-analysis showed that ECMO could not reduce the mortality of patients with COVID-19-related ARDS (116). In a recent cohort study, the mortality rate of COVID-19-related ARDS adult patients treated with ECMO was less than 40%, which is similar with the mortality rate of non-COVID-19-related ARDS cases, supporting the application of ECMO in COVID-19-related ARDS (117,118). Though the research evidence for the application of ECMO to children is little, ECMO is still widely used in the treatment of PARDS. A cohort study showed that ECMO did not improve the survival rate of children with hypoxic respiratory failure, and there was no obvious benefit to clinical improvement, weaning from ventilator or discharge (119). Further randomized trials are needed to confirm the efficacy of ECMO to help determine the treatment plan.

Inhaled nitric oxide

Inhaled Nitric Oxide can promote selective vasodilation of the lungs and improve the oxygenation of blood (120). However, studies showed that inhaled NO does not bring benefits to PARDS (121,122). PALICC recommends it for salvage treatment of severe PARDS or as a transition to ECMO treatment (72).

Conclusions

Children with COVID-19 are mostly mild, severe patients are few. The proportion of complicated ARDS varies greatly in different studies. Due to the lack of clinical data, the actual incidence and mortality are not clear. At present, the gold standard for the diagnosis of novel coronavirus infection is nucleic acid testing. The diagnostic criteria for ARDS are not uniform, and the PALICC standard is often used as a reference in clinical practice to identify, diagnose and treat children with ARDS early. There is no specific antiviral drug used in pediatric patients, only recommended for severe and critically ill children, and their efficacy needs to be further proved by randomized trials. Ventilation support is the fundamental treatment for children with ARDS, but there is no recommendation for the best ventilation mode, and whether COVID-19-related ARDS is an atypical subset in ARDS needs further study. More high-quality studies are still needed to provide evidence in the future.

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