Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

The use of convalescent plasma for pediatric patients with SARS-CoV-2: A systematic literature review

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19), a severe illness leading to pneumonia, multiorgan failure, and death. With this study, we performed a systematic review of the literature and ongoing clinical trials on convalescent plasma therapy in pediatric patients with COVID-19. The electronic databases Medline PubMed, Scopus, and Web Of Science were searched. Also, clinical trials registries were searched for potentially eligible studies. A total of 90 records were retrieved after duplicate removal. Eight studies were case reports of children treated with convalescent plasma therapy (14 children, age range, 9 weeks to 18 years); 5 children had a chronic disease. During the hospital stay, 5 received drugs (e.g., remdesivir) in addition to convalescent plasma therapy. No convalescent plasma therapy-related adverse events were reported in 5 studies and 3 made no mention of adverse events. Seven studies concluded that convalescent plasma therapy is or could be a useful therapeutic option; one study made no claims. Only 3 of the 13 retrieved trials underway were planned exclusively for children. This is the first systematic review of the literature regarding convalescent plasma therapy for COVID-19 in children. We found insufficient clinical information on the safety and efficacy of convalescent plasma therapy in children. Nevertheless, the positive outcomes of the few case reports published to date suggest that convalescent plasma therapy may be of potential benefit. Further research with well-designed and powered clinical trials is needed.

1. Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated in the city of Wuhan in Hubei province, China, in late 2019. This virus is the cause of coronavirus disease 2019 (COVID-19), a severe illness characterized by pneumonia with increased infiltration of inflammatory cells and higher levels of pro-inflammatory cytokines (cytokine storms). Such events may lead to acute pulmonary injury, acute respiratory distress syndrome (ARDS), multiorgan failure, and ultimately death [1–3]. During the first three months of 2020, SARS-CoV-2 infection began to spread worldwide. It was finally classified by the World Health Organization (WHO) as a Public Health Emergency of International Concern. At the time of writing, nearly 50 million people have been infected by the virus and approximately 1,25 million have died (WHO. Coronavirus disease [COVID-19] outbreak, accessed 09/11/2020) [4]. The median age of patients who died due to severe COVID-19 during the first pandemic wave (March-June 2020) was 78 years (interquartile range [IQR], 67–87), according to the U.S. Centers for Disease Control and Prevention (CDC) [5]. Patient age progressively declined over the summer months due to the lack of adoption by younger individuals of minimum preventive measures (use of masks and social distancing) [5]. Even with the decreasing age of symptomatic COVID-19 patients during the second pandemic wave, symptomatic cases among children remain rare for still largely unknown reasons. Nonetheless, cases of multisystem inflammatory and Kawasaki syndrome in children and adolescents have been reported [6].

While there are various treatment options for SARS-CoV-2, no effective vaccine or drug against the virus is currently available [7].

Abbreviations: CPT, convalescent plasma therapy; RBD, receptor-binding domain; RT-PCR, real-time reverse transcription-polymerase chain reaction.

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Table 1
Characteristics of case reports of children treated with convalescent plasma.

Author (year)	Design	Country	Case study	Comorbidity	Clinical condition	Diagnostic approach	Treatment	Reason for CP* treatment	Outcome	Comments
Jin H., et al. (Sep 2020) [20]	Case report	USA	Case 1−10-year-old male; excluded: Case 2−24-year-old man; Case 3−40-year-old man	Hereditary spherocytosis + X-linked agammaglobulinemia (XLA)	Initial symptoms: 10 dys before hospitalization; chest X-ray: right middle and lower lobe infiltrates	At admission: negative naso-pharyngeal swab RT-PCR;*** day 19: positive bronchoalveolar lavage RT-PCR***	10-day course of remdesivir; 2 units 200 mL unmixed ABO-compatible CP* (days 22 and 23)	Minimal improvement on supportive therapies	Recovered after receiving CP* (6 dys).	CPT may help neutralize virus, shorten duration of illness, also in later stages of COVID-19
Figlerowicz M, et al. (July 2020) [21]	Case report	Poland	6-year-old girl	Aplastic anemia with severe pancytopenia	Hepatomegaly and bilaterally enlarged kidneys; COVID-19-associated severe aplastic anemia	RT-PCR*** test on nasopharyngeal swab.	IVIG, lopinavir-ritonavir (10 mg + 2.5 mg twice daily). At 5 wks: CP* with antibodies against IgG titer 1:700 once in a 200 mL/dose	Poor effect of treatment: IVIG, lopinavir-ritonavir + steroid	Negative SARS-CoV-2 RNA in nasopharyngeal swabs (3 wks); hematologic parameters (pancytopenia) did not improve; no adverse events	In patients with pancytopenia, transfusion of CP* could be an option
Shankar AU, et al. (2020) [22]	Case report	India	4-year-old girl	Acute lymphoblastic leukemia	Chest X-ray: bilateral fluffy opacities; hypoxia with increasing oxygen requirement to 7 L/min with face mask	RT-PCR*** for SARS-COV-2 RNA from nasopharyngeal swab	CP* 15 mL/kg on day 8 and 9. Lopinavir-ritonavir and remdesivir dexamethasone (0.2 mg/kg) and IVIG (1 g/kg)	Children with cancer (high-risk population); severe COVID-19 associated pneumonia	Remarkable improvement with reduction in respiratory rate, work of breathing and oxygen requirement (10 dys) No transfusion reaction	Positive outcome following use of IVIG, steroids and CP* alone
Schwartz SP, et al. (Oct 2020) [17]	Case report (n = 4)	USA	1) 15-year-old obese Hispanic male; 2) 16-year-old obese Asian male; 3) 5-year-old Hispanic female; 4) 12-year-old obese Hispanic female	None	Acute respiratory failure requiring high-flow nasal cannula (HFNC) at admission	Anti-SARS-CoV-2 antibodies targeted to RBD** of SARS-CoV-2 spike protein	CP* units transfused: Case 1) no. 2 (RBD** binding titer 1:160; same donor); Remdesivir. IV anakinra. Case 2) no. 2, 10 mL/kg (titer unknown). remdesivir. Case 3) no. 2 (separate donors; titer 1:1,280). remdesivir Case 4) no. 2 (titer: Unit 1 = 1: 2,560, Unit 2 = 1:640). remdesivir. IV methylprednisolone	CPT* as a treatment strategy for severe disease	Discharged home after CP*: 7 dys; 5 dys; 23 dys; 10 dys, respectively. Off oxygen support. 4) binding titer: unit 1 = 1:2,560, unit 2 = 1:640 No adverse events	CPT* is feasible therapy for critically ill pediatric patients
Rodriguez Z, et al. (Sep 2020) [23]	Case report	USA	9-week-old female	Trisomy 21; congenital heart disease	Cardiopulmonary failure secondary to unrepaired congenital heart disease exacerbated by COVID-19	SARS-CoV-2 nucleic acid testing of nasopharyngeal swab	Remdesivir (5 mg/kg) 2 aliquots of CP* from 2 donors (10 mL/kg per aliquot; donor no. 1 had IgG titer 1:12724 and neutralizing titer 1:126; donor no. 2 had IgG titer 1:816 and neutralizing titer 1:50) from 2 COVID-19 recovered donors	Deteriorating clinical status because lack of response to remdesivir (5 mg/kg per day) on hospital day 15 and 2.5 mg/kg per day on hospital days 16−25).	Uneventful complete recovery (47 dys)	CP* may be safe and effective treatment option in SARS-CoV-2 infection refractory to remdesivir.
		USA		None						

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Design	Country	Case study	Comorbidity	Clinical condition	Diagnostic approach	Treatment	Reason for CP* treatment	Outcome	Comments
Diorio C, et al (Sep 2020) [18]	Case report		N = 4 patients, 14–18 years old; CD4, CD15, CD17, CD25#		Intubation and ventilation; two required extracorporeal membrane oxygenation	RT-PCR*** testing of respiratory tract mucosa	Patient CD4 received CP* 2 mL/kg Patients CD15, CD17, CD25 received CP* 4 mL/kg (RBD**-specific antibody titer levels <1:160)	Life-threatening COVID-19-associated respiratory disease	Donor for patient CD25# had higher SARS-CoV-2 RBD** antibody titers (>1:6000) than donor for other patients; no adverse event	CP* may be of greatest benefit early in illness
Greene AG, et al (Jun 2020) [19]	Case report	USA	11-year-old female	None	Toxic shock-like syndrome; LV systolic function mildly decreased based on decreased shortening fraction	RT-PCR*** positive for SARS-CoV-2	Furosemide, enoxaparin, tocilizumab, CP*, remdesivir, steroids, IVIG	Signs of distributive shock, multi-organ injury, systemic inflammation associated with COVID-19	Improved dramatically (24 h)	Close follow-up for children presenting with fever lasting 3 dys
Balashov D, et al. (Nov 2020) [24]	Case report	Russia	9-month-old girl	Juvenile myelomonocytic leukemia; hematopoietic stem cell transplantation	Polysegmental bilateral viral pneumonia with 60 % damage of lung tissue	RT-PCR***, throat swab positive for SARS-CoV-2 on day 99 after hematopoietic stem cell transplantation	Tocilizumab (10 mg/kg), CP* (10 mL/kg; 3 doses; titers 1:160, 1:160 and 1:80)	Secondary immunodeficiency	Full resolution of lung lesions; complete elimination SARS-CoV-2 4 mths after first detection CT* well tolerated	SARS-CoV-2 CP* in combination with other therapeutic approaches possible curative options

Legend: *CP denotes convalescent plasma; **RBD receptor-binding domain; ***RT-PCR real-time reverse transcription-polymerase chain reaction; #antibody titers expressed as reciprocal serum dilution against SARS-CoV-2 antigens in four children.

Passive immunotherapy using hyperimmune convalescent plasma (HCP) from SARS-CoV-2 recovered donors has been largely explored [8–10] and reviewed [11]. Previous RCTs in adults with COVID-19 infection did not show any beneficial effects of CP [12–15]. In addition, a Cochrane review supports uncertainty about the safety and efficacy of therapy in COVID-19 adults with CP [11]. Unfortunately, little data for the pediatric population exist. To fill this gap, we conducted a systematic review the literature and ongoing clinical trials on the use of HCP in pediatric patients with COVID-19 infection.

2. Methods

2.1. Search strategy

The electronic databases Medline PubMed Advanced Search Builder, Scopus, and Web Of Science were searched (until November 1, 2020) using medical subject headings (MeSH) terms and text words (their combinations and truncated synonyms) as appropriate: [HYPERIMMUNE PLASMA or CONVALESCENT PLASMA] and [PEDIATRIC OR CHILD] and [COVID-19 or SARS-COV-2]. When available articles were retrieved, the abstracts were screened after removal of duplicate articles. The full text was analyzed and the references were screened for further articles missed in the primary search. This review is not limited to the geographical area or gender. Inclusion criteria were: children with COVID-19 (or SARS-COV-2), in which convalescent plasma (or hyperimmune plasma) was used as treatment. Studies reporting the results of controlled trials, case-control studies, cohort studies, with synthesized data were included. The search was limited to articles published in English. Exclusion criteria were: studies published only as abstracts, letters or conference proceedings, discussion papers, animal studies, or editorials. Initial screening of titles identified potentially relevant studies, followed by screening of abstracts and then full-text review. All titles and abstracts were independently evaluated by two reviewers (MZ, MF), not blinded to authors, journals, results for consistency of inclusion/exclusion and any disagreement was solved by consensus. If the two review authors did not reach an agreement, a third review author was consulted to solve disagreement. No ethical approval was required for this study.

2.2. Study review and data extraction

Two independent reviewers (MZ, MF) evaluated the articles potentially meeting the inclusion criteria and retrieved the full text. Studies that did not fulfil all inclusion criteria were excluded; reasons for exclusion are reported. Table 1 presents the articles excluded from the review because not pertinent to the present study. Full texts were screened, and bibliographic details, as well as data regarding study design, participants, disease severity, intervention, and outcomes were recorded on predefined forms. When data from the same cohort were presented in more than one article, only the reports that most directly evaluated therapy with convalescent plasma (or hyperimmune plasma) and COVID-19 (or SARS-COV-2) in children (age, 0–18 years) [16] were included. All data, numerical calculations, and graphic extrapolations were independently confirmed. We did not deal with missing data. Due to the lack of study homogeneity, a narrative synthesis of the results was conducted.

2.3. Ongoing trials involving pediatric patients

We searched the clinical trials registries (censored 5th November 2020) for eligible studies under way or planned to investigate the use of CPT for COVID-19 infection in children. The six online databases used for this research were https://clinicaltrials.gov/; https://eudract.ema.europa.eu/; https://www.clinicaltrialsregister.eu/; https://www.who.int/ictrp/network/en/; http://www.chictr.org.cn/abouten.aspx; https://www.irct.ir/.

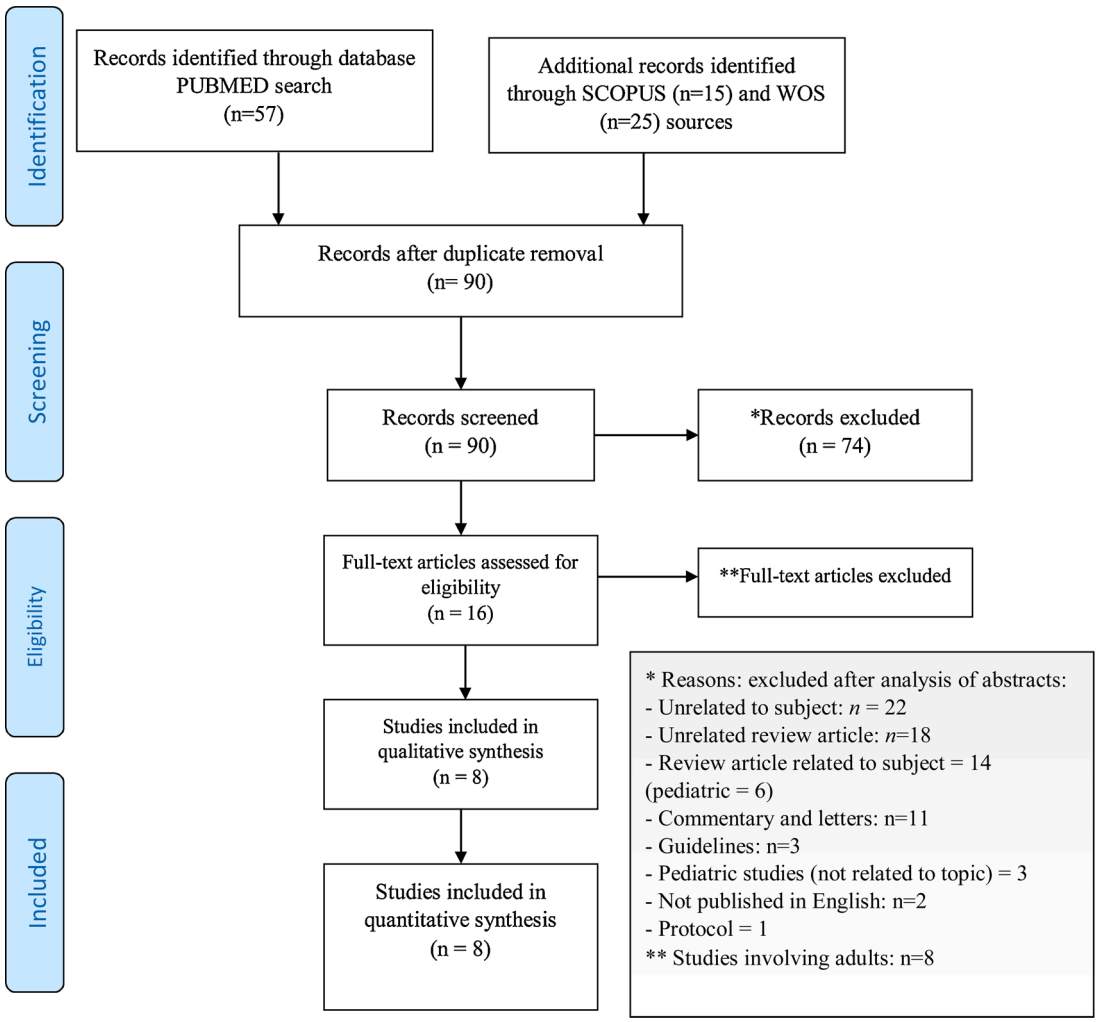

Fig. 1. PRISMA 2009 Flow Diagram.

3. Results

The initial search yielded 90 records as detailed in the PRISMA flow diagram (Fig. 1). Further screening of abstracts excluded 74 records unrelated to the topic (n = 22), unrelated reviews (n = 18), related reviews (n = 14; in childhood n = 6), commentaries or letters (n = 11), guidelines (n = 3), unrelated studies involving children, and studies not published in English (n = 2), and protocol (n = 1). Eight of the remaining 16 full-text records were excluded because the study population was adults (Supplementary Table 1). The 8 other records were case reports involving 14 children. The study population ranged in size from 1 to 4 children (age, 9 weeks to 18 years). Table 1 presents the characteristics of the studies included in the final review. Three case reports included patients (n = 9) without comorbidity [17–19]; 5 reported on patients (n = 5) with a comorbid condition: one each with agammaglobulinemia [20], aplastic anemia and severe pancytopenia [21], acute lymphoblastic leukemia [22], trisomy 21 with congenital heart disease [23], and juvenile myelomonocytic leukemia [24].

Clinical conditions at admission before treatment were severe, including pneumonia [20,22,24], respiratory failure [17,18], and (multi)organ failure [21,23,19]. Among the additional drug treatments administered during hospital stay, the most frequent was remdesivir (n = 5) [20,22,17,23,19]. Five case reports described the use of CP antibodies against SARS-CoV-2 IgG [21,17,23,18,24], whereas 3 did not [20,22,19]. No CPT-related adverse events were reported in 5 studies [21,17,18,24,22], and 3 studies made no mention of adverse events [20,23,19]. Patient outcomes were reported as recovery and/or discharge from hospital (n = 6) [20,22,17,23,19,24] or as amelioration of markers of SARS-CoV-2 infection [21,18]. Based on clinical observations, 2 case reports concluded that CPT is a useful option [22,17], 5 concluded that it could be a useful choice [20,21,23,18,24], and 1 case report made no statement [19].

Table 2 presents the ongoing and planned clinical trials (n = 13). Most are registered in the United States (n = 8), followed by the UK (n = 2), Canada, Pakistan, and Brazil. Ten involve both pediatric and adult populations [25–34]. One trial did not state the upper limit of age at enrollment [29]. Finally, 3 trials are planned specifically to involve children (total of 160 participants), 2 in the United States [35,36] and 1 in Canada [37]. Two trials are currently in Phase 1 [35,36] and 1 trial is in Phase 2 [37] (total of 160 participants). The unit of measure of CP infusion is defined as "Unit" (200–250 ml) in 1 trial and as dosage per kg of body weight (5–10 ml/kg) in 2 trials.

4. Discussion

This is the first systematic review of the literature investigating CPT for COVID-19 in children. All children had serious COVID-19, some with severe concomitant conditions and treated with various drugs. Most studies reported no CPT-related adverse events. We found insufficient information to compare the evidence for the efficacy of CPT. Among the registered clinical trials (mainly with clinicaltrials.gov), very few have been designed exclusively for children. The broad clinical interest in this

Table 2
Characteristics of ongoing clinical and preclinical trials of convalescent/hyperimmune plasma treatment against COVID-19 (updated on November 05, 2020).

Trial no.	Country	Objective	Design	Phase(s)	Last update	Indication	Age Eligible for Study	Study population	Schedule	Donor titer
NCT04377672 [35]	USA	Safety of CP* administration; prevent or lessen disease severity	Interventional (clinical trial)	Phase 1	June 2, 2020	High risk of developing COVID-19 due to recent exposure	1 mth - 18 yrs	30	1−2 unit (200−250 mL per unit) of CP*	>1:320
NCT04377568 [37]	Canada	CP* for hospitalized children	Multicenter, open-label, randomized controlled trial	Phase 2	October 8, 2020	Hospitalized with COVID-19 illness	< 18 yrs	100	One infusion of CP* 10 mL/kg, up to a maximum of 500 m L	–
NCT04462848 [36]	USA	Safety and pharmacokinetics	Interventional (clinical trial); single group assignment)	Phase 1	July 8, 2020	Cardiovascular disease, lung disease, immunosuppression	1 mth - 17 yrs	30	CP* 5 mL/kg. Maximum volume 500 m L	
NCT04352751 [34]	Pakistan	Real-life setting clinical data in local population; evidence-based management of disease condition	Interventional (clinical trial)	Not Applicable	September 29, 2020	Severe or critical illness	18−55 yrs (adults)	2000	Children: CP* 15 ml/kg if <35 kg body weight. Adults: CP* max 450 - 500 ml once in all adults.	NA
NCT04360486 [25]	USA	Treatment option for patients with severe COVID-19 infection	Expanded access open-label, single-arm, multi-site protocol	–	April 27, 2020	Severe or life-threatening	Child, adult, older adult	–	–	–
NCT04374370 [26]	USA	Expanded access to CP*	–	–	May 5, 2020	Severe Acute Respiratory Syndrome	6−99 yrs	–	–	–
NCT04458363 [27]	USA	Safety of CP* for children	Interventional (clinical trial); randomized	Early Phase 1	July 7, 2020	Severe COVID-19 disease	<22 Yrs (child, adult)	50	10 mL/kg/dose (up to 2 units per dose); two doses per patient for a total dose of 20 mL/kg	–
NCT04528368 [28]	Brazil	Efficacy and safety of CP*	Interventional (clinical trial)	Phase 2	August 27, 2020	No indication of ventilatory support	Child, adult, older adult	60	400 mL of CP*	≥ 1: 320
NCT04361253 [29]	USA	Early addition of CP* to standard treatment improves clinical outcome	Prospective randomized, double-masked, placebo-controlled trial	Phase 3	May 18, 2020	Active COVID-19 infection in hospitalized patients	Age >1 yr	220	250 mL, max500 mL	–
NCT04376034 [30]	USA	Help fight infection in patients with COVID-19	Interventional (clinical trial), non-randomized, prospective	Phase 3	May 6, 2020	Mild, moderate and severe/ critical severity	31 dys and older	240	10 mg/kg up to 2 units of CP*	
NCT04381936 [31]	UK	Prevention of death in patients with COVID-19	Randomized trial	Phase 3	September 29, 2020	Patients with COVID-19 in hospital care	Child, adult, older adult	15,000	275 ml ± 75 ml per day on study days 1 and 2 (minimum 12-h interval)	
NCT04349410 [32]	USA	Fleming method for tissue and vascular differentiation and metabolism	Randomized trial	Phase 3	October 29, 2020	Patients with COVID-19	Child, adult, older adult	1800	CP* 2-units infused over 4-h	1:320
ISRCTN50189673 [33]	UK	To compare several different treatments potentially useful for patients with COVID-19	Interventional, randomized adaptive trial	Recruiting	October 06, 2020	COVID-19 (clinically suspected or laboratory-confirmed), and in hospital	Child, adult	–	–	–

Legend: * CP denotes convalescent plasma.

vulnerable patient subpopulation is scarce.

The prevalence of COVID-19 in children and adolescents is relatively low, accounting for about 2.4 % of all reported cases [38]. Although most children rarely progress to severe disease, there is concern for an inflammatory cascade [39]. Between January and June 2020, 55,270 children/adolescents diagnosed with and 3,693 hospitalized for COVID-19 were included in a large-scale multinational cohort study. While the mortality rate due to COVID-19 is negligible in this age group, complications including pneumonia, ARDS, and multisystem inflammatory syndrome should not be underestimated [40]. Early identification of COVID-19 and prompt treatment are essential, especially in children with underlying/comorbid disease(s) [38].

Our review revealed a wide range of medications for the inpatient management of pediatric COVID-19. An international network cohort study, performed in children/adolescents diagnosed with and/or hospitalized for COVID-19 at age <18 years, reported a variety of adjunct therapies: systemic corticosteroids (6.8 %), famotidine (9.0 %), antithrombotic therapy, antibiotics, and immunoglobulins [40].

The U.S. Food and Drug Administration (FDA) approved remdesivir for emergency use in children hospitalized with severe suspected or laboratory-confirmed COVID-19 [41]. Parenteral remdesivir has been approved by the European Medicines Agency for pediatric and adolescent patients (≥12 years, body weight ≥40 kg), and has shown potential benefits [42]. Some limitations may regard neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU) patients with severe disease (mechanical ventilation or extracorporeal membrane oxygenation [ECMO]).

CPT can be administered in children with rapid exacerbation of conditions and those with severe and critical diseases [43]. However, the currently available scientific literature is limited to case reports. Research providing higher quality evidence for the efficacy and safety of CPT in the treatment of pediatric COVID-19 infection has been planned [44] or is still in the protocol phase.

The main limitations and biases of the present study are that it includes only clinical case reports. Another bias (bias of reporting) is that only cases with a positive outcome have been reported, precluding representativeness of the whole pediatric population treated with CP.

5. Conclusions

Although COVID-19 is rare in childhood, children with chronic illness are vulnerable and may require treatment. We found no high quality studies investigating the efficacy and safety of CPT for COVID-19 in children and adolescents. Although available reports in pediatric age are case reports and case series (reporting bias), they have the potential to stimulate future research based on well-designed and powerful studies.

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CRediT authorship contribution statement

Marco Zaffanello: Conceptualization, Data curation, Writing - original draft. **Giorgio Piacentini:** Supervision, Validation, Writing - review & editing. **Luana Nosetti:** Data curation, Investigation, Writing - original draft. **Massimo Franchini:** Writing - original draft, Methodology, Writing - review & editing.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.transci.2020.103043.

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