Original Article

COVID-19 treatment in children: A systematic review and meta-analysis

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Abstract

Background: Exact information about the efficacy of various medications proposed by regulatory bodies in children with COVID-19 is limited due to the lack of controlled trials in the existing literature. **Methods:** Different electronic databases (MEDLINE, EMBASE, Web of Science, COCHRANE CENTRAL, LitCovid, medRxiv, and bioRxiv) were searched for articles describing the management of COVID-19 cases in children with 18 shortlisted medications. Prospective/retrospective studies/case series (with at least 20 cases) reporting COVID-19 in patients aged ≤14 years were searched to collect information regarding clinical details and severity of participants, medications used, and outcome. The pooled estimate of these parameters across studies was performed using a random-effect or fixed-effect meta-analysis depending on the degree of heterogeneity. **Results:** From a total of 5794 records, 97 studies/case series (8243 patients) fulfilled the eligibility criteria and were included in this systematic review. A total of 21% children received at least one medication specifically used for COVID-19. While antivirals were used in 15.3% of children, remedesivir was the most commonly used antiviral drug in 6.2% of included children without many reports of serious adverse effects. There was a more prevalent use of anti-inflammatory medications including corticosteroids (27.8%, $P = 0.01$). Total 91% of severe cases described in literature in children received some anti-inflammatory medications. Among them, corticosteroids (17%) and Intravenous immune globulin (IVIG) (17.5%) were the most predominant followed by interferon (4.2%), tocilizumab (1.5%), and anakinra (0.8%). The most predominant therapy among multisystem inflammatory syndrome in children (MIS-C) cases were IVIG (81%), followed by aspirin (67%), corticosteroids (64%), inotropes (62%), and anticoagulation (56%, mostly low molecular weight heparin, LMWH). Overall mortality was only 1.3%, but when we analyzed separately including only cases with moderate and severe disease, the mortality rate was 4.6%. **Conclusion:** Among pharmacological modalities, anti-inflammatory agents like corticosteroids and antivirals like remdesivir have the most promising evidence for severe cases of pediatric COVID-19. Intravenous immunoglobulin and other anti-inflammatory/immunomodulatory agents like anakinra, aspirin, and anticoagulants have important therapeutic role in cases with MIS-C. Most of the mild cases recover with conservative treatment only.

Keywords: Hydroxychloroquine, lopinavir/ritonavir, remdesivir, ribavirin; SARS-CoV-2, tocilizumab, MIS-C

Introduction

After its discovery in December 2019 in Wuhan, China, it has been more than one and a half years now; still, the world has not recovered from the COVID-19 pandemic. India is among one of the worst hit countries by COVID-19 second wave and a large number of pediatric severe COVID-19 cases as well

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as multisystem inflammatory syndrome in children (MIS-C) cases were seen in the second wave in India as compared to the first wave of the pandemic.[1] Although various countries have prepared a number of effective COVID-19 vaccines for adults, for the pediatric population, only recently Drugs Controller General of India (DCGI) granted emergency approval of COVISHIELD and COVAXIN for pediatric patients aged more than 12 years.[2] Similarly, no magic bullet against COVID-19 could be discovered until now, although remdesivir, casirivimab/imdesivimab, ivermectin, baricitinib, and tofacitinib have attracted much attention.[3-5] In adults, a large number of uncontrolled and controlled trials, as well as meta-analyses have been completed, but in children, such good-quality studies are yet to be completed.[6–8] Initially, children were considered to have less risk for developing COVID-19 and especially a severe illness, but recent data reveals they are particularly prone to develop MIS-C and the third wave may specifically affect children more. Although India has started a pediatric trial of COVAXIN for children aged 6–12 years, but in the near future, mass vaccination of children seems unlikely.[9] Most studies and meta-analyses performed in children till now have focused predominantly on clinical features and outcome, but only vaguely mentioned the treatment regimens adapted.[10,11] We have collated information regarding various medications tried in all the published studies in children with COVID-19 in this systematic review for the first time and in later part also described their mechanism of action as well as other clinical aspects of managing pediatric cases of COVID-19.

Methods

We performed this systematic review to collate all reports regarding the efficacy of various medications in children with confirmed COVID-19 infection from the currently available literature. Accordingly, the primary aim of this systematic review was to provide a pooled estimate of the efficacy of various medications in children with SARS-CoV-2 infection. A meta-analysis of observational studies in epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed while conducting the study.

A predefined search strategy was developed first. Three investigators performed independently a literature search in MEDLINE/PUBMED, Web of Science, EMBASE, CENTRAL (Cochrane central register of controlled trials), LitCovid, medRxiv, and bioRxiv for original articles] cross-sectional studies, retrospective/prospective studies, randomized controlled trials (RCTs)] and case series published between 1st December 2019 to 15th June 2021, without using any language restrictions (translation performed with Google Translate). The search strategy was targeted to include children aged less than or equal to 14 years with confirmed COVID-19. The terminologies used were divided into three basic groups: study population (children/pediatric/infant/adolescent/child), terms describing or related to COVID-19 (also SARS-CoV-2, coronavirus, 2019 nCoV), and terms describing management/treatment/medication names (treatment, management, also remdesivir, casirivimab, imdesivimab, favipiravir, ivermectin, doxycycline, azithromycin, hydroxychloroquine, lopinavir/ritonavir, tocilizumab, interferon, dexamethasone, intravenous immunoglobulin (IvIg), heparin, ribavirin, and name of other medications tried in COVID-19). Using these MeSH terms, specific search strategies were developed for each search engine. The electronic search was later supplemented by a manual search of the references of the included articles to identify additional cases. Such a search strategy was employed to identify all studies describing COVID-19 in children for initial screening.

Study selection

As the preliminary search revealed no randomized controlled trials and only a few uncontrolled interventional trials/case series describing the efficacy of a particular drug as the primary objective of the study in children; hence, we intended to screen all articles describing COVID-19 cases in children. We specifically focused on the section of each article describing the management of pediatric participants and recovery/mortality rate, as well as complications attributed to medications administered. We even screened the studies enrolling both adults and children and included them in the review, if adequate information was available regarding pediatric participants separately.

After preliminary literature search and based on the current evidence, we shortlisted 14 medications, which were either previously considered probably efficacious in COVID-19 (although the benefit of some of these drugs was later refuted by controlled trials in adults) and which are currently approved by the US Food and Drug Administration (FDA) for use in children or considered efficacious even if not approved by FDA and used in various centers. These 14 medications selected are listed in Table 1. Although the mode of respiratory support including inhaled oxygen administration by face mask/nasal cannula/non-rebreathing mask, noninvasive or invasive mechanical ventilation, inotropes, and other supportive measures are equally important, we decided to limit the scope of our review to pharmacological measures only. All types of study design starting from RCTs, prospective cohort study, cross-sectional study, case-control study, retrospective case series including at least 20 participants describing the management of children with COVID-19 were included in the analysis. The review also included those studies which mentioned about the management of MIS-C in children. Correspondences or letters fulfilling the above criteria were excluded from the review. Narrative or systematic reviews, meta-analysis, editorials, perspectives, conference proceedings, and studies describing other serotypes of coronaviruses were excluded from this study. The review excluded case reports and small case series describing less than 20 children as they were likely to increase heterogeneity and impair the correct estimation of the pooled estimate. The study also excluded those articles describing only epidemiological or clinical features of children with COVID-19, but no specific information or only vague information is available regarding pharmacological interventions.

Table 1: Pooled estimates of the frequency of administration of various medications in children with COVID-19 and mortality rates in these subgroups

Name of medication	Predominant type of cases included	Pooled estimate for proportion of cases receiving the medication (in %) (95% CI)	Heterogeneity (I^2%)	*P* for I^2
Remdesivir	Severe	6.6 (4.9-8.3)	31	0.06
Favipiravir	Mild/moderate	1.5 (0.4-2.1)	51	0.005
Ritonavir/ Lopinavir	Severe	0.5 (0.2-1.3)	32	0.05
Ribavirin	Moderate and severe	0.3 (0.2-1.0)	46	0.01
Oseltamivir	Moderate and severe	1.4 (0.6-3.1)	57	0.001
Umifenavir	Moderate and severe	0.2 (0.1-0.7)	54	0.001
Hydroxychloroquine/Chloroquine	Mild (52%) moderate (9%) severe (39%)	9.9 (4.5-13.1)	36	0.05
Antibiotics	Mild (23%) moderate (39%) severe (38%)	33.1 (22.9-43.4)	59	0.001
Azithromycin	Mild and moderate	13.2 (8.4-19.6)	46	0.009
Corticosteroid	Severe/MIS-C	17.2 (11.6-23.5)	27	0.01
Tocilizumab	Severe/MIS-C	1.5 (0.4-2.1)	39	0.01
IVIG	Severe/MIS-C	17.5 (10.2-25.9)	38	0.01
Anakinra	Severe/MIS-C	0.8 (0.3-1.4)	29	0.027
Infliximab	Severe/MIS-C	0.4 (0.2-0.7)	41	0.02
Aspirin	Severe/MIS-C	7.1 (4.2-12.9)	28	0.07
Enoxaparin	Severe/MIS-C	3.2 (1.7-6.3)	25	0.09
Interferon	Moderate and severe	4.2 (2.1)	27	0.08
Convalescent plasma	Severe	0.1 (0.05-0.3)	35	0.05
Herbs/home remedies/other	Mild	7.9 (3.4-11.8)	61	0.001

The review also excluded those studies which have only used medications other than the above listed 14 medications, currently shown to have no definite evidence and most probably won't be used in the future in any of the centers, as they are of little relevance clinically now. However, the studies which have mentioned the use of other medications along with the 18 medications shortlisted were included in the analysis, and the information about other medications was collated into one single group as described in Table 1. Each of the articles included underwent a quality check as per a predefined set of criteria and validated guidelines. Independently, two researchers first screened the title and abstract to select the articles describing COVID-19 cases in children. Subsequently, the reviewers went through the full text of all articles to screen for those articles which have described the management of COVID-19 with any of the above listed 14 medications.

Data extraction and quality assessment

A predesigned, standardized, well-structured proforma was developed for data extraction. Two investigators independently reviewed the eligible articles and extracted data from their full text. The extracted data included as much information available from the following: the number of children with COVID-19, age group, and other demographic details of these children, the severity of COVID-19 illness, number of asymptomatic cases, number of participants who received various medications, and respiratory support, drug-related complications, recovery rate, and mortality rate, apart from the study site, study period, sample size, study design, and other details of study method. A third independent investigator rechecked the completeness and accuracy of extracted data. If both investigators disagreed on some topic, then a consensus decision was achieved by discussing it with the third investigator. Every effort was made to prevent duplication of data and every case included in the final analysis was ensured not to be part of another series. ROBINS-I tool was used to assess the risk of bias of the included nonrandomized trials and observational studies.

Data synthesis and statistical analysis

Appropriate descriptive statistics were used to represent various parameters and wherever feasible, pooled estimates, with 95% confidence intervals (CIs) of these parameters were estimated. Categorical variables were presented as frequency (percentage) and 95% CI, whereas continuous variables were presented as mean with standard deviation or median with interquartile range. Meta-analysis of data regarding various parameters was performed using REVMAN 5.4 software. We utilized a random/fixed-effect model depending on the degree of heterogeneity for various parameters. Heterogeneity in studies was assessed by utilizing Higgins and Thompson's I^2 method and Chi-square test on Cochran's Q statistics. Egger's test was used to assess the presence of publication bias.

Results

After a primary search, a total of 5794 publications were retrieved. Among these, 2849 were duplicates and hence removed accordingly. The eligibility of the remaining 2945 papers was evaluated initially from titles and abstracts and 2464 irrelevant articles were excluded according to the title, article type, and abstract [Figure 1]. For full-text review, 481 articles were selected. Out of these, ultimately 97 articles were found

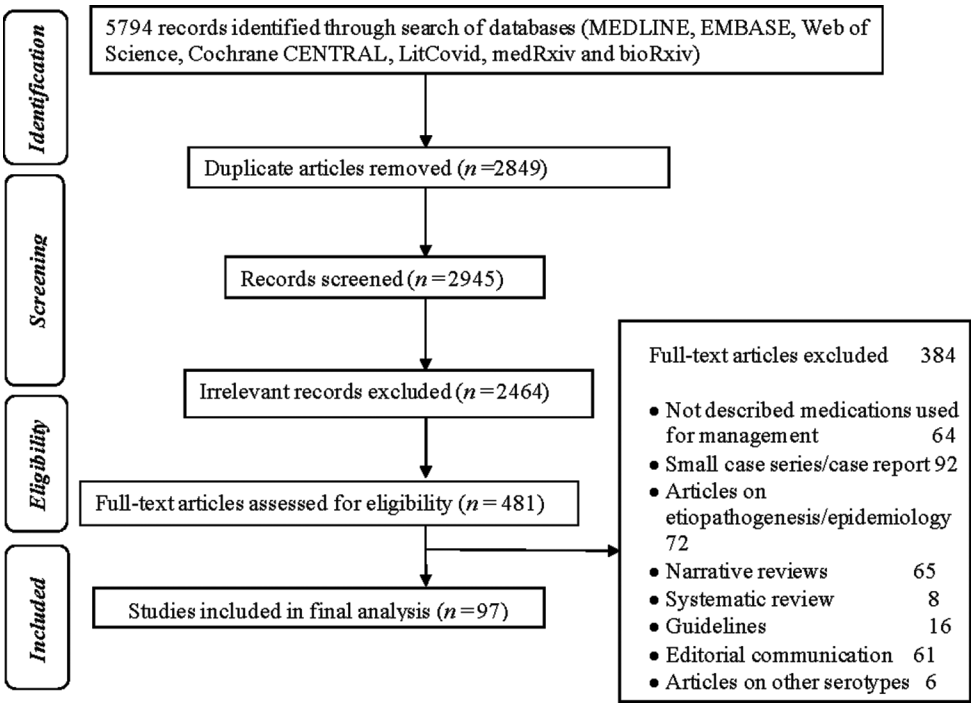

Figure 1: Flow diagram of the study selection process

to provide information regarding treatment modalities in 8243 children, out of which 43 (0.5%) children died. Ultimately, these 97 prospective/retrospective studies were included in the final analysis.[12–46] Out of the 97 studies, 23, 29, and 45 were of fair, good, and poor quality.

Out of the 8243 children described in these 97 studies, 58% were male. While 12% of cases described in these studies were asymptomatic and mostly did not receive any medications except hydroxychloroquine in few studies, 39%, 28%, and 21% of children were in mild, moderate, and severe/critical category. Total 79% children were managed conservatively/with symptomatic treatment only, apart from respiratory support as required, and rest 21% children additionally received at least one medication specifically used for COVID-19 (excluding antibiotics in 33% and herbs/home remedies in 7.9% of children). Overall mortality was only 1.3%, but when we analyzed separately including only cases with moderate and severe disease, the mortality rate was 4.6%.

We then meta-analyzed the individual prevalence of administration of various medications. Although substantial heterogeneity was observed between studies describing these features, no significant publication bias was observed in Egger's test ($P > 0.05$). While antivirals were used in 15.3% of children, remedesivir was the most commonly used antiviral drug in 6.2% of included children without many reports of serious adverse effects. Favipiravir, oseltamivir, ritonavir/lopinavir, ribavirin, and umifenavir were used in 1.5%, 1.4%, 0.5%, 0.3%, and 0.2% children, respectively. However, most studies after October 2020 mainly focused on remedesivir and some on favipiravir, but recently in 2021, most adult and pediatric studies even did not mention the use of favipiravir, as its efficacy also became controversial with more expanding knowledge. Since the majority of cases who received antivirals belonged to the moderate and severe category of illness, the mortality rate among recipients was higher than the overall sample population (4.2% vs. 1.3%, $P = 0.001$). Azithromycin (13%) was the most common antimicrobial used. While in 2020, a number of studies mentioned the use of antimalarial like hydroxychloroquine in 9.9% of cases collectively, doxycycline and ivermectin use was found to be described only in very few recent series in children.

On the contrary, recent studies suggested more prevalent use of anti-inflammatory medications including corticosteroids (27.8% vs. 15.3% for antivirals, $P = 0.01$). Moreover, 91% of severe cases described in literature in children received some anti-inflammatory medications. While overall corticosteroids (17%) and IVIG (17.5%) were used in an almost equal proportion of cases, this might be due to the fact that the majority of the publications describing children with severe illness included children with MIS-C like presentation. Interferon was used in 4.2% of patients, while tocilizumab (1.5%) and anakinra (0.8%) were also used in a minority proportion of cases.

Convalescent plasma therapy, which was previously considered an attractive therapeutic option, was found to be utilized in a few studies (5 children with a severe illness out of 121 children with COVID-19 in four studies). While aspirin was used in 7.1% of children, heparin was used only in 3.2% of children and predominantly their use was described in patients with MIS-C.

Complications attributed to administered medications were only rarely explained in the published studies and we could detect only two cases of cardiac arrhythmias attributed to hydroxychloroquine.

Exact modes of respiratory support provided to children with moderate and severe COVID-19 have been described in 43 studies. In these studies, 21% of children required some form of respiratory support (12% and 9% of children required oxygen inhalation and mechanical ventilation respectively) and 4.6% of children succumbed. Ionotropic/vasopressor medications were required in 11.6% of patients. However, this finding cannot be extrapolated to the whole population, as mild cases were not part of this cohort.

Subgroup analysis in multisystem inflammatory syndrome in children patients

We performed a subgroup analysis including studies with at least 20 MIS-C patients and included 917 patients from 27 articles. Overall, 79% of these patients required intensive care unit admission. The most predominant therapy was IVIG (81%), followed by aspirin (67%), corticosteroids (64%), inotropes (62%), and anticoagulation (56%, mostly LMWH). Apart from remedesivir as antiviral used in 9% of cases, a range of anti-inflammatory biological agents were also used, including tocilizumab (27%), anakinra (10%), and infliximab (9%) in less proportion of cases. Overall, 33% required mechanical ventilation, and 6% required extracorporeal membrane oxygenation (ECMO).

Discussion

This review summarizes the pooled experience of all the clinical studies with various medications for the treatment of pediatric COVID-19. Initial clinical studies were found to have stressed on antivirals other than remdesivir like ribavirin, lopinavir/ritonavir, and oseltamivir, as at that time, the evidence for treatment in COVID-19 was still in the preliminary stage and hence various studies followed different treatment protocols. Recent clinical studies were also found to have focused on anti-inflammatory medications like corticosteroid, intravenous immunoglobulin, tocilizumab, and interferon, apart from remdesivir, given the increased incidence of MIS-C reported in recent studies.[47] Recent articles suggest the use of remedesivir only in severe cases and even in adults, the RECOVERY trial has shown that although it reduces the duration of intensive care unit (ICU) stay, it does not reduce mortality.[48] Hydroxychloroquine was found to be utilized in studies predominantly completed before July 2020, as subsequently, various studies showed this drug to be not efficacious at best and harmful otherwise in severe cases of COVID-19 in adults.[49] Similarly, a number of studies from developing countries have suggested the efficacy of ivermectin and doxycycline, especially in 2021.[50-52] For this reason, few recent articles mentioned the use of ivermectin and doxycycline in children, but the universal use of this medication is still controversial. We could not find much data for use of casirivimab/imdevimab in children <12 years, as it is yet to be FDA approved. Similarly, the recently DCGI approved medication, 2-deoxy-D-glucose in India produced by Defence Research and Development Organisation (DRDO) can be used for patients aged 4 years or more, although more trials are undergoing for this medication.[53]

In a nutshell, while the cumulative data suggest the use of hydroxychloroquine, antivirals like ritonavir/lopinavir, etc., were used in earlier studies, but information explored from WHO and various guidelines based on large RCTs and systematic reviews suggest apart from remedesivir, corticosteroid, IVIG, tocilizumab, anakinra, infliximab, aspirin and heparin, other medications cannot be recommended in COVID-19 cases in children of any severity.[54] Evidence for favipiravir, doxycycline, ivermectin, casirivimab, imdesivimab, 2DGO, and other promising biological agents like baricitinib, tofacitinib, and bevacizumab is still very scarce in literature. With the publication of more studies in future months regarding these drugs, consensus guidelines published by regulatory bodies somewhat based on a mix of evidence-based medicine and good practice points extrapolated from adult literature is likely to change.

Data regarding the use of LMWH in children were found to be scarce in our review, although pulmonary microembolism has been considered as a potential mechanism behind the respiratory distress in COVID-19 for a few months now and in adults, LMWH is used in the majority of centers worldwide. We could not collect much information regarding the efficacy of vitamins like vitamin C, vitamin D, and zinc, as most of the studies did not specifically mention how many patients received these medications. But in some of the centers, they used it as off-label because of lack of adverse effects. We have also not assessed the efficacy of hydroxychloroquine and other drugs for prophylaxis of low-risk/high-risk contacts of confirmed COVID-19 cases, as this was out of the scope of our review. The mortality rate for children who received antivirals and anti-inflammatory medications was significantly higher than the overall sample population (0.5%). This could be probably because the studies which described the children receiving these medications predominantly included children with more severe illness and hence the relatively high mortality rate. The same hypothesis can explain the higher mortality rate among the children who required various respiratory supports like oxygen inhalation, noninvasive, and invasive mechanical ventilation. Lastly, we did not collect information regarding homeopathic, ayurvedic, and other indigenous treatment modalities and mainly focused on allopathic medications, as it was out of the scope of our review and evidence regarding the efficacy of these other indigenous modalities is still lacking even in adults. We included the children who received these drugs into one combined category in our review and most of these children were either suffering from mild illness or asymptomatic.

The large meta-analysis including 7780 pediatric patients although described briefly on treatment modalities, but only described medications received in 614 children.[55] Irfan *et al.*[56] included

9935 patients in their systematic review in January 2021, but we included slightly fewer patients as we focused on the treatment of COVID-19 only and excluded the studies which have inadequate information regarding treatment modalities, unlike the previous two reviews which focused on clinical features. Still, our systematic review is the largest review till date to focus on various treatment modalities in the maximum number of children. However, the various treatment modalities described in both the systematic reviews and relative frequency of use of various medications remain similar in the previous systematic reviews and our review.

The meta-analysis performed on remdesivir in adults showed it has a modest yet significant reduction in mortality and significantly improves the time to recovery, as well as significantly reduced risk of adverse events and serious adverse events.[57] A recently published meta-analysis on tocilizumab in severe COVID-19 in adults did not show conclusive evidence favoring its use. All-cause mortality, risk of ICU admission, and requirement of mechanical ventilation were similar between tocilizumab and control groups.[58] Similarly, the systematic review on corticosteroids in COVID-19 in adults showed the results from retrospective studies were heterogeneous and difficult to infer of a definitive protective benefit with corticosteroids. But RECOVERY trial found a significantly better outcome with dexamethasone, mostly in severe cases. Similar systematic reviews are yet to be performed in children in the absence of completed controlled trials with published results.[59]

The most promising evidence, as we have already mentioned before, exists for antivirals like remdesivir, although controlled trial results are available in adults and RCTs are undergoing in children.[60] Multiple trials on different other therapeutic options are being conducted, the results of which are likely to modify evidence-based management guidelines of COVID-19 cases.

Remdesivir is a broad-spectrum antiviral agent, initially synthesized and developed as a treatment for Ebola virus infection by Gilead Sciences in 2017.[61] Its antiviral mechanism is mainly due to delayed chain cessation of the nascent viral RNAs.

Animal experiments in mice infected with Middle East respiratory syndrome coronavirus (MERS-CoV) demonstrated that remdesivir effectively reduces viral load in lung tissue, improved lung function, and reduced pathological damage occurring to lung tissue. Wang *et al*.[62] showed remdesivir is potent in blocking SARS-CoV-2 infection even at a low range of micromolar concentrations, with a high selectivity index. Initially, Grein *et al*.[63] demonstrated the efficacy of remdesivir in an adult with COVID-19 pneumonia. Later a randomized, double-blind, placebo-controlled, multicenter, phase III clinical trial in China also further strengthened this evidence.

Remdesivir has the best favorable evidence in therapy against SARS-CoV2, based on up-to-date evidence available till now. It has *in vitro* activity against many novel coronaviruses, including SARS-CoV2, and currently, large multicentric phase 3 randomized clinical trials are underway. In murine models, its use results in decreased viral lung titers, and it prevented pulmonary hemorrhage.[64] Its safety profile is also attractive: Its propensity for liver or kidney toxicity is low compared to other antivirals. There are case reports of successful use in SARS-CoV2.

Remdesivir is the first drug to be approved by The FDA for COVID-19, especially for severe cases. The FDA granted an emergency use authorization for remdesivir for both adults and children with suspected/confirmed severe COVID-19 disease on 1$_{st}$ May 2020, as it seems to boost recovery in these patients.[65] However, safety and effectiveness in children have not been assessed rigorously and the above-mentioned dosing has been derived based on pharmacokinetic data obtained from adult healthy volunteers.[66]

Chloroquine and hydroxychloroquine have long been used in the treatment of malaria, rheumatoid arthritis, and Systemic lupus erythematosus (SLE). There was initial hype about this drug, but recently several studies and a meta-analysis refuted the previous hypothesis.[67] There is some evidence that chloroquine and hydroxychloroquine can reduce cytokine storms. According to one analysis, the main cause of death of COVID-19 patients is related to the triggering of the cytokine storm, which contributed to acute respiratory distress.[68]

The initial hype regarding the use of hydroxychloroquine, labeled as a wonder drug for prophylaxis and treatment, is now under debate after the influential multinational registry analysis showed hydroxychloroquine or chloroquine with or without a macrolide did not provide any survival benefit, decreased in-hospital survival, and increased frequency of ventricular arrhythmias when used for the treatment of COVID-19. Although later this study was retracted, the same day on which another major influential article showing harmful effects of angiotensin-converting enzyme (ACE) inhibitors was retracted, WHO still discontinued major trials exploring its efficacy and the FDA even revoked the emergency status of this drug. In India, however, Indian Council of Medical Research (ICMR) continues to recommend hydroxychloroquine at least for prophylaxis and even for mild disease.[69]

Before this study, another open-labeled nonrandomized study demonstrated improved virologic clearance with hydroxychloroquine compared to controls receiving standard supportive care. Another study demonstrated that *in vitro* hydroxychloroquine is more potent than chloroquine. The efficacy of combined hydroxychloroquine and azithromycin on SARS-CoV-2 was tested *in vitro*, which showed a synergistic effect and led to a significant inhibition of viral replication.[70]

An open-label nonrandomized clinical trial was conducted for hydroxychloroquine and azithromycin as a treatment option in adults. The study concluded that hydroxychloroquine treatment was significantly associated with viral load reduction or disappearance and the effect was reinforced by azithromycin.[71]

The Indian Ministry of Health and Family Welfare guidelines for the management of COVID-19 advise the use of lopinavir/ritonavir only after informed consent for severe cases and warned of severe adverse effects with prolonged therapy.[18] A trial of lopinavir and ritonavir in adults with severe COVID-19 showed no benefit with lopinavir-ritonavir treatment beyond standard care.[72]

The Zhejiang University School of Medicine suggested the use of nebulized interferon-alpha2b and oral lopinavir/ritonavir (LPV/RTV) along with corticosteroids for complications like Acute respiratory distress syndrome (ARDS), encephalitis, multisystem inflammatory response, hemophagocytic lymphohistiocytosis syndrome or septic shock, and intravenous immunoglobulin for severe cases.[73] Another study with clinical analysis of children found no significant difference of the days from onset to RNA or nucleic acid amplification test turning negative after the treatment, and the days of hospital stay between the interferon, interferon plus ribavirin, and interferon plus LPV/RTV groups.[74]

The use of convalescent plasma, which contains antibodies from recovered patients by transferring passive immunity, may help in suppressing the viremia. A meta-analysis of studies, including 714 patients with SARS or severe influenza has shown that treatment with convalescent plasma and immunoglobulins helped to decrease mortality.[75] Intravenous immunoglobulin has been tried in a few patients in China at a dose of 0.3–0.5 g/kg/day with some benefits.

Casirivimab/imdevimab is an artificial "antibody cocktail" which has been shown to reduce COVID-19-related hospitalization or emergency room visits in people at high risk for disease progression within 28 days after treatment. It consists of two monoclonal antibodies, casirivimab (REGN10933) and imdevimab (REGN10987), which must be mixed, the intent behind that being to prevent mutational escape, and accordingly, it is available as a co-formulated product. These are recombinant human Immunoglobulin G1 (IgG1) monoclonal antibodies targeting the receptor-binding domain of the spike protein of SARS-CoV-2.[3]

Doxycycline inhibits SARS-CoV-2 entry into the cell by inhibiting MMP-9, IL-6, and NF-κB, required for this purpose. It also increases the entry of zinc into these cells, which inhibits viral growth.[51] Ivermectin also has been shown to inhibit viral replication *in vitro*.[52] A recent scoping review exploring ivermectin monotherapy, doxycycline monotherapy, and ivermectin and doxycycline combination therapy including 8754 adult patients from 19 articles found that some studies concluded in favor of the intervention and some studies displayed no significant benefit. They concluded that the evidence was not strong enough to either promote or refute their efficacy in COVID-19 management.[50]

2-DG (2-deoxy-D-glucose) selectively gets accumulated in the infected cells and inhibits aerobic glycolysis, thereby inhibiting viral replication. Based on successful results in the form of better symptom improvement and requirement of less time receiving supplemental oxygen and excellent safety profile, DCGI provided emergency authorization to this medication. Pediatric trial results are still awaited.[53]

In our review, we categorized all herbal medicines into one category and most of these herbal medicines have been used in studies from China. Several herbal medicines have been reported to have antiviral activity against SARS coronavirus, like scutellariae radix, artemisiae annuae, and armeniacae semen. The herbal formulae most commonly used for the treatment of pediatric COVID-19 are armeniacae semen, but evidence regarding their benefit is still inconclusive.[76-80]

In the first wave and recently declining the second wave, according to the latest data in India, around 39 crore COVID-19 testing has been performed and around 2.98 crore positive cases have been reported officially.[81] While only 0.5% of cases were of less than 14 years of age, still that accounts for around 1.5 lakh pediatric cases. As MIS-C reporting is not that much stringent in our country and many of these children are COVID Reverse transcription polymerase chain reaction (RT-PCR) negative, so the true COVID burden might be way higher in children. India has already provided 27 crore COVID vaccine doses to people aged >18 years and 22 crore people have received at least one vaccine. In the upcoming few months, the majority of the adult population will be vaccinated, as new vaccines like SPUTNIK V have also been approved and production of COVAXIN and COVISHIELD have been expedited.[82] As most experts believe that the third wave of the pandemic is almost inevitable in India within a few upcoming months, as it has already hit many countries like the UK, by that time, only children are most likely to be left unvaccinated.[83,84] Children are as susceptible as adults and older individuals to develop an infection but not a severe disease. Although it is highly unlikely that the third wave will exclusively affect children in India, it seems reasonable to say it will predominantly affect the pediatric population. Taking that into account, central and state governments have initiated building infrastructures like Pediatric Intensive Care Units (PICUs) and skilled health care personnel in various states across the country. But as most new medications and vaccines are not yet tried in children/trials is undergoing (like the recently initiated trial of PFIZER vaccine and COVAXIN in children), children will be deprived of the benefits of these new medications like the artificial antibody cocktails. Currently, regulatory bodies like ICMR, National Medical Commission (NMC), and Indian Academy of Pediatrics (IAP), as well as AIIMS, New Delhi, and other Institute of National Importances (INIs) in India have come across various guidelines for children with COVID-19 based on good practice points and current evidence.[85] Most of these guidelines recommend the use of corticosteroids in moderate COVID pneumonia, only if rapid progression and to start supplemental oxygen if SpO2 <94%. However, for severe disease in children, remedesivir, corticosteroid, and awake proning in older children, as well as HFNC/NIV/invasive mechanical ventilation, inotropes and restrictive fluid therapy have been

advised. Dexamethasone 0.15 mg/kg/dose q12hourly (maximum 6 mg)/1–2 mg/kg/day of methylprednisolone are the preferred corticosteroids. Similarly, in cases with MIS-C, apart from other supportive organ supports, IVIG 2 gram/kg over 24-48 h is also to be added in case of life-threatening conditions, cardiac dysfunction, coronary involvement, or multiple organ dysfunction syndrome (MODS), according to these guidelines. If there is no improvement or worsening, then a repeat dose of IVIG or methylprednisolone at 10-30 mg/kg/day for 3-5 days is to be administered. In cases, still unresponsive to the above treatment, anakinra or infliximab can be tried. Aspirin at 3-5 mg/kg/day is used when there is thrombocytosis or coronary aneurysm Z score ≥2.5 and enoxaparin 1 mg/kg twice daily subcutaneous (SC) is used when there is thrombosis, left ventricular ejection fraction (LVEF) <35% or coronary aneurysm Z score ≥10. As there is no routine indication of anticoagulants in children with COVID-19 like adults, this might explain the lower prevalence of its use in our review. More randomized trials are urgently needed specifically targeting pediatric population and especially those with MIS-C.[86,87]

While almost all of these studies included in the review were performed in tertiary care hospitals, well-planned research pertaining to primary care management is still lacking from India and abroad. However, various regulatory bodies like ICMR, MOHFW, and INIs like AIIMS, New Delhi have come up with guidelines for home isolation of asymptomatic and mild cases and management of mild cases in home and primary care center for children. Most of these guidelines have consensus decisions on few good practice points. In the primary care setting, the health practitioner should focus on ample rest, adequate hydration, and feeding for children and if infected adults and uninfected children are in the same family, then isolation of children if possible. Symptomatic management is also important for mild cases, which includes oral paracetamol (10-15 mg/kg/dose) for fever and cough suppressants like cetirizine or home remedies as deemed suitable. While unnecessary use of antibiotics like oral azithromycin, amoxiclav, doxycycline, or ivermectin is not supported by these guidelines, corticosteroid and remedesivir should never be tried at home without evidence of pneumonia. As gastrointestinal symptoms are more common in children, ORS and zinc need to be prescribed when clinically indicated in such cases. While the routine monitoring for danger signs like persistent fever beyond one week, desaturation on pulse oximetry or breathlessness is important as in adults, in children, additional monitoring for signs and symptoms of MIS-C needs to be taught to health care workers in primary health settings and parents. Whenever danger signs occur, routine hematological, biochemical testing, chest X-ray, coagulogram, and inflammatory markers need to be performed and the child needs to be admitted in the hospital. If home monitoring is not possible, even mild cases with comorbidities like chronic lung disease, symptomatic heart disease, chronic kidney disease, and neurological disorders should be admitted. Whenever possible, in these admitted cases, nebulization needs to be avoided and if inhaled medications are indicated, then preferably MDI and spacer should be used. Awake proning and 6MWT are only indicated for older children >12 years of age.

There are several limitations of our systematic review and meta-analysis. First of all, a randomized controlled trial with the primary objective directed toward determining the efficacy of any particular drug in children was lacking. Poor study quality of many included studies, retrospective study design, and significant heterogeneity compromised the reliability of pooled estimate results obtained in the meta-analysis. Second, mild COVID-19 cases in children usually do not make their way into published literature, especially in the later part of the pandemic, so our review results at best holds good for moderate and severe cases only. The unusually high rate of use of various pharmacological agents is due to the significant number of severe cases in the study participants of our review and certainly does not represent the true community scenario. The review included all the studies performed from December 2019 till now and over these months, the evidence approving/refuting various drugs and operational guidelines by various regulatory bodies have changed many times. Some of the drugs like hydroxychloroquine and azithromycin, which were included in the review, have been practically disapproved currently by FDA and other health authorities for use in confirmed COVID-19 cases. The drugs for which breakthrough positive evidence have been found recently in adults, controlled trials are ongoing in children like those for remdesivir and favipiravir and the results are not available yet. Many included studies described vividly the clinical manifestations, but treatment details were only scanty. The study investigators also followed different institutional guidelines and sometimes personal preferences for choosing the treatment regimens, thus compromising the reliability of outcome results. The severity of participants in various studies also differed widely and some studies tended to use antivirals even for mild cases, while other studies preserved them for severe cases only. This caused difficulty in pooling the results across these studies. Most of the pediatric studies have used anti-inflammatory therapies in children with MIS-C, but some of the earlier studies did not specifically mention that, as an increased prevalence of this entity became evident to clinicians after the study was completed. Viral clearance time has not been mentioned separately for various specific medications in most studies. Thus, it is difficult to extrapolate whether various medications change the natural course of illness, as most pediatric COVID-19 cases are less severe, with a better recovery rate as compared to the adult population. Last, the scope of our systematic review was to focus on pharmacological modalities and not on the mode of respiratory support, inotropes, and other supportive care. Although the review briefly touched on these modalities, more clinical trials and systematic review in this regard is also needed urgently. Still, this is the first systematic review in children that focused specifically on management aspects of COVID-19 and provided a comprehensive overview to clinicians at this challenging time regarding experience with various medications tried till now.

Conclusion

Among pharmacological modalities, anti-inflammatory agents like corticosteroids and antivirals like remdesivir have the most promising evidence for severe cases of pediatric COVID-19. Intravenous immunoglobulin, other anti-inflammatory/immunomodulatory agents like anakinra, aspirin, and anticoagulants have an important therapeutic role in cases with MIS-C. Most of the mild cases recover with conservative treatment only.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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