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ORIGINAL ARTICLE

Pediatric clinical trial profile for COVID-19 at ClinicalTrials.gov: a systematic review

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Abstract

Introduction: COVID-19 is an extremely serious infectious disease. However, few studies have focu-sed on the drug treatment of pediatric patients affected by COVID-19. **Objective:** Thus, this study conducted a review of clinical trials registered in the Clinical Trials database on drug treatment in pe-diatric patients with COVID-19. **Methods:** A systematic search was conducted in the Clinical Trials database (https://clinicaltrials.gov/) using the web tracking technique to collect registered clinical tri-als that conducted drug treatment in pediatric patients aged 0 to 17 years. After the drugs used were identified, their dosage and other pertinent information were obtained from the DrugBank databases (https://go.drugbank.com) and the DrugBase (https://www.drugbase.de). **Results:** Eight clinical trials were found in the research, classified as completed and 34 in progress, aimed at pediatric patients. The United States was the country that most research involving the drug use in patients with pedia-tric COVID-19. Hydroxychloroquine was the most observed drug in the treatment of pediatric pa-tients, followed by remdesivir. An increase in phase 3 and randomized trials was also observed among ongoing research when compared to completed research. **Conclusion:** Compared to adults, pedia-tric COVID-19 has distinct treatment needs. Thus, it is important to complete the clinical trials de-scribed in the present study, in addition to more randomized clinical trials, before any therapy or other objects related to the clinical management processes for COVID-19 can be properly recom-mended and applied in pediatric treatment.

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INTRODUCTION

Second survey released by the Johns Hopkins University of Medicine (https://coronavirus.jhu.edu/)[1] during the month of April 2021, the COVID-19 pandemic caused fur coronavirus SARS-CoV-2 hit approximately 136 million people, with more than 2 million nine hundred thousand deaths confirmed around the world. Although the syndrome respiratory caused by this illness can be of extreme gravity, its manifestation in individuals infected is variable, involving since cases asymptomatic, until deaths that consolidate in few days, especially at absence of treatment intensive[2]. Factors as age advanced age (>60-70 years), diabetes, diseases heart disease, hypertension , or other types of illness chronicles, it seems contribute to raising the risk associated with COVID-19, but deaths and/ or severe cases of the disease already were described in people young people enjoying full conditions physical and health[2].

Manifestations clinics as far away incubation period, strong infectivity, symptoms Resumen clinicians symptoms, fever and cough, in addition to shortness of breath, vomiting, diarrhea, myalgia and fatigue, are symptoms common associated with COVID-19[2-3]. In in relation to your treatment, management clinical is generally directed towards supportive measures[4-5], such as oxygen therapy, fluid administration, and antimicrobials for infections bacterial secondary[6]. even if without evidence robust results clinicians satisfactory, some medicines he comes being used to stop the progression of the disease. Drugs like oseltamivir along with antibiotics[3], Remdesivir and chloroquine[7-8], hydroxychloroquine[9], lopinavir-ritonavir and interferon-α 2b[3], in addition to Nitazoxanide they are being used and studied mainly in adults[10], Bearing in mind that people of any age are susceptible to COVID-19 and that it has been spreading quickly fur world thanks to the emergence of new strains viral , becomes critical at low prevalence of studies about pediatric COVID-19 in compared to adults[11-13].

Although the manifestations COVID-19 clinics are considered any less aggressive at population pediatric, children under 2 years old are most prone to frames most severe.[14-15]. The use of antiviral therapy in children has been considered, according to some protocols[16]. The antiviral Remdesivir, as such as hydroxychloroquine, for example, were considered as options therapeutics in children according panel multicentric[16]. However, new studies still need to be directed to understand how the disease affect the population pediatrics and regarding the use of agents with potential activity against SARS-CoV-2, since the drugs aforesaid were applied in protocols non-validated for adults[17]. With that, note the importance of analyzing the current use of drugs in the treatment of COVID-19 in patients pediatric patients, making the main objective of the present study the survey and analysis of trials clinicians registered in the Clinical Trials database (https://clinicaltrials.gov/) finished and in progress, in addition to evaluating those with approach drug therapy and which included in your samples, children.

METHODS

The present study it ‘s about a revision systematic testing clinicians registered in the international Clinical Trials database (https://clinicaltrials.gov/)[17] on the treatment medicated in patients pediatric patients with COVID-19. As pediatrics, we define patients aged 0 to 17 years.

You essay used in this job were obtained through a search systematized in the database using you descriptors *“Covid-19”* and *“SARS-CoV-2”* in the search field identified as *“Condition or disease”*, limiting the search date to up to *October 08, 2020*. the present search he was carried out in two moments distinct to characterize separately you essay clinicians Classified as *“completed ”* or *“ in progress”*.

To search for studies with the status *“completed”*, we used you following filters in the search form: *“Status: suspended, terminated or completed”*; *“Child (birth-17)”*; *“Sex: all”* and *“Study type: Interventional (Clinical Trial)”*. Now for the studies in progress, the following filters were used: *“Status: recruiting”*; *“Child (birth-17)”*; “ *Sex: all”*; *“Study type: Interventional (Clinical Trial)”*. No other filters for language restrictions , disease conditions, results or search locations he was applied at data selection.

after identification preview of studies clinicians and drugs associates, we perform new searches on DrugBank (https://go.drugbank.com)[18] and DrugBase (https://www.drugbase.de)[19] for details about your dosage known in relation to population pediatric.

RESULTS

During the execution of this revision in the Clinical Trials database were identified 130 trials clinicians treatment related patient medication pediatric patients with COVID-19, 16 of which were completed and 114 in progress . After application of filters for each group, eight (n=8) trials were obtained clinicians completed and thirty - four (n=34) in progress, as introduced at Figure 1.

All the raw data from the research carried out in the Clinical Trials database (https://clinicaltrials.gov/) are available in Supplementary Material S1 and S2.

Distribution of trials clinics by country

Among you eight (n=8) trials concluded with patients pediatric patients , five (n=5) were performed us United States, being you too much performed at South Korea, Egypt and Iran. with respect to the essay clinicians in progress , the United States and Egypt registered the same number of studies within the analysis performed , or that is, eight (n=8) trials clinicians in each country. In then China and Pakistan stand out with three (n=3) studies registered each. In Iran and Mexico there were two (n=2) studies of each country registered and how much to the too much countries included, one (n=1) survey in each there was been registered. These data can be seen at

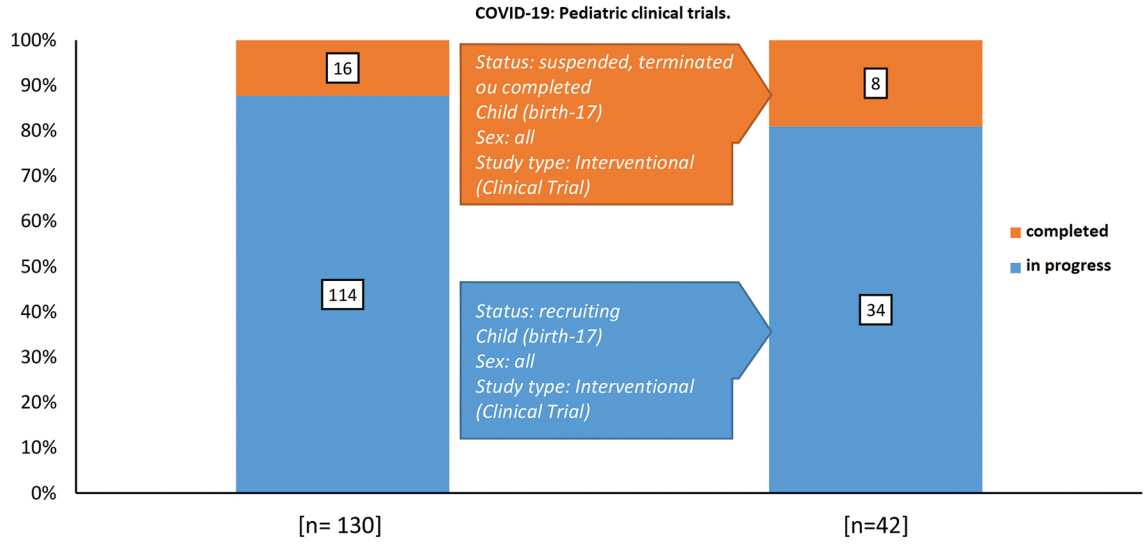

Figure 1. Distribution of trials clinicians completed and in progress in the ClinicalTrials.gov database for the treatment of COVID-19 / SARS-CoV-2 as of October 8 , 2020.

Figure 2. It is worth noting that no had test records clinicians completed or in progress in Brazil in this range age in October 2020 with Clinical Trials (https://clinicaltrials.gov/)[17].

Distribution of trials drug clinicians used

A total of 19 drugs many different were associated with the treatment of COVID-19 in patients pediatrics based on Wow research in Clinical Trials.

In essay clinicians completed involving patients pediatricians, we observed one larger prevalence of hydroxychloroquine in studies with individual use (n=4) or in association with other drugs (n=3), such as Favipiravir (n=1), Azithromycin (n=1) or Lopinavir/Ritonavir (n=1). In addition Furthermore, Remdesivir was the second damn it most studied in researches completed with patients pediatrics in the period evaluated, the others being drugs observed (Ivermectin, Azithromycin, Tocilizumab and Lopinavir/Ritonavir) present in a uniform among the studies (Figure 3).

So as us results , hydroxychloroquine and remdesivir were the drugs predominant us essay clinicians in progress within the period analyzed, with five (n=5) and four (n=4) studies in progress respectively. Ivermectin (n=3), Nitazoxanide (n=3), Lopinavir/Ritonavir (n=2), Azithromycin (n=1) and Tocilizumab (n=1) also were gifts among the drugs most observed us studies no completed (Figure 3).

Distribution of trials clinical trials by phases and type of research

According to analyzed data at gift research, among studies Classified as completed in the database, six trials clinicians (n=6) were finalized in your phases 2 and/or 3, while two trials (n=2) no presented Details about the research phase. In addition addition, five essay clinicians (n=5) were identified as randomized While three (n=3) as non-randomized (Figure 4).

Already among the studies in progress, thirteen (n=13) essays clinicians were observed at phase 3 and two (n=2) in the phase 4. Also we observed an increase expressive of rehearsals randomized, totaling 85.3% (n=29) of the 34 studies found (Figure 4).

DISCUSSION

The fast global spread of COVID-19 makes priorities you intense community efforts medical and scientific at identification of strategies preventive and treatment effective in promoting the development of a management doctor suitable. Although the pandemic related to SARS-CoV-2 already you have more than a year and what information relatively wide be available to patients adults, the characteristics epidemiological and clinical in children, which include therapeutic data, even no were totally defined for COVID-19[3].

As already observed in others essay reviews clinicians related to the treatment of COVID-19[20-21], chloroquine / hydroxychloroquine is the drug most observed in the Clinical Trials database at essay clinicians involving SARS-CoV-2. According to DrugBase, Chloroquine (CQL) is a drug used primarily as prophylaxis in the treatment of malaria[22], being also widely known for its effectiveness in the treatment of autoimmune diseases as lupus, arthritis rheumatoid and in illnesses dermatological. In the latest decades, studies evidenced CQL as an agent potential in the therapeutic arsenal against some types of cancer and as a possible antiviral[22-24]. Because it is a weak base, CQL focuses on in organelles that have low pH like endosomes, lysosomes and Golgi vesicles, being able to raise the pH in such structures[25]. Despite CQL 's mechanism of action, not be fully understood, studies

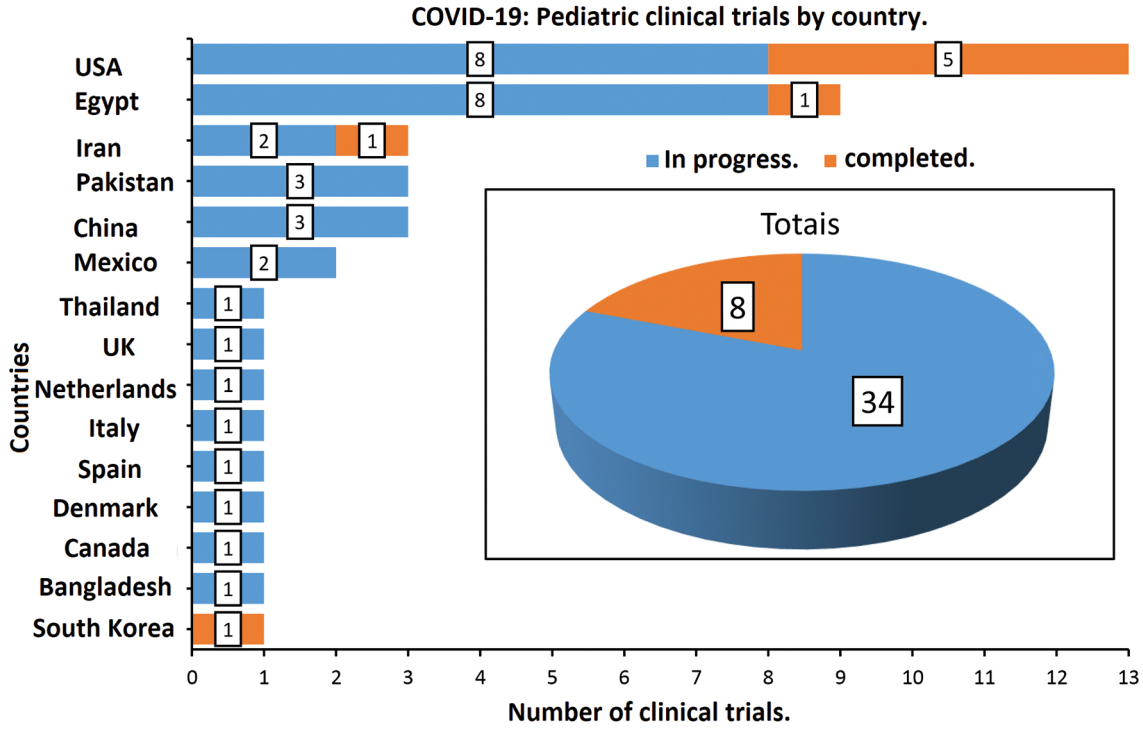

Figure 2. Distribution by country of all you essay clinicians completed and in ClinicalTrials.gov database progress for COVID -19/SARS-CoV-2 treatment as of *October 8*, 2020.

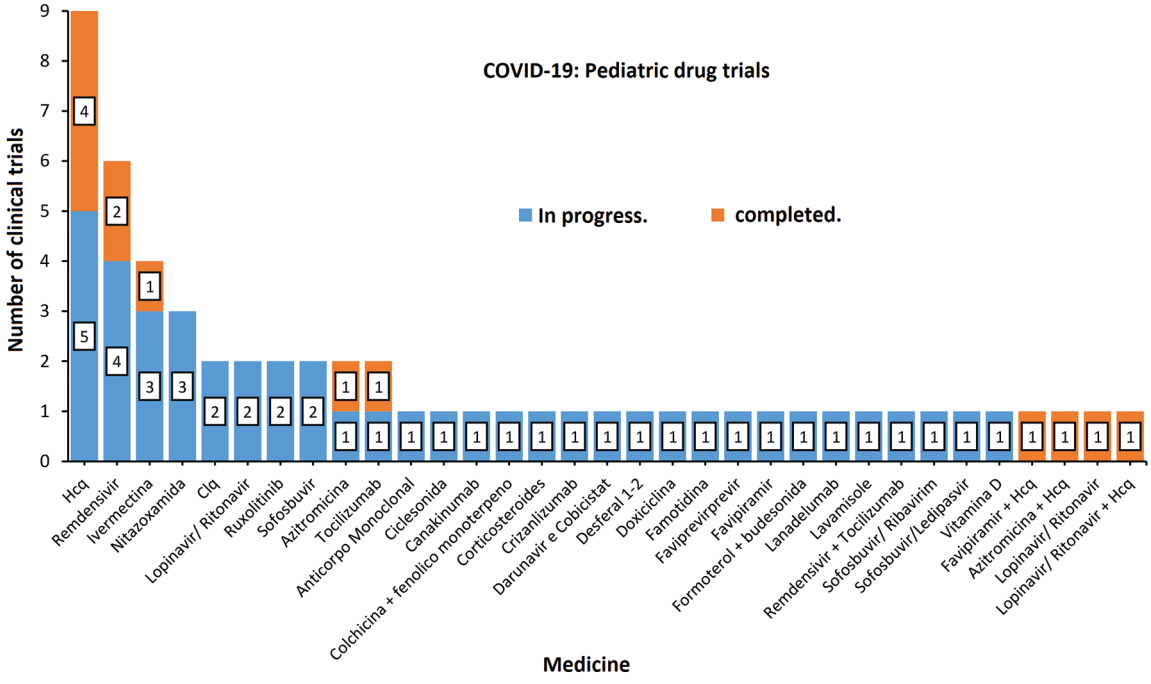

Figure 3. Distribution by drug of all essay clinicians completed and in ClinicalTrials.gov database progress for COVID -19 / SARS-CoV-2 treatment as of *October 8, 2020*.

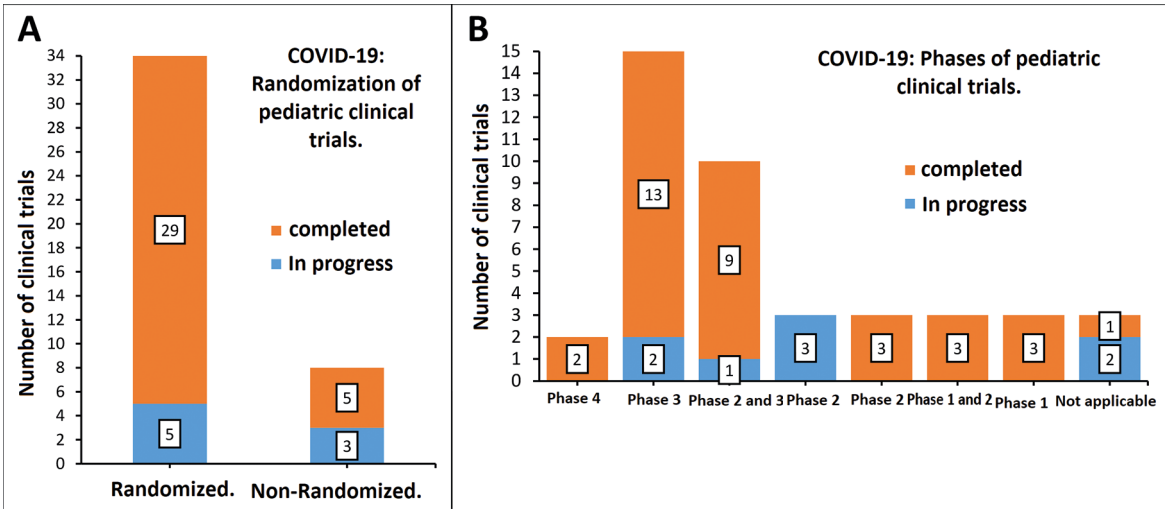

Figure 4. Distribution by research phases and randomization of all essay clinicians completed and in ClinicalTrials.gov database progress for COVID -19 / SARS-CoV-2 treatment as of October 8 , 2020. In (A) are the essay clinicians distributed by presence / absence of randomization , in (B) the essay clinicians by research phases.

in vitro independent evidenced your inhibition of viral replication[25-26] and its possible acting at infection by SARS-CoV-2, interfering mainly at glycosylation of the ACE-2 cell receptor (*angiotensin-converting enzyme 2*), hindering viral entry[25] by not receptor glycosylation that prevents your interaction with the SARS-CoV-2 S surface protein, which may impacts negatively the link virus -receptor and later prevent infection[27]. In addition addition, the inhibition of endosome acidification promoted by CQL also could block the replication of the coronavirus[28]. Hydroxychloroquine (HCQ) is a derivative of CQL and as to the role of hydroxychloroquine in infections caused by CoVs, like yours mechanism of action is identical to that of CQL, it is believed that its antiviral activity too be the same[9,29]. However, studies recent he comes demonstrating The ineffectiveness of those medicines in the treatment of COVID-19.

Bhagteshwar Singh et al[30] in analyzing ten studies (n=10) and to compare the use of HCQ with the treatment pattern no HCQ or placebo noted few or none difference at death from any cause. Also observed that HCQ can to do few or none difference at probability of a negative PCR for SARS -CoV-2 in samples respiratory symptoms on the 14th day of administration. You researchers also observed that HCQ probably results in few or none difference at progression to ventilation mechanics or in the time of improvement clinic When compared to treatment pattern without HCQ or placebo. In addition Furthermore, they showed that HCQ probably results at a risk increased risk of adverse event development, but may to do few or none difference in the risk of serious adverse events[30]. In addition of this study, different reviews systematic were published examining the treatment of COVID-19 with HCQ/ CQL, mainly in patients adults. in the biggest part, your conclusions coincide with those described by Bhagteshwar Singh et al.[30], not showing none benefit of HCQ for the reduction of mortality from COVID-19[31-34].

Even with the growing number of articles demonstrating the inefficiency in the treatment of patients adults with COVID-19[30-34], CQL/HCQ was suggested as alternative therapy for patients who do not are candidates for the antiviral Remdesivir, in case of unavailability or While you patients await administration of Remdesivir, however, this same panel multicentric contraindicates the use of HCQ alone or in combination with azithromycin , for the treatment of COVID-19 outside of a trial clinical[16]. In addition addition, the present panel stresses that the therapies antivirals for COVID-19 no are necessary for the great most patients pediatricians and that the evidence on the use of medicines suggested continue The evolve quickly, generating the need for updates in the guidelines provided constantly.

CONCLUSION

Through a search systematic in the Clinical Trials database (https://clinicaltrials.gov/)[17], this revision recovered forty - two (n=42) trials clinicians who evaluated interventions for prevention or coronavirus treatment in patients pediatric using many different drugs. In general, the use of antimalarials, mainly Hydroxychloroquine, and the antivirals Remdesivir and Lopinavir/Ritonavir, in addition to anti- inflammatory drugs and azithromycin, were observed in the treatment of children infected by SARS-CoV-2. However, research recent he comes evidencing The lack of drug efficacy reported in the process therapeutics of COVID-19 in patients adults, which generates one larger worry and uncertainties in your application in patients

pediatric. Thus , it becomes important to conclude the tests clinicians described in the present study, in addition to essay clinicians randomized, before any therapy or other objects related to the management processes clinical trial for COVID-19 can be adequately recommended and applied in the treatment pediatric.

LIMITATIONS

The present study had some limitations , being conducted within the time limit described.

INTEREST CONFLICTS

You authors declare there is no conflict of interest.

CONTRIBUTION STATEMENT

MRZC , *LT* and *FBM* conceived The original idea. *FBM* supervised the project. *MRZC* and *LT* contributed to the collection, preparation and analysis of data. *DSS*, DBA, *KFK*, *RP* and *FBM* contributed to the interpretation of results. *DSS* and *FBM* took the lead at manuscript writing. All you authors provided critical feedback and helped shape the research, analysis, and manuscript.

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