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Research Article

Scientific Evidences about the Pharmacological Therapy for COVID-19 in Children

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Abstract

Introduction: The acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19) arised in 2020 as a pandemic and in spite of the consequences there are not yet any drug to face this problem.

Objective: To identify in the scientific literature evidences about the pharmacological therapy for COVID-19 in children.

Method: This is an integrative review of the literature carried out from SPIDER instrument and conducted in June 2020, at the PubMed from the use of descriptors "coronavirus infections, child e drug therapy". After the filter from the inclusion and exclusion criteria, were used and analyzed through an instrument, five articles summarized in synoptic table.

Results: The selected articles pointed to the use of antivirals drugs (Lopinavir-ritonavir (LPV/r), antibiotics (Vancomycin and Amikacin), antimalarial drugs (Hydroxychloroquine), immunomodulatory (Interferon α - 1b) and herbal medicine (Lianhuaqingwen) in the pharmacological management of children with COVID-19.

Conclusion: As it is a new stump of novel coronavirus, its necessary the accomplishment of clinical trial that guide the evidence-based practice.

Keywords: *Evidence-Based Medicine; Child Health; Coronavirus Infections; Drug Therapy; Review*

Introduction

The several acute respiratory syndrome for coronavirus (SARS-CoV-2) is the focus of global attention [1] since the several cases of patients with pneumonia in Wuhan-Hubei, in China, were identified at the end of December 2019 [2,3].

Characterized as highly infectious disease [4,5], the COVID-19 can be classified as light, common, grave and criticism. The both of two types have a good prognosis, however the last two could culminate in systematic organ dysfunction [6], that characterize the urgency to find appropriate drugs [3].

The clinical manifestations of novel coronavirus include fever, non-productive cough, dyspnea, tachypnea, myalgia, fatigue and diarrhea [7-9] and though it might affect all age-groups [10], as indicated for different studies [2,10,11], the manifestations are lighter in children the in adults. However, the symptomatology in children is distinguished from adults in context of respiratory infections, what demonstrates the necessity of paying attention in children with COVID-19 [11].

Despite the pneumonia for novel coronavirus be a serious illness, with high lethality rate [3], until now there has been no pharmacological treatment clinically effective against the COVID-19 [2,3,12], although various studies are ongoing [12].

The care for patients with COVID-19 are limited to symptomatic treatment [3], being raised as measured of support the administration of oxygen, intravenous therapy, hydro electrolytic correction and of disorders with acids and bases [10].

Considering the epidemiological importance of novel coronavirus, is compelling to find appropriate medicines to face this problem [3].

At that, it is important the development of researches about the pharmacological management for COVID-19, since these studies have potential to contribute with the care to patient until a specific medication for novel coronavirus be developed, favoring the best of Evidence-Based Health Care, with direct reflection in health and quality of life of patient.

Purpose of the Study

The purpose of this study is to identify in the scientific literature evidences about the pharmacological therapy for COVID-19 in children.

Materials and Methods

Integrative review of the literature carried out in June 2020 about the scientific literature evidences about the pharmacological therapy for COVID-19 in children. This is an important method because it allows systematically the analysis of literature about a specific topic, promoting the investigation about published researches, the remaining gaps and the disclosure of data produced for other authors [13].

To guide the elaboration of research question and to conduct the searches was used the tool SPIDER, which consist of five elements: Sample, Phenomenon of Interest, Design, Evaluation and Research type [14]. In the face of it, was formulated the following leading question: What are the scientific evidences (E) about the pharmacological therapy for COVID-19 (PI) in children (S)?

Considering the phases of integrative review [15], the elaboration of research question (PI) has been succeeded by the following actions: search or sampling in literature, anchored by inclusion and exclusion criteria (S/D/R); data collection (S); critical analysis of included studies (E); discussion of results (E); and presentation of review.

The data collection was conducted from three times. The first one consisted in an uprising of studies in the PubMed database from the descriptors "coronavirus infections, child e drug therapy", consulted in Medical Subject Headings (MeSH), in National Library. The crossings of descriptors occurred by using the Boolean Operator AND: coronavirus infections AND child AND drug therapy. Was not held any restriction in selection, considering the option "all fields" in the searches.

Were found 108 materials, filtering by the following inclusion criteria: articles published fully, available online, in English. It is worth highlighting that because the novel coronavirus is a new theme, were included in the selection only studies published in 2020. Were excluded articles whose results weren't related to drug treatment in children with the diagnosis of COVID-19. From these criteria, were rejected 71 articles (10 because did not the full text; 60 because weren't related to SARS-CoV-2, but other types of coronavirus and 1 because it wasn't published in English) and pre-selected 37.

The second phase of data collection was guided for a protocol drawn by authors. So, the 37 pre-selected articles were submitted to a read carefully of tittle and abstract and has been selected the studies that had children among the subjects and which fall within the drugs related to infection by novel coronavirus. This new selection resulted in 20 articles.

In the third phase of data collection, which was also based in cited protocol, the 20 articles initially selected were submitted to a new analysis, at which the fully studies were critically read. After that, were excluded 15 articles because they didn't addressed specifically the drugs in the context of novel coronavirus and selected 5 articles to compose the sample of this review.

The selected articles were evaluated and classified with respect to level of evidence considering the system proposed by Oxford Centre for Evidence-based Medicine [16] whom classify the evidences in 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4 and 5.

Because this study did not involve human, it was not necessary to submit to the Committee on Ethics in Research. However, was complied the Brazilian Law number 9.610, from 19 February 1998 [17], which regulates the copyright and were considered the ethical principles that concern to preservation of autonomy. Thus, the authors consulted were adequately mentioned.

Results

The 5 selected articles were fully read and, after that, was filled out an instrument with the summarization of these studies for the following information: identification (ID), authorship, tittle, journal/magazine, objective, type of survey and sample, which is presented in table 1. In table 2 are presented the level of evidence and the results of each one of article consulted.

ID	Authorship	Tittle	Jornal/magazine	Objective	Type of survey and sample
01	Wang., *et al*. [19]	Clinical Outcomes in 55 Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Who Were Asymptomatic at Hospital Admission in Shenzhen, China	*The Journal of Infectious Diseases*	To present the epidemiological and clinical outcomes in 55 asymptomatic carriers who were laboratory confirmed to be positive for SARS-CoV-2 through nucleic acid testing of pharyngeal swab samples	Prospective cohort with 55 patients
02	Ye., *et al.* [3]	Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019	*European Review for Medical and Pharmacological Sciences*	To investigate whether lopinavir/ritonavir (LPV/r) in combination with other pneumonia-associated adjuvant drugs has a better therapeutic effect on COVID-19.	Case control study with 47 patients
03	Aghdam; Jafari; Eftekhari [20]	Novel coronavirus in a 15-day-old neonate with clinical signs of sepsis, a case report	*Infectious Disease*	To introduce the case of a 15-day-old neonate with the novel coronavirus and with clinical signs of sepsis.	Case report of a neonate
04	Hrusak., *et al.* [18]	Flash survey on severe acute respiratory syndrome coronavirus-2 infections in pediatric patients on anticancer treatment	*European Journal of Cancer*	To flash survey on COVID-19 incidence and severity among children on anticancer treatment	Ecological study with approximately 10.000 patients
05	Lin., *et al.* [11]	The isolation period should be longer: Lesson from a child infected with SARS-CoV-2 in Chongqing, China	*Pediatric Pulmonology*	To relate the case of a 7-year-old child with SARS-CoV-2 infection	Case report with 1 patient

Table 1: *Summarization of selected studies for this review regarding to authorship, tittle, journal/magazine, objective, type of survey and sample.*

ID	Level of evidence	Level of recommendation	Results
01	2B	B	• Lopinavir-ritonavir was offered for 7 days to a 2-year-old child.
02	3B	B	• Lopinavir-ritonavir resulted in good answers in remission of fever and in ammunition. The examen blood suggested that the number of patients with ALT and AST abnormal in test group has not significantly increased with the treatment duration and the corresponding percentage was smaller than in control group; in patients who received the combined treatment LPV/r, the fast remission can be observed in some clinical symptoms such as abnormality of leukocytes, lymphocytes and C-reactive protein. The results showed that the abnormal proportion of leukocytes, lymphocytes, PCR and PLT in test group was generally lower than in the control group after three treatments.
03	4	C	• Vancomycin, amikacin and oseltamivir: The recovery gradually began after the second day of admission. respiratory distress and stains resolved. The oral feeding began and was tolerated.
04	2C	B	• Hydroxychloroquine • Lopinavir- ritonavir
05	4	C	• Lianhuaqingwen: Chinese herbal medicine administered either in oral as granule. • Nebulization for interferonα- 1b • Oseltamivir: The oral intake may not reduce the replication of SARS -CoV- 2.

Table 2: *Summarization of selected studies for this review regarding to the level of evidence and results.*

The most researches (n = 3) was carried out in China, initially the epicenter of the pandemic [2,3] and as indicated in table 2, the majority (n = 3) was classified with degree of recommendation B, from the level of quality of scientific evidence assessed [16]. Only one of the studies [18] presented a significant sample, with 10.000 participants, which were part of a multicenter study in 25 countries. However, all of them presented theoretical foundation in analysis and in results. Regarding to approach, was predominant (n = 3) the quantitative, with different kinds of methods.

The results related to objective of this review were summarized in table 2, that also contains the level of evidence and the level of recommendation. The drugs cited in treatment of children with COVID-19 belong to the class of antiviral [3,11,18-20], antibiotics [20], drugs to combat malaria [18], immunomodulator [11] and phytotherapy medication [11], which were: Lopinavir-ritonavir (LPV/r) [3,18,19]; Oseltamivir [11,19]; Vancomycin [19]; Amikacin [19]; Hydroxychloroquine [18]; Interferon α - 1b [11] and Lianhuaqingwen [11].

It is also worth highlighting that the although the selected articles have presented the drugs managed to children with COVID-19, only one of them [3] has focused on evaluation of the effectiveness of a specific drug (LPV/r) in context of novel coronavirus. In three studies [3,11,20] are presented the conclusions related to drugs cited and two of the selected articles [18,19] remained only in the descriptive approach, and that was the limitation of these studies, described in table 3, which shows the recommendations from consulted authors and the limitations identified by authors of this review.

ID	Recommendations	Limitations
01	There were none.	It wasn't specified the number of children and their ages.
02	To apply widely the combined treatment LPV/r in the treatment of patients with infection by COVID-19; Do not use antibiotics for more than five days to avoid the occurrence of new infections; The therapy in combination with broad spectrum antibiotics must be avoided; The glucocorticoids can be used in a short period of time (3-5 days) small doses, not exceeding 1-2 mg per kg per day, depending on the situation of patient.	There are some limitations which referred to reduced size of the sample of control group; Lack data during treatment make the results imprecise, and none statistical analysis was done in relation to side effects of LPV/r in gastrointestinal via, such as diarrhea. Therefore, in future analysis, the sample size must be expanded to make the results more precise and a systemic study can be carried out about LPV/r and the possibility of side effects in gastrointestinal via in patients with infection by COVID-19.
03	There were none.	It does not address the specific effects of drugs.
04	There were none.	It was restricted to children in anti-neoplastic treatment.
05	There were none.	It didn't do an analysis about all of used drugs.

Table 3: *Summarization of selected studies for this review regarding the recommendations and limitations identified.*

The combined treatment LPV/r was the most cited [3,18,19], which had been cited as effective in the remission of fever and ammunition [3]. Thus, in a case-control study [3] the results indicated that, in comparison with control group, the patients from test group returned to normal body temperature in less time (test group: 4,8 ± 1,94 days vs. control group: 7,3 ± 1,53 days, p = 0,0364), and these results suggest that the patients who were treated with LPV/r combined with adjuvant drugs associated to pneumonia had more possibility to returning to normal body temperature than that who were treated only with adjuvant drugs.

It has been shown [3] that the combined treatment LPV/r is able to reduce the abnormal values of biochemical indices to the detriment of the isolated adjuvant therapy as it was observed that the abnormal proportion of leukocytes, lymphocytes PCR and PLT in the test group was generally smaller than in the control group after three treatments. In addition, the abnormal proportion of lymphocytes, Hb, granulocytes and PCR in the test group has been gradually reduced from first to third measurement. The number of days required to nCoV-RNA became negative was shorter in the test group (7,8 ± 3,09 days) than in the control group (12,0 ± 0,82 days), with p = 0,0219.

It was also identified [3] that the combined use of LPV/r with adjuvant drugs does not represent adverse effects, toxic neither collateral of liver, since biochemical tests showed that the abnormal percentage of ALT and AST in the test group was smaller than in the control group.

In relation to antibiotics, although one of the studies [3] have recommended that these drugs mustn't be used and, if it were used, the use should not exceed 5 days because of the risk of new infections [3], in another study [20] the authors showed that the combined use of antibiotic and antiviral was responsible for gradual recovery of newborn after the second day of admission, been resolved the stains and the respiratory distress. Besides, the oral feeding began and was tolerated.

Concerning to Oseltamivir, cited in two of the studies [11,19], it was observed that it can't reduce the replication of SARS-CoV-2 [11]. In addition, depending on the situation of patients, the glucocorticoids can be used for a short period of time (3 - 5 days) in doses that not exceeding 1 - 2 mg/kg/day [3].

Discussion

Since the novel coronavirus was advertised as a pandemic by World Health Organization (WHO) in March 2020 [21], several studies have been developed [12] aiming to present pharmacological treatments clinically proven to this problem.

Although there is no specific medicine available against COVID-19 [3], authors [22,23] are manifesting about a strategy known as "repositioning/ reutilization", which is related to discovery of action of drugs already existing for diseases beyond them which they were originally developed, what is related to drugs cited in this review.

As it is related to an RNA virus, such as HIV [3], the viral replication of novel coronavirus is associated to hydrolysis of protease, into a form which is possible to avoid the viral replication through the inhibition of this process [3]. The LPV/r is an inhibitor of protein [24] and one of medicines currently used in the treatment of second line of retroviruses and, in the context of HIV, interferes in protease causing deregulation of structural and functional protein in the core of the virus, contributing for the generation of immature viral particles and non-infectious, inhibiting the replication of HIV [25,26]. Considering the possibility of reducing the viral load of HIV-positive patients, its efficiency has already been described in different studies [24-27].

What about the SARS-CoV-2, was revealed by a study [28] which dealt with therapies directed to the novel coronavirus that non-structural proteins codified by genome of this virus are protagonists in the viral lifecycle and that the connection in proteases SARS-CoV-2

can be used as potentially antiviral. At that, authors [3] recommends that shall be taken into consideration the possibility that antiviral which already been approved, or which are in development to treatment of infections caused by HIV and other viral infections, such as the LPV/r, which is one of HIV protease inhibitors.

Several studies indicate the effectiveness of combination of these drugs in reducing of viral load and improvement of immunity, even when this medicine is used without the combination of other antiviral [25]. In a metanalysis [27] which aimed to evaluate the efficacy and safety of LPV/r in people infected by HIV, the authors concluded that it's an effective therapy, also with significant effect in prevent of vertical transmission. In a research [29] which specifically addressed the infection by HIV in children and teenagers, was demonstrated that better results were obtained when the protease inhibitors were included in therapeutics, culminating with more viral suppressive in patients treated.

Although there are already evidences about the use of LPV/r can reduce the development of acute respiratory distress syndrome and the mortality caused by the infection by SARS [30], there are still not many scientific productions about these medicines in the treatment of SARS-CoV-2, since the virus is a stump discovered recently. However, studies [31,32] have already identified the efficacy of lopinavir, LPV/r in reduction of viral load and better results in patients with COVID-19, with reduction of necessity of invasive ventilation. In spite of all these evidences, the Brazilian Society of Pediatrics [33] does not recommend the use of these antiretroviral in children.

Concerning to Oseltamivir [11,19], which is indicated in the treatment of SRAG by influenza virus [34], acts by inhibiting the neuraminidase enzyme of influenza virus, which is essential both for viral entry into non-infected cells and liberation of viral particles and further expansion of etiologic agent in organism [35], with recommendation of use in cases of Influenza-like Syndrome in pediatrics early, preferably during the first 48 hours from the beginning of symptoms, because the early start of treatment with this medicine can reduce the duration of symptoms and complication of infection [36].

In discussing this medicine in the treatment of children with suspect of COVID-19, the Brazilian Society of Pediatrics [33] recommends the use empirical, independent of severity of the case, and drug should be kept until the result of PCR for coronavirus and if the virology for influenza are positive.

Even knowing that in viral infections the antibiotics are ineffective [37], in Influenza-like Syndrome is recommended treatment adjunct of antibiotics and antiviral [38] and, in relation to COVID-19, in the protocol of clinical management of COVID-19 in specialized attention, published by Brazilian Ministry of Health [39], is recommended association of antibiotics with antiviral treatment as an way of to prevent or to treat a possible bacterial infection associate.

In a research [40] carried out in a pediatric hospital from Portugal with children and teenagers affected by influenza, the author identified that in 63% of the cases were prescribed antibiotics, and she considered this rate high, so she warned about the need for introducing antibiotics only when there will be suspect of bacterial infection at the same time than influenza infection. Similar result was observed in a retrospective cohort [41] conducted in a pediatric hospital from United States, which revealed that is high the number of people with viral infection been treated with antibiotics together with antiviral.

Such findings support the positioning of authors [42] who on addressing the viral infections in pediatric disclose that coronavirus is one of the main etiological agents in infections of children, and the inflammatory process of nasal mucosa is an important cause of obstruction in sinuses and auditory tube, in addition to being able to happen secondary bacterial infection, with necessity of antibiotic therapy in parallel to treatment with antiviral. In the face of such evidences, the Brazilian Society of Pediatrics [33] recommends the use of antibiotics when there is a suspicion of bacterial infection and warns that the therapeutic must be individual.

The drug used against malaria cited in this review (hydroxychloroquine) [18] was in the center of discussions about the treatment to cases of novel coronavirus and has been highlighted in different studies [43-47], which it was considered an alternative for COVID-19. Although there are *in vitro* studies which show the effectiveness of hydroxychloroquine in inhibition of viral replication [48], there are too researches [44,45,47] that show important adverse effects related to the use of this medicine. Besides, in one of studies [46] in which was observed decrease of viral load in patients was highlighted the existence of some biases such as the fact of hydroxychloroquine has been used in association with azithromycin, the lack of a control group to comparison of results and a small sample. In relation to these results, the Brazilian Society of Immunology [49] concluded that the recommendation of use of this medicine in cases of COVID-19 is still early and are necessary more researches about it.

It should be stressed that the Brazilian Society of Pediatrics [48] in scientific opinion about the use of hydroxychloroquine in treatment of children and teenagers with COVID-19, does not recommend its use because it considers that there aren't data that have support to safety and effectiveness of its administration in pediatric patients with COVID-19, independent of severity of the case.

The interferon α, the drug of choice in treatment of children affected by hepatitis B virus [50], acts in regulation of cell growth [51], with antiviral effects, antiproliferative and immunomodulator [52]. It uses in cases of novel coronavirus has not been yet documented in literature. However, in a study [53] which aimed to clarify the pulmonary manifestations related to its use was showed that has been progressively reported cases of pulmonary toxicity assigned to interferon α, with clinical manifestations which vary from asymptomatic case to grave answers where there is a risk of death. Considering such evidences and the known deleterious effects of novel coronavirus in the pulmonary system, the use of interferon α must be cautious, and it is not recommended its administration in pediatric patients [33].

In China, country where the pandemic had beginning [2,3] and main origin of articles selected for this review, the traditional medicine is an important alternative of care in different contexts of diseases for millenniums [54], being the phytotherapy one of possibilities of treatment of COVID-19. Faced with this, was highlighted the use of Lianhuaqingwen [11], which have been already studied in a randomized clinical trial in the context of chronic obstructive pulmonary disease [55] and has been proved effective in the treatment of this illness because it can reduce the liberation of inflammatory mediators and, consequently, to reduce the systemic inflammation and in airway. In treatment of influenza revealed have antiviral activity and relevant impacts in immune system [56].

Specifically about cases of novel coronavirus, studies [57,58] showed its effectiveness too. A research [57] which aimed to demonstrate the antiviral activity of this herbal medicine indicated that is possible a significant inhibition of SARS-CoV-2, important reduction of pro-inflammatory cytokines and abnormal morphology of viral particles in cells, allowing to authors conclude that the Lianhuaqingwen is one of strategies to control the COVID-19.

Such results are similar those released in a randomized clinical trial [58] which aimed to determinate the safety and efficacy about the use of Lianhuaqingwen in patients with COVID-19 and that presented as outcome recovery significantly larger in the group test, beyond reduced time to recovery among patients who received this medicine and improve in computerized tomography manifestations, without serious adverse events.

There are several researches in progress to evaluate the efficacy and safety of drugs in different classes to patients with COVID-19 [59]. It´s necessary the conduction of controlled or randomized studies, with high number of patients for the presented evidences in this review are really strong and able to guide the clinical practice and the decision taking.

Conclusion

The scientific evidences about pharmacological therapy for COVID-19 points to the use of different classes of drugs, with emphasis in antiviral (here represented by combination of LPV/r and Oseltamivir) for therapeutic of children with novel coronavirus. In addition to these, stands out the use of antibiotics, drug against malaria, immunomodulatory and phytotherapies.

Despite all of the discussed drugs have presented a positive aspect in the context of treatment of children with COVID-19, is early to say that such medicines are the best option of pharmacological management of novel coronavirus in pediatric, and its necessary the conduction of other researches about this theme. In the face of this conclusion, it's recommended the realization of clinical studies, controlled and randomized to support strong evidences, guiding the best evidence-based practice.

Bibliography

1. Zhou P., *et al*. "Discovery of a novel coronavirus associated with the recent pneumonia out- break in humans and its potential bat origin". *Nature* 579 (2020): 270-273.

2. Wang D., *et al*. "Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China". *The Journal of the American Medical Association* 323 (2020): 1061-1069.

3. Ye XT., *et al*. "Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019". *European Review for Medical and Pharmacological Sciences* 24 (2020): 3390-3396.

4. Data from the official website of the National Health Commission.

5. Special Expert Group For Control Of The Epidemic Of Novel Coronavirus Pneumonia Of The Chinese Preventive Medicine Association. "[An update on the epidemiological characteristics of novel corona- virus pneumonia COVID-19]". *Zhonghua Liu Xing Bing XueZaZhi* 41 (2020): 139-144.

6. Guan W., *et al*. "Clinical characteristics of 2019 novel coronavirus infection in China". *The New England Journal of Medicine* (2020).

7. Wu YC., *et al*. "Overview of the 2019 novel coronavirus (2019-nCoV): the pathogen of severe specic contagious pneumonia (SS- CP)". *Journal of the Chinese Medical Association* (2020).

8. Chen N., *et al*. "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". *Lancet* 395 (2020): 507-513.

9. Li Q., *et al*. "Early transmission dynamics in Wuhan, China, of Novel Coronavirus-infected pneumonia". *The New England Journal of Medicine* 382 (2020): 1199-1207.

10. Lu Q and Shi Y. "Coronavirus disease (COVID-19) and neonate: what neonatologist needs to know". *Journal of Medical Virology* (2020).

11. Lin J., *et al*. "The isolation period should be longer: Lesson from a child infected with SARS-CoV-2 in Chongqing, China". *Pediatric Pulmonology* (2020): 1-4.

12. Maguire BJ and Guérin PJ. "Um protocolo de revisão sistemática vivo para registros de ensaios clínicos covid-19". *Wellcome Open Research* 5 (2020): 60.

13. Ramalho Neto JM., *et al*. "Meleis' Nursing Theories Evaluation: integrative review". *Revista Brasileira de Enfermagem* 69.1 (2016): 162-168.

14. Cooke A., *et al*. "Beyond PICO: The SPIDER Tool for qualitative evidence synthesis". *Qualitative Health Research* 22.10 (2012): 1435-1443.

15. Souza MT., *et al*. "Integrative review: what is it? How to do it?" *Einstein* 8.1-1 (2010): 102-106.

16. Oxford Centre for Evidence-based Medicine: levels of evidence (2009).

17. Brasil. "Lei Nº 9.610, de 19 de fevereiro de 1998.Altera, atualiza e consolida a legislação sobre direitos autorais e dá outras providências". *Diário Oficial da União* (1998).

18. Hrusak O., *et al*. "Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment". *European Journal of Cancer* 132 (2020): 11e16.

19. Wang Y., *et al*. "Clinical Outcomes in 55 Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Who Were Asymptomatic at Hospital Admission in Shenzhen, China". *The Journal of Infectious Diseases* (2020): 1-5.

20. Aghdam MK., *et al*. "Novel coronavirus in a 15-day-old neonate with clinical signs of sepsis, a case report". *Infectious Diseases* (2020): 1-3.

21. World Health Organization (WHO). Rational use of personal protective equipment forcoronavirus disease 2019 (COVID-19) (2020).

22. Nishimura Y and Hara H. "Drug repositioning: current advances and future perspectives". *Frontiers in Pharmacology* 9 (2018): 1068.

23. Pushpakom S., *et al*. "Drug repurposing: progress, challenges and recommendations". *Nature Reviews Drug Discovery* 18 (2019): 41-58.

24. Sheahan TP., *et al*. "Comparative therapeutic efcacy of remdesivir and combination lopinavir, ritonavir, and inter- feron beta against MERS-CoV". *Nature Communication* 11 (2020): 222.

25. Sabbatani S., *et al*. "[First evalua- tions of LPV/RTV (Kaletra) efcacy on HIV-pos- itive patients treated with multiple drugs]". *Le Infezioni in Medicina* 11 (2003): 18-24.

26. Bongiovanni M., *et al*. "Lopinavir/ritonavir vs. indi- navir/ritonavir in antiretroviralnaive HIV-infectedpatients: immunovirologicaloutcomeandsideeffects". *Antiviral Research* 62 (2004): 53-56.

27. Huang X., *et al*. "Efficacy and biological safety of lopinavir/ritonavir based anti-retroviral therapy in HIV-1-infected patients: a meta-analysis of randomized controlled trials". *Scientific Reports* 5 (2015): 8528.

28. Li G and Clerc ED. "Therapeutic options for the 2019 novel coronavirus (2019-nCoV)". *Nature Reviews Drug Discovery* 19 (2020): 149-150.

29. Sánchez PR., *et al*. "Impact of lopinavir-ritonavir exposure in HIV-1 infected children and adolescents in Madrid, Spain during 2000-2014". *PLoS One* 12.3 (2017): e0173168.

30. Chu CM., *et al*. "HKU/UCH SARS Study Group". *Thorax* 59 (2004): 252-256.

31. Wu C., *et al*. "Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China". *JAMA Internal Medicine* (2020).

32. Paules CI., *et al*. "Coronavirus Infections-More Than Just the Common Cold". *JAMA - The Journal of the American Medical Association* 323.8 (2020): 707-708.

33. Sociedade Brasileira de Pediatria (SBP). COVID-19 em crianças: envolvimento respiratório (2020).

34. Lana RM., *et al.* "The novel coronavirus (SARS-CoV-2) emergency and the role of timely and effective national health surveillance". *Cad Saúde Pública* 36.3 (2020): e00019620.

35. Ministério da Saúde. Biblioteca Virtual em Saúde. Qual a diferença do Oseltamivir em relação aos antivirais usados para tratamento de Herpes e HIV? Qual o mecanismo de ação de cada um deles? (2020).

36. Sociedade de Pediatria de São Paulo. Recomendação: uso de oseltamivir em pediatria (2020).

37. Fundação Oswaldo Cruz (Fiocruz). Antibióticos são eficazes na prevenção ou tratamento de Covid-19? (2020).

38. Ministério da Saúde. Síndrome gripal e síndrome respiratóriaaguda grave: classificação de risco e manejo do paciente (2020).

39. Ministério da Saúde. Protocolo de Manejo Clínico da Covid-19na Atenção Especializada". 1. edition. rev. – Brasília: Ministério da Saúde (2020).

40. Devesa Neto VSF. "A realidade da prescrição de oseltamivir em crianças internadas num hospital pediátrico terciário". *Disponível* (2020).

41. Williams JTB., *et al.* "Rising Oseltamivir Use Among Hospitalized Children in a Postpandemic Era". *Hospital Pediatrics* 6.3 (2016): 172-178.

42. Pitrez PMC and Pitrez JLB. "Acute upper respiratory tract infections - outpatient diagnosis and treatment". *The Journal of Pediatrics* 79.1 (2003): S77-S86.

43. Geleris., *et al*. "Observational study of hydroxychloroquine in hospitalized patients with Covid-19". *The New England Journal of Medicine* (2020).

44. Borba., *et al*. "Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial". *JAMA Network Open* 3 (2020): e208857.

45. Tang., *et al*. "Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial". *British Medical Journal* 369 (2020): m1849.

46. Gautret., *et al*. "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial". *The International Journal of Antimicrobial Agents* 56.1 (2020): 105949.

47. Rosenberg., *et al*. "Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State". *The Journal of the American Medical Association* 323.24 (2020): 2943-2502.

48. Sociedade Brasileira de Pediatria (SBP). Cloroquina/Hidroxicloroquina para o tratamento da COVID-19 em crianças e adolescentes: Parecer Científico da Sociedade Brasileira de Pediatria (2020).

49. Sociedade Brasileira de Imunologia (SBI). Cloroquina/Hidroxicloroquina para o tratamento da COVID-19 (2020).

50. Ministério da Saúde. "Protocolo clínico e diretrizes terapêuticas para o tratamento da hepatite viral crônica B e coinfecções". Brasília: MS (2011).

51. Stark GR., *et al.* "How cells respond to interferons". *Annual Review of Biochemistry* 67 (1998): 227-264.

52. Ministério da Saúde. Protocolo Clínico e Diretrizes Terapêuticas para o Tratamento da Hepatite Viral Crônica B e Coinfecções (2020).

53. Garib JR and Teixeira R. "Pulmonary manifestations associated with the current treatment of chronic hepatitis C". *Revista Médica de Minas Gerais* 23.2 (2013): 235-239.

54. Vieira AJ., *et al*. "Introdução da fitoterapia chinesa noSistema Único de Saude (SUS)". *Revista Saúde em Foco* (2018): 10.

55. Dong L., *et al*. "Effect of Lianhuaqingwen Capsules on Airway Inflammation in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease". *Hindawi* (2014): 11.

56. Ding Y., *et al*. "The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function BMC Complement". *Alternative Medicine* 17.1 (2017): 130.

57. Runfeng L., *et al*. "Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2)". *Pharmacological Research* 156 (2020): 104761.

58. Hu K., *et al*. "Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial". *Phytomedicine* 16 (2020): 153242.

59. Núcleo de Evidências da Coordenação de Evidências e Informações Estratégicas paraGestão em Saúde do Departamento de Ciência e Tecnologia da Secretaria de Ciência,Tecnologia, Inovação e Insumos Estratégicos em Saúde. Revisão rápida sobre alternativas terapêuticas paracoronavírus humano – Atualização (2020).

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