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Original Article

Evaluation of Changing Drug Preferences During the COVID-19 Pandemic in a Tertiary Childrens Hospital

Bir Üçüncü Basamak Çocuk Hastanesinde, COVID-19 Pandemisi Sırasında Değişen İlaç Tercihlerinin Değerlendirilmesi

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ABSTRACT

Objective: There is currently no drug that is effective against the coronavirus disease-2019 (COVID-19) and no consensus was present regarding the treatment. In this cross-sectional study, we aimed to evaluate the progress of the treatment process of patients with COVID-19 since the first day of pandemic in our country and the changes in the process.

Method: This single-center cross-sectional study was conducted from March 11 through November 30, 2020, in University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, a 400-bed tertiary care hospital in İzmir, Turkey. Treatment options in all hospitalized children with COVID-19 were evaluated.

Results: Evaluation of our clinical treatment algorithm from March to December, it was seen that the majority of the patients did not need any specific treatment and recovered only with supportive treatment. Because of the recommendations of the COVID-19 guidelines, no efficacy has been detected during the oseltamivir treatment and there was a significant decrease in use of azithromycin and hydroxychloroquine. Favipiravir is still the first choice of drug for patients with COVID-19.

Conclusion: World Health Organization, the Infectious Diseases Society of America, and Surviving Sepsis guidelines indicate that their investigational treatments should only be used in certain clinical trial setting. Supportive care is still the main therapeutic option in COVID-19.

Keywords: Antiviral drug, coronavirus disease-2019 (COVID-19), pandemic, favipiravir

ÖZ

Amaç: Günümüzde koronavirüs hastalığı-2019'a (COVİD-19) karşı kanıtlanmış etkili bir ilaç ve de tedavi konusunda fikir birliği yoktur. Bu nedenle, kesitsel çalışmada, ülkemizde pandeminin ilk gününden itibaren COVİD-19 hastalarının tedavi sürecinin ilerleyişini ve süreçteki değişiklikleri değerlendirmeyi amaçladık.

Yöntem: Bu tek merkezli kesitsel çalışma, 11 Mart-30 Kasım 2020 tarihleri arasında İzmir, Türkiye'de 400 yataklı üçüncü basamak bir hastane olan Sağlık Bilimleri Üniversitesi Dr. Behçet Uz Çocuk Hastalıkları ve Cerrahi Eğitim ve Araştırma Hastanesi'nde gerçekleştirildi. Hastanede yatan tüm COVİD-19'lu çocuklarda tedavi seçenekleri değerlendirildi.

Bulgular: Mart-Aralık ayları arasında klinik tedavi algoritmamız değerlendirildiğinde, hastaların çoğunluğunun herhangi bir spesifik tedaviye ihtiyaç duymadığı ve sadece destek tedavisi ile iyileştiği görüldü. COVİD-19 kılavuzlarının önerileri hızla güncellenmiş ve nihayetinde oseltamivir tedavisinin etkinliği olmadığı saptanmıştır. Bununla birlikte pandemi ilk günlerinden bu yana azitromisin ve hidroksiklorokin kullanımında belirgin azalma olmuştur. Favipiravir ise COVİD-19 hastaları için hala ilk ilaç seçimidir.

Sonuç: Kılavuzlarda, tüm tedavi alternatiflerinin yalnızca belirli klinik araştırma ortamlarında kullanılması gerektiğini göstermektedir. Destekleyici bakım, COVİD-19'da hala ana tedavi seçeneğidir.

Anahtar kelimeler: Antiviral ilaç, koronavirüs hastalığı-2019 (COVİD-19), pandemi, favipiravir

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INTRODUCTION

Since the beginning of the pandemic, coronavirus disease-2019 (COVID-19) has progressed in very different clinical courses in children. Children were reported to have lower number of symptoms compared to adults and the attributable mortality rates in the children are extremely lower compared to adults [1]. Currently, effective drug against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not available. Because of the changes in clinical findings over time and the detection of new symptoms, and demonstration of wide variance between countries in terms of treatment guidelines, these guidelines have been updated in time [2]. Lack of evidence concerning both the efficacy and possible harmful effects of these medications, and also the unfavourable risk - to - benefit ratio of supportive care as the primary management strategy used for most pediatric patients especially outside the setting of a clinical trial required urgent action [3]. On May 01, 2020, the Food and Drug Administration (FDA) issued an emergency use authorization for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease [4].

There is no consensus on the treatment for COVID-19 in children as well as adults and current management is still controversial. Many studies have reported that children with severe and critical COVID-19 were treated with supportive care alone, whereas numerous ongoing studies for adults are trying to determine whether any pharmacological treatment is available [5,6].

This cross-sectional study aimed to evaluate drug options used for the treatment of pediatric patients with COVID-19 for about a year from the onset of the pandemic, and the variability of this treatment process according to clinical experience.

MATERIALS and METHODS

This single-center cross-sectional study was conducted from March 11, 2020 through November 30, 2020, in pandemic clinics, which is a tertiary childcare hospital in İzmir, Turkey. All patients diagnosed with COVID-19 under the age of 18 were included in the study. Patients diagnosed with Multisystem Inflammatory Syndrome in Children were excluded from the study.

The patients were diagnosed as COVID-19 based on the presence of clinical characteristics consistent with COVID-19 in children, SARS-CoV-2 polymerase chain reaction (PCR) positivity detected in nasopharyngeal swab samples, and/or the presence of SARS-CoV-2 antibodies as of August 1, 2020 [7].

Data of the patients were collected from medical records, including information on demographic and clinical characteristics (age, gender, symptoms, medical history), underlying diseases or comorbidities (i.e., heart disease, chronic lung disease, developmental delay, hematological disease, epilepsy), the results of chest X-ray and thorax computerized tomography, the indications for the treatment applied, clinical outcomes with the admission date, the time elapsed from the disease onset to the confirmation of the diagnosis and length of the hospital stay.

Statistical Analysis

Collected data were analyzed with SPSS Software version 20 (IBM Corporation, Armonk, NY, USA). Categorical variables were analyzed using relative frequencies, while continuous variables using median or mean (depending on whether they show normal distribution) values. Categorical variables such as ratio of underlying disease, and ratio of pulmonary involvement were compared using Pearson χ^2 and Fisher's Exact tests. The significance level was taken as $p \leq 0.05$.

Study protocol was approved by the University of Health Sciences Turkey, İzmir Dr Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (decision no: 474, date: 17.12.20).

RESULTS

The study enrolled 301 hospitalized children with COVID-19 including 156 (51.8%) male, and 145 (48.2%) female patients with an overall mean age of 98.3±67.6 months (range 1 month to 17 years). Seventy-seven (25.6%) patients had, while majority of the patients (224/301, 74.4%) had not an underlying disease. The most common concomitant chronic medical conditions were neuro-developmental diseases (mental motor retardation, developmental delay, and cerebral palsy) (21/77, 27.2%), followed by asthma (9/77, 11.6%), epilepsy (8/77, 10.3%), and obesity (8/77, 10.3%). The most common underlying diseases were congenital heart diseases (n=7, 9%) and malignancy (n=7, 9%), followed by other rheumatologic diseases, hematologic diseases, and metabolic diseases (Table 1).

Pulmonary involvement was found in 80 (26.5%) of the 301 COVID-19 patients. Eighty-seven (28.9%) patients received any drug for COVID-19 according to

the national guideline, and the remaining patients were followed up without specific treatment. Twenty-four (31.2%) with, and 63 (28.1%) patients without underlying diseases were treated with antiviral agents, with a statistically significant intergroup difference regarding antiviral drug usage (p>0.05). Significantly higher number of (n=44: 53.8%) patients with pulmonary involvement used antiviral drug compared to the patients without (p<0.001).

The drugs administered during the pandemic included hydroxychloroquine (HCQ), oseltamivir, azithromycin, and favipiravir. Because of the varying clinical approaches, at the beginning of the pandemic oseltamivir was used only in three patients. Two of these patients were given oseltamivir in combination with the HCQ and azithromycin. Azithromycin was used in 23 (7.6%) patients. The use of azithromycin was at its peak during April (n=14/37: 37.8%) and May (n=5/33: 15%). Following April, these treatment strategies were discontinued in subsequent months due to changes in knowledge and experiences with COVID-19. Only one patient per month received azithromycin treatment in the months that followed. HCQ treatment was utilized in a total of 68 patients. Its use peaked in May (n=16/68: 23.5%), but gradually decreased in ongoing months and discontinued throughout the pandemic. During this period, use of favipiravir became prominent for patients older than 12 years of age in our clinical practice and two of 24 patients (8.3%) in September and 15 of the 82 patients (18.3%) in November were treated with favipiravir. Monthly distribution of specific antiviral therapies used is shown in Figure 1.

A total of 81 patients received antibiotic therapy for respiratory tract infections, the most commonly used antibiotics were 3rd generation cephalosporin (n=40 :13.2%), amoxicillin - clavulanate (n=32 :10.2%), and ertapenem (n=18 :6%). Considering the distribution of antibiotics by months the distribution rates were the highest in March (n=1/1 :100%) and April (n=18/37 :48.6%). There was also a decrease in the rate of antibiotic use in the following months.

Most of the patients (n=214 :71 %) were followed up without specific treatment for COVID-19. Consequently, the number of patients without any specific medications increased in the following months. While the rates of supplying nonspecific treatment ranged from 60% to 68% from March to August, the rates of patients without specific treatment increased to 81-86% in the final three months of the study (Figure 2).

DISCUSSION

In this study, our treatment experiences for the hospitalized children with COVID-19 were reviewed. While at the beginning of the COVID-19 pandemic, HCQ was used in 9-16% of the patients, this rate decreased dramatically during the subsequent months. Moreover, after the recommendation of favipiravir use for COVID-19 in September 2020 by the national and international guidelines, it was administered in 8.2% of the patients in November 2020. In addition, the rates of the patients followed up with only supportive treatment increased during the following months of the pandemic as a result of our clinical experiences accumulated during the course of the disease. Treatment approaches did not differ according to the concomitant diseases of the

Table 1. Clinical and demographic characteristics of 301 patients enrolled to the study

Characteristics and underlying medical conditions	Patients, n (%)
Age (months), mean	98.3±67.6 (1 month -17 years)
Female, n (%)	145 (48.2)
Comorbities, n=77	
Neurodevelopmental diseases, n (%)	21 (27.2)
Asthma, n (%)	9 (11.6)
Epilepsy, n (%)	8 (10.3)
Obesity, n (%)	8 (10.3)
Congenital heart diseases, n (%)	7 (9)
Malignency, n (%)	7 (9)
Rheumatological diseases, n (%)	4 (5.1)
Miscellaneous*, n (%)	13 (16.9)

*Including neutropenia, idiopatic thrombocytopenia, metabolic diseases, Down syndrome, psoriasis, immune deficiency, Becker's muscular dystrophy, type 1 diabetes mellitus

patients, while significantly higher number of patients with pulmonary involvement were treated with antiviral agents (p<0.001).

Today, there is still no targetted treatment for pediatric COVID-19 cases and experiences are ever changing. The Ministry of Health firstly published the guideline for pediatric patients on March 23, 2020 in Turkey [8] and the treatment algorithm in our clinic was planned according to this guideline. In the first six months of the pandemic, the number of hospitalized-patients was high due to the follow-up of the clinical findings and the uncertainty about the prognosis. Simultaneously, greater number of patients received higher doses of targeted drugs and

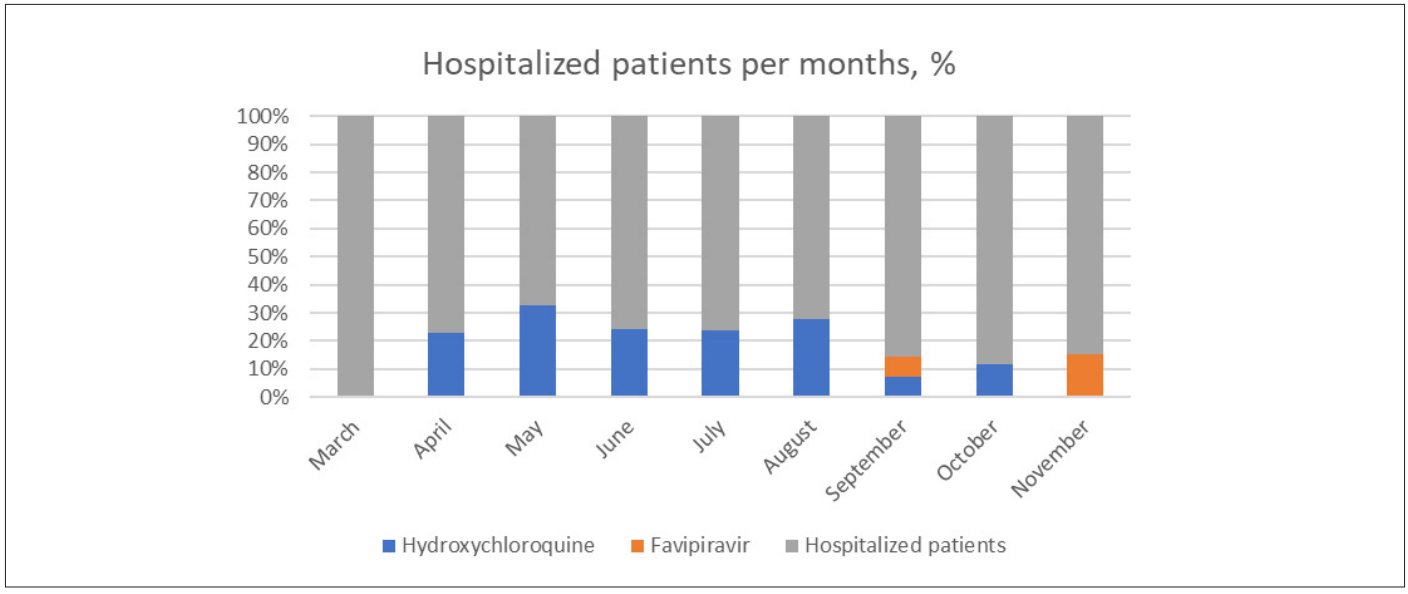

Figure 1. Monthly disease - specific therapies

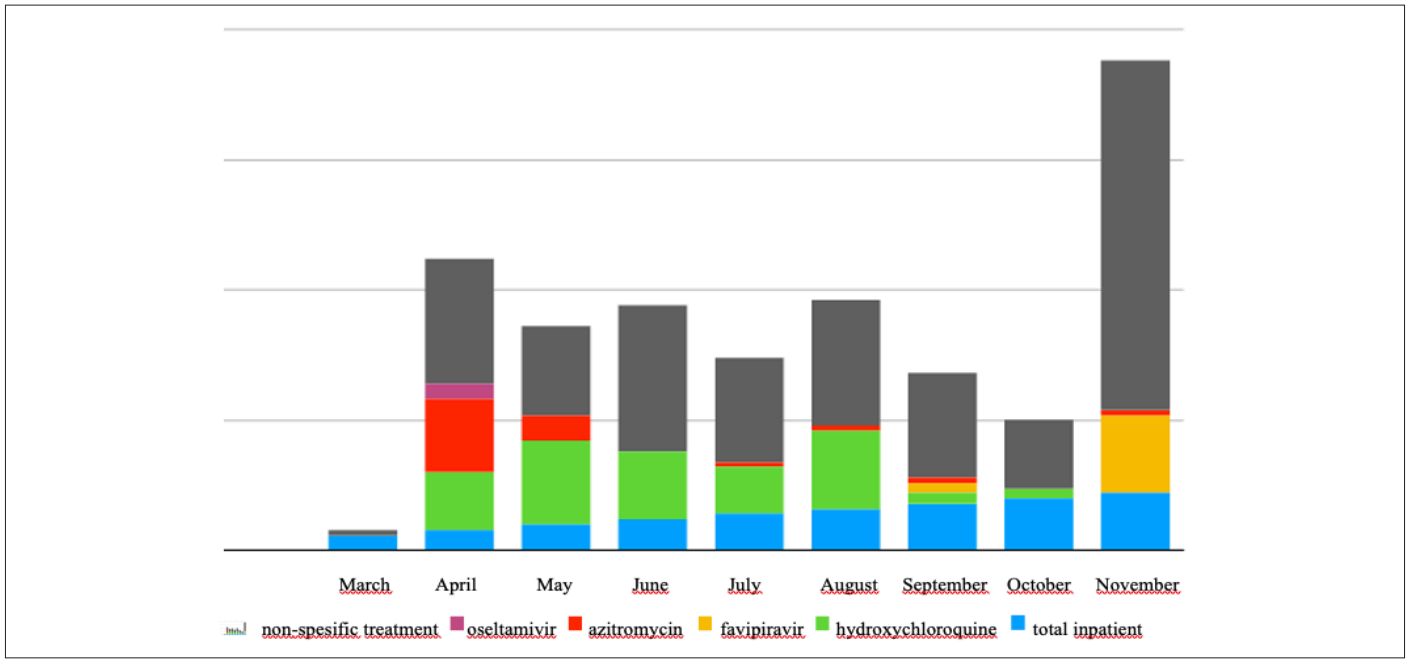

Figure 2. Rates of patients without specific treatment

drug combinations in accordance with guidelines. Our treatment approaches have evolved due to the rising number of patients and increased clinical experience. There was a significant decrease in the targeted drug used and the number of in-patients in the last three months according to the recent guidelines.

Treatment process for COVID-19 varies in different countries, and the the World Health Organization (WHO) has published several interim reports based on previous human coronavirus outbreaks [9]. In these temporary WHO guidelines, the COVID-19 treatment recommendation is mostly supportive and treatment decisions should be made on a case-by-case basis, such as starting antimicrobial treatment in selected cases [10].

The clinical manifestation of COVID-19 may be like other upper respiratory tract infections [3]. During the initial phase of pandemic, oseltamivir was administered in compliance with the guidelines, since COVID-19 could not be distinguished from influenza virus infection, increased incidence rates of co-infections with influenza and COVID-19 were reported [11]. The guideline of Turkish Ministry of Health published on April 2, 2020, recommended addition of oseltamivir to the treatment in cases where COVID-19 disease cannot be distinguished from seasonal influenza infection; and the drugs HCQ ± azithromycin, lopinavir/ritonavir were included in the treatment protocol. However, due to global studies, our guideline was updated periodically and lastly published on September 26, 2020 [12]. COVID-19 guideline released by the Ministry of Health for the treatment of pediatric patients was updated as HCQ, favipiravir, lopinavir/ritonavir. Since oseltamivir failed to be effective against COVID-19, it was excluded from the guidelines after the influenza session passed away [13].

In the early stages of the pandemic, HCQ was preferred in patients with widespread lung involvement at our center. Initially, The Infectious Diseases Society of America (IDSA) recommended the usage of chloroquine with or without azithromycin, lopinavir-ritonavir, tocilizumab, and convalescent plasma in the context of clinical studies [14], while advocating against azithromycin treatment with HCQ due to the increased risk of prolongation of the Q-T interval. In the following days, also azithromycin was removed from the current Ministry of Health treatment guidelines, and our practice [12].

While HCQ has antiviral and immunomodulatory efficacy, the benefits of its use for COVID-19 are still controversial in practice [15]. In the study of Gautret et al. [16], the efficacy of co-administration of HCQ and azithromycin was evaluated and it was emphasized that a higher rate of PCR negativity was detected on days 3 to 6 after HCQ treatment. In this study, the usage of azithromycin with HCQ was associated with more viral clearance in a short period of time than HCQ alone [16]. However, an observational study found no evidence of antiviral clearance with HCQ and azithromycin in 11 hospitalized patients and it was stated that QTc prolongation, which is a side effect of both drugs, may be seen at a higher rate [17].

In a randomized, double-blind, phase 2b study, Borba et al. [18] indicated the safety and efficacy of low/high HCQ dosage regimens in 81 patients with severe COVID-19 infection. While all patients received a combination of ceftriaxone and azithromycin, 89.6% of the patients received only oseltamivir. As a result of the study, it was found that mortality and complications as QT prolongation were more common in those receiving high-dose HCQ treatment. The combination of high-dose chloroquine, azithromycin, and oseltamivir might cause an increase in mortality rates [18]. According to the conclusions of these clinical studies and relevant publications, HCQ and azithromycin combination therapy was discontinued after April 2020.

Antiviral agents such as oseltamivir, ribavirin, remdesivir, lopinavir/ritonavir have been used to reduce viral load without any significant treatment benefit [19]. According to the WHO guideline published on December 17, 2020, children were not included in the randomized controlled trials for HCQ, lopinavir/ritonavir, and remdesivir [20]. However, remdesivir has been approved by the FDA for the treatment of suspected or laboratory-confirmed COVID-19 disease in adults and children who have been hospitalized with severe disease [7].

In the open-label comparative controlled study by Cai et al., [21] favipiravir was preferred due its faster viral clearance and improved chest computed tomography changes compared to lopinavir/ritonavir [21]. However, this was not a randomized and double-blinded study as most of the other studies in the literature. The efficacy of favipiravir against COVID-19 has not been proven in the other two randomized clinical trials [22,23] and studies on its efficacy are still ongoing. During the first 6 months of the pandemic, favipiravir, which is not approved for children under 12 years of age, has become a prominent treatment in our clinical practice since September 2020, after it was recommended in the international guidelines. However, WHO, IDSA, and Surviving Sepsis

guidelines generally agree that all of these investigational treatments should only be evaluated on a patient-by-patient basis [24,25].

Study Limitations

There are several limitations to our study. As a retrospective study, it has limitations when compared to randomized clinical trials, and it only included patients from one single center. Moreover, in the current study, treatment options were not evaluated according to clinical severity of COVID-19, and the concomitant chronic medical conditions of the patients. However, it should be emphasized that the study is one of the rare studies in which the changes in treatment strategies as a result of modifications in recommendations of guidelines during the ongoing pandemic and also the enhanced observations about the recently emerged disease of the current medical center were taken into consideration in pediatric patients with COVID-19.

CONCLUSION

In conclusion, based on our observations from the onset of the pandemic to December 2020, despite some of the proposed antiviral drugs, the majority of the children with COVID-19 did not get any treatment. Over the course of a year, our therapeutic approaches have changed considerably, but there is still a paradox about the specific treatment due to a lack of evidence and data coming from randomized studies. However, supportive care of pediatric cases is still the main therapeutic option as in the literature.

Ethics

Ethics Committee Approval: Study protocol was approved by the University of Health Sciences Turkey, İzmir Dr Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (decision no: 474, date: 17.12.20)

Informed Consent: Cross-sectional study.

Peer-review: Internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: E.C., E.K., E.B., Ş.Ş., M.Y.Ç., M.D., A.A.K., K.A., N.B., İ.D., Concept: E.C., Design: E.C., N.B., İ.D., Data Collection and/or Processing: E.C., E.K., E.B., Ş.Ş., M.Y.Ç., M.D., A.A.K., K.A., Analysis and/or Interpretation: E.C., N.B., İ.D., Literature Search: E.C., E.K., E.B., Ş.Ş., M.Y.Ç., M.D., A.A.K., K.A., Writing: E.C., N.B., İ.D.

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REFERENCES

1. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109(6):1088-95. doi: 10.1111/apa.15270.
2. Esposito S, Noviello S, Pagliano P. Update on treatment of COVID-19: ongoing studies between promising and disappointing results. Infez Med. 2020;28(2):198-211. Available at: https://www.infezmed.it/media/journal/Vol_28_2_2020_10.pdf
3. Chiotos K, Hayes M, Kimberlin DW, Jones SB, James SH, Pinninti SG, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. J Pediatric Infect Dis Soc. 2020;9(6):701-15. doi: 10.1093/jpids/piaa045.
4. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment
5. National Institutes of Health. "Coronavirus disease 2019 (COVID-19) treatment guidelines." (2020). Available at: https://www.covid19treatmentguidelines.nih.gov/ on 11/24/2020
6. Meo SA, Klonoff DC, Akram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. Eur Rev Med Pharmacol Sci. 2020;24(8):4539-47. doi: 10.26355/eurrev_202004_21038.
7. Interim Guidelines for COVID-19 Antibody Testing. Interim Guidelines for COVID-19 Antibody Testing in Clinical and Public Health Settings. Updated Aug. 1, 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html
8. Turkish Ministry Of Health Guideline. Available from: https://www.ekmud.org.tr/files/uploads/files/Saglik-Bakanligi-COVID-19-rehberi-23032020.pdf
9. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance; 2020. Available from: https://apps.who.int/iris/handle/10665/331446
10. Tobaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA, et al. Therapeutic Management of COVID-19 Patients: A systematic review. Infection Prev Pract. 2020;2(3):100061. doi: 10.1016/j.infpip.2020.100061.
11. Turkish Ministry of Health Guideline. Available from: https://www.ekmud.org.tr/files/uploads/files/COVID19-%20HastaYonetimi-Tedavisi.pdf?1
12. Turkish Ministry of Health Guideline. Available from: https://www.ekmud.org.tr/files/uploads/files/covid-19-immun%20plazma%20rehberi-v5-26_10_2020.pdf
13. Srinivas P, Sacha GL, Koval C. Antivirals for COVID-19. Cleve Clin J Med. 2020. https://doi.org/10.3949/ccjm.87a.ccc030
14. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr. 2020;16:223-31. https://doi.org/10.1007/s12519-020-00343-7

15. Dragojevic Simic V, Miljkovic M, Stamenkovic D, Vekic B, Ratkovic N, Simic R, et al. An overview of antiviral strategies for coronavirus 2 (SARS-CoV-2) infection with special reference to antimalarial drugs chloroquine and hydroxychloroquine. Int J Clin Pract. 2021;75(3):e13825. doi: 10.1111/ijcp.13825.

16. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949. doi:10.1016/j.ijantimicag.2020.105949

17. Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with Severe COVID-19 infection. Med Mal Infect. 2020;50(4):384. doi: 10.1016/j.medmal.2020.03.006.

18. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, 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 Netw Open. 2020;3(4):e208857. https://doi.org/10.1001/jamanetwor kopen.2020.8857.

19. Carlotti APCP, Carvalho WB, Johnston C, Rodriguez IS, Delgado AF. COVID-19 Diagnostic and Management Protocol for Pediatric Patients. Clinics (Sao Paulo). 2020;75:e1894. doi: 10.6061/clinics/2020/e1894.

20. Agarwal A, Rochwerg B, Lamontagne F, Siemieniuk RA, Agoritsas T, Askie L. A living WHO guideline on drugs for covid-19. BMJ. 2020;370:m3379. doi: 10.1136/bmj.m3379.

21. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing). 2020;6(10):1192-8. doi: 10.1016/j.eng.2020.03.007.

22. Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. Clinical outcomes and plasma concentrations of BaloxavirMarboxil and Favipiravir in COVID-19 patients: an exploratory randomized,controlled trial. Eur J Pharm Sci. 2021;157:105631.

23. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. 2020. http://dx.doi.org/10.1101/2020.03.17.20037432.

24. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America guidelines on the treatment and Management of Patients with COVID-19. 2020;ciaa478. doi: 10.1093/cid/ciaa478.

25. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis campaign: guidelines on the Management of Critically ill Adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020;48(6):e440-69. https://doi.org/10.1097/CCM.0000000000004363.