sciencedirect.com

Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis

32-40 minutes

Abstract

Background

For the past few months, HMOs have faced crowded emergency rooms and insufficient hospital and intensive-care-unit beds, all from the worst pandemic of this century, COVID-19.

Methods

In a large HMO in Brazil, our approach was to allow treating physicians to prescribe antiviral medications immediately at presentation, and prednisone starting on day-6 of symptoms to treat pulmonary inflammation. We implemented this COVID-19

protocol for outpatients and studied 717 consecutive SARS-CoV-2-positive patients age 40 years or older presenting at our emergency rooms.

Results

Use of hydroxychloroquine (HCQ), prednisone or both significantly reduced hospitalization risk by 50–60%. Ivermectin, azithromycin and oseltamivir did not substantially reduce risk further. Hospitalization risk was doubled for people with type-2 diabetes or obesity, increased by two-thirds for people with heart disease, and by 75% for each decade of age over age 40. Similar magnitudes of reduced risk with HCQ and prednisone use were seen for mortality risk, though were not significant because of only 11 deaths among the 717 patients. No cardiac arrhythmias requiring medication termination were observed for any of the medications.

Conclusions

This work adds to the growing literature of studies that have found substantial benefit for use of HCQ combined with other agents in the early outpatient treatment of COVID-19, and adds the possibility of steroid use to enhance treatment efficacy.

- Previous
- Next

Abbreviations

HMO

Health Maintenance Organization

1. Introduction

Mankind has been facing one of the greatest challenges of the XXI century: a pandemic [1] caused by a new virus, SARS-CoV-2, thought to be transmitted by airborne particles and droplets and contact with contaminated surfaces or objects [2]. Clinical manifestations of coronavirus disease 2019 (COVID-19) patients

range from asymptomatic to mild non-specific signs and symptoms to severe pneumonia with organ function damage and eventual mortality [3,4]. There is a clear need to try to stop disease progression as early in the disease process as possible. Infected patients with comorbidities such as heart failure, type-2 diabetes, asthma or chronic obstructive pulmonary disease and obesity, and patients over sixty years of age are at substantially higher risk to develop severe disease and tend to have higher risks of death [[5], [6], [7]]. Many drugs have been tried in hospitalized patients, with largely discordant results [[8], [9], [10], [11]]. Randomized double-blind controlled trials demonstrating benefit or lack of benefit of drugs in high-risk outpatients will not be available any time soon, as many clinical sites are still recruiting patients [12]. Early outpatient illness is very different than hospitalized severe disease and treatment therefore will differ between these two distinct groups. Relatively little is established about utility of medications in early outpatient treatment. Currently [13,14] it is understood that COVID-19 is at least a four-phase illness: phase 1 is viral replication, followed by pulmonary inflammation in phase 2, “cytokine storm” and acute respiratory distress in phase 3, and disseminated multi-organ involvement in phase 4. For treatment at the beginning of the illness, there are indications that chloroquine and especially hydroxychloroquine (HCQ) may be beneficial [[15], [16], [17], [18]], but no specific antiviral medications have demonstrated proven efficacy as yet [19,20]. Recently, the Brazil Federal Committee for Medicine has approved the prescription of chloroquine and HCQ for clinically suspected COVID-19 patients at the physician’s discretion with informed consent [21] and the Health Ministry has also endorsed the use of these medications [22]. Brazil has the highest rate in South America in the ranking of COVID-19 deaths, with more than 4.2 million people infected in the country [23] in circumstances of a large population still to be affected and with economic difficulties resulting in inadequate social distancing. Data over March–May from the Federal Health Ministry [24] show that more than 90% of hospitalized patients with severe respiratory distress who were tested were positive for SARS-CoV-2, with less than 5% detected with influenza. Therefore, we assumed in clinical

practice that most patients coming to the emergency room with influenza-like symptoms would have COVID-19. With all that, we developed a protocol for early recognition and treatment of high-risk patients (in our population, age greater than 40 years because of generally poorer health standards, or with comorbidities) who would come to our outpatient network of emergency rooms with influenza-like symptoms: fever, cough, myalgia and headache, among others, and receive early treatment, provided to patients at the first doctor visit, using physician discretion from among HCQ, azithromycin, ivermectin, oseltamivir, zinc sulfate, nitazoxanide and prednisone (the last starting on day-6 of symptoms). We evaluate here risks of subsequent hospitalization based upon outpatient use of these various medications.

2. Methods

Patient data were analyzed from electronic charts of health maintenance organization (HMO) Hapvida Saúde, the largest Brazilian HMO with 6 million members spread over five regions of the country. Data were collected after informed consent and Institutional Ethics Committee (4.087.824 CEP-University Fortaleza UNIFOR) approval for this study. To-date, during the pandemic, more than 300 000 monthly emergency room (ER) consults have occurred. Patients were all seen at the ERs of the widespread country hospital network and admitted if indicated. At the beginning of the pandemic in Brazil, late March–April 2020, the north and northeast cities were more affected, with a great number of ER consults and hospital and intensive-care-unit admissions. A protocol for early treatment of COVID-19 was developed by a team of senior HMO medical staff and started in early May; it included clinical recognition of the commonly described main COVID-19 signs and symptoms, and protocol criteria assessment for hospital admission vs outpatient care. Patients coming with influenza-like symptoms such as fever, sore throat, myalgia, arthralgia or coryza would enter the COVID-19 protocol. Patients presenting with hypoxia, defined as the need of oxygen to maintain an oxygen saturation greater than 92%, respiratory rate of or greater than 24 respirations/minute, hypotension defined as systolic pressure less

than 90 mm Hg or diastolic pressure less than 60 mm Hg, or with confusion or extreme lethargy were immediately admitted to the hospital. The remaining patients over age 40 or with comorbidities were defined as high-risk and treated as outpatients. The protocol specifics were chosen by the attending physician, and all of its steps were monitored for quality assurance. The protocol was largely automated through on-screen suggestions and physician choice boxes leading to successive screens, medication prescription choices, etc. After discharge from the ER, patients received paper charts instructing them on isolation, symptoms to expect and medications to use, and QR codes for telemedicine, chat or phone consults. Patients were instructed to return if symptoms of dyspnea, confusion or lethargy occurred. Telemedicine was also always available to HMO patients on the HMO website. For discharged patients, the COVID-19 protocol included (all as oral medications), as chosen by doctors and patients: HCQ as first-line treatment, if used (400 mg bid day 1, 400 mg qd days 2–5), prednisone (1 mg/kg qd x 5 days, maximum 80 mg/day, no taper), azithromycin (500 mg qd x 5 days), ivermectin (12 mg qd x 2 days), plus symptom relievers. Zinc sulfate, oseltamivir and nitazoxanide were also available to be prescribed but were used infrequently. As doctors quickly found that most of the prescribed HCQ was not available at common drugstores, if prescribed it was decided to offer the drug free of charge to all patients who only had to sign informed consent to receive it. Data were collected from the HMO database for consecutive patients registered from May 11th to June 3rd, 2020. We selected all patients 40 years and older who tested positive for SARS-CoV-2 using a real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens [25]. To be clear, while all relevant patients with clinically likely COVID-19 were offered treatment by the HMO, for the present report, we analyzed all those patients whose infections were subsequently confirmed by laboratory assay. The collected data included patient characteristics and comorbidities, age, gender, history of type-2 diabetes, hypertension, cardiac illness, pulmonary disease, other conditions, and facts of hospital

admission and death. Collected data were analyzed with multivariate unconditional logistic regression models to determine associations with medication use as well as other risk factors for hospital admission and death. Age (in decades) and presentation delay (days) were treated as continuous covariates whereas all other variables were dichotomous. In addition to the medications, all of the presentation characteristics and comorbidities in Table 1 were examined for statistical significance and for confounding adjustment. Death outcomes were those considered to be due to complications associated with COVID-19. A two-sided p-value less than 0.05 was considered statistically significant.

Table 1. Characteristics of tested-positive Covid-19 patients treated under the new Hapvida Brazil HMO protocol.

	Given none of the medications (n = 122)	**Given neither HCQ nor Prednisone (n = 244)**	**Given both HCQ and Prednisone (n = 159)**	**Given HCQ Only (n = 175)**	**Given Prednisone Only (n = 139)**	**F (**
Age (mean, years) (10–90 %iles)	51.3 (41–70)	52.0 (41–71)	50.4 (41–60)	50.3 (41–61)	48.8 (4–59)	5 (
Presentation delay[a] (mean, days) (10–90 %iles)	4.1 (1–8)	4.2 (1–8)	4.5 (1–8)	4.4 (1–9)	5.6 (1–10)	4
Sex (% Female)	59.0	54.5	45.9	48.0	59.0	5
Hospitalized (%)	27.0	24.2	10.1	14.3	10.1	1
Ventilated (%)	4.9	3.3	2.5	1.1	3.6	2
Died (%)	3.3	2.9	0.6	0.6	1.4	1
Cough (%)	69.7	67.2	73.0	74.9	66.9	7

	Given none of the medications (n = 122)	Given neither HCQ nor Prednisone (n = 244)	Given both HCQ and Prednisone (n = 159)	Given HCQ Only (n = 175)	Given Prednisone Only (n = 139)	F (r
Fever (%)	52.5	59.4	66.7	65.7	61.9	6
Myalgia (%)	37.7	37.7	44.7	53.1	36.0	4
Sore Throat (%)	17.2	19.3	23.9	29.1	26.6	2
Headache (%)	36.1	35.7	41.5	39.4	41.0	3
Diarrhea (%)	7.4	7.4	8.2	11.4	11.5	9
Shortness of Breath (%)	26.2	30.3	28.9	28.0	20.9	2
Type 2 Diabetes Mellitus (%)	14.8	18.4	15.1	21.7	11.5	1
Obesity (BMI>30, %)	10.7	7.8	6.9	20.6	5.0	1
Heart Disease (%)	21.3	29.9	31.4	41.1	18.8	3
Pulmonary Disease (%)	6.6	4.5	1.3	4.0	3.6	3
Given Azithromycin (%)	0.0	43.4	50.3	65.7	58.3	5
Given Ivermectin (%)	0.0	24.2	77.4	42.9	59.7	4

	Given none of the medications (n = 122)	Given neither HCQ nor Prednisone (n = 244)	Given both HCQ and Prednisone (n = 159)	Given HCQ Only (n = 175)	Given Prednisone Only (n = 139)	F (I
Given Oseltamivir (%)	0.0	9.0	7.5	26.3	7.9	1

a

Number of patients with data on date of start of symptoms, 113, 222, 152, 168, 134 and 676 in the respective columns.

3. Results

From May to June, 24 927 patients were included in the COVID-19 protocol, 56% from the northeast Brazil states of Ceará, Bahia and Pernambuco. Seven hundred seventy-two patients (3.1%) were admitted to the hospital and 52 died (6.7% of those hospitalized, 0.2% of the whole cohort). Within the cohort of 24 927 patients, because of scarcity of the tests and without selection by disease severity, 3307 had testing for SARS-CoV-2 performed; 1570 were age 40 years or over and 715 (45%) of these patients had positive RT-PCR assays for SARS-CoV-2. We also included 2 patients who had positive SARS-CoV-2 serology (Table 1). Three hundred seventy-two patients were female (52%); the mean age was 50.6 years (range 40–93 years). The average delay from the start of symptoms to ER visit was 4.6 days. Common presenting symptoms included shortness of breath (198, 28%), cough (504, 70%), fever (452, 63%), myalgia (306, 43%) and sore throat (173, 24%); 221 (31%) patients had histories of cardiovascular disease, 123 (17%) had diabetes type 2, 73 (10%) were obese and 25 (3.5%) had chronic pulmonary disease. There were 114 hospital admissions (16%) and of these, 19 (17%) patients required mechanical ventilation and 11 (9.6%) patients died. The median time between start of symptoms and hospital admission was eight days; between hospital admission and death was seven days. One hundred

twenty-two of the 717 patients received none of the medications, and 33 (27%) of them required hospitalization.

Associations with fact of eventual hospitalization are given in Table 2. The multivariate logistic regression model presented in the table shows that age, obesity (BMI > 30) and dyspnea were very substantial risk factors for hospital admission. Each additional decade of age over age 40 multiplied the risk of admission by a factor of 1.75. Use of prednisone and use of HCQ were both associated with significantly reduced risk, and both drugs used together seemed to perform slightly better than either one alone. When the analysis was restricted to exclude patients hospitalized within five days, thus not eligible to receive prednisone, the results were essentially unchanged. History of pulmonary disease, presentation delay, or presentations with cough, myalgias, sore throat, headache or diarrhea were not associated with risk of hospitalization. Presentation with fever, however, had OR = 1.93 (95%CI 1.18–3.14), p = .0085, but did not change the associations seen in Table 2, and with consideration for multiple comparisons of the various patient characteristics, may not be statistically significant. Based on the model of Table 2, we also examined use of azithromycin, OR = 0.93 (95%CI 0.60–1.45) and use of ivermectin, OR = 1.17 (95%CI 0.72–1.90). Zinc prescription was not given on its own and where prescribed was highly correlated with other medication use and had little independent information for estimation of its own association in the adjusted model. When the model of Table 2 was performed including only individuals who had a history of at least one condition of obesity, diabetes or heart disease (73 hospitalized patients and 232 not hospitalized), the associations with the medications largely remained: for both HCQ + prednisone, OR = 0.33 (95%CI 0.14–0.81), p = .015; for HCQ alone, OR = 0.41 (95%CI 0.20–0.83), p = .013; and for prednisone alone, OR = 0.75 (95%CI 0.29–1.93), p = .55. We also examined the model of Table 2 for the three medication exposures vs receipt of no medications at all. For both HCQ + prednisone, OR = 0.29 (95%CI 0.14–0.58), p = .00053; for HCQ alone, OR = 0.32 (95%CI 0.17–0.63), p = .00081; and for prednisone alone, OR = 0.37 (95%CI 0.18–0.77), p = .0082. Similar

magnitudes of association as these were seen for these medications among all 717 subjects for death as the outcome, but the small numbers of deaths precluded statistical significance of these associations. However, the strongest predictors of mortality overall were obesity, OR = 13.0 (95%CI 2.35–72.3), p = .0033, and diabetes, OR = 4.65 (95%CI 1.20–18.1), p = .027. We observed no cardiac arrhythmia events requiring medication termination for any of the medications used in the 717 patients that we analyzed, and no deaths attributable to such arrhythmias.

Table 2. Multivariate logistic regression risk factors for hospitalization of tested-positive Covid-19 outpatients at Hapvida HMO, Brazil.

Exposure	Regression Exposure Units	Average of or Number Not Hospitalized (n = 603)	Average of or Number Hospitalized (n = 114)	OR (95% Confidence Interval)	*P*-val
Age at diagnosis (continuous)	Per decade	49.4	57.1	1.75 (1.42–2.16)	$10^{-6.}$
Gender	Female vs Male	314 vs 289	58 vs 56	0.87 (0.56–1.35)	.52
Dyspnea at diagnosis	Yes vs No	148 vs 455	50 vs 64	2.07 (1.32–3.26)	.0017
Obesity	Yes vs No	55 vs 548	18 vs 96	2.38 (1.24–4.57)	.0090
Diabetes Mellitus Type 2	Yes vs No	83 vs 520	40 vs 74	2.11 (1.26–3.52)	.0045
Heart Disease	Yes vs No	162 vs 441	59 vs 55	1.67 (1.03–2.70)	.037
Prescription of both hydroxychloroquine and prednisone	Both vs not both	143 vs 460	16 vs 98	0.40 (0.21–0.75)	.0042

Exposure	Regression Exposure Units	Average of or Number Not Hospitalized (n = 603)	Average of or Number Hospitalized (n = 114)	OR (95% Confidence Interval)	*P*-val
Prescription of hydroxychloroquine only	Yes vs no	150 vs 453	25 vs 89	0.45 (0.25–0.80)	.0065
Prescription of prednisone only	Yes vs no	125 vs 478	14 vs 100	0.51 (0.26–0.99)	.049

4. Discussion

SARS-CoV-2 will cause greater mortality than any recent contemporary pandemic; only when the pandemic ends it will be possible to assess the full health, social and economic impact of this global disaster [[26], [27], [28]]. Preliminary data show that in developed countries, the impact will be huge. But in developing countries, where public health systems already face great challenges to provide basic health care to all in need, the impact will be several times greater [[26], [27], [28]]. These problems will not be solved anytime soon. In the midst of the SARS-CoV-2 pandemic, a feasible approach, with inexpensive drugs, relying on syndromic signs and symptoms rather than scarce laboratory tests may help many patients and will be even more important in developing countries. Around the world there are already over 28 million confirmed COVID-19 cases [29]. Brazil has the third-largest number, with 4.2 million cases and 128 000 deaths as of September 9th [29]. If this trend continues, in about six months, Brazil will have the worldwide largest number of deaths of any country.

In March 2020, the World Health Organization recommended the use of medications oseltamivir and antibiotics [30]. On March 28, 2020, the FDA issued an emergency use authorization for remdesivir and HCQ for patients in both clinical trials and with severe hospitalized disease [31]. Since then, pharmacological

treatments have been controversial. On June 15 the FDA retracted its earlier authorization and on July 1 posted warnings about its use, leaving HCQ outpatient use not supported [32]. Countries such as China and India have issued guidelines supporting the use of chloroquine or HCQ in COVID-19 [33,34]. Evidence of the real-world unimportance of arrhythmia and other cardiovascular adverse-event endpoints of HCQ and HCQ + AZ use is given in the large Oxford-based record-linkage study [35] and in a study of 40% of the English population [36]. Understanding the pathophysiology of COVID-19 in the different clinical stages of the disease is important, as treatments will change according to progression of the disease [13]. Our study showed that HCQ alone, prednisone alone, and HCQ plus prednisone did better than standard treatment for early stage COVID-19. It may be that the corticosteroid benefit involves low levels of type I and III interferons juxtaposed to elevated chemokines and high expressions of IL-6. Reduced initial innate antiviral defenses allow the virus to multiply, followed after a few days by relatively excess inflammatory cytokine production, allowing for steroids to reduce the latter in the early features of COVID-19, before appreciable pneumonia has occurred [37]. Hydroxychloroquine has a number of suggested beneficial actions for early COVID-19, not least of which is its non-immunosuppressive immunomodulatory activity [38].

Because all treatments have costs and benefits, treating all high-risk patients early would take a major effort from Brazil's Universal Public System (SUS) and its private HMOs, but would be much less expensive than hospital-based inpatient treatment, which would probably be impossible on the scale needed. Our study showed that about 10% of high-risk outpatients over age 40 treated with prednisone still required hospitalization, which is substantially better than the 24% among untreated patients, thus even this treatment plan could create a large hospital-bed demand. However, we found that even in hospital, these treated patients do better and their mortality is much lower.

In an ideal world, large randomized double-blinded controlled clinical trials establish evidence, but take time to complete and

many are not large enough for the randomization to be sufficiently effective in reducing biases. To-date, treatment protocols have proposed drugs with antiviral activity, and with anti-inflammatory responses, such as therapeutic regimens of IFN-α+lopinavir/ritonavir and IFN-α+lopinavir/ritonavir + ribavirin, among others. While cost-effectiveness of these regimens have been challenged, HCQ is generic and has been prescribed for malaria for decades, as it has antiviral and anti-inflammatory properties. On March 27th, 2020 the Brazilian Federal Health Authority issued a note saying that it would treat severely ill patients in the Public System with HCQ [39]. On May 20th, the same authority issued another note that HCQ would be available for physicians to prescribe for outpatients and mild cases, according to symptoms and severity [22]. Prednisone is also generic and inexpensive and has been used for many decades and does not interact adversely with HCQ.

Our results demonstrate a positive benefit of HCQ and prednisone in decreasing hospital admissions in a high-risk population over 40 years of age with RT-PCR-positive SARS-CoV-2 infection when started at first doctor visit. A high-risk outpatient benefit of HCQ use has been summarized elsewhere [35] but to our knowledge this is the first time that efficacy of outpatient prednisone use has been reported. Use of these medications also showed some evidence of reduced mortality in the study group, and larger studies of mortality will be needed to validate this finding. We observed that outpatient hospitalizations of the larger group of suspected COVID-19 ER patients, from the same HMO database before vs after the protocol started, March–April vs May, decreased significantly, 23% vs 9%, and mortality declined from 1.75% to 1.39%. For May, our HMO data also show that the mortality was less than COVID-19 mortality for Brazil as a whole.

Our study has several limitations. This is a retrospective, chart-based study, and even though our initial sample of patients was large, with almost 25 000 patients, few of these patients were tested due to the scarcity of RT-PCR tests. Then, we chose to study only tested-positive SARS-CoV-2 patients to make sure we were

dealing with confirmed cases of COVID-19. Limiting analyses to patients greater than 40 years of age further reduced our sample size. Nevertheless, our experience of approaching and treating patients with influenza-like symptoms in this era of pandemic SARS-CoV-2 is useful and more generally applicable. In one State Hospital Network of the cohort this spring, more than 90% of patients admitted to the hospital with appreciable respiratory distress had positive RT-PCR for SARS-CoV-2 [40], so it seems reasonable to infer that it would be similar for patients with influenza-like illness presenting at the emergency room. Also, our study involved a range of treatment medications assigned by HMO physicians using their clinical judgements, rather than mandated by study design. Clinical treatment decisions allow for the possibility that sicker patients get more or more aggressive treatments, creating the potential of confounding by indication. The comorbidity distributions of the various treatments as shown in Table 1 suggest that except for shortness of breath, patients not treated with HCQ or prednisone may have been slightly less symptomatic than treated patients. However, this would if anything have tended to reduce the magnitude of risk lowering that we found for these medications toward the null. A pattern of chronic comorbidity differences is not apparent in the table; nevertheless, our results were adjusted for those comorbidities where associations with risk of hospitalization were observed (Table 2). In spite of the aforementioned, our study was large enough to have observed statistically significant results and was based on actual clinical conditions and data recorded in active clinical charts, to enable reasonable inference about lack of reporting biases in the analyzed data.

Our analyses thus show that it is possible to give HCQ with companion medications in an early stage protocol that proves to be safe, and warnings about cardiac arrhythmia adverse events are unnecessary unless significant contraindications are known. Treatment-failure mortality, while small, is still the major concern of patient management. Our new protocol is continuing in clinical practice in our HMO, and we hope for it to be more generally applied across the rest of Brazil as quickly as possible.

5. Conclusion

We found early outpatient use of HCQ and prednisone, both as individual prescriptions and used together, to lower the risk of hospitalization in symptomatic high-risk COVID-19 patients presenting for primary care at the emergency rooms of our large HMO in Brazil. Other than the small numbers of treatment failure, no potentially life-threatening adverse events were recorded with medication treatment. These medications were found to be safe and beneficial for early high-risk outpatient treatment of COVID-19.

Financial support

None.

CRediT authorship contribution statement

Silvia Nunes Szente Fonseca: Conceptualization, Investigation, Resources, Data curation, Writing - original draft, Project administration. **Anastasio de Queiroz Sousa:** Investigation, Resources, Data curation, Writing - review & editing. **Alexandre Giandoni Wolkoff:** Conceptualization, Investigation, Resources, Data curation, Writing - review & editing, Project administration. **Marcelo Sampaio Moreira:** Investigation, Resources, Data curation, Writing - review & editing. **Bruno Castro Pinto:** Investigation, Resources, Data curation, Writing - review & editing. **Christianne Fernandes Valente Takeda:** Investigation, Resources, Data curation, Writing - review & editing. **Eduardo Rebouças:** Investigation, Resources, Data curation, Writing - review & editing. **Ana Paula Vasconcellos Abdon:** Investigation, Resources, Data curation, Writing - review & editing. **Anderson L.A. Nascimento:** Investigation, Resources, Data curation, Writing - review & editing. **Harvey A. Risch:** Conceptualization, Investigation, Data curation, Formal analysis, Writing - review & editing.

Declaration of competing interest

Dr. Risch acknowledges past advisory consulting work with two of

the more than 50 manufacturers of the various medications analyzed herein. This past work was not related to any of these medications and was completed more than two years ago. He has no ongoing, planned or projected relationships with any of these companies, nor any other potential conflicts-of-interest to disclose. None of the other authors have any potential conflicts of interest to disclose.

Acknowledgements

The authors wish to acknowledge the valuable contributions of Ana Briza Campelo Mourão Leopoldo, Caroline de Alencar Santana Monteiro, Jose Amilton Matos Cavalcante Júnior, Rudy Diavila Bingana, Thuliermes Lopes Pamplona, Jamile Nayara da Silva, Fábio Henrique Rodrigues de Souza, José Cristian Brandão Mendes, Iury Handric da Penha Teixeira, Alexmar Matos Queiroz, Bruno Bezerra M. Cavalcante, Francisco Jadson Franco Moreira, Antonio Jefferson Ribeiro Soares, Maria Rejane Maia Pinheiro de Abreu, Alex Jones Flores Cassenote, Tibor Schuster and Alain Benvenuti. Special thanks to Jorge Pinheiro Koren de Lima, MD, and Candido Pinheiro Koren de Lima, MD, for exceptional support and decisive actions for COVID-19 pandemic preparedness.

References

[1]

Who**WHO/Europe | Coronavirus disease (COVID-19) outbreak - WHO announces COVID-19 outbreak a pandemic [Internet]**

[2]

Cdc**Interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings [internet]. Coronavirus disease 2019 (COVID-19)**

[3]

H. Ge, X. Wang, X. Yuan, G. Xiao, C. Wang, T. Deng, *et al.***The epidemiology and clinical information about COVID-19**

Eur J Clin Microbiol Infect Dis, 39 (2020), pp. 1011-1019

[4]

W. Guan, Z. Ni, Y. Hu, W. Liang, C. Ou, J. He, *et al.***Clinical characteristics of coronavirus disease 2019 in China**

N Engl J Med, 382 (18) (2020), pp. 1708-1720

[5]

S. Bialek, E. Boundy, V. Bowen, N. Chow, A. Cohn, N. Dowling, *et al.***Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020**

MMWR Morb Mortal Wkly Rep, 69 (2020), pp. 343-346

[6]

Z. Wu, J.M. McGoogan**Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention**

J Am Med Assoc, 323 (2020), pp. 1239-1242

[7]

C. Wu, X. Chen, Y. Cai, J. Xia, X. Zhou, S. Xu, *et al.***Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in wuhan, China**

[8]

P. Gautret, J.-C. Lagier, P. Parola, V.T. Hoang, L. Meddeb, M. Mailhe, *et al.***Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial**

[9]

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, *et al.***Compassionate use of remdesivir for patients with severe covid-19**

N Engl J Med, 382 (2020), pp. 2327-2336

[10]

L.R. Baden, E.J. Rubin**Covid-19 - the search for effective therapy**

N Engl J Med, 382 (2020), pp. 1851-1852

[11]

J.M. Sanders, M.L. Monogue, T.Z. Jodlowski, J.B. Cutrell**Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review**

J Am Med Assoc, 323 (2020), pp. 1824-1836

[12]

ClinicalTrials.gov [internet]. Search of: COVID-19 - list results

Downloaded June, 15 (2020)

[13]

H.K. Siddiqi, M.R. Mehra**COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal**

J Heart Lung Transplant, 39 (2020), pp. 405-407

[14]

J.J.H. Park, E.H. Decloedt, C.R. Rayner, M. Cotton, E.J. Mills**Clinical trials of disease stages in COVID 19: complicated and often misinterpreted**

[15]

R. Barbosa Esper, R. Souza da Silva, F. Teiichi Costa Oikawa, M. Machado Castro, A. Razuk-Filho, P.B. Batista Jr., *et al.***Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine**

[16]

J.C. Lagier, M. Million, P. Gautret, P. Colson, S. Cortaredona, A. Giraud-Gatineau, *et al.***Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a retrospective analysis**

Trav Med Infect Dis (2020 Jun 25), p. 101791

[17]

T.D.A. Ly, D. Zanini, V. Laforge, S. Arlotto, S. Gentile, H. Mendizabal, *et al.***Pattern of SARS-CoV-2 infection among dependant elderly residents living in retirement homes in Marseille, France, March-June 2020**

[18]

A. Ip, J. Ahn, Y. Zhou, A.H. Goy, E. Hansen, A.L. Pecora, *et al.***Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: a multi-center observational study**

[19]

M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, *et al.***Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro**

Cell Res, 30 (2020), pp. 269-271

[20]

X. Yao, F. Ye, M. Zhang, C. Cui, B. Huang, P. Niu, *et al.***In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)**

[21]

Conselho Federal de Medicina**Processo-consulta CFM nº8/2020 - parecer CFM nº4/2020. Tratamento de pacientes portadores de COVID-19 com cloroquina e hidroxicloroquina [Internet]. 2020**

[22]

Ministério da Saúde Brasil**Orientações do Ministério da Saúde para Manuseio Medicamentoso Precoce de Pacientes com Diagnóstico da COVID-19 [Internet]. Brasília;**

[23]

Coronavírus brasil [internet]

Downloaded June, 15 (2020)

[24]

Infogripe- Monitoramento de casos reportados de síndrome respiratória aguda grave (SRAG) hospitalizados

Downloaded June, 17 (2020)

[25]

L. Kucirka, S. Lauer, O. Laeyendecker, D. Boon, J. Lessler**Variation in false negative rate of RT-PCR based SARS-CoV-2 tests by time since exposure**

Ann Intern Med, August 18 (2020), p. 2020

[26]

Z. Barnett-Howell, A.M. Mobarak**The benefits and costs of social distancing in rich and poor countries**

[27]

United Nations Development Programme**Socio-economic impact of COVID-19**

Downloaded June, 16 (2020)

[28]

M. Nicola, Z. Alsafi, C. Sohrabi, A. Kerwan, A. Al-Jabir, C. Iosifidis, *et al.***The socio-economic implications of the coronavirus pandemic (COVID-19): a review**

Int J Surg, 78 (2020), pp. 185-193

[29]

Johns Hopkins Coronavirus Resource Center**COVID-19 map - johns hopkins coronavirus resource center**

Johns Hopkins Coronavirus Resource Center (2020)

[30]

World Health Organization**Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. World Health Organization**

[31]

U.S. Food and Drug Administration (FDA)**Alert - June 15, 2020: based on FDA's continued review of the scientific**

evidence available for hydroxychloroquine sulfate (HCQ) and chloroquine phosphate (CQ) to treat COVID-19, FDA has determined that the statutory criteria for EUA as outlined in Section 564(c)(2) of the Food, Drug, and Cosmetic Act are no longer met

Downloaded June, 17 (2020)

[32]

U.S.Food and Drug Administration**FDA news release. Coronavirus (COVID-19) update: daily roundup June 15, 2020**

[33]

National China Health Office Medical Letter**184. Notice on issuing the new coronavirus pneumonia diagnosis and treatment plan (trial version 7)**

Mar, 3 (2020), p. 2020

[34]

Government of India, Ministry of Health and Family Welfare**Directorate General of Health Services (EMR division). Clinical Management Protocol: COVID-19**

[35]

H.A. Risch**Early outpatient treatment of symptomatic, high-risk covid-19 patients that should be ramped-up immediately as key to the pandemic crisis**

[36]

C.T. Rentsch, N.J. DeVito, B. MacKenna, C.E. Morton, K. Bhaskaran, J.P. Brown, *et al.***Hydroxychloroquine for prevention of COVID-19 mortality: a population-based cohort study**

[37]

L. Kolilekas, K. Loverdos, S. Giannakaki, L. Vlassi, A. Levounets, E. Zervas, *et al.***Can steroids reverse the severe COVID-19 induced 'cytokine storm'? J Med Virol 2020. June 12, 2020**

[38]

L. Durcan, M. Petri**Immunomodulators in SLE: clinical evidence and immunologic actions**

J Autoimmun, 74 (2016), pp. 73-84

[39]

Brasil. Nota informativa Nº 5/2020-DAF/SCTIE/MS. NOTA INFORMATIVA. Brasília

[40]

Brasil. Boletim Epidemiologico . Doença pelo Novo Coronavirus.(COVID-19). Perfil Epidemiologico Dos Pacientes Hospitalizados por Syndrome Respiratória Aguda Grave (SRAG) no Estado do Ceará. 05 de maio de 2020/pagina9/36

View Abstract