Review

Pharmacy and Therapeutics Committee Preparedness Plan for COVID-19

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ABSTRACT

As the Pharmacy and Therapeutics (P&T) committee acts as an advisory committee on therapeutic options, it is important during pandemics, such as the current Coronavirus disease 2019 pandemic, to quickly search the evidence, be able to select the most appropriate therapies despite the limited evidence, and make appropriate decisions related to which drugs to procure and stock. Potential therapies and recommendations to the P&T committee at a large healthcare institution as means of a preparedness plan are reviewed here.

Keywords: Pharmacy and theraputics committee, COVID-19, preparedness plan

INTRODUCTION

On December 31, 2019, a pneumonia of unknown cause in Wuhan, China was reported to the World Health Organization's Country Office.[1] The Coronavirus disease 2019 (COVID-19) quickly turned into a global concern with its rapid spread.

After the initial outbreak in China, many other countries have also documented cases, spreading to more than 202 countries, with 754,948 confirmed cases globally and 36,571 deaths as of March 31, 2020. The highest numbers of confirmed COVID-19 cases were reported from China, Italy, United States, Spain, Germany, and Iran.[2] Mortality rates have been reported to be same between Italy and China reaching 2.3%, the top two affected countries in this pandemic.[3]

On March 2, 2020, the Saudi Ministry of Health announced its first case of COVID-19 in the kingdom, in a Saudi patient whom had returned from Iran.[4] At the time of submitting this paper, the total number of cases had increased to 1563 as of March 31, 2020. Of particular concern to the country during this pandemic is the high influx of Muslims to the country for pilgrimage; therefore, as a precautionary measure the Saudi government decided to suspend the Umrah pilgrimage and revisit the decision periodically.[5] This was followed by other strict measures to combat the virus, such as closing schools and curfews in most of its major cities.

At the National Guard Health Affairs (NGHA) in Riyadh, Saudi Arabia, any global outbreak brings back memories of the hospital's shutdown during the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreak in the summer of 2015,[6] that experience built a sense of accountability and resilience to contain MERS-CoV and any other similar outbreaks in the future. The hospital's leadership continued to take measures to break the transmission and ensure vigilance and preparedness for other infectious outbreaks. Very soon after the outbreak of COVID-19, the institution provided guidelines for employees travelling to any of

the affected countries, suspended the fingerprint biometric attendance system, and held online educational awareness sessions about COVID-19.

The World Health Organization has developed a critical preparedness, readiness, and response actions for COVID-19 plan, with guidance based on the following four transmission scenarios for COVID-19[7]:

1. Countries with no cases (no cases);
2. Countries with 1 or more cases, imported or locally detected (sporadic cases);
3. Countries experiencing cases clusters in time, geographic location, and/or common exposure (clusters of cases); and
4. Countries experiencing larger outbreaks of local transmission (community transmission).

At this time Saudi Arabia is in scenario 3. Under the guidance, there is a link to a clinical management tool specifically for COVID-19 and under module 7 (antimicrobial therapies) they state there are no known effective antivirals for COVID-19.[7]

As an integral part of the hospital's steering committees, the pharmacy & therapeutics (P&T) committee, is charged with providing advice to the rational use of medications throughout the institution; our P&T committee at NGHA discussed our COVID-19 preparedness plan from a pharmacologic therapeutic prospective. The NGHA is one of the largest healthcare institutions in Saudi Arabia, with a bed capacity of 3577 collectively between its medical cities.

The aim of this plan was to identify all potential treatments, review the available evidence, and provide advice to the hospital's committee on decisions related to drug therapy based on resources, the limited evidence at the time and the current national COVID-19 situation.

METHODS

The preparedness plan development included assembling a multidisciplinary team, identifying and reviewing evidence on potential treatments, treatment selection, and finally continuous assessment of stocks and logistical considerations.

Identifying Treatment Options and Evidence Review

The main central region P&T coordinator conducted a systematic review of published studies on PubMed, to identify studies examining therapeutic drugs for treatment of COVID-19. Key words used were "2019 novel coronavirus," "Wuhan virus," "COVID-19," and "SARS-CoV-2." All theory based, in vitro, animal, or human studies proposing potential therapies published between December 2019 and March 2020 were included. All articles were screened for treatment modalities in patients treated in the current outbreak, so descriptive observational studies were included. Studies on therapeutic drugs used in SARS-CoV and MERS-CoV were excluded.

Studies were categorized into human studies in patients infected with current COVID-19, in vitro studies, and studies that were based on theoretic efficacy. For articles published in Chinese, translation was done through google translate. Outcomes were listed, if reported in the study. Formulary status and cost of the potential drug therapies were also added to support the committee's decision.

Together, the chair of the P&T, the pharmaceutical planning department, and the pharmacoeconomic center, reviewed recommendations and continuous evaluation of the therapeutic options and measures that needed to be taken.

RESULTS

A total of 1528 articles were related to COVID-19 on PubMed as of March 26, 2020. Only 20 were related to therapeutics and were used for a full review. A list of identified studies is in Table 1. The majority were (ahead of print), had only abstracts available, or were in Chinese language.

Of 20 studies included, 14 were in patients in the current COVID-19 outbreak, two were in vitro studies, and four were articles reviewing theoretic concepts for treating COVID-19. Of 14 observational studies, one was in the United States, one in Singapore, one in France, one in Korea, and all the rest in China.

Drug Selection

The list of the studies was used to formulate recommendations to the hospital's P&T committee on increasing stock and availability of certain drugs as a mean of preparedness for the worsening of COVID-19 outbreak. Because of the limited number of cases locally at the time of developing this plan and the strict quarantine measures taken by the government, the criteria for selection was as follows: only select treatments that were used in clinical studies during the outbreak, which showed relative effectiveness, no reported harm, and were easily accessible (i.e., available locally).

Most of the studies did not report any clear outcomes and no conclusions could clearly be drawn, but drugs that were used in current COVID-19 patients were recommended to be stocked, except for remdesivir as it is not available on the market except through special access and published data were only from one patient.[8]

The list of drugs from in vitro studies or theoretically based were listed to clarify that there was still not enough evidence to recommend them in light of the availability of the other treatments. A decision was made not to recommend these drugs at the time of this review.

Recommended drugs based on the mentioned criteria

The following drugs were recommended: chloroquine, hydroxychloroquine + azithromycin, lopinavir/ritonavir, oseltamivir, and ribavirin.

DISCUSSION

The role of P&T committees during this pandemic is to provide continuous advice on emerging therapies and contain misinformation or exaggeration of proposed therapies that may have not proven any efficacy yet. As healthcare resources can become compromised during these times, institutions need to concentrate their efforts on ensuring continuous supply of supportive medications and be ready to face the challenging situation of distributional justice, having to choose between allocating resources to treatments that provide care to patients that show better hopes of survival.

P&T committees need to meet more frequently to assess the situation and plan for the worst-case scenario. At the time of this review, many proposed therapies were under investigation; however, very few besides lopinavir/ritonavir, chloroquine, ribavirin, and hydroxychloroquine + azithromycin, were clinically used or had any reported outcomes. Institutions need to explore potential unproven therapies carefully while weighing priorities and its burden on resources.

Drug Logistical Considerations

Frontline doctors from Wuhan describe the lack of drugs as a problem during the outbreak.[9] Drug shortages are expected as supplies of active pharmaceutical ingredients are interrupted by closure of factories in China, which in turn supply 70% of raw material to India one of the largest suppliers of generic drugs in the world.[10]

Therefore, beside antiviral directed treatments, identifying supportive drugs needed for infected patients may be more important during the pandemic, and assessing adequate stocks as demand is expected to increase. Shortages and lack of adequate planning may on its own increase mortality significantly. Efforts to identify early signs of supply chain shortages in supportive drugs, such as fluids and electrolytes, anti-inflammatories, steroids, and antibiotics for secondary infections, should continuously be assessed by the committee together with monitoring emerging logistical constrains and stock levels.

From the very start of the outbreak continues communication and coordination between P&T committee and our Pharmaceutical Planning Department (PPD) was almost on a daily basis, to ensure adequate stocks and prepare for increase in demand. The PPD reported during this time a surge in demand for the potential COVID-19 drugs in the market, but despite that, no increase in consumption at our institution was noted at the time of writing this paper. The PPD did however report a significant increase in drug transportation fees for a couple of drugs in the market, which affected net price for some other drugs procured by PPD.

Forecasting and estimating number of patients

Earlier during the outbreak, the Reproduction number (R) was reported to be 2.2,[11] R is the average number of individuals to whom each infector will transmit the virus. When R is greater than 1, sustained transmission can occur; if R is less than 1, then chains of transmission will simply halt. Special about COVID-19 is the fact there is a significant number of asymptomatic infected individuals, known as recessive infections, that act as a source of infection during the outbreak, and therefore forecasting can be challenging. More recent reports show the R has dropped to less than 1 in most municipalities in China. A Chinese group developed a model to forecast the trend of COVID-19 infections, based on the (susceptible exposed infectious recovered) model. This model considers the COVID-19 transmission mechanism, infection spectrum, and prevention and control procedures. They predicted the inflection point of the epidemic has passed, but had not ended.[12] In another predictive paper, the authors predicted the outbreak would end in China after March 20, 2020, and it did.[13]

Researchers explain why containment efforts can only help delay the spread and buy us time to prepare, and how these efforts will not prevent a pandemic.[14] As Saudi Arabia has only sporadic cluster cases at this time, with known exposure through travel, it is hard to predict the number of patients and rough estimates can only be done based on other country's experiences.

Italy's experience might serve as a good predictor for a worse-case scenario where the numbers of infected showed an exponential growth. From February 22, 2020 to March 11, 2020, the number of cases went from seven confirmed to 10,149 cases. Together with reports form a systematic review of clinical features of COVID-19 patients describing 20% required treatment in the intensive care unit,[15] a worse-case scenario estimate number of patients that would be considered sever and be candidates for antiviral therapy can be made.

Accessibility and Cost

Of the potential treatments for COVID-19, hydroxychloroquine/chloroquine + azithromycin are the cheapest regimens, while lopinavir-ritonavir was more expensive with less supporting evidence on better outcomes compared with hydroxychloroquine + azithromycin. See Table 2 for cost of drug regimens.

All the recommended drugs are registered with the Saudi Food and Drug Authority with multiple suppliers locally listed.

Tocilizumab had no clinical studies in human, and its theoretic use in COVID-19 is based on relieving the cytokine storm syndrome not on any antiviral effect. It is

Table 1.—Summary of articles related to CODID-19 therapeutic options

Title/Reference	Type of Study/ Number of Patients	Drug Regimen	Country	Outcome	Formulary Status
Human Clinical Studies					
Lopinavir-Ritonavir					
A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19[37]	99 patients	Lopinavir-ritonavir	China	Treatment with lopinavir-ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90–1.72). Mortality at 28 days was similar in the lopinavir-ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). In a modified intention-to-treat analysis, lopinavir-ritonavir led to a median time to clinical improvement that was shorter by 1 day than observed with standard care (hazard ratio, 1.39; 95% CI, 1.00–1.91)	Yes
Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore[22]	Patients in current outbreak $n = 5$	Lopinavir-ritonavir	Singapore	For 3 of 5 patients, fever resolved and supplemental oxygen requirement was reduced within 3 days, whereas 2 deteriorated with progressive respiratory failure	Yes
Clinical characteristics of laboratory confirmed positive cases of SARS-CoV-2 infection in Wuhan, China: a retrospective single center analysis[23]	Patients in current outbreak $n = 32$ (received the antiviral)	Lopinavir-ritonavir	China-Wuhan	Could not be determined, but 1 patient showed improvements in his chest radiographs. And patients who were not prescribed lopinavir-ritonavir and patients prior to being prescribed lopinavir-ritonavir tended to have worse manifestations on their chest radiographs (14/16, 87.5%).	Yes
Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multicenter study in Wenzhou City, Zhejiang, China[25]	Patients in current outbreak	Lopinavir-ritonavir	Wenzhou City, Zhejiang, China	Ongoing	Yes
Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR[35]	1 patient	Lopinavir-ritonavir	Korea	Coronavirus viral loads significantly decreased and no or little coronavirus titers were observed	Yes

Table 1 continues on next page.

Table 1.—Continued.

Title/Reference	Type of Study/ Number of Patients	Drug Regimen	Country	Outcome	Formulary Status
Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study[38]	16 patients	Arbidol combined with lopinavir-ritonavir	China	The COVID-19 could not be detected for (75%) of patients' nasopharyngeal specimens in the combination group after seven days, compared with (35%) of in the monotherapy group ($p < 0.05$). After 14 days, 16 of 17 (94%) and 9 (52.9%) of 17 COVID-19 could not be detected ($p < 0.05$). The chest CT improved for (69%) of patients in the combination group after 7 days, compared with (29%) of the monotherapy group ($p < 0{\cdot}05$)	Arbidol: no
Remdesivir					
First case of 2019 novel cornavirus in the united states[8]	Patient in current outbreak $n = 1$	Remdesivir	USA	Patient improved and alive	No Not yet available, under clinical trials (Glilade)
Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China[24]	Patients in current outbreak $n = 31$ (pediatric)	Supportive only	Northern China	No deaths	
Oseltamivir					
Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China[26]	Patients in current outbreak $n = 138$	Oseltamivir	Wuhan, China	No effective outcomes were observed Mortality 4.3 %	Yes
Clinical characteristics of Coronavirus Disease 2019 in China[27]	1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces	35.8% received oseltamivir	China	No direct conclusion Mortality 2.5%	Yes

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Table 1.—Continued.

Title/Reference	Type of Study/ Number of Patients	Drug Regimen	Country	Outcome	Formulary Status
Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study[21]	$n = 99$	Oseltamivir (75 mg every 12 hours, orally), ganciclovir (0.25 g every 12 hours, intravenously), and lopinavir and ritonavir tablets (500 mg twice daily, orally). The duration of antiviral treatment was 3–14 days (median 3 days [interquartile range 3–6]).	Wuhan, China	Not specifically reported, but mortality was 11%	Yes
Chloroquine and hydroxychloroquine					
Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies[34] (as press release no full publication)	100 patients	Chloroquine	10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo	Chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course (results given through news briefing, not published)	Yes
Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial[36]	26 patients	Hydroxychloroquine and azithromycin	France	At day 6 postinclusion, 100% of patients treated with hydroxychloroquine and azithromycin combination were virologically cured compared with 57.1% in patients treated with hydroxychloroquine only, and 12.5% in the control group ($p < 0.001$)	Yes
Ribavirin					
Clinical characteristics of imported cases of COVID-19 in Jiangsu Province: a multicenter descriptive study[28]	80 patients	Ribavirin antiviral therapy for 3–12 days	Jiangsu, China	21 cases were discharged from the hospital, and no patient died. The average length of stay for discharged patients was 8 days	Yes
In vitro					
Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro[29]	In vitro	Remdesivir and chloroquine	China	Remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro	Remdesivir: No chloroquine: yes

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Table 1.—Continued.

Title/Reference	Type of Study/ Number of Patients	Drug Regimen	Country	Outcome	Formulary Status
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)[39]	In vitro	Hydroxychloroquine and chloroquine	China	Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro	Yes
Theoretical					
COVID-19: combining antiviral and anti-inflammatory treatments[30]	In vitro modeling	Baricitinib, ruxolitinib, fedratinib	UK	Theoretical	Baricitinib: no Ruxolitinib: yes Fedratinib: no
Broad spectrum antiviral agent niclosamide and its therapeutic potential[31]	Theoretical	Niclosamide	USA	Theoretical	Yes
Learning from the past: possible urgent prevention and treatment options for Severe Acute Respiratory Infections caused by 2019-nCoV[32]	Theoretical	Remdesivir	USA	Theoretical	No Not yet available, under clinical trials (Glilade)
Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies[33]	Theoretical, based on cytokine storm syndrome	Convalescent plasma Interleukin-6 antibody blocker (tocilizumab) Stem cell therapy	China	Theoretical convalescent plasma: but used in SARS successful Tocilizumab: clinical trial ongoing (only for severs cases)	Tocilizumab: yes

Table 2.—Cost of potential COVID-19 drug regimens/patient in Saudi Arabia and the United States, listed in ascending manner

Drug Dosage Form Available	Proposed Regimen and Duration for Adult Patients	Unit price (USD)*	Unit price (SAR)**	Cost/Patient/ Course of Therapy: USA	Cost/Patient/ Course of Therapy: Saudi Arabia
Azithromycin tablet 250 mg	500 mg on day 1, followed by 250 mg × 4 days	$2.55	0.67	$15.3	4.02 SAR
Chloroquine phosphate tablet 250 mg	500 mg BID × 5 days	$4.84	0.2428	$96.8	4.856 SAR
Hydroxychloroquine sulfate tablet 200 mg	200 mg TID × 10 days	$1.83–$4.36	1.2358	$54.9–$130.8	37.074 SAR
Oseltamivir 75 mg	75 mg BID × 5 days	$13.66–$15.46	6.8	$136.6–$154.6	68 SAR
Ribavirin 200 mg capsule	400 mg every 8 hours for at least 3 days, then 1200 mg orally twice a day, for a total of 7–10 days	$8.27	1.875	$545.82	123.75–157.5 SAR
Lopinavir 200 mg/ritonavir 50 mg	400 mg/100 mg BID × 14 days	$10.24	12.44	$573.44	696.64 SAR
Tocilizumab 400/20 mL	One dose 400 mg may be given a second dose	$138.35 per mL	2979.23/ vial	$2767–$5534	2979.23–5958 SAR

BID: twice daily; SAR: Saudi Arabian Riyal; TID = three times daily; USD: United States Dollars.
* Prices of drugs in USA obtained from Lexicomp.[40] Prices of lowest generic listed.
** Saudi prices listed as per NGHA acquisition.

an expensive drug, but was available on our formulary and no accessibility problems were noted at the time; however, no recommendation to increase stocks was made because of limited evidence and high cost.

CONCLUSIONS

Summary of recommendations made to P&T committee

1. Increase existing stocks of the following drugs: lopinavir/ritonavir, chloroquine, ribavirin, hydroxychloroquine, azithromycin, and oseltamivir.
2. To estimate the number of patients that would require antiviral drugs based on the local number of affected cases, predictions using other countries' trends, and an estimation of 20% of cases being moderate to severe, and to review this decision periodically based on trend of actual number of cases.
3. All listed potential treatments should be secured in controlled area in the pharmacy to control the stock and restricted in the electronic healthcare system.
4. Increase supply of all supportive treatments as follows:
   - Fluids: crystalloids (normal saline and Ringer's lactate) and electrolytes
   - Vasopressors (i.e., norepinephrine, epinephrine, vasopressin, and dopamine)
   - Low-molecular-weight heparin and heparin
   - Proton-pump inhibitors
   - Sedatives
   - Albumin
   - Neuromuscular blockade (e.g., cisatracurium)
   - Corticosteroids
5. To develop an antiviral protocol for COVID-19 treatment, to include patient criteria for treatment and recommended doses
6. Daily stock monitoring of the potential treatments listed

Monitoring emerging therapies

The rapid Chinese researchers' response to the outbreak made the virus genome sequence quickly available (GenBank ID: MN908947.3).[16] In which high-sequence homology was found to be shared with SARS-CoV. As a result, most of what has been published are theoretic proposed treatments based on previous studies targeting SARS-CoV and MERS-CoV.

Many clinical trials are undergoing to determine possibly effective therapies, which have included the following drugs: lopinavir plus ritonavir and arbidol, remdesivir, darunavir and cobicistat, favipiravir, ruxolitinib, baloxavir, marboxil, hydroxychloroquine, camrelizumab, tocilizumab, and immunoglobulin. No recommendations to procure or increase stock of any of these medications were made at this time.[17–20]

As the P&T committee acts as an advisory committee on therapeutic options, it is important during such epidemic outbreaks to quickly search the evidence, be able to debunk misinformation, select the most appropriate therapies despite the limited evidence, and conduct ongoing surveillance for emerging therapeutic options and make appropriate decisions.

The main challenge at the time of this research was most articles were published in Chinese language and available only as abstracts. Most studies were of very poor to poor quality with limited number of patients to clearly extrapolate effectiveness.

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