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Review

Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)

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Reviews in Cardiovascular Medicine

The SARS-CoV-2 virus spreading across the world has led to surges of COVID-19 illness, hospitalizations, and death. The complex and multifaceted pathophysiology of life-threatening COVID-19 illness including viral mediated organ damage, cytokine storm, and thrombosis warrants early interventions to address all components of the devastating illness. In countries where therapeutic nihilism is prevalent, patients endure escalating symptoms and without early treatment can succumb to delayed in-hospital care and death. Prompt early initiation of sequenced multidrug therapy (SMDT) is a widely and currently available solution to stem the tide of hospitalizations and death. A multipronged therapeutic approach includes 1) adjuvant nutraceuticals, 2) combination intracellular anti-infective therapy, 3) inhaled/oral corticosteroids, 4) antiplatelet agents/anticoagulants, 5) supportive care including supplemental oxygen, monitoring, and telemedicine. Randomized trials of individual, novel oral therapies have not delivered tools for physicians to combat the pandemic in practice. No single therapeutic option thus far has been entirely effective and therefore a combination is required at this time. An urgent immediate pivot from single drug to SMDT regimens should be employed as a critical strategy to deal with the large numbers of acute COVID-19 patients with the aim of reducing the intensity and duration of symptoms and avoiding hospitalization and death.

Keywords

SARS-CoV-2; COVID-19; hospitalization; mortality; ambulatory treatment; anti-infective; anti-inflammatory; antiviral; corticosteroid; antiplatelet agent; anticoagulant; sequenced multidrug therapy

The pandemic of SARS-CoV-2 (COVID-19) is advancing unabated across the world with each country and region developing distinct epidemiologic patterns in terms of frequency, hospitalization, and death. There are four pillars to an effective pandemic response: 1) contagion control, 2) early treatment, 3) hospitalization, and 4) vaccination to assist with herd immunity (Fig. 1). Additionally, when feasible, prophylaxis could be viewed as an additional pillar since it works to reduce the spread as well as incidence of acute illness. Many countries have operationalized all four pillars including the second pillar of early home-based treatment with distributed medication kits of generic medications and supplements as shown in Table 1. In the US, Canada, United Kingdom, Western European Union, Australia, and some South American Countries there has been three major areas of focus for pandemic response: 1) containment of the spread of infection (masking, social distancing, etc., 2) late hospitalization and delayed treatments (remdesivir, convalescent plasma, antiviral antibodies), and 3) vaccine development (Bhimraj et al., 2020; COVID-19 Treatment Guidelines, 2020). Thus the missing pillar of pandemic response is early home-based treatment (as seen in Fig. 1).

The current three-pronged approach has missed the predominant opportunity to reduce hospitalization and death given the practice of directing patients to self-isolation at home. Early sequential multidrug therapy (SMDT) is the only currently available method by which hospitalizations and possibly death could be reduced in the short term (McCullough et al., 2020a). Most COVID-19 patients with progressive symptoms who arrive to hospital by emergency medical services do not require intubation or pressors initially in the field (Yang et al., 2020). Once hospitalized, if oxygen is required the mortality rate rises to ~12% (Palazzuoli et al., 2020). Approximately one quarter require mechanical ventil ation, advanced circulatory support, or renal replacement therapy and in that group the mortality exceeds 25% (S. Gupta et al., 2020a,b). Our observations suggest a majority of hospitalizations could be avoided with a first treat-at-home strategy with appropriate telemedicine monitoring and access to oxygen and therapeutics. Patients will have the best chance of therapeutic gain when trea ted before there is significant progression of disease (Argenziano et al., 2020; McCullough et al., 2020b; Rhodes et al., 2017).

The majority serious viral infections require early treatment with multiple agents and this approach has not been applied in trials of COVID-19 sponsored by governments or industry. Since COVID-19 syndrome is characterized by early exponential viral proliferation, cytokine-mediated organ damage and dysfunction, and endothelial injury with proximal platelet aggregation with thrombosis, (Fig. 2) it is not realistic to assume a single drug or antibody could comprehensively handle all of these manifestations. At this time there are no reports of conclusive randomized trials of oral ambulatory therapy for COVID-19 and none are expected in the short term. Most oral therapy trials reported to date have been small, underpowered, unblinded, relied on biased physician assigned endpoints, or in some cases, have been administratively stopped early without scientific justification or safety concerns.

Because COVID-19 is highly communicable, many U.S. ambulatory clinics do not care for patients with COVID-19 and studies suggest there has been little or no attempt to provide outpatient therapy to patients in the period before hospitalization (Price-Haywood et al., 2020). As the most notable early closure of a critically needed trial was U.S. National Institutes of Health study of hydroxychloroquine (HCQ) and azithromycin in ambulatory COVID-19 patients after 30 days with only 20 of 2000 budgeted patients enrolled (National Institutes of Health, 2020a,b). There has been no substantive federal effort since then on ambulatory trials and thus any future results are not expected in a time frame to influence public health policy (World Health Organisation, 2020). At the time of this writing, there are no planned trials of SMDT regimens designed to manage early viral replication, cytokine storm, and thrombosis in ambulatory patients with COVID-19 (Fig. 3). Hence, there is an urgent need for innovative early SMDT in COVID-19 to achieve the goal of reducing the intensity and severity of symptoms and lessening the risk of hospitalization or death. This outpatient ambulatory push could have a dramatic impact on reducing the strain on healthcare systems.

In the absence of evidence from or a commitment to clinical trials of early therapy, other scientific information on the pathophysiology, treated natural history, and clinical judgement together must guide contemporary ambulatory management of COVID-19 (McCullough et al., 2020b). Observational studies reporting outcomes in patient populations managed consistently with empirically derived early intervention regimens currently provide an acceptable level of evidence for safety and efficacy of these widely available, inexpensive and safe alternatives to the current standard of non-intervention (Khan et al., 2020). Based on pathophysiology and observational data, each physician and patient using shared decision making set the course for COVID-19 management: watch-

Table 1. Listing of early home-based treatment kits provided for acute COVID-19 illness by various countries.

Country	Drugs and supplements	References
Algeria	Chloroquine/Hydroxychloroquine	(Belayneh, 2020)
Argentina	Ivermectin	(Mega, 2020)
Brazil	Hydroxychloroquine, Ivermectin, Azithromycin (Vitamin D and zinc only for those who can afford)	(Coronavirus a Tarde, 2020; Ministério da Saúde, 2020)
Bangladesh	Ivermectin, Doxycycline	(Trial Site News, 2020)
Cameroon	Chloroquine/Hydroxychloroquine	(Belayneh, 2020; Bösmüller et al., 2020)
China	Chloroquine/Hydroxychloroquine plus other traditional medicine up to 23 different Chinese herbal medicines	(Fan et al., 2020)
Colombia	Ivermectin	(Mega, 2020)
Egypt	Chloroquine/Hydroxychloroquine	(Mohhamad, 2020)
France	Hydroxychloroquine, Azithromycin, and Lopinavir-Ritonavir	(Gérard et al., 2020)
Ghana	Chloroquine/Hydroxychloroquine	(Isaac, 2020)
India	Hydroxychlorquine, Ivermectin, alone or in combination with other drugs	(Vora et al., 2020)
Korea	Hydroxychloroquine	(Hong et al., 2020)
Mexico	Ivermectin, hydroxychloroquine	(Pacheco, 2020)
Morocco	Chloroquine/Hydroxychloroquine	(Brian, 2020; McFadyen et al., 2020; Mussa, 2020)
Mozanbique	Chloroquine/Hydroxychloroquine	(Belayneh, 2020; McFadyen et al., 2020)
Nigeria	Chloroquine/Hydroxychloroquine	(Felix, 2020; McFadyen et al., 2020)
Peru	Ivermectin, Azithromycin	(Diario oficial del bicentenario, 2020; Trial Site News, 2020)
Senegal	Chloroquine/Hydroxychloroquine	(Huaxia, 2020; McFadyen et al., 2020)
South Africa	Chloroquine/Hydroxychloroquine	(Katharine , 2020; McFadyen et al., 2020)
Spain	Patients who are already taking hydroxychloroquine within or outside of clinical trials for COVID-19 as well as patients undergoing chronic treatment with these drugs should continue taking them and, in any case, maintain their usual follow-ups with their doctors	(Agencia Española de Medicamentos y Productos Sanitarios, 2020)
Taiwan	Hydroxychloroquine	(Sheng, 2020)
Uganda	Chloroquine/Hydroxychloroquine, Azithromycin	(McFadyen et al., 2020; The Independent, 2020)
USA	No kits provided from public health agencies, Association of American Physicians and Surgeons Home COVID-19 Treatment Guide recommendends adjuvant neutraceuticals, and sequenced multidrug therapy by prescription	(AAPS, 2020)

ful waiting in self-quarantine or empiric treatment with the aim of lessening the intensity and duration of symptoms and reducing the risk of hospitalization and death (Gopalakrishnan et al., 2020). Fortunately, most healthy individuals with COVID-19 under age 50 years have a self-limited illness and no specific treatment is advised in the absence of severe symptoms. However, they should be advised that development of lower respiratory symptoms warrant evaluation of oxygenation status and consideration chest imaging which may prompt interventions with documentation of hypoxemia or pulmonary infiltrates.

However, those over age 50 and or those with one or more comorbidity have increased risks for hospitalization and death over 1% which increase substantially up to 40% with advancing age and more medical illnesses (obesity, diabetes mellitus, heart disease, pulmonary disorders, renal disease, and malignancies) and thus, warrant early ambulatory treatment according to best medical judgement weighing the benefits and risks of oral therapy. SARS-CoV-2 as with many viral infections, may be amenable to multiple drugs early in its course but is less responsive to the same treatments when administration is delayed and given in the hospital (Vaduganathan et al., 2020). Innovative SMDT regimens for COVID-19 utilize principles learned from hospitalized patients as well as data from treated ambulatory patients.

For the ambulatory patient with recognized signs and symptoms of COVID-19 on the first day (Fig. 2), often with nasal real-time reverse transcription or oral antigen testing not yet performed, the following three therapeutic principles apply (Centers for Disease Control and Prevention, 2020) : 1) combination anti-infective therapy to attenuate viral replication, 2) corticosteroids to modulate cytokine storm, and 4) antiplatelet agent/antithrombotic therapy to prevent and manage micro- or overt vascular thrombosis. For patients with cardinal features of the syndrome (fever, viral malaise, nasal congestion, loss of taste and smell, dry cough, etc) with pending or suspected false negative testing, therapy is the same as those with confirmed COVID-19.

1. Reducing viral spread and contamination

A major goal of self-quarantine is control of contagion (Nussbaumer-Streit et al., 2020). While there has been a great emphasis on masking and social distancing in congregate settings, many sources of information suggest the main place of viral transmission occurs in the home (respiratory, contact, oral-fecal) (Jef-

Fig. 1. The four pillars of pandemic response to COVID-19. The four pillars of pandemic response to COVID-19 are: 1) contagion control or efforts to reduce spread of SARS-CoV-2, 2) early ambulatory or home treatment of COVID-19 syndrome to reduce hospitalization and death, 3) hospitalization as a safety net to prevent death in cases that require respiratory support or other invasive therapies, 4) natural and vaccination mediated immunity that converge to provide herd immunity and ultimate cessation of the viral pandemic.

ferson et al., 2020; Xu et al., 2020). Masks for all unaffected contacts within the home as well as frequent use of hand sanitizer and hand washing is mandatory in the setting when one or more family members falls ill. Sterilizing surfaces such as countertops, door handles, phones, and other devices is advised. When possible, other close contacts can move out of the house and seek shelter free of SARS-CoV-2. Findings from multiple studies indicate that policies concerning control of the spread SARS-CoV-2 are only partially effective and extension into the home as the most frequent site of viral transfer is reasonable (Hsiang et al., 2020; Xiao et al., 2020). One of the great advantages of home treatment of COVID-19 is the ability of an individual or family unit to maintain isolation and complete contact tracing. If therapy is offered in the home with delivery of medications, then trips to urgent care centers, clinics, and hospitals can be reduced or eliminated. This limits spread to drivers, other patients, staff, and healthcare workers. On the contrary, therapeutic nihilism on the part of primary care physicians and health systems drives anxiety and panic among patients with acute COVID-19 who feel abandoned, making them more likely to break quarantine and seek aid at urgent care centers, emergency rooms and hospitals.

SARS-CoV-2 exists outside the human body in a bioaerosol of airborne particles and droplets. Since exhaled air in an infected person is considered to be "loaded" with particulate inoculum, each exhalation and inhalation in theory reinoculates the nasopharynx and tracheobronchial tree (Chen, 2020). We propose that fresh circulating air could reduce reinoculation and potentially lessen the severity of illness and possibly limit household spread during quarantine (Melikov et al., 2020). This calls for open windows, fans for aeration, or spending long periods of time outdoors away from others with no face covering in order to disperse and not reinhale the viral bioaerosol. These are principles used in the hospital with negative pressure ventilation deployed in isolation rooms to reduce bioaerosol contagion.

2. Adjunctive nutraceuticals

There has been considerable interest and study of the use of micronutrients and supplements for COVID-19 prophylaxis and treatment in combination with anti-infectives as first proposed by Zelenko and colleagues (Derwand et al., 2020). In general these agents are not curative but assist in treatment regimens to augment the therapeutic response. The aim of supplementation is to replenish in those with deficiencies associated with COVID-19 mortality, and to aid in reducing viral replication and tissue damage. Zinc deficiency is common among adults (Sharma et al., 2020). Zinc alone is a potent inhibitor of viral replication. Zinc in combination with hydroxychloroquine (HCQ) is potentially synergistic in reducing viral replication since HCQ is a zinc ionophore facilitating intracellular entry and inhibition of intracellular viral replication (Derwand and Scholz, 2020). This readily available nontoxic therapy could be deployed at the first signs of COVID-19 (Rahman

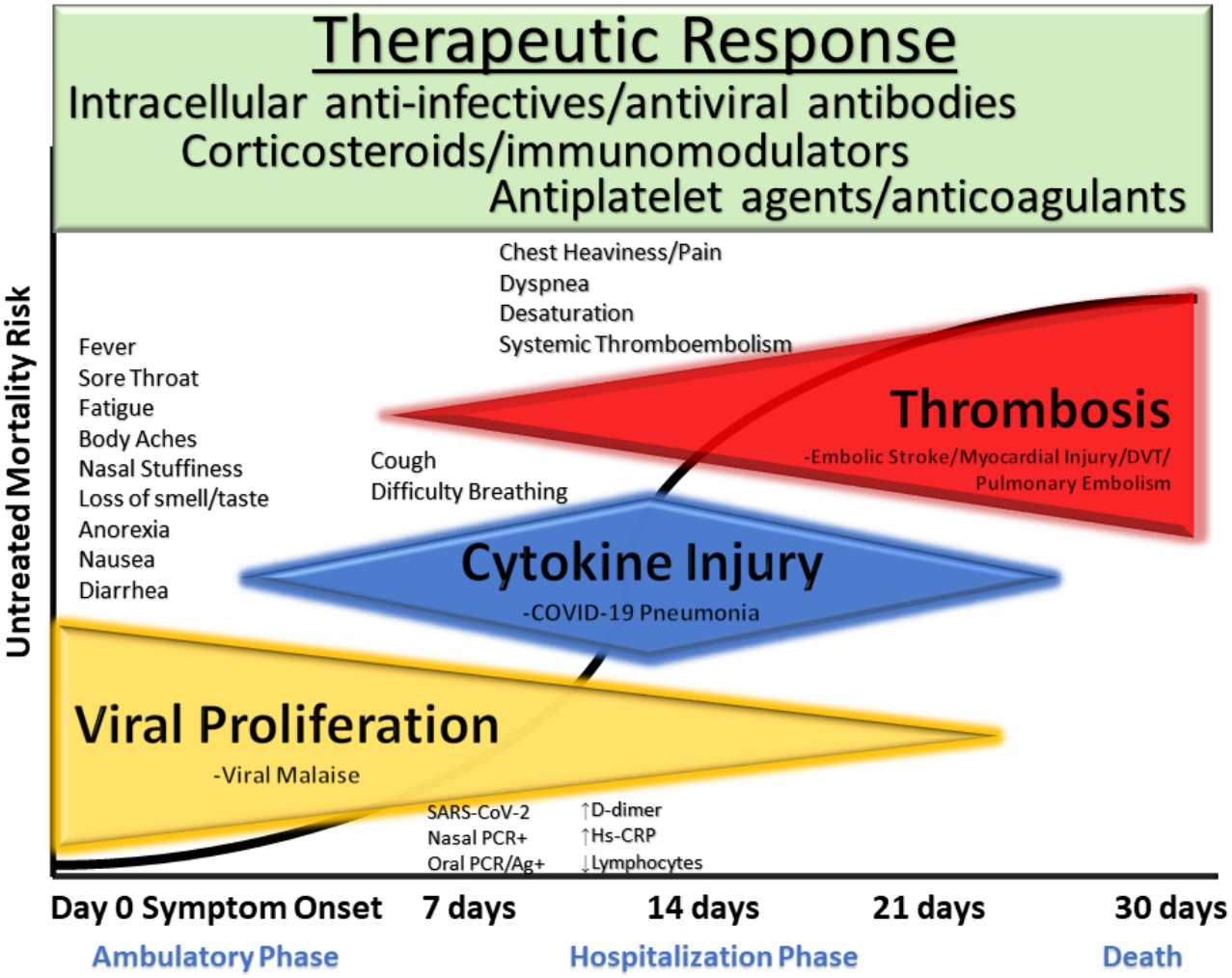

Fig. 2. Major dimensions of COVID-19 infection that call for a multi-drug strategy in the early ambulatory period with available medications including anti-infectives (hydroxychloroquine, ivermectin, azithromycin, doxycycline), corticosteroids, and anti-platelet drugs and anticoagulants. The three dimensions of the infection and their time-course allow for the sequenced multi-drug approach to be utilized with the goal of reducing hospitalization and death.

and Idid, 2020). Zinc sulfate 220 mg (50 mg elemental zinc) can be taken orally per day (Pormohammad et al., 2020).

Vitamin D deficiency has been associated with increased COVID-19 mortality and is commonly confounded by increasing age, obesity, diabetes, darker skin tones, and lack of fitness (Meltzer et al., 2020; Pereira et al., 2020) With good rationale, one small, randomized trial of vitamin D_3 supplementation found reduced mortality in patients with COVID-19 (Entrenas et al., 2020; Zhang et al., 2020a). The suggested dose is 5000 IU of vitamin D_3 per day.

Vitamin C has been used in a variety of viral infections and could be useful in combination with other supplements in COVID-19 (Carr and Rowe, 2020). Multiple randomized trials of vitamin C given intravenously or orally are planned or in progress at the time of this writing (Beigmohammadi et al., 2020; Liu et al., 2020) A reasonable dose would be vitamin C 3000 mg po qd.

Quercetin is a polyphenol that has a theoretical mechanism of action that could reduce the activity of a SARS-CoV-2 entry through the ACE2 receptor, inhibit viral proteases via conveyance of zinc, and attenuate inflammatory responses mediated through interleukin-6 (Bastaminejad and Bakhtiyari, 2020; Cione et al., 2019; Dabbagh-Bazarbachi et al., 2014; Derosa et al., 2020). The mechanisms of action favorably affect viral replication and immune response, so it is conceivable that this agent taken in combination with others discussed could play an assistive role in reducing early viral amplification and tissue damage (Colunga Biancatelli et al., 2020). The suggested dose of quercetin is 500 mg po bid.

3. Anti-infective therapy with intracellular activity

Quickly reducing the rate, quantity, and duration of viral replication, is a goal of antiviral therapy aimed at starting on the first day of symptomatic illness. The compelling rationale for prompt therapy is to minimize the degree of direct viral injury to the respiratory epithelium, vascular endothelium, and organs (Izzedine et al., 2020). Maladaptive host responses dependant on replication of SARS-CoV-2 could be attenuated by early initiation of combination anti-infectives including activation of inflammatory cells, cytokines, endothelial injury, and thrombosis (Singhania et al., 2020). Because SARS-CoV-2 infection is associated with severe disease and increased mortality in patients over age 50 years and those with one or more comorbidities, clinicians should use of at least two commercially available, anti-infective agents where it is

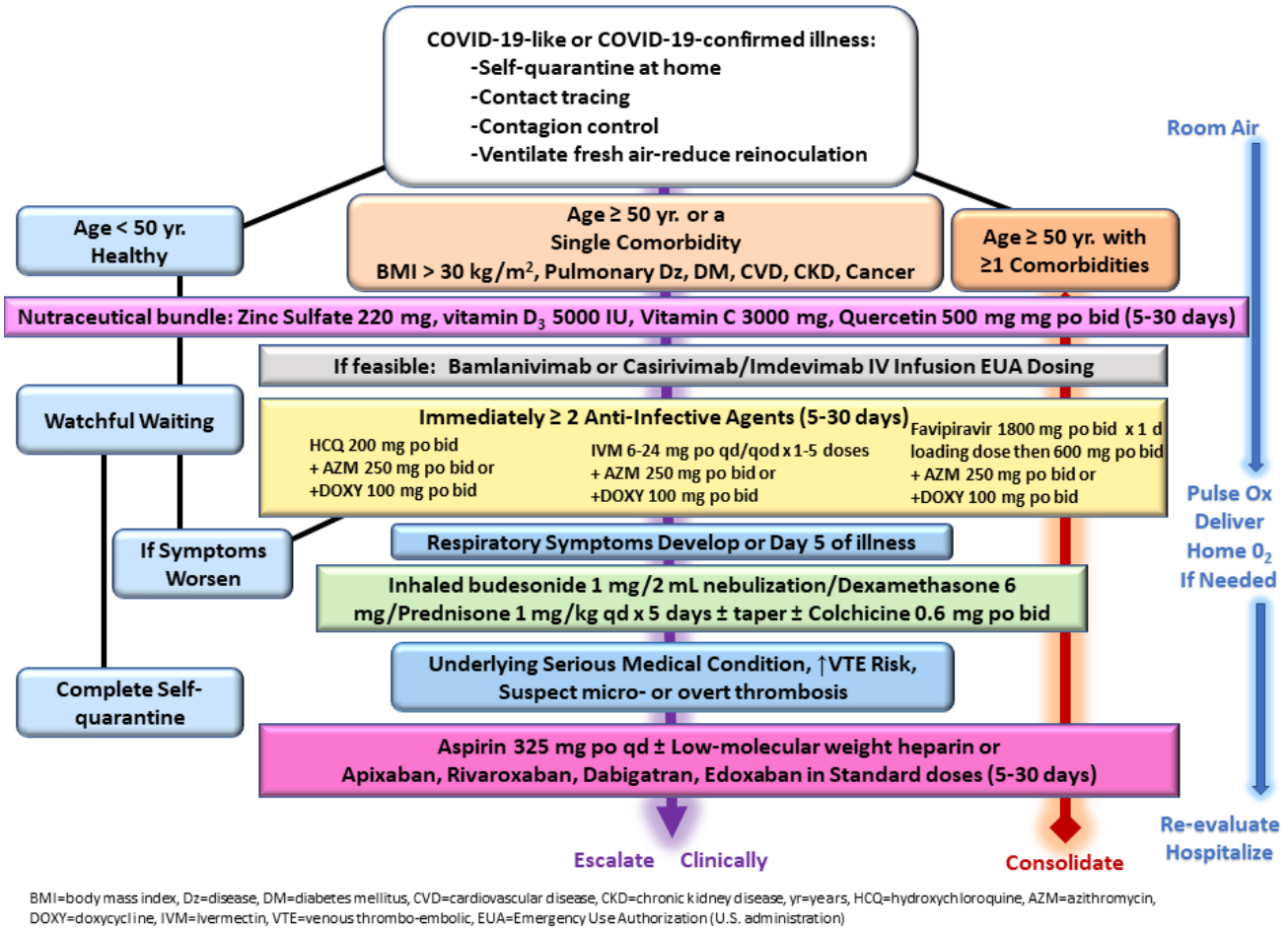

Fig. 3. Sequential multidrug treatment algorithm for ambulatory acute COVID-19 like and confirmed COVID-19 illness in patients in self-quarantine. Yr = year, BMI = body mass index, Dz = disease, DM = diabetes mellitus, CVD = cardiovascular disease, chronic kidney disease, HCQ = hydroxychloroquine, IVM = ivermectin, Mgt = management, Ox = oximetry, reproduced with permission from reference.

appropriately considered clinically indicated, medically necessary "off-label" prescription (Shojaei and Salari, 2020). Conversely, the decision to withhold oral therapy early in a potentially fatal illness should be made in a shared-decision making process with the patient given the full understanding that the natural untreated history of COVID-19 in high risk adults includes the risk of hospitalization, hospital-acquired complications, and death. The physician and patient should understand that the only method by which a hospitalization could be avoided would be the empiric use of SMDT that have a reasonable chance of success with acceptable safety. Recent expanded use authorization of IV administration of bamlanivimab is another option available to a limited number of patients, but supplies will be insufficient to treat everyone who meets the broad criteria for the therapy, so availability of oral alternatives remains essential.

4. Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial/anti-inflammatory drug that impairs endosomal transfer of virions within human cells. HCQ is also a zinc ionophore that conveys zinc intracellularly to block the SARS-CoV-2 RNA-dependent RNA polymerase which is the core enzyme of the virus replication (te Velthuis et al., 2010). A continuously updated synthesis of HCQ studies supports the following (COVID-19 Treatment, 2020): 1) 63% of studies of HCQ administered late in the hospital course have demonstrated benefit, 2) 100% of the early treatment studies have demonstrated benefit with a composite 64% relative risk reduction in the progression of disease, hospitalization, and death (Arshad et al., 2020; Mikami et al., 2020; Prodromos and Rumschlag, 2020; Rosenberg et al., 2020). The small randomized trials to date are inconclusive for the following reasons: 1) no placebo control, 2) unblinded, 3) altered primary endpoints, 4) biased unblinded physician assigned endpoints (such as need for oxygen), 5) markedly truncated sample sizes and administrative termination of trials, 6) pretreatment with other antivirals.

Hydroxychloroquine was approved by the U.S. Food and Drug Administration in 1955, has been used by hundreds of millions of people worldwide since then, is sold over the counter in many countries and has a well characterized safety profile (Fram et al., 2020; Schrezenmeier and Dörner, 2020). Asymptomatic QT prolongation is well-recognized though an infrequent (< 1%) occurrence with HCQ (Prodromos et al., 2020). In those with glucose-6-phosphate dehydrogenase deficiency HCQ should not be used (Aguilar, 2020). In the setting of acute severe COVID-19 illness, symptomatic arrhythmias can develop in the absence of HCQ and are attributed to cytokine storm and critical illness (Elsaid et al., 2020). Data safety and monitoring boards have not declared safety concerns in HCQ clinical trial published to date. Rare pa-

tients with a personal or family history of prolonged QT syndrome, those on additional QT prolonging, contraindicated drugs (e.g. dofetilide, sotalol), should be treated with caution and a plan to monitor the QTc in the ambulatory setting. A typical HCQ regimen is 200 mg bid for 5 to 30 days depending on continued symptoms.

5. Ivermectin

Ivermectin (IVM) is a broad spectrum anti-parasitic agent that has been shown to have anti-viral activity against a range of viruses including recently, SARS-CoV-2 (Heidary and Gharebaghi, 2020). This drug is well tolerated, has a high therapeutic index and proven safety profile with over 3.7 billion treatments, and has been used alone or combined with either doxycycline or azithromycin in early clinical studies of patients with COVID-19 (Rahman et al., 2020). There are a number of randomized and prospective studies and all have shown efficacy in clinical outcomes at the time of this report (Alam et al., 2020; Chowdhury et al., 2020; Gorial et al., 2020; Khan et al., 2020; Nunez et al., 2020). Hence, it is reasonable in patients where HCQ cannot be used and favipiravir is not available, that IVM (200-600 mcg/kg [6-36 mg] single oral dose given daily or every other day for 2-3 administrations) could be the base of SMDT intended to reduce viral replication early in the course of COVID-19. However, uncertainty remains at this time concerning optimal dosing and schedule (Schmith et al., 2020). In the ICON study, IVM use in the hospital was associated with a 48% relative risk reduction in COVID-19 mortality (Rajter et al., 2020). Currently, there are 36 randomized clinical trials of ivermectin alone or in combination for ambulatory and hospitalized patients listed on clinicaltrials.gov.

6. Favipiravir

Favipiravir is an oral selective inhibitor of RNA-dependent RNA polymerase, and is approved for ambulatory use in COVID-19 in multiple countries (Coomes and Haghbayan, 2020). Favipiravir is safe and it shortens viral nasal shedding to less than 7 days in most studies (Ivashchenko et al., 2020; Pilkington et al., 2020). A dose administration could be 1600-1800 mg po bid on day 1, following by 600-800 mg po bid for 14 days depending on the dose sizes available in 30 different countries (Li et al., 2020). At the time of this writing, there are large ambulatory clinical trials in progress but are not expected to report in time to aid in the crisis at hand in the U.S.

7. Antibiotics with intracellular anti-infective activity

Azithromycin (AZM) is a commonly used macrolide antibiotic that has antiviral properties mainly attributed to reduced endosomal transfer of virions as well as established anti-inflammatory effects (Pani et al., 2020). French reports indicated that AZM in combination with HCQ was associated with reduced durations of viral shedding, fewer hospitalizations, and reduced mortality as compared to those untreated (Lagier et al., 2020; Million et al., 2020). In a large observational inpatient study (n = 2451), those who received AZM alone had an adjusted hazard ratio for mortality of 1.05, 95% CI 0.68-1.62, $P = 0.83$ (Colunga Biancatelli et al., 2020). The combination of HCQ and AZM has been considered a standard of care outside the US for COVID-19 in more than 300,000 older adults with multiple comorbidities (Risch, 2020). AZM like HCQ can prolong the QTc in $< 1\%$ of patients, yet has demonstrated safety in co-administration with HCQ (Huang et al., 2020). A reasonable regimen is 250 mg po bid for 5 to 30 days for persistent symptoms or evidence of bacterial superinfection.

Doxycycline is another common antibiotic with multiple intracellular effects that may reduce viral replication, cellular damage, and expression of inflammatory factors (Malek et al., 2020; Sodhi and Etminan, 2020). It has been shown to have in vitro activity against COVID-19 at clinically used concentrations, acting in post-entry stages of the infection with SARS-CoV-2 in Vero E_6 cells (Gendrot et al., 2020). It has also been shown to concentrate in the lungs at levels twice that of plasma. When combined with ivermectin early in the infection it appears to enhance efficacy to near complete eradication of COVID-19 in less than 10 days. This drug has no effect on cardiac conduction and has the main caveat of gastrointestinal upset and esophagitis. Both AZM and doxycycline has the advantage of offering antibacterial coverage for superimposed bacterial and atypical infection in the upper respiratory tract (Ailani et al., 1999). Doxycycline can be dosed 200 mg po followed by 100 mg po bid for 5 to 30 days for persistent symptoms or evidence of bacterial superinfection.

8. Antibody therapy

Recently, bamlanivimab a monoclonal antibody directed against the SARS-CoV-2 spike protein has been approved for the early ambulatory treatment of COVID-19. In the BLAZE-1 randomized trial, the pooled secondary endpoint of COVID-19 hospitalizations occurred 4/136 and 7/69 of the Bamlanivimab and placebo groups respectively (Chen, 2020). While these results are not considered conclusive nor robust, given the emergency context, bamlanivimab is authorized for COVID-19 patients who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 or hospitalization. The authorized dosage for bamlanivimab is a single IV infusion of 700 mg administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. The infusion should occur over an hour with another hour of monitoring for systemic reactions (expected $< 5\%$).

A humanized antibody blend of casirivimab and imdevimab has also received emergency approval in the United States and for a similar population as bamlanivimab. This pair of antibodies binds at different regions of the SARS-CoV-2 spike protein. This antibody combination is dosed 1,200 mg of casirivimab and 1,200 mg of imdevimab together as a single IV infusion over at least 60 minutes with another hour of monitoring for reactions (Regeneron Pharmaceuticals, Inc., 2020). In the phase II program, the secondary endpoint of hospitalization occurred in 8/434 and 10/231 of casirivimab/imdevimab and placebo groups, respectively. These results should be interpreted with caution and cannot be characterized as being conclusive or robust, yet as with all therapies discussed in this paper, casirivimab/imdevimab can be integrated into an innovative sequenced multi-drug regimen for SARS-CoV-2 infection.

If SARS-CoV-2 is diagnosed by rapid testing in a facility that performs antibody infusion such as an emergency room, urgent care center, or clinic, it is reasonable to start COVID-19 with the antibody infusion. Conversely, if it can be safely arranged by home infusion while maintaining quarantine, physicians may prescribe this therapy to augment the effects of longer courses of oral treat-

ment. At this time, it is unattractive to ask a patient to break quarantine and risk spread of infection to drivers and healthcare personnel in order to receive an outpatient infusion.

9. Corticosteroids

The manifestations of COVID-19 that prompt hospitalization and that may well lead to multi-organ system failure are attributed to a cytokine storm. The characteristic profile of an acutely ill COVID-19 patient includes leukocytosis with a relative neutropenia. Among COVID-19 patients, serum IL-6 and IL-10 levels are elevated in the critically ill (Han et al., 2020). In COVID-19, some of the first respiratory findings are cough and difficulty breathing. These features are attributable to inflammation and cytokine activation. Early use of oral corticosteroids is a rational intervention for COVID-19 patients with these features as they would be in other inflammatory lung disorders (Kolilekas et al., 2020; Singh et al., 2020). Inhaled budesonide 1 mg/2 mL via nebulizer or 200 mcg/inhaler up to every four hours can be utilized however, there are no published reports of efficacy in COVID-19. The RECOVERY trial randomized 6425 hospitalized patients with COVID-19 in a 2 : 1 ratio to open label dexamethasone 6 mg po/IV qd for up to 10 days and found dexamethasone reduced mortality, HR = 0.65, 95% CI 0.51-0.82, $P < 0.001$ (Horby et al., 2020) . Concordantly, a meta-analysis involving 1703 critically ill COVID-19 patients found a 36% relative risk reduction in death (Sterne et al., 2020). Safety concerns regarding prolonged viral replication with steroids have not been substantiated (Masiá et al., 2020). A clinical extension of these findings is administration of steroids in COVID-19 patients at home on day five or beyond with moderate or greater pulmonary symptoms (Szente Fonseca et al., 2020). Dexamethasone 6 mg po qd or prednisone 1 mg/kg can be given orally per day for five days with or without a subsequent taper.

10. Colchicine

Colchicine is a non-steroidal anti-mitotic drug used in gout and pericarditis which blocks metaphase of inflammatory cells by binding to the ends of microtubules preventing their intracellular assembly. The GRECCO-19 randomized open-label trial in 105 hospitalized patients with COVID-19 (treated with HCQ and AZM in 98 and 93% respectively) found that colchicine was associated with a reduction in D-dimer levels and improved clinical outcomes (Deftereos et al., 2020). The clinical primary end point (2-point change in World Health Organization ordinal scale) occurred in 14.0% in the control group (7 of 50 patients) and 1.8% in the colchicine group (1 of 55 patients) (odds ratio, 0.11; 95% CI, 0.01-0.96; $P = 0.02$) (World Health Organisation, 2020). Because the short-term safety profile is well understood, it is reasonable to consider this agent along with corticosteroids in an attempt to reduce the effects of cytokine storm and myopericarditis. A dosing scheme of 0.6 mg po bid x 3 days then 0.6 mg po qd for 30 days can be considered.

11. Antiplatelet agents and antithrombotics

Multiple studies have described increased rates of pathological macro and micro-thrombosis (Bösmüller et al., 2020; McFadyen et al., 2020). COVID-19 patients have described chest heaviness associated with desaturation that suggests the possibility of pulmonary thrombosis (Bhandari et al., 2020). Multiple reports have described elevated D-dimer levels in acutely ill COVID-19 patients which has been consistently associated with increased risk of deep venous thrombosis and pulmonary embolism (Artifoni et al., 2020; Chan et al., 2020; Mestre-Gómez et al., 2020). Autopsy studies have described pulmonary micro thrombosis and overt embolism with deep venous thrombus found in over half of fatal COVID-19 cases (Ackermann et al., 2020; Burlacu et al., 2020). These observations support the hypothesis that a unique endothelial injury and thrombosis are playing a role in oxygen desaturation, a cardinal reason for hospitalization and supportive care (Zhang et al., 2020b). Because thromboxane A_2 is markedly upregulated with SARS-CoV-2 infection, early administration of aspirin 325 mg per day is advised for initial antiplatelet and anti-inflammatory effects (Chow et al., 2020; Glatthaar-Saalmüller et al., 2017; A. Gupta et al., 2020a; Turshudzhyan, 2020). Ambulatory patients can also be treated with subcutaneous low-molecular weight heparin or with oral novel anticoagulant drugs (apixaban, rivaroxaban, edoxaban, dabigatran) in dosing schemes similar to those used in outpatient thromboprophylaxis. In a retrospective study of 2773 COVID-19 inpatients, 28% received anticoagulant therapy within 2 days of admission, and despite being used in more severe cases, anticoagulant administration was associated with a reduction in mortality, HR = 0.86 per day of therapy, 95% CI: 0.82-0.89; $P < 0.001$. Contemporary use of in hospital anticoagulants has remained in ~30% of cases (Vahidy et al., 2020) . Pre-emptive use of low molecular weight heparin or novel anticoagulants have been associated with $>$ 50% reduction in COVID-19 mortality (Billett et al., 2020). Anticoagulants also reduce death in COVID-19 hospitalized patients with thrombotic complications, elevated D-dimer levels, and higher comorbidity scores (Tang et al., 2020) . Finally, many acutely ill outpatients also have general indications or risk for cardioembolic/venous thromboembolic prophylaxis applicable to COVID-19 (Moores et al., 2020; Ruocco et al., 2020). There are ambulatory randomized trials of aspirin and novel oral anticoagulants underway. However, given reports of catastrophic stroke and systemic thromboembolism and the large reductions in mortality for both prophylactic and therapeutic use, administration of aspirin 325 mg po qd for all COVID-19 high-risk patients and systemic anticoagulation is prudent in patients with a history of heart, lung, kidney, or malignant disease (Yamakawa et al., 2020).

12. Delivery of oxygen and monitoring

Telemedicine is a tractable means for the initial evaluation and management of COVID-19 allowing the patient to remain in self-quarantine at home. Clinical impressions of the patient can be gained with audio and video feeds. Key supplemental information includes self/family measurement of vital signs and temperature. A significant component of safe outpatient management is maintenance of arterial oxygen saturation on room air or prescribed home oxygen (oxygen concentrators) under direct supervision by daily telemedicine with escalation to hospitalization for assisted ventilation if needed. Self-proning could be entertained for medically sophisticated patients with good at-home monitoring (Westafer et al., 2020) .

The interventions discussed in this review could be extended to seniors in COVID-19 treatment units within nursing homes and other non-hospital settings. In addition to oral medications, these centers could deliver intravenous fluid and parenteral medications (i.e. bamlanivimab, casirivimab/imdevimab), oxygen, and assisted pressure ventilation with the goal of reducing the risk of

hospital transfer.

13. Summary

The SARS-CoV-2 outbreak is a once in a hundred-year pandemic that has not been addressed by rapid establishment of infrastructure amenable to support the conduct of large, randomized trials in outpatients in the community setting. The early flu-like stage of viral replication provides a therapeutic window of tremendous opportunity to potentially reduce the risk of more severe sequelae in high risk patients. Precious time is squandered with a "wait and see" approach in which there is no anti-viral treatment as the condition worsens, possibly resulting in unnecessary hospitalization, morbidity, and death. Once infected, the only means of preventing a hospitalization in a high-risk patient is to apply treatment before arrival of symptoms that prompt paramedic calls or emergency room visits. Given the current failure of government support for randomized clinical trials evaluating widely available, generic, inexpensive therapeutics, and the lack of instructive outpatient treatment guidelines (U.S., Canada, U.K., Western EU, Australia, some South American Countries), clinicians must act according to clinical judgement and in shared decision making with fully informed patients. Early SMDT developed empirically based upon pathophysiology and evidence from randomized data and the treated natural history of COVID-19 has demonstrated safety and efficacy. In newly diagnosed, high-risk, symptomatic patients with COVID-19, SMDT has a reasonable chance of therapeutic gain with an acceptable benefit-to-risk profile. Until the pandemic closes with population-level herd immunity potentially augmented with vaccination, early ambulatory SMDT should be a standard practice in high risk and severely symptomatic acute COVID-19 patients beginning at the onset of illness.

Footnote: To understand which drugs are being used in the early treatment of COVID-19 in these countries' websites of government agencies such as Brazil, Peru, Spain, Taiwan, and USA were searched. We also looked for researchers published in PUBMED by China, France, India, Korea, and African countries. Additional Information was also obtained from reliable sources of internet such as Argentina, Bangladesh, Colombia, Mexico and African Countries.

Author contributions

PAM wrote the first draft and created the figures, all authors provided critical edits and comments, PEA did the final proofreading and key finalization of the text. SR created the first draft of the table.

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