Research Article,

Innovative Early Sequenced Multidrug Therapy for Sars-Cov-2 (Covid-19) Infection to Reduce Hospitalization and Death

Peter A. McCullough, MD, MPH, [1][2][3]

[1]Baylor University Medical Center,

[2]Baylor Heart and Vascular Institute,

[3]Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX

Abstract:

The SARS-CoV-2 viral pandemic is creating surges of COVID-19 hospitalizations and excess mortality. Watchful waiting and late-stage hospitalization have failed to resolve the crisis due to the complex and multifaceted pathophysiology of COVID-19 illness including viral mediated organ damage, cytokine storm, and thrombosis. Patients endure long untreated periods before succumbing to hospitalization and delayed treatment. Thus, early innovative, sequenced multidrug regimens have the best chance of success and are prudent as the next direction in randomized trials and advanced practice. Early management includes: 1) nutraceuticals, 2) combination anti-infective therapy, 3) corticosteroids, 4) antiplatelet agents/antithrombotics, 5) supportive care including supplemental oxygen, monitoring, and telemedicine. An immediate pivot from therapeutic nihilism to innovative sequenced multidrug regimens is required as the only strategy to reduce hospitalization and death in current acute cases of COVID-19.

Key words: SARS-CoV-2; COVID-19; hospitalization; mortality; ambulatory treatment; anti-infective; anti-inflammatory; corticosteroid; antiplatelet agent; anticoagulant; multidrug regimen

Interoduction:

The pandemic of SARS-CoV-2 (COVID-19), is rapidly expanding across the world with each country and region developing distinct epidemiologic patterns in terms of frequency, hospitalization, and death. The United States ranks among the worst ten large countries in the world for COVID-19 deaths per million populations despite having sophisticated hospitals and technology. The common feature of the laggard countries is the absence of government/medical society support for home treatment for COVID-19. Other countries including China, Japan, India, Russia, and others, that have handled COVID-19 more successfully have emphasized home treatment with available anti-infectives and other agents. In the US there has been three major areas of focus for the National Institutes of Health, Centers for Disease Control, Food and Drug Administration, and the Infectious Diseases Society of America: 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.[i] [ii] This three-pronged approach has missed a large opportunity to reduce hospitalization and death given the long-phase of illness spent in isolation at home. Early home treatment is the only current option to reduce hospitalizations and possibly death in the short term.[iii] Most patients who arrive to the hospital by emergency medical services with COVID-19 do not require intubation or pressors in the field.[iv] Once hospitalized, the mortality rate if oxygen is required is ~12%.[v] Approximately one quarter requires mechanical ventilation, advanced circulatory support, or renal replacement therapy and in that group the mortality exceeds 25%.[vi] [vii] These observations suggest a majority of hospitalizations could be avoided with a treat-at-home first approach with appropriate telemedicine monitoring and access to oxygen and therapeutics that have the best chance of success when administered early in the course of the infection.[viii]

[ix] [x] Most serious viral infections require early treatment with multiple agents and this approach has not been tested in government or industry sponsored trials of COVID-19. Since COVID-19 syndrome is characterized by early exponential viral replication, cytokine storm, and thrombosis, (Figure 1) it is not realistic for a single drug or designer antibody to comprehensively handle all of these manifestations. At this time with over 40 million cases and 1 million deaths worldwide, there are no large, conclusive randomized trials of oral ambulatory therapy for COVID-19.[xi] Most trials reported to date have been small, underpowered, unblinded, biased by physician assigned endpoints, or have been administratively stopped early without scientific justification or safety concerns. Because COVID-19 is highly communicable, many ambulatory clinics do not care for patients and reports indicate there has been little or no attempt outpatient therapy offered to patients in the period before hospitalization.[xii] The National Institutes of Health administratively terminated its trial of hydroxychloroquine (HCQ) and azithromycin in ambulatory COVID-19.[xiii] After 30 days the trial was folded due to lack of enrollment with only 20 of 2000 patients recruited and no safety concerns reported.[xiv] No sufficiently large (N~20,000) trials of oral therapy are planned to meaningfully impact clinical practice of COVID-19 outpatients.[xv] At the time of this writing, there are no experimental drug trials designed to manage viral replication, cytokine storm, and thrombosis in ambulatory patients with COVID-19. Hence, there is an urgent need for innovative early sequenced multidrug regimens using existing agents to come forward for COVID-19 to achieve the goal of reducing the intensity and severity of symptoms and lessening the risk of hospitalization or death. In the absence of evidence from clinical trials, other data on the pathophysiology, treated natural history from community and hospital cases, and clinical judgement should guide contemporary ambulatory management of COVID-19.[ix] Many studies of available nutraceuticals and oral drugs have reported associations with favorable outcomes.[lvi] These associations could be due to the nutraceutical or drug it self, or could be explained by selection bias. Meaning the patient or the physician via co-selection for early treatment partially explains the beneficial effect. In the setting of an emergency fatal pandemic, the explanation is less important than the actual result.

Those patients who receive forms of early therapy discussed in this paper have statistically significant reductions in the intensity and severity of symptoms, hospitalization, and death.

In shared decision-making, each physician and patient set the course for COVID-19 management: watchful waiting in self-quarantine or empiric treatment.[xvi] Fortunately, most healthy individuals with COVID-19 under age 50 with no medical problems have a self-limited illness and no specific treatment is warranted beyond nutraceuticals to replace potential baseline deficiencies. However, those over age 50 years and or those with one or more comorbidity have increased risks for hospitalization and death over 1% and increase substantially with age and baseline medical illnesses (obesity, diabetes mellitus, heart disease, pulmonary disorders, renal disease, and malignancies). For such patients and those who present with severe symptoms, prompt oral ambulatory treatment should be started according to best medical judgement weighing the benefits and risks. SARS-CoV-2 as with many viral infections may be amenable to multiple drugs early in its course but is probably not responsive to the same treatments when administration is given late in the hospital.[xvii] For the ambulatory patient with recognized signs and symptoms of COVID-19 on the first day (Figure 1), often with nasal real-time reverse transcription or oral antigen testing not yet performed, the following four therapies should be applied[xviii]: 1) nutraceuticals, 2) combination anti-infective therapy, 3) corticosteroids, 4) antiplatelet agent/antithrombotic therapy. For patients with cardinal features of COVID-19-like illness (fever, body aches, malaise, fatigue, nasal congestion, loss of taste and smell, etc) with pending or suspected false negative testing, therapy is the same as those with confirmed COVID-19.

Vitamins and Micronutrients:
There has been considerable interest and study of the use of nutraceuticals for COVID-19 prophylaxis and treatment in combination with anti-infectives as first proposed by Zelenko and colleagues.[xix] In general these agents are not curative but may be assistive in addressing deficiencies associated with COVID-19 mortality. Additionally, nutraceuticals discussed may aid in reducing viral replication and tissue damage. Zinc in combination with hydroxychloroquine or ivermectin is potentially synergistic in reducing viral replication by reducing the activity of polymerases.[xx] [xxi] This readily available nontoxic

micronutrient should be deployed at the first signs of COVID-19.[xxii] Zinc sulfate 220 mg (50 mg elemental zinc) can be taken daily.[xxiii] Vitamin D deficiency is common and has been associated with increased COVID-19 mortality and is commonly confounded by increasing age, obesity, diabetes, and lack of fitness.[xxiv] [xxv] A pilot trial of vitamin D supplementation suggested a reduced mortality in treated patients with acute COVID-19.[xxvi] 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.[xxvii] Presently, multiple randomized trials of vitamin C given intravenously or orally are planned or in progress.[xxviii] [xxix] A reasonable dose would be vitamin C 3000 mg po qd.

Quercetin is a polyphenol with theoretical mechanisms of action that could reduce the activity of a SARS-CoV-2 entry through the ACE2 receptor, inhibit viral proteases, and attenuate interleukin-6-mediated inflammatory responses.[xxx] [xxxi] Since this is only agent that would work at multiple levels of viral replication and immune response, it is conceivable that taken in combination with other nutraceuticals quercetin may play an assistive role in reducing early viral tissue damage. The suggested dose of quercetin is 500 mg twice daily.

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.[xxxii] 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.[xxxiii] 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 treatment. 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.

Combination Anti-Infective Therapy:
Immediately reducing the rate, quantity, and duration of viral replication, is a goal of anti-infective therapy started on the first day of symptoms. The rationale for immediate treatment is to lessen the degree of direct viral injury to the respiratory epithelium, vascular endothelium, and organs.[xxxiv] Maladaptive host responses that depend on replication of SARS-CoV-2 could be attenuated by early combination anti-infectives including activation of inflammatory cells, cytokines, endothelial injury, and thrombosis.[xxxv] Because SARS-CoV-2 infection is potentially fatal in patients over age 50 years and or with one or more comorbidities the use of at least two commercially available, anti-infective agents is appropriately considered clinically indicated, medically necessary "off-label" use.[xxxvi]

Antimalarials:
Hydroxychloroquine (HCQ), is an antimalarial/anti-inflammatory drug that impairs endosomal transfer of SARS-CoV-2 virions within human cells.[xxxvii] 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.[xxxviii] An online assemblage of HCQ studies is updated continuously and analysis of the findings support the following[xxxix]: 1) 63% of studies of HCQ late in the hospital course have demonstrated benefit, 2) 100% of the early treatment studies have been positive with a composite 64% relative risk reduction in the progression of disease, hospitalization and death.[xl] [xli] [xlii] The small randomized trials to date are inconclusive for the following reasons: 1) lack of placebo control, 2) no study drug accountability, 3) lack of blinding, 4) altered primary endpoints, 5) biased unblinded physician assigned endpoints (such as need for oxygen), 6) markedly truncated sample sizes due to premature administrative closure of enrollment, 7) pretreatment with other antivirals. HCQ 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 even in the setting of critical COVID-19 illness.[xliii] [xliv] Asymptomatic QT prolongation is a well-recognized and infrequent complication of HCQ. In the setting of critical illness, COVID-19 in the absence of HCQ or other QT-prolonging drugs has been associated with of the QT interval lengthening and polymorphic ventricular tachycardia. This has been attributed to cytokine storm and critical illness.[xlv] Thus far, data safety and monitoring boards have found no safety concerns in any monitored clinical trial of HCQ. Rare patients 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 cautionary plan of QTc monitoring in the ambulatory setting. A typical HCQ regimen is 200 mg bid for 5 to 30 days depending on continued symptoms.

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.[xlvi] This drug is well tolerated and has been combined with either doxycycline or azithromycin in early clinical studies of patients with COVID-19. While there are relatively few studies with clinical outcomes at the time of this report, it is reasonable in patients where HCQ cannot be used and favipiravir is not available, that IVM (200-400 mcg/kg [6-18 mg] single oral dose given every day or every other day for 3 dose administrations) could be the base of a multidrug regimen intended to reduce viral replication early in the course of COVID-19. However, there are considerable questions at this time on optimal dose and schedule.[xlvii] In the ICON study, IVM use in the hospital was associated with a 48% relative risk reduction in COVID-19 mortality.[xlviii] At the time of this writing, there are no large-scale, placebo-controlled trials of IVM in ambulatory treatment of COVID-19.

Favipiravir:

Favipiravir an oral selective inhibitor of RNA-dependent RNA polymerase is approved to treat COVID-19 in the ambulatory and hospital setting in China, Russia, and India.[xlix] Favipiravir has been shown to safe and it markedly reduced the time of viral nasal shedding to less than 7 days in most studies.[l] [li] Favipiravir should not be prescribed to women of childbearing potential. 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 where it is used to treat influenza.[lii] At the time of this writing, there are ambulatory clinical trials in progress, but they are not expected to report soon enough to impact the pandemic.

Azithromycin:

Azithromycin 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.[liii] French reports indicated that azithromycin in combination with HCQ was associated with truncated viral shedding, fewer hospitalizations, and reduced mortality combination with HCQ as compared to those untreated.[liv] [lv] Combination HCQ and azithromycin therapy has been utilized for acute COVID-19 in over 300,000 older adults with multiple comorbidities.[lvi] Azithromycin can prolong the QTc in <1% of patients and had been shown to be safe in co-administration with HCQ.[lvii] Azithromycin provides additional coverage of bacterial upper respiratory pathogens that could potentially play a role in concurrent or secondary infection. Thus, AZM can manage acquired or concurrent pneumonia with atypical organisms.[lviii] A reasonable regimen is 250 mg po bid for 5 to 30 days for persistent symptoms or evidence of bacterial superinfection.

Doxycycline:

Doxycycline is another common antibiotic with multiple intracellular effects that may reduce viral replication, cellular damage, and expression of inflammatory factors.[lix][lx] This drug has no effect on cardiac conduction and has the main caveat of gastrointestinal upset and esophagitis. Doxycycline has the advantage of offering upper respiratory antibacterial coverage with a high degree of activity against many common respiratory pathogens.[lxi] One of many dosing schemes is 200 mg po followed by 100 mg po bid for 5 to 30 days for persistent symptoms or evidence of bacterial superinfection.

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.[lxii] In COVID-19, some of the first respiratory findings are nasal congestion, cough, and wheezing. These features are due to excess inflammation and cytokine activation. Pre-hospital use of oral corticosteroids is a rational intervention for COVID-19 patients with these features as they would be in acute asthma or reactive airways disease.[lxiii][lxiv] The RECOVERY trial randomized 6425 hospitalized patients with COVID-19 in a 2:1 ratio to 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.[lxv] A meta-analysis involving 1703 critically COVID-19 patients found a 36% relative risk reduction in mortality.[lxvi] There are no justified safety concerns regarding prolonged viral replication with steroids.[lxvii] A clinical extension of these findings would be to employ steroids in COVID-19 patients at home on day five or beyond with moderate or greater pulmonary symptoms. Inhaled budesonide several times per day, dexamethasone 6 mg po qd, or prednisone 1 mg/kg po qd for five days with or without a subsequent taper could all be considered in the multidrug regimen.

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.[lxviii] 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 = .02).[lxix] 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 an myopericarditis. A dosing scheme of 0.6 mg po bid x 3 days followed by 0.6 mg po qd for 30 days can be considered.

Antiplatelet Agents and Antithrombotics:

Multiple reports have described SARS-CoV-2 induced hemagglutination and pathological macro and micro-thrombosis.[lxx][lxxi][lxxii] COVID-19 patients have described chest heaviness associated with desaturation that suggests the possibility of pulmonary micro-thrombosis.[lxxiii] Multiple reports have described elevated D-dimer levels in acutely ill COVID-19 patients which has been consistently associated with thromboembolic complications and death.[lxxiv][lxxv][lxxvi] Autopsy studies have described pulmonary micro-thrombosis in COVID-19.[lxxvii] These observations support the notion that endothelial injury, hemagglutination, and thrombosis are playing a role oxygen desaturation, a cardinal feature of COVID-19 pneumonia.[lxxviii] Because thromboxane A_2 is markedly regulated with SARS-CoV-2 infection, aspirin 325 mg per day can be administered as an initial antiplatelet and anti-inflammatory agent for 30 days.[lxxviii][lxxix][lxxx] Ambulatory patients can be additionally treated with subcutaneous low-molecular weight heparin or with short-acting novel anticoagulant drugs in dosing schemes similar to those use 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, anticoagulation 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 ~30% of cases,[lxxxi] however, pre-emptive use of low molecular weight heparin or novel or anticoagulants have been associated with >50% reduction in mortality.[lxxxii] Anticoagulants

particularly reduce mortality in COVID-19 hospitalized patients with thrombotic complications, elevated D-dimer levels, and higher comorbidity scores.[lxxxiii lxxxiv lxxxv] There are ambulatory randomized trials of aspirin and novel anticoagulants underway; however, given the large and substantial 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.

Delivery of Oxygen and Monitoring:

Early home treatment allows high-risk patients to recover in self -quarantine without risking spread of the virus to drivers, healthcare workers, and other patients in clinics and hospitals. Telemedicine is a reasonable platform for the initial evaluation and management of COVID-19. Clinical impressions of the patient can be gained with audio and video feeds. Key supplemental information includes self/family measurement of vital signs, temperature, and pulse oximetry.[lxxxvi]

Summary:
The SARS-CoV-2 outbreak is a once in a hundred pandemic that does not appear to be amenable to large, randomized trials conducted in outpatients. Because the illness gives a long window for treatment at home before late hospitalization, there is a therapeutic window of opportunity. Once infected, the only means of preventing a hospitalization in a high-risk patient is to apply treatment as an outpatient. Given the current failure of randomized clinical trials and the lack of instructive outpatient treatment guidelines, clinicians must act according to clinical judgement and in shared decision making with patients. Early sequenced, antibody and oral multidrug therapy based upon pathophysiology, treated natural history, and limited clinical trials in COVID-19 has a reasonable chance of success with an acceptable benefit-to-risk profile. Until the pandemic closes with vaccine-facilitated herd immunity, early ambulatory treatment should be considered in high risk acute COVID-19 beginning at the onset of illness.

Figure 1. Major dimensions of COVID-19 infection that call for a multi-drug strategy in the early ambulatory period with available medications
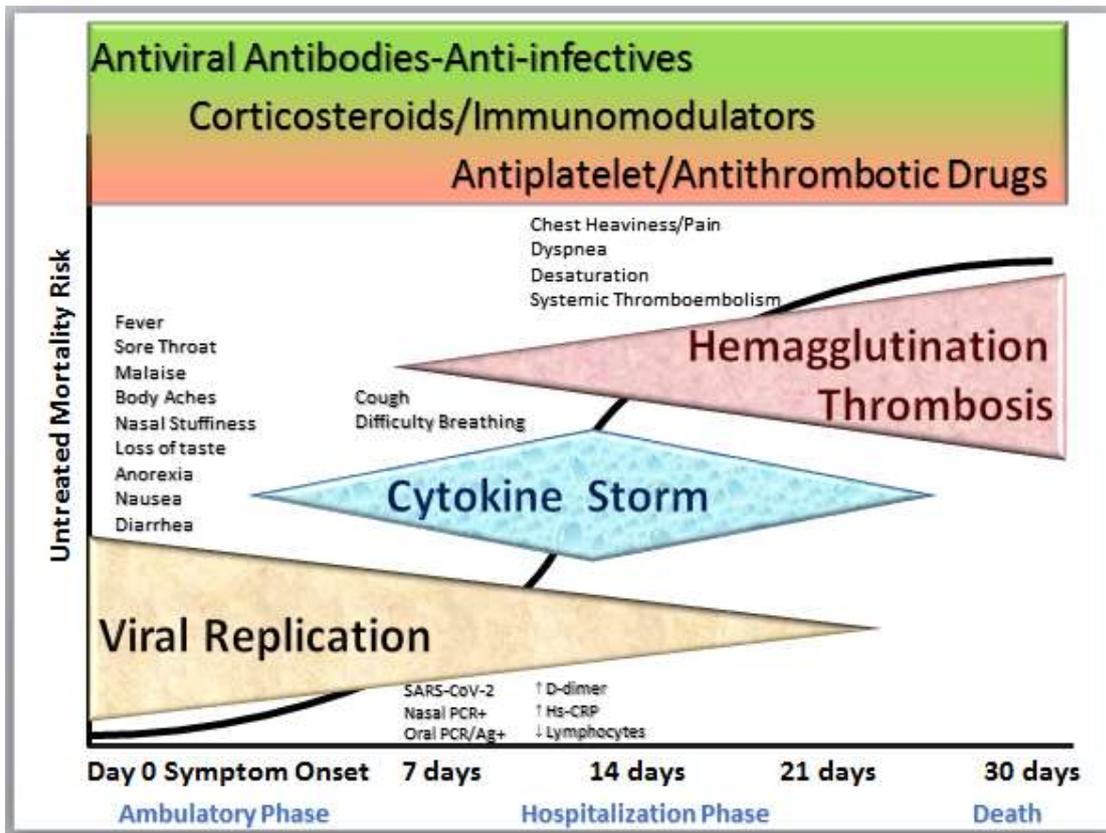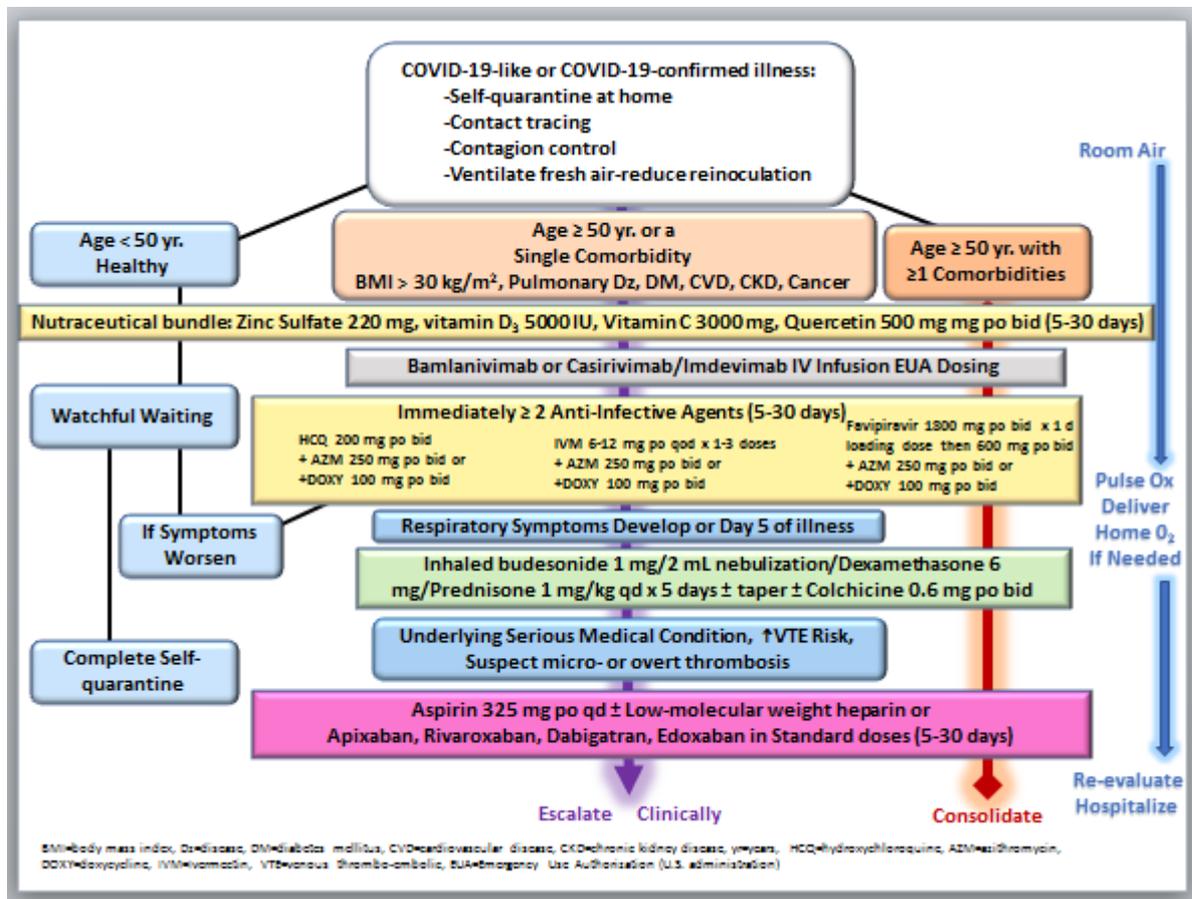
Figure 2. Treatment algorithm for COVID-19 like and confirm COVID-19 illness in ambulatory patients at home in self-quarantine. Yr=year, BMI=body mass index, Dz=disease, DM=diabetes mellitus, CVD=cardiovascular disease, chronic kidney disease, HCQ=hydroxychloroquine, IVM=ivermectin, AZM=azithromycin, DOXY=doxycycline, Mgt=management, Ox=oximetry, EUA=Emergency Use Authorization (U.S. administration)

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