Early Treatment of the Inflammatory Stage of COVID-19 and its rationale

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Abstract

COVID-19 is typically an acute infection caused by SARS-CoV-2 virus that lasts 2-3 weeks. However, in some instances the disease may worsen and lead to Acute Respiratory Distress Syndrome (ARDS) and multisystem damage that can result in long term disability or even death if not treated early and effectively.

This article focuses on the early inflammatory phase of COVID-19, which typically starts about a week after the onset of first symptoms associated with the initial viral stage. A readily accessible treatment option comprising well-known glucocorticoids, antihistamines, leukotriene antagonists and anticoagulants is included, and its rationale is given. This treatment option is especially relevant for general practitioners and emergency room clinicians and can be initiated prior to the need for hospitalization and in most cases may also prevent it.

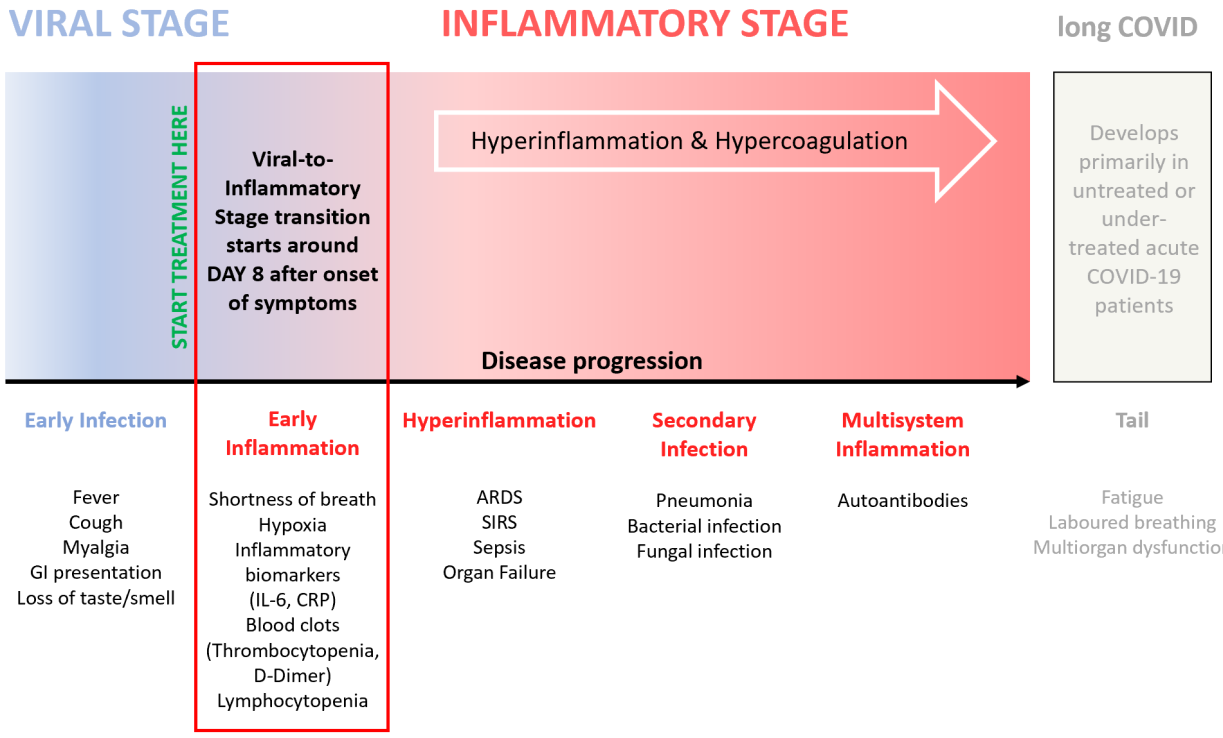

Figure 1: Viral-to-Inflammatory Stage Transition around Day 8 of symptomatic disease is an underutilized treatment window that may prevent escalation of the disease into hospitalization and death. Adapted from Griffen et al. [1].

The Two Major Stages of COVID-19:

In order to understand what treatment strategies are available to the medical community for treating or potentially preventing COVID-19 illness, it is essential to have a basic understanding of the disease course. COVID-19 exhibits distinctive stages (Figure 1) [1] and management of each stage is highly specific. The disease progresses through two major stages – the initial VIRAL STAGE (early infection) and subsequent INFLAMMATORY STAGE that can have multi-phasic course and complex manifestations.

The early **VIRAL STAGE** (early infection): SARS-CoV-2 infection begins with inhalation of viral-laden aerosols into the nasopharynx. These viral particles use spike protein for the attachment to membrane-anchored angiotensin-converting enzyme 2 (ACE2). This triggers endocytosis of SARS-CoV-2 allowing for host cell invasion and subsequent viral replication within the infected cells. ACE2 is expressed in the respiratory, gastrointestinal and reproductive tracts, skin, kidneys, heart, liver and neural tissues, and on endothelial cells, which explains the varied list of symptoms that can accompany COVID-19.

The viral incubation period until symptoms begin to appear ranges from 2-14 days and is dependent on age, comorbidities and the SARS-CoV-2 variant; the median time is 4-5 days [2]. If there are no symptoms by day 14 post-infection, it is unlikely that the person will develop symptomatic disease.

In symptomatic cases, viral replication dramatically increases 1-3 days post-infection and peaks around days 3-4 [1], which suggests that individuals are most infectious at this time. Early symptoms can include headache, fever, flu-like muscle and joint aches, extreme fatigue, dermatologic manifestations, and sometimes loss of taste or smell. In mildly infected patients, the viral load is generally below detection limit by day 10 after first presentation of symptoms, which corresponds with elevated serum immunoglobulin IgM and IgG [3, 4, 5], and 90-99% of recovered patients possess highly protective neutralizing immunoglobulins within 4 weeks of infection [6]. Severely infected or immune-compromised individuals may continue to have detectable viral RNA until day 20 and may even remain PCR positive weeks after hospital discharge.

The early viral stage usually lasts about 5 days after contracting the virus. People can either be asymptomatic, or display a mild fever, dry cough, aches and pains, gastrointestinal presentation, and sometimes loss of taste and smell. Mild to moderate illness including mild pneumonia reportedly accounts for 81% of cases [2].

The **INFLAMMATORY STAGE** can progress through increasingly complex phases that involve progressively more organ systems. The transition from the initial viral stage to the subsequent inflammatory stage typically occurs around the 8^{th} day post symptom onset and represents a considerable treatment opportunity window.

The suggested treatment protocol included at the end of this article is therefore named "8th day therapy protocol". It is also included as a convenient supplementary 1-page handout.

The **early inflammation phase** can occur between days 7-14 after onset of symptoms [1]. The patient may display shortness of breath and low levels of blood oxygen; chest X-rays and CT scans can reveal abnormalities in the lungs. Illness including dyspnea, hypoxia and more than 50% lung involvement on imaging reportedly accounts for 14% of cases [2]. Immune dysregulation during this phase can be diagnosed with circulatory biomarkers such as elevated pro-inflammatory molecules (IL-6 > 40 pg/mL, CRP $\geq$ 10 mg/L), blood clotting (< 150,000 thrombocytes/mm^3), fibrinolysis (D-Dimer $\geq$ 0.5 mg/L), lymphopenia (<1500 cells/mm^3) and eosinopenia (<450-550 cells/mm^3) [7]. If untreated, the patient can progress to the **hyperinflammation phase** that may result in ARDS, systemic inflammatory response syndrome (SIRS), or sepsis that can lead to cardiac and renal failure. Critical illness including respiratory failure, shock or multiorgan dysfunction reportedly accounts for 5% of cases, and the case fatality ratio at this phase is 2.3% [2].

The **secondary infection phase** in prolonged disease can lead to pneumonia and other secondary bacterial and fungal infections and is believed to be due to ongoing viral- or therapy-induced immune suppression.

The **multisystem inflammation phase** appears to be an autoimmune phenomenon that is hypothesized to be attributed to hyperstimulation of the immune system and/or molecular mimicry that leads to the production of autoantibodies [8].

The **tail phase**, sometimes referred to as "long COVID", is not well understood. Patient symptoms most frequently include fatigue and labored breathing. MRI scans have identified multiorgan dysfunction suggestive of ongoing inflammation many months after the onset of early infection [9]. Three different mechanisms have been proposed: post-viral fatigue syndrome, autoimmune-mediated responses, and/or persistent virus infection [10]. This phase appears to be related to untreated or insufficiently treated early acute disease.

Progression through early inflammation to hyperinflammation:

Inflammation is the innate immune system's defensive response to early SARS-CoV-2 infection and is essential for initiating long-term protective immunity provided by immunoglobulins and immune cells with cytotoxic capabilities. This innate inflammatory response against SARS-CoV-2 is initiated by sentinel cells of the mucosal immune system, which include epithelial cells lining the respiratory tract and underlying mast cells, dendritic cells, macrophages and granulocytes such as eosinophils. These cells express membrane and cytoplasmic pattern-recognition receptors (PRRs) that enable

them to recognize SARS-CoV-2. In turn, they become activated to release inflammatory cytokines, chemokines, vasoactive lipids and proteins, reactive oxygen species (ROS) and proteases, all of which are necessary for ensuring an effective innate host response against the pathogen. The release of pro-inflammatory cytokines (i.e. TNF-α, IL-1 and IL-6) by these sentinel cells alerts and activates neighboring cells to respond to infection. These cytokines are also responsible for initiating the acute-phase response, which includes initiating the release of acute-phase proteins such as CRP from the liver, fever and sickness behaviour (i.e. anorexia, muscle and joint aches, fatigue and depression). Sentinel cells also release chemokines that recruit effector neutrophils and monocyte-derived macrophages from the circulation to the respiratory battlefront. They also secrete ROS that possess antimicrobial and cytotoxic properties.

When mast cells become activated, either by PRRs or Fc receptors that bind to SARS-CoV-2-specific immunoglobulins, they release vasoactive lipids (i.e. prostaglandins, thromboxanes, prostacyclins and leukotrienes). These lipids contribute to immune cell trafficking and activation, the fever response, and platelet aggregation that can lead to clotting to prevent vascular leakage from damaged blood vessels. Mast cell granules also contain complement proteins C3 and C5, and proteases that convert C3 and C5 into bioactive C3a and C5a following degranulation. In addition to being vasoactive, these C3a and C5a anaphylatoxins have a variety of other functions that can include activating the complement system, initiating the release of vasoactive histamine from mast cells and eosinophils, and recruiting effector neutrophils. Mast cell granules also contain kallikrein proteases that act on hepatic kininogens to produce bradykinin, which is also vasoactive and is involved in neutrophil recruitment and activation [11].

It is essential that the inflammatory response be tightly regulated during early COVID-19 to ensure it effectively destroys SARS-CoV-2, initiates protective long-term immunity, and minimizes collateral tissue damage. Immune dysregulation is believed to be the cause of progression from early inflammation to hyperinflammation and later phases of COVID-19 [7, 12]. Two overlapping hypotheses have been brought forward to explain this dysregulation. The first being the “cytokine storm” hypothesis, whereby high levels of circulating pro-inflammatory cytokines are thought to be responsible for the multisystem pathological manifestations of COVID-19. This uncontrolled inflammation contributes to vascular leakage within the lungs and cell necrosis that results in autoinflammation [13]. The second hypothesis, referred to as the “bradykinin storm”, highlights the importance of reduced availability of lung epithelial cell ACE2 during SARS-CoV-2 infection. ACE2 is physiologically responsible for inactivating vasoactive angiotensin II and bradykinin. When ACE2 function is impaired, this is associated with acute lung damage and inflammation resulting in fluid retention and decreased gas permeability. Overexpression of IL-6 also leads to increased expression of epithelial cell bradykinin receptors and downregulation of the bradykinin suppressor

SERPINA12, which means epithelial cells are more responsive to vasoactive bradykinin during the cytokine storm [13].

Early treatment of the inflammatory stage:

Clearly, this disease is complex, incompletely understood and involves many mediators, all of which contribute to the pathology. At the outset, there were no gold-standard, randomized, double-blind, placebo-controlled trials that established treatment, especially for the post-viremic stage of the disease. Thus, desperate patients were simply told, “go home, take Tylenol and return if your breathing becomes difficult”. This approach has been completely inadequate and has allowed a critical treatment window to be missed. As daunting as it may be, physicians and other health care workers around the world have stepped up and tried a wide range of therapies where none existed previously. Some of their protocols have now been published, while many others have appeared in case reports, or in pre-prints. It is beyond the scope of this document to address all the reports of successful treatments for the inflammatory phase. Nevertheless, we feel obliged to share enough information to help the average family doctor keep their patients alive and out of the hospital. We conclude with a description of an unremarkable but remarkably successful therapy using over the counter antihistamines and glucocorticoids. The time at which family doctors might apply critical pharmacological therapy is the early inflammation phase, which some refer to as Day 8. It is at this point that patients often start to improve, or enter the serious hyperinflammatory phase, diving into more severe pulmonary incapacitation and potentially death. At this point, mast cells may come to the forefront through mast cell activation syndrome (MCAS), which has an incidence of ~17% in COVID-19 subjects, similar to that of the proportion of subjects who progress beyond mild COVID-19. According to this scheme, mast cells become intensely involved in the disease process discharging copious quantities of the many mediators described above. With the multitude of active substances released in this highly inflammatory process, physicians have tried many different therapeutic approaches that are commonly used for treating the inflammation associated with rheumatoid arthritis, asthma, chronic obstructive pulmonary disease (COPD) or systemic lupus erythematosus (SLE). Drugs common to a number of useful protocols include glucocorticoids, antihistamines and leukotriene antagonists and anticoagulants.

Glucocorticoids**:** A specter of glucocorticoids such as prednisone, hydrocortisone, and dexamethasone are commonly used in family medicine, and in fact, are the standard of care for many inflammatory conditions. Glucocorticoids are now a widely accepted treatment for COVID-19. The RECOVERY Trial provided support for the use of oral glucocorticoids, as dexamethasone resulted in a significantly reduced mortality rate [14]. In addition, there have also been reports of inhaled budesonide’s success. For example, Ramakrishnan et al. [15] conducted an open-label parallel-group phase 2 randomised controlled trial of inhaled budesonide, compared with usual care, in adults

within 7 days of the onset of mild COVID-19 symptoms; urgent care visits occurred in 14% of control subjects and only 1% of budesonide subjects.

Antihistamines: In a similar way, family doctors have extensive experience in using antihistaminic medications to treat mast cell and eosinophil hypersensitivity reactions, and this is the standard of care in such situations. Many doctors have also reported benefits of using antihistamines for treating COVID-19; among the many successful therapies, glucocorticoids and antihistamines are among those most often reported. Antihistamines act as histamine (H) receptor antagonists and target different H receptors. There are four types of H receptors: H1 receptors are abundant on vascular smooth muscle, mast cells, endothelial cells and in the brain; H2 receptors are expressed in gastric mucosa, cardiac muscle and in the brain, H3 presynaptically act as autoreceptors, and H4 receptors are expressed by various immune cells including mast cells, eosinophils and neutrophils. Only H1 and H2 antagonists are well developed and readily available; fortunately, these have been reported to be useful in the treatment of COVID-19. An example of antihistamine success is described by Morán Blanco et al. [16], who tested the effect of H1 receptor antagonists (Dexchlorpheniramine, Cetirizine, or Loratadine) on 84 residents (mean age 85 years old) in two nursing homes in Yepres, Spain; in 25 subjects, Azithromycin was added. No hospitalizations or deaths occurred in this treatment group, although they all had positive test results for COVID-19 by the end of the study period. In the comparison group of 1084 subjects living under similar conditions in Albacete, about 200 km away, the death rate was 28%. Similar observations have been made with respect to H2 receptor antagonists. Initial anecdotal reports of observations of COVID-19 patients in Wuhan, China and New York already taking Famotidine for stomach acid control found a lower incidence of death than those not taking this H2 receptor antagonist. Hogan et al. [17] also studied the effectiveness of dual blockade with H1 and H2 receptor antagonists in a group of 110 COVID-19 positive inpatients (mean age 64 years old, ethnic makeup was majority Black with the balance White and other) with severe and critical pulmonary symptoms. The patients were given both Cetirizine and Famotidine for ≥ 48 h, in addition to standard of care therapy. The primary endpoint was death, which was found to be 16% when do not resuscitate patients were included, and 8% when they were not; this compares with 30.9% (in Atlanta critical ICU-only patients), 23.6% in Louisiana, 21% in New York City, 25.7% in the RECOVERY trial in the United Kingdom and 21.9 and 28.3% in Wuhan, China. Overall, Hogan et al. found that the combination of Cetirizine and Famotidine resulted in about one-third fewer deaths.

It is important to point out that some other reports about antihistamine treatment have been less positive. A Famotidine study by Yeramaneni and colleagues [18] is one such example. These authors identified patients who tested positive for SARS-CoV-2 and monitored the 30-day all-cause mortality as the primary outcome. In-hospital Famotidine use, regardless of dose or route, within 24 hours of hospital admission served as primary intervention. Post-match 30-day mortality was 15.1% amongst Famotidine users versus 9.5% for non-Famotidine users (P = .007). Unfortunately for

this study, the Famotidine users were on average 6 years older ($P < .0001$), with higher WHO disease severity score ($P < .0001$). This, together with late therapy initiation, might explain the perceived lack of Famotidine benefit.

The question about whether H receptor blockade is critical for Famotidine efficacy, or if it involves an off-target mechanism has been explored by Malone et al. [19] using computer-assisted interrogation of Famotidine to identify potential binding sites. After articulating four potential mechanisms and conducting the experiments, these authors ruled out three off-target sites and concluded that Famotidine was indeed acting through its well-known H receptor blocking action. On the basis of this report, and the other evidence regarding antihistamines, we suggest that both H1 and H2 receptor antagonists, or inverse agonists, should be considered in the treatment of patients with established COVID-19 in the post-viremic stage.

Leukotriene antagonist: Once the role of mast cells and their release of various mediators in the hyperinflammatory pulmonary phase of COVID-19 was appreciated, it was logical to hypothesize a specific role of leukotrienes, and to suggest testing efficacy of a leukotriene antagonist to mitigate disease severity. In support of this, Montelukast has been shown to alter the pulmonary response to antigen, tissue eosinophilia and IL-5 expression by inflammatory cells and decreased elevated levels of IL-1β and IL-8 in humans with viral upper respiratory tract infections [20]. In a more recent study, Khan et al. [21] conducted a retrospective analysis in which 30 patients who received Montelukast at the direction of their doctors were compared with 62 patients who did not receive this drug. All patients identified were confirmed to have a diagnosis of COVID-19. The patients who received Montelukast were started on day 1 of hospital admission with the standard oral dose of 10 mg/day, and none had previously been treated with the drug. Clinical status was assessed according to the COVID-19 Ordinal Scale for clinical improvement. Clinical deterioration from day 1 to day 3 occurred in 10% of the Montelukast treated patients as compared to 32% in nontreated patients ($p = 0.022$). Despite the imperfect match between the Montelukast and control groups, we take this as good support for the consideration of this leukotriene antagonist for the treatment of COVID-19. A randomized clinical trial (NCT04389411) is in progress with a projected completion date of December 2021. While we await these results, it may be unethical to deprive patients of treatment with Montelukast.

Anticoagulants: The role of thrombosis in COVID-19 is essential and has been reviewed by Hanff et al. [22]. Clearly thrombosis contributes to the pathology during the inflammatory phase of the disease. Meizlish et al. [23] tested the effects of both anti-coagulant therapy (Enoxaparin or Heparin) and anti-platelet therapy (81 mg Aspirin) in a large, retrospective study of 2,785 hospitalized adult COVID-19 patients, and both treatments were shown to be effective in lowering the mortality rate. In spite of the fact that this was a retrospective study, the indisputable death endpoint increases the

validity of the study. In terms of practicality, aspirin is far more convenient to administer and much less expensive than either Enoxaparin or Heparin.

The 8th day therapy protocol:

A common theme among the many treatment protocols that have been shared internationally is aggressive multi-targeted treatment in the early phase of COVID-19 [24]. A key consideration is that these treatments employ well-known drugs with modest risks of adverse effects in comparison to the high risk of morbidity and death associated with COVID-19 when it is allowed to progress untreated or under-treated.

An example protocol that has recently gained attention is that of Dr. Shankara Chetty, a family physician in South Africa [25], who has had extensive experience with a treatment combination based on glucocorticoids, H receptor blocking agents, leukotriene antagonists and Aspirin in his COVID-19 patients.

Dr Chetty's protocol focuses on the 8th day after onset of COVID-19 symptoms, which approximates the early inflammatory phase. This 8th day protocol does not cover the initial viral phase, which requires a somewhat different approach. Of course, it is preferable to start the treatment at the viral stage of the disease. Yet, many patients contact their family practitioner several days after their first symptoms, which reduces the effectiveness of protocols focusing on the viral stage of COVID-19.

As the transition from the initial viral stage to the early inflammatory stage typically occurs around day 8 after the first symptoms, it is essential for the treating physician to establish as precisely as possible the first day of symptoms. The patient should be alerted of the date when a possible sudden aggravation of symptoms may occur, and shortness of breath is typically associated with this aggravation.

The "8th Day Therapy" encompasses 4 distinct interventions listed below. Possible drug interactions need to be carefully assessed:

<u>Intervention #1 Corticosteroids</u>: The goal is to mitigate the inflammatory reaction by attenuating the release of inflammatory mediators and to prevent immune dysregulation such as a possible subsequent cytokine storm. Medication: Prednisone 80 mg daily for 1 week. Note: Increase dose rapidly to get symptomatic relief quickly. CRP and IL-6 values must show quick decline. Dose will vary according to SARS-CoV-2 variants and severity of the inflammatory reaction. Can go as high as 100 mg tid for first few days. Wean off cautiously when CRP and IL-6 are normal or patient is well for a few days.

<u>Intervention #2 Antihistamines</u>: The goal is to block histamine that has been released. H1 antagonist: Promethazine 25 mg tid x 5 days or Levocetirizine 5 mg bid x 1 month following Promethazine to reduce somnolence. H2 antagonist: Cimetidine 400 mg daily x 1 month, or another H2 blocker such as Famotidine is suitable.

Intervention #3 Leukotriene antagonist: The goal is to block leukotrienes that have been released. Montelukast 10 mg bid x 5 days then daily x 1 month.

Intervention #4 Anticoagulants: The goal is to avoid thrombosis. ASA (Aspirin/acetylsalicylic acid) 325 mg daily x 1 month. Add Ribaroxaban (Xarelto) 15 mg bid if D-dimer is elevated; decrease to 15 mg once daily x 1 month when D-Dimer returns to normal.

Additional interventions may be needed, according to clinical judgement, for bacterial co-infection or other complications.

Discussion:

The classic presentation of early stage COVID-19 includes flu-like symptoms, fever, shortness of breath and fatigue that lasts 5-7 days. The majority of patients then improve and go on to recovery. Often in this stage of the disease, little is offered but supportive medications such as Acetaminophen. Usually, the patient is left with no instructions other than to self-isolate and only present to the emergency room if they become worse. This is consistent with the COVID-19 Clinical Management Living Guidance of the WHO [26].

In a minority of patients, the early inflammatory phase of COVID-19 begins to present around the 8th day from when the very first symptoms of the disease began. Increasing shortness of breath is the symptom which heralds this change, and often drives the patient to primary care or emergency room physicians to seek help. This change in status can be rapid and devastating in some patients.

It is practice in some places to use protocols in the early disease, which include anticoagulants and steroids, or even antiviral early treatments, however, this is generally not the norm.

The 8th day is a crucial time that requires the immediate addition of appropriate medications to target the causes of this sudden downward turn in clinical status of the patient. Aside from benefiting the patient, possibly being lifesaving and preventing long COVID syndrome, this timely treatment can help avoid hospital admission and unnecessary pressure on the healthcare system. It also markedly reduces costs to both, the system and the patient.

In this paper, we have presented and discussed a therapeutic strategy using a combination of medications including high dose glucocorticoids, antihistamines, leukotriene antagonists and anticoagulants. These medications are well-known and frequently used world-wide in any medical practice and are indeed the standard of care in diseases which are the results of similar pathophysiological mechanisms as those

found in this phase of COVID-19. The relatively high doses are used for only a short period of time (3-5 days) and are often safely used by physicians for longer periods of time in escalations of severe autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus.

While analyzing the pathophysiology and pharmacology related to the early inflammatory phase of COVID-19, this article explains how common medications best address the symptoms that are developing in these patients. It also explains why it is crucial to both educate the patient to be on high alert for the onset of possible day 8 worsening of symptoms, and for the physician in charge to begin these medications immediately. This practice has the potential to significantly decrease the risks of hospitalizations, intensive care unit admissions, patient ventilation, long COVID-19 syndrome and death.

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DR CHETTY'S 8TH DAY THERAPY FOR COVID-19

This one-pager summarizes the therapy adopted by Dr Shankara Chetty, from South Africa, to help prevent COVID-19 from progressing towards severe disease. The document focuses on the 8th day onwards of COVID-19, i.e. the inflammatory phase. It does not cover the initial viral phase, for which early treatment protocols already exist and can be prescribed before. The document is for information only, not for therapeutic advice. If you catch COVID-19, please seek immediate medical help.

The 8th Day Therapy aims at mitigating a possible hypersensitivity reaction, that can trigger an inappropriate immune response, including a possible subsequent cytokine storm. This transition from the initial viral phase typically occurs on Day 8 after the first symptoms. It's essential for the treating physician to establish as precisely as possible the first day of symptoms, to alert the patient of the date when a possible sudden aggravation of symptoms may occur. Shortness of breath is typically associated with this aggravation.

The 8th Day Therapy encompasses 4 distinct interventions. They sometimes follow a previously prescribed early treatment protocol. Possible drug interactions need to be carefully assessed.

Intervention #1: Corticosteroids

Goal: To stop the hypersensitivity reaction, to stop the release of mediators and to prevent an inappropriate immune response, including a possible subsequent cytokine storm.

Medication: Prednisone 80mg dly x 1 week.

Note: Increase dose rapidly to get symptomatic relief quickly. CRP and IL6 values must show quick decline. Dose will vary according to variants and severity of reaction. Can go as high as 100mg tds for first few days. Wean off cautiously when CRP and IL6 are normal or patient is well for a few days. Those with prolonged reactions are difficult to wean, so consider adding Azathioprine 50mg dly to decrease steroid requirements.

Intervention #2: Anti-histamines

Goal: To clear the histamines that have been released.

Medications:

H1: Promethazine 25mg tds x 5 days or Levocetirizine 5mg bd x 1 month to follow Promethazine

H2: Cimetidine 400mg x 1 month or another H2 blocker

Other anti-histamine drugs can be suitable

Intervention #3: Anti-leukotrienes

Goal: To clear the leukotrienes that have been released.

Medication: Montelukast 10mg bd x 5 days then dly x 1 month

Intervention #4: Blood Thinners

Goal: to clear platelet activating factors

Medications:

Aspirin 325 mg dly x 1 month.
Add Xarelto 15 mg bd if D.Dimer is raised; decrease to 15 mg dly x 1 month once D.Dimer is normal

Optional Interventions

- Add appropriate antibiotics for those with fever, bacterial co-infection or raised Procalcitonin levels
- Add Venteze syrup PRN for those suffering from asthma
- Add Ivermectin 12 mg dly x 5 days in those with cough, dyspnea or decreased oxygen saturation
- Fluvoxamine may be a suitable drug, yet Dr Chetty has so far no experience with it.

By Dr Shankara Chetty, MD, with the editorial assistance of JP Kiekens / covexit.com
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***For any questions, please use this form**.*