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The Advent of COVID-19; Periodontal Research Has Identified Therapeutic Targets for Severe Respiratory Disease; an Example of Parallel Biomedical Research Agendas

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The pathophysiology of SARS-CoV-2 infection is characterized by rapid virus replication and aggressive inflammatory responses that can lead to acute respiratory distress syndrome (ARDS) only a few days after the onset of symptoms. It is suspected that a dysfunctional immune response is the main cause of SARS-CoV-2 infection-induced lung destruction and mortality due to massive infiltration of hyperfunctional neutrophils in these organs. Similarly, neutrophils are recruited constantly to the oral cavity to combat microorganisms in the dental biofilm and hyperfunctional neutrophil phenotypes cause destruction of periodontal tissues when periodontitis develops. Both disease models arise because of elevated host defenses against invading organisms, while concurrently causing host damage/disease when the immune cells become hyperfunctional. This represents a clear nexus between periodontal and medical research. As researchers begin to understand the link between oral and systemic diseases and their potential synergistic impact on general health, we argue that translational research from studies in periodontology must be recognized as an important source of information that might lead to different therapeutic options which can be effective for the management of both oral and non-oral diseases. In this article we connect concepts from periodontal research on oral inflammation while exploring host modulation therapy used for periodontitis as a potential strategy for the prevention of ARDS a deadly outcome of COVID-19. We suggest that host modulation therapy, although developed initially for management of periodontitis, and which inhibits proteases, cytokines, and the oxidative stress that underlie ARDS, will provide an effective and safe treatment for COVID-19.

Keywords: COVID-19, SARS-CoV-2, periodontal research, ARDS, PMN hyperactivation

INTRODUCTION

The outbreak of viral pneumonia cases from SARS-CoV-2 was first reported by the Chinese government in December 2019 (1). As with other viral diseases SARS-CoV-2 can cause various respiratory infections, including multifocal interstitial pneumonia which was leading to admission to intensive care and death in infected patients (2). This infection, named Coronavirus disease 2019 (COVID-19) (3), can cause complications including the development of acute respiratory distress syndrome (ARDS); an often fatal disorder (2, 4).

ARDS is caused by many pathogens including influenza and coronavirus. Although its precise pathophysiologic mechanisms are not completely clear, it could be the result of direct damage caused by the viral pathogen and then, more importantly, the triggering of a complex dysregulation of the inflammatory environment (5, 6). Indeed, it has been argued that the host-mediated lung and other tissue damage has more to do with the massive infiltration of polymorphonuclear neutrophils (PMNs) in the lungs rather than purely direct viral effects in relation to morbidity and mortality (4, 6, 7).

Immuno-Inflammatory Pathogenesis of COVID-19

Data from cohorts of critically ill patients with COVID-19-related pneumonia provide evidence of cytokine profiles like those of hyperinflammatory states seen in bacterial and viral pneumonias (4, 8). SARS-CoV-2 invades the host cell by binding of its viral spike glycoprotein to the host's cellular receptor for ACE2. Once in the cell, the virus may "deceive" the immune system through strategies that prevent pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) from recognizing pathogen-associated molecular patterns (PAMPs) and will start replicating freely within the infected cells using their own organelles and other cellular components (9). In addition, SARS- CoV-2 has also evolved strategies that interfere in the production of type I/III IFN which are essential for the development of effective immunity (9). As a result of this state of unchecked replication, SARS-CoV-2 can reach high titres shortly after initial infection that leads to an exponential production of PAMPS, cell damage and release of damage-associated molecular patterns (DAMPS), all of which triggering a hyperactive inflammatory responses (10).

The attachment of SARS-CoV-2 to ACE2 for host cell entry leads to down-regulation of ACE2 and a subsequent increase of angiotensin II (ANGII) (11–16) which dysregulate the renin-angiotensin system (RAS) (17). In elevated levels, ANGII acts as a pro-inflammatory mediator that ultimately activates NFκB, disintegrin, and metalloprotease 17 (ADAM17) (18). This activated pro-inflammatory environment triggers the production of reactive oxygen species (ROS), fibrosis, matrix metalloproteinases (MMPs), production of cytokines such as IL-6 and IL-8 by macrophages and recruitment of PMNs. The virus also activates NFκB (11, 15) that amplifies downstream signaling for cytokine production (14, 15). The release of cytokines activates pathogenic T helper type 1 (Th1) cells rapidly which then secrete additional pro-inflammatory cytokines (11, 12, 19). This is followed by additional infiltration of macrophages and PMNs into alveolar cavities where they begin to contribute to the hyper-inflammatory response (11, 14, 15). ANGII is also known to trigger the coagulation cascade by activating platelets through surface AngII receptors binding and inducing platelet shape change (20) both of which associated with thrombosis (21). In summary, SARS-CoV-2 binding to ACE2 for cell invasion is likely the first step for activation of the cytokine storm which releases uncontrolled levels of cytokines, including IL-1β, 1L-6, IL-8, and IL-10 (22), that prime the host for development of hyperactive inflammatory responses. Manifestation of the cytokine storm is extremely complex but in general in addition to virus-induced infiltration of inflammatory cells to the lungs causing oxidative stress and initial inflammation it relies on even more PMN infiltration into the lung whereby cytokines, MMPs, PMN elastase, ROS, and nitric oxide (NO) are released into the inflamed tissue (22, 23) causing diffuse alveolar damage, pulmonary edema, pulmonary fibrosis, acute lung tissue destruction, multiple organ failure and death. These developments essentially describe ARDS as seen in patients suffering from COVID-19 (11–16).

PMNs are the first and most numerous innate immune cells to reach the infection site and therefore play a central role in the resolution of inflammation through specific mechanisms of virus inactivation including the release of MMPs, cytokines, ROS, peroxidases and PMN extracellular traps (NETs) (24). This is of course protective. But PMNs can also become "hyperactive," and when this happens, PMNs contribution to antiviral defense can cause harmful effects to the host including the development of pneumonia and ARDS (25–27). Paradoxically then, despite the critical roles played by PMN cells insofar as clearance of viral pathogens and other infectious disease is concerned it's recognized that excessively sensitized/activated PMN responses promote a vicious cycle of inflammatory damage to the very tissues to which they were dispatched as a consequence of a PMN-induced cytokine storm (24). Notably, MMP-2 and−9 destroy the extracellular matrix in the lungs by degrading collagen found in the basement membrane comprising their parenchymal architecture (22). The virucidal effects of ROS and the recruitment and activation of even more PMNs through the production of cytokines can perpetuate the hyperinflammatory response thereby leading to lung and other tissue injuries including the development of vasculitides and thrombotic conditions characteristic of ARDS (24, 27). In addition, ROS production further increases vascular and epithelial permeability, allowing for continuous infiltration of PMNs and serosanguinous exudates into the alveolar space (27). Finally, the formation of NETs aided by activated platelets in response to endothelial damage, ROS and IL-1β production and virus replication may increase the risk of thromboembolic events in COVID-19 patients by triggering complement activation and further fuelling the coagulation cascade (9) (**Figure 1**).

A summary of the role of PMNs on the severity of COVID-19 in recent studies is shown in **Table 1**.

To prevent this, we hypothesize that any treatment which could prevent excess PMN infiltration and hyperactivation while also blocking excessive levels of MMP activity, elastase activities

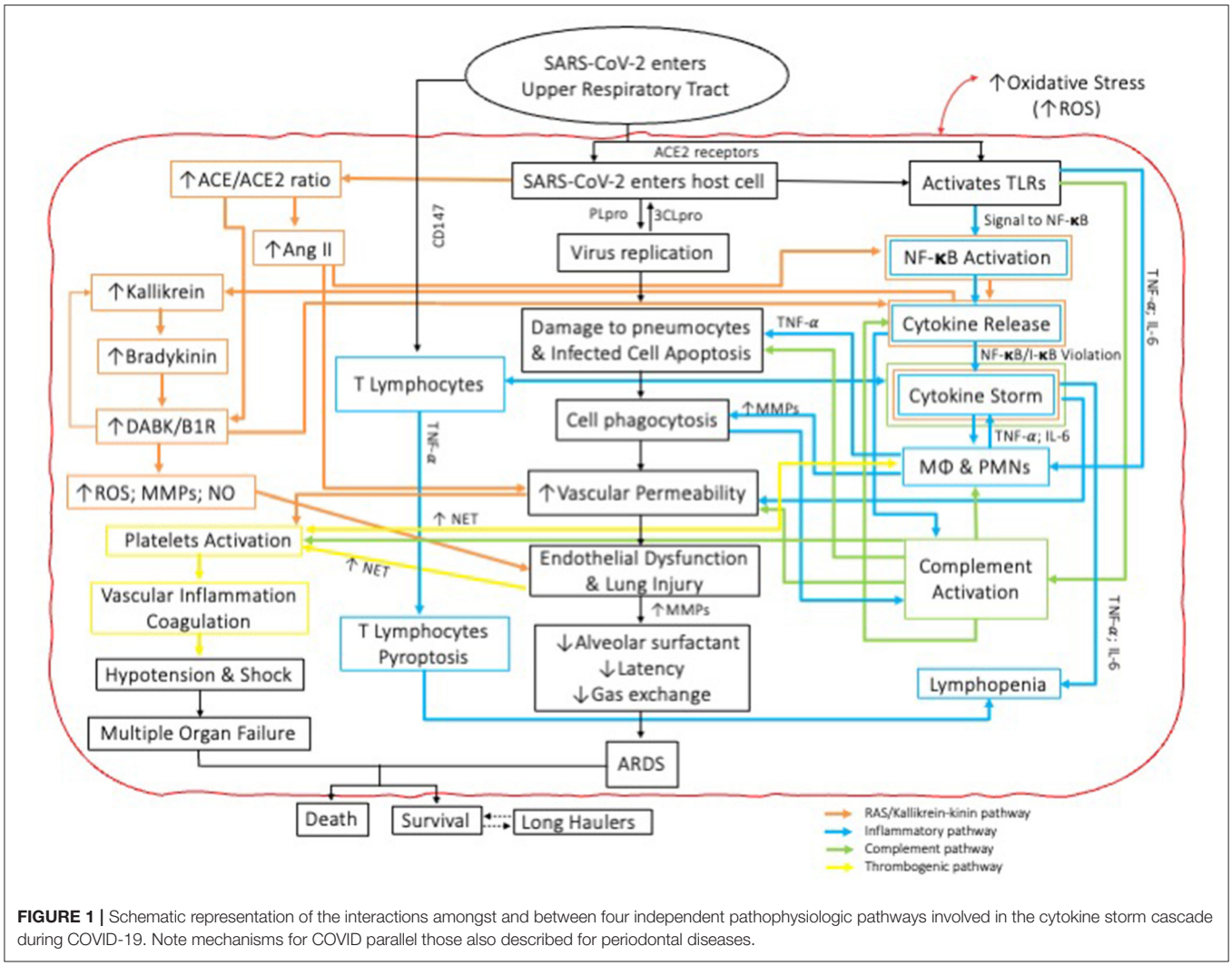

FIGURE 1 | Schematic representation of the interactions amongst and between four independent pathophysiologic pathways involved in the cytokine storm cascade during COVID-19. Note mechanisms for COVID parallel those also described for periodontal diseases.

and simultaneously reducing excessive ROS levels or activity might represent a useful approach to the prevention and/or amelioration of the morbidity and mortality associated with the cytokine storm/ARDS in patients with COVID-19.

Links Between Oral Inflammation and Systemic Disease

As researchers begin to understand the link between oral and systemic diseases more clearly and their potential synergistic impact on general health, we argue that translational research from studies in periodontology must be recognized as an important source of information that might lead to new and different therapeutic options which can be effective for the management of both oral and non-oral diseases.

While evidence of associations between periodontal diseases and systemic conditions have long been noted (36), there has been increased interest in determining the underlying mechanisms that might explain the oral-systemic pathophysiology. We suggest that a causal and indeed bidirectional link may exist between periodontitis and systemic non-communicable diseases. However, we also have to recognize that they could also be manifestations of common underlying pathophysiological mechanisms. This said, these two concepts are not mutually exclusive, and therefore we must emphasize that both putative mechanisms could be involved in those associations, as demonstrated by studies that show bidirectionality of association. For instance, early epidemiological studies have demonstrated the bidirectional adverse interrelationship between an altered host inflammatory response in PD and the metabolic imbalance in diabetes (37) while more recently, a causal association was demonstrated between periodontitis and chronic kidney diseases mediated *via* oxidative stress (38), which seems highly relevant to this argument. We also point out that oxidative stress is a key element of PMN hyperfunctionality related to overproduction of ROS and downregulation of endogenous antioxidants such as NrF2 mediated expression of superoxide dismutase (39). Inflammation is therefore the common factor amongst periodontitis and the chronic diseases of aging, or simply "the disease" (40). Insofar the individual's susceptibility to systemic diseases, our research support the hypothesis that PD sensitizes or primes the peripheral innate immune system, and predominantly the

TABLE 1 | Summary of the role of PMNs on the severity of COVID-19 in recent studies.

As predictors of poor outcomes	Higher PMN counts in non- survivors than in survivors (4)
	Increased NET formation associated with COVID-19–related ARDS (28)
	Increased NET formation as a potential biomarker for disease severity (28)
	PMN-to-lymphocyte ratio as the most promising predictive factor for critical illness incidence of COVID-19 pneumonia (29)
	Markers of PMN activation amongst the most potent discriminators of critical illness (30)
	PMN activation preceding the onset of critical illness and predicting mortality (30)
	Higher levels of specific markers of NETs in patients receiving mechanical ventilation than in those breathing room air (31)
	Neutrophilia observed In the last 24 h preceding death (32)
	NETs infiltrate in lungs of patients with a fatal outcome (32)
	Dramatic increase of PMNs with COVID-19 severity and ARDS (33)
	Increased number of circulating PMNs as an indicator of worse outcomes (2)
Linked to dysregulated immune response	Blood PMNs produce high levels of NETs; NETs are highly detected in the tracheal aspirate and lung tissue (34)
	SARS-CoV-2–activated PMNs induce lung epithelial cell death through the release of NETs (34)
	PMN activation-associated signatures prominently enriched in severe patient groups (35)
	Dysregulated NET formation in lungs (6)

PMNs in such a manner as to allow those cells to trigger and/or exacerbate inflammatory diseases in distant organ systems (41).

Periodontal Disease-Induced Immunopathology and COVID-19

The oral cavity is unique in that the teeth are the only structures in the body that *de facto* protrude through the lining epithelium, in this case the gingival tissues. As such a unique seal exists between the gingiva and tooth surfaces and therefore between the oral cavity and its contents thereby preventing ingress of microbial or other pathogens into the body (42). This biologic seal, specifically a connective tissue and epithelial attachment to cementum, is not perfect and is permeable even in health but moreso in states of inflammation. To enhance protection from pathogens, cells of the innate immune system such as PMNs, are recruited constantly to the oral cavity as part of a healthy and self-limiting inflammatory response against the challenges imposed by the oral microorganisms found in the dental biofilm (43). Interestingly, while bacteria or their by-products may lead to periodontal tissue damage, the host immunoinflammatory response to microorganisms in dental biofilms, when uncontrolled, is considered the main cause of periodontal pathogenesis (40, 44), something akin to destruction of lung tissues observed in ARDS. In parallel to what is seen in ARDS, the initial host immune response starts when PRRs expressed in the membrane of epithelial cells and gingival fibroblasts interact with PAMPs, including lipopolysaccharide (LPS) found in the cell wall of specific periodontal bacteria (45). LPS is considered a potent ligand for TLR4 (46) and activation of both the TLR2 and TLR4 pathways has been described in studies with *Porphyromonas gingivalis* (47). PAMP-TLRs binding and MyD88 signaling results in the activation of the downstream signaling pathways associated with inflammation and upregulation of pro-inflammatory transcription factors, such as NFκB (48), leading to the release of inflammatory cytokines and chemokines (49, 50). The most common cytokines involved in this process are TNF-α, IL- 1β, IL-6, and IL-8 (51, 52), while chemokines include CXCL8/IL-8, CCL2, CCL3, and CCL5 (49, 50) and their release causes vasodilation and chemical gradients that facilitate the migration of leukocytes, mostly PMNs from the vasculature to the site of injury (53). Infiltration of such inflammatory cells leads to release of ROS, MMPs and NETs, as well as to chemotaxis and phagocytosis as defense mechanisms against infection and inflammation (54–58). However, as periodontal diseases are not considered as a classic bacterial infection but rather a dysbiotic disease such mechanisms are necessary but possibly not sufficient to cause disease (59). Periodontal dysbiosis leads to a disturbance of the local homeostasis and immune subversion that increases microbial colonization, virulence, and persistence to disease, and result in persistent recruitment of PMNs (60) with hyperfunctional or hyperactive phenotypes (43, 54–56, 61–63). Similar to what happens in patients with COVID-19, these now hyperactivated PMNs pour out high levels of ROS and degradative enzymes along with ever increasing levels of proinflammatory cytokines (55, 56, 62). These actions lead to severe destruction of the connective tissues about the affected teeth leading to pain, bleeding and ultimately tooth loss (58, 64).

This phenotype of hyperinflammatory PMNs has also been observed to play an important role in the pathogenesis of systemic diseases such as diabetes and cardiovascular disease, suggesting an epidemiological association between periodontal diseases and systemic conditions (65, 66). More importantly, these hyperactivated phenotypes have been observed in severe cases of COVID-19 (67, 68), as well as in aging-related conditions (69). Therefore, the presence of periodontitis in patients who are infected with SARS-CoV-2 could represent an as yet unrecognized comorbidity that could contribute to more severe symptoms of COVID-19. While there are now emerging scientific publications that align with this suggestion (70, 71), it still stands in the grounds of scientific inference. Two plausible mechanisms may explain this association: one being related to the periodontitis-induced inflammatory response; a pre-existing pro-inflammatory state. This could act synergistically and therefore amplify the systemic inflammatory response induced by infection with SARS-CoV-2. Another possibility includes the notion there could be a genetic predisposition of the host to

develop hyperinflammatory conditions that are favorable to both the development of PD or COVID-19. Regarding the former, our team's previous research has shown that an increase in the level of hyperactivated PMNs in bone marrow and blood can be caused by periodontal inflammation and that this predisposes to an exacerbated PMN response to distant inflammatory conditions. In other words, PD primes the immune system and thus intensifies the overall innate immune response, thus exacerbating general inflammatory disease (41) including COVID-19.

Similarly, in an experimental study of the respiratory mucosa before, during, and after respiratory syncytial virus (RSV) infection in humans, participants who succumbed to infection had more activated PMNs in their airways before exposure to the virus than those who staved off infection. After viral exposure, a reduction in antiviral response in the neutrophilic mucosal environment was observed, more specifically suppression of interleukin-17 (IL-17), followed by disease onset. The authors hypothesized that primed PMNs, typically associated with immune response to previous bacterial infections might increase the individual's susceptibility to symptomatic viral infections and potentially even COVID-19 (72). A strong hyperactivation phenotype in peripheral PMNs has already been directly associated with severe cases of COVID-19, including increased phagocytosis, degranulation and chemotaxis, and increased expression of genes involved in pro-inflammatory cytokine release. Within these severe cases, the emergence of an immature PMN population, characteristic of emergency myelopoiesis, was the main difference observed between the immune responses in fatal and non-fatal cases of COVID-19 (73). NET formation in tissue injury and thrombotic complications are additional pathogenic mechanisms whereby circulating PMNs can lead to more severe COVID-19 (6, 28, 31, 32, 34). This highlights another potential mechanisms linking PD as a potential comorbidity in COVID-19 cases: the pro-thrombotic state as a result of PD-associated haemodynamic, endothelial, and inflammatory triggers that may lead to an abnormality in the coagulation or fibrinolysis system (74).

From Bench to Chairside With a Bridge to the Bedside—Host Modulation Therapy (HMT)

We suggest that the SARS-CoV-2 pandemic has highlighted the need for a greater understanding of the role of PMNs in combating viral infections, as COVID-19-related PMN-mediated inflammation in the lungs can be life-threatening (6). While supporting the potential role of PD-related innate immune response in systemic inflammatory conditions, our team proposes the use of host modulation therapy (HMT), as designed initially for treatment of PD for treatment of systemic inflammatory diseases that interact with PD (41), as well as in the prevention and treatment of ARDS, given the similarity of the underlying inflammatory mechanisms. Hereunder we describe the tenets of HMT.

HMT has been established in periodontology as a successful therapeutic approach for management of chronic periodontal and refractory periodontal diseases, all of which are PMN-mediated disorders. This therapy, pioneered by our group (notably Dr. Golub's group), was a paradigm shift in periodontal therapy for using tetracycline-based molecules and *not* reliant on their antimicrobial properties, to downregulate the activities of PMN-derived MMPs, suppression of inflammatory cytokines, and for quenching of ROS (75–78). In relation to periodontitis, work has focused on the use of subantimicrobial dose doxycycline (Periostat®), but higher dose use over a short term is certainly feasible when treating extreme cases of inflammation as in the acute stage of COVID-19. This has also led to the development of effective treatment for rosacea using sub-antimicrobial-dose doxycycline slow release form (Oracea®/Aprillon®) (79) More recently, this concept was boosted by Serhan's studies on pro-resolving lipid mediators in which he argues that a failure in resolution of inflammation rather than its hyperactivation leads to chronic inflammation (80, 81). Pre-clinical studies have shown that treatment with lipid mediators after experimentally induced periodontitis in animals was associated with bone loss prevention, regeneration of periodontal tissues and bacterial shifts in the subgingival microbiota (82–84). In humans, differences in pro-resolving lipid mediator profiles were observed between periodontally healthy and periodontitis participants and thus associated with the state of periodontal inflammation (85). These targets are important factors contributing to the breakdown of periodontal tissues, but also to other tissues being attacked by dysregulated inflammation-mediated destruction observed in periodontitis and ARDS (including stimulation of the vasculitides). Along similar lines, our group has shown that the flavonoids, resveratrol, and curcumin, downregulate ROS-mediated oxidative stress, inhibit ROS production/activity, and inhibit pro-inflammatory cytokine formation in animal model studies of periodontitis, which should protect tissues under inflammatory attack (86, 87). In animals subjected to cigarette smoke inhalation, we showed that resveratrol effectively blocks the harmful effects of aryl hydrocarbons found in cigarette smoke and the environment, which could be very important inasmuch as smoking represents a significant comorbidity for COVID-19 and is also a major risk factor for periodontitis and favor healing (88, 89). There is also evidence animal model data showing that by using HMT, the development of ARDS can be blocked (90, 91).

We suggest that the effectiveness of HMT could be independent of the type of infectious virus because it targets the host's cellular mechanisms that propagate ARDS (and of course PD) and not only the virus itself. Therefore, we suggest that mutations of the virus should be equally less material insofar as the putative effectiveness of HMT in prevention and treatment of ARDS. Recent evidence showed that tetracyclines have *in vitro* activity in post-entry stages of the infection with SARS-CoV-2 (92) and resveratrol blocks replication of coronavirus and other respiratory viruses (93, 94). We propose that the use of drug/nutraceutical HMT described initially for periodontitis could reduce morbidity, mortality, and possibly longer-term sequelae of COVID-19.

The concept of HMT emerged for the treatment of periodontitis almost 40 years ago, after the identification of host-response mechanisms as the mediators of the destruction

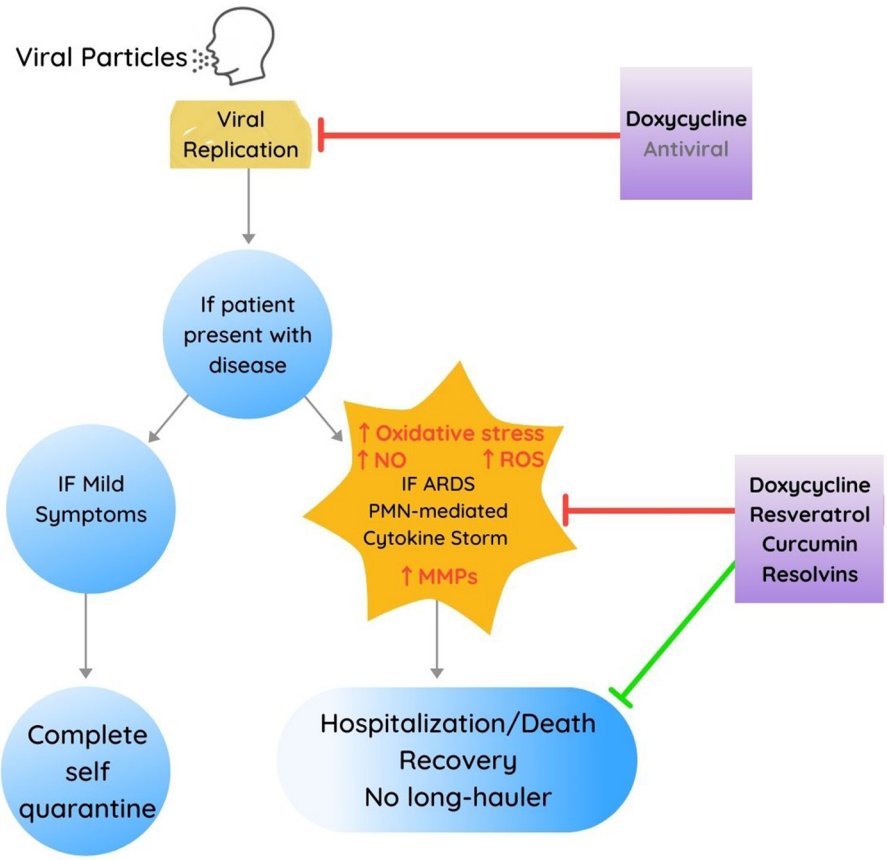

FIGURE 2 | Proposed multidrug treatment approach, developed in part from therapeutic targets identified for management of periodontal diseases for each phase of Covid-19 presenting both inhibitory (in red) and stimulating or improvement-associated effects (in green). Note also that the use of antivirals (other than doxycycline) is depicted in a slightly faded font to delineate that these other therapeutics were not developed from or based on periodontal research investigations.

of the collagen-rich periodontal tissues and subsequent experiments with systemic drugs that inhibited collagen- and bone-destructive enzymes. Around the same time HMT was shown to be effective for downregulation of pathologically elevated levels of inflammation in systemic conditions such as arthritis, cancer, lung and cardiovascular diseases and rosacea (95). Based on this concept, we have presented evidence, described initially in the periodontal research literature, about the protective properties of a new approach to therapy, HMT, that fits precisely the treatment needs of patients with COVID-19/SARS-CoV-2 infection. And, unlike other medications being investigated for the treatment of COVID-19-mediated lung disease there are virtually no concerns about potential toxicity.

The rationale for this proposed treatment approach is based on the use of some or all the compounds identified above to inhibit the cytokine storm/ARDS, including PMN-mediated hyperinflammatory responses and tissue destruction and including the development of thromboembolic disorders. This approach should reduce hospitalization, ICU admissions, and death associated with COVID-19 markedly as suggested in **Figure 2**.

CONCLUSION

We suggest that we've demonstrated how research focused initially on oral inflammatory diseases has illuminated therapeutic targets that can be attacked by relatively simple and safe compounds, thereby reducing hospitalization, morbidity and mortality associated with COVID-19.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HT, LG, MGo, and MGl contributed to conception and design of the study. NF, LG, HT, and MGl, contributed to the experimental analyses and performance. EC and HT wrote the first draft of the manuscript while all others wrote or edited sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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