Medical Research Archives

RESEARCH ARTICLE

COVID-19: Using the Right Tools at the Right Time

Daniel O. Griffin[1,2]

[1]Department of Medicine, Division of Infectious Diseases, Columbia University, College of Physicians and Surgeons, New York, NY 10032, [2]ProHealth NY Lake Success, NY,

* dg2810@cumc.columbia.edu

ESMED
European Society of Medicine

OPEN ACCESS

Published: August 31, 2022

Citation: Griffin O Daniel, 2022. COVID-19: Using the Right Tools at the Right Time, Medical Research Archives, [online] 10(8). https://doi.org/10.18103/mra.v10i8.3041

DOI
https://doi.org/10.18103/mra.v10i8.3041

ISSN: 2375-1924

ABSTRACT

COVID-19, caused by SARS-CoV2, first described in several cases of pneumonia in Wuhan, China in December 2020 has now become a disease that is now present throughout the world. Multiple evidence-based measures and therapeutics are now available for the prevention and treatment of COVID-19. Many therapeutics have been studied and some even continue to be used without compelling evidence to suggest efficacy. Critical to the prevention and successful identification of treatments for COVID-19 has been an appreciation of the multiple stages of this disease. A previous paper published in February 2021 presented a consensus framework of relevant stages of COVID-19 authored by 35 physicians and scientist from multiple disciplines and countries. This framework included: three periods: the period of pre-exposure, the incubation period, the period of detectable viral replication, and five phases: the viral symptom phase, the early inflammatory phase, the secondary infection phase, the multisystem inflammatory phase, and the tail phase. This common terminology has served as a framework to guide COVID-19 therapeutics studied or currently in use. We now have a greater understanding of this disease and an update framework with two preclinical periods, the Pre-exposure Period and the Incubation Period, followed by four clinical phases, the Early Viral Upper Respiratory Non-hypoxic Phase, the Early Inflammatory Lower Respiratory Hypoxic Phase, the Secondary Symptomatic Phase and the Late Phase. We also have more evidence regarding the role of improved ventilation, the effectiveness of different masks, several highly effective vaccines, and a few effective antiviral, immunomodulatory, and supportive therapies. As there has been substantial progress made in understanding this disease and the role of various interventions, both nonpharmacological and pharmacological and changes over time in characteristics of SARS-CoV-2 such as a shorter incubation period and different susceptibility to various therapeutics, it is appropriate to put forth this update.

Key words: COVID-19, SARS-CoV2, Phases, Cytokine Storm

Introduction:

COVID-19 is likely to remain a problem in varying degrees for many years to come despite mitigation strategies, various therapeutics, and vaccines. We have learned a tremendous amount in a short period the disease COVID-19 and SARS-CoV-2 the pathogen driving this disease, since it was first recognized in late 2019.[1] It is anticipated that we will continue to make advances that will positively impact society's experience with this pathogen. As we move forward, we will need to remember the importance of timing but updating the framework can contribute to our continued progress. The three periods were initially described as the Pre-exposure period, the Incubation period, and the Detectable Viral Replication Period. This then lead, with some overlap, into the five clinical phases: the Viral Symptom Phase, the Early Inflammatory Phase, the Secondary Infection Phase the Multisystem Inflammatory Phase and the Tail Phase. As our understanding has evolved it make sense to simplify this framework into the two preclinical periods, the Pre-exposure Period and the Incubation Period, followed by four clinical phases, the Early Viral Upper Respiratory Non-hypoxic Phase, the Early Inflammatory Lower Respiratory Hypoxic Phase, the Secondary Symptomatic Phase and the Late Phase. (Figure 1)

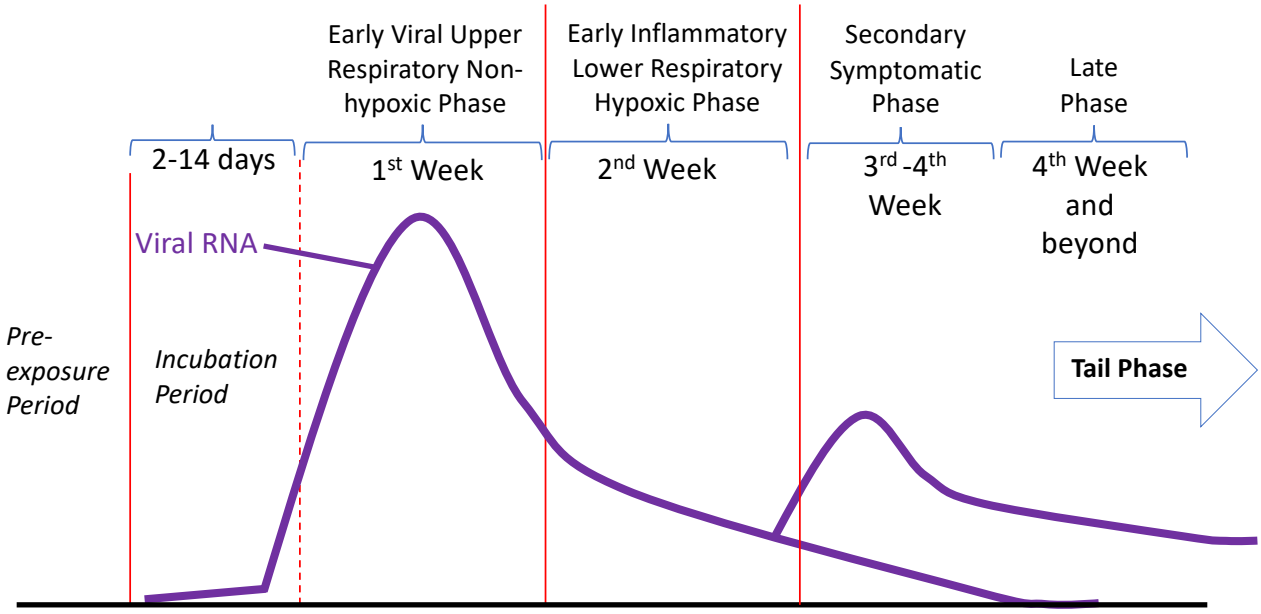

Figure 1. Time course of COVID-19 divided into the two preclinical periods, the Pre-exposure Period and the Incubation Period, followed by four clinical phases, the Early Viral Upper Respiratory Non-hypoxic Phase, the Early Inflammatory Lower Respiratory Hypoxic Phase, the Secondary Symptomatic Phase and the Late Phase.

This framework is complementary to the stages of different severity described by Centers for Disease Control, National Institutes of Health, and the World Health Organization with progression from mild and moderate COVID-19 (equating to Early Viral Upper Respiratory Non-hypoxic Phase) to severe and critical COVID-19 (Early Inflammatory Lower Respiratory Hypoxic Phase).[2] A lack of appreciation of how critical timing was with regard to the efficacy of different interventions lead to negative results and may have resulted in us failing to appreciate the efficacy of therapeutics such as monoclonal antibodies and small molecule antivirals that were initially studied in the later hospital period after the important window of viral replication.[3,4]

Methods:

This article followed the publications and postings on preprint servers as well as manually searched for articles related to SARS-CoV-2 and COVID-19 indexed on PubMed or posted on preprint servers 1 December 2019 through 1 July 2022. Articles were included if they provided relevant information and were judged to be consistent and of adequate quality. Of these, 121 articles were selected, reviewed, and are referenced in this paper.

COVID is not a linear disease and has several characteristic stages. This updated review will reference these stages and what evidence-based interventions are now available and during what stage of disease they are associated with benefit or harm. These periods and phases are the two preclinical periods: the Pre-exposure Period and the Incubation Period, followed by four clinical phases: the Early Viral Upper Respiratory Non-hypoxic Phase, the Early Inflammatory Lower Respiratory Hypoxic Phase, the Secondary Symptomatic Phase and the Late Phase.

Pre-exposure Period

During the Pre-exposure Period both nonpharmaceutical and pharmaceutical interventions have been demonstrated to provide benefit but not without some cost or challenge involved. Masks, distancing, ventilation, cleaning, and hygiene measures, optimizing management of pre-existing conditions, and the use of certain pharmaceutical intervetions.[5] (Figure 2.) We should probably start with a comment on a significant communication problem that has plagued and will continue to challenge us if not addressed. This is the very confusing and binary view of pathogens with respiratory routes of transmission having either droplet or airborne aerosol transmission. In a well-ventilated healthcare facility it might be reasonable institute certain types of infection control precautions based on their relative effectiveness in reducing transmission, their ability to be practically implemented and their cost.[6] It is now clear that infectious agents, including SARS-CoV-2 cannot be neatly divided into the dichotomy of droplet versus airborne with a special separation of 2 meters or 6 feet providing absolute protection, particularly in poorly ventilated indoor settings.[7] It is not clear that any nuance in this area is helpful. For the purposes of science communication, the term respiratory transmission may end up being the most helpful terminology to use going forward.

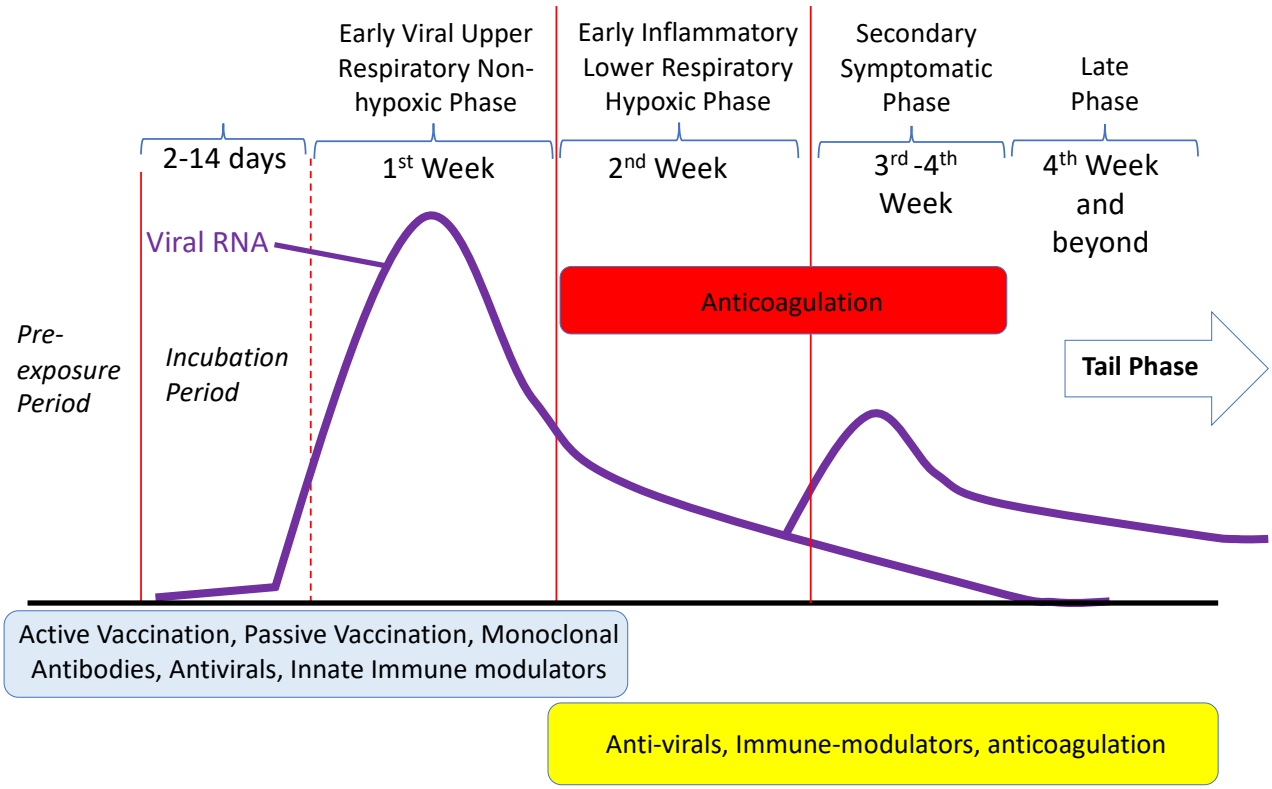

Figure 2. Timing of interventions during the time course of COVID-19.

Different types of masks are associated with reduction in the relative risk of infection with SARS-CoV-2.[8,9] The efficacy of different masks for personal protection is dependent ventilation.[10] As the pandemic has evolved and society's willingness to mask has decreased the concept of one-way masking, where only the concerned or vulnerable person is wearing a mask has become more important. In these settings a 'higher quality' N95 or KN95 mask is recommended.[11] Governmental

and community encouragement of physical distancing in the form of 'social distancing' or 'physical distancing' has been associated with a reduction in case numbers and there have been subsequent rises in case counts upon relaxation of restrictions.[12] Several studies have suggested an increased risk of transmission indoors, particularly in environments with poor ventilation.[13]

Our most powerful interventions have been pharmaceutical, involving both active immunization (vaccination) and passive immunization (monoclonal antibodies). Available vaccines for COVID-19 have been remarkably effective for reducing the risk of severe and critical COVID-19 associated hospitalizations and deaths.[14-18] A challenge for science communication is that many expected the COVID-19 vaccines would provide robust protect against infection or even a positive test and have lost confidence when they get infected or hear of vaccinated individuals getting COVID-19. One of the most effective ways of increasing vaccine acceptance is a discussion between patients and clinicians.[19] A highly effective approach for augmenting vaccination in higher risk individuals or those unable to get the protection from vaccination has been the administration of long-acting monoclonal antibodies such as tixagevimab-cilgavimab.[20,21]

Incubation Period

The Incubation Period is the time from exposure to symptoms and extends for 2-14 days.[22] While newer variants may be associated with more people developing symptoms and turning positive in the first few days after an exposure there are still individuals not testing positive until near the end of this 14 day period.[23] If a person reaches day 14 and is not testing positive, the likelihood of having acquired an infection has most likely passed.[23] A well described aspect of SARS-CoV-2 is its ability to generate subclinical or asymptomatic infection with transmission despite no obvious symptoms.[24-26] Asymptomatic transmission from patients prior to or without ever progressing through the early clinical phases as was documented in the Diamond Princess Cruise Ship Cohort and in other contract tracing and modeling studies.[27,28]

Early Viral Upper Respiratory Non-Hypoxic Phase

The Early Viral Upper Respiratory Non-Hypoxic Phase is the first clinical stage when individuals test positive develop upper respiratory and other viral symptoms. This phase largely equates to the mild or moderate stage of COVID-19, but it is critical for clinicians and researcher to realize that certain individuals will progress to severe or critical COVID-19. COVID-19, during the early Viral Upper Respiratory Non-hypoxic Phase, presents as an influenza-like viral illness with fever, headache, sore throat, nasal congestion, rhinorrhea, cough, myalgia, fatigue, loss of taste and smell and gastrointestinal symptoms.[1,29,30] Certain biomarkers and clinical features including patient age and comorbidities have predictive value regarding the risk of progression from this phase to severe disease but the severity of symptoms during this period do not reliably predict progression or lack of progression and a risk assessment if critical.[31-33]

Multiple well designed clinical trials have demonstrated that this is the critical period to initiate antiviral therapies, such as direct-acting small molecule inhibitors or monoclonal antibodies. A wait and see approach based on the severity of first week symptoms can result in missed opportunities, hospitalization, progression to severe and critical COVID-19 and death.[34] Multiple well designed randomized placebo controlled multicenter prospective trials have reinforced the importance of timing for antiviral therapeutics demonstrating efficacy only if started early and lack of efficacy and potential harm and if initiated after the period of viral replication, such as when patients are requiring mechanical ventilation.[35,36]

The timing of symptom onset and test positivity may be influenced by the specific viral variant, prior infection, vaccination status or the specific host that is infected.[37] Viral replication may be detectable as early as 1 day after exposure, peaking at different times with different variants and in different hosts.[38] The level of viral RNA copies rises from undetectable to millions of RNA copies per microliter or nasal or oropharyngeal samples and then decreases but in many case the levels may drop and then rise during the acute 14 days of illness.[39-42] Some individuals, with or without therapy may have high levels of detectable viral RNA and culturable virus beyond 14 days.

It is during the Early Viral Upper Respiratory Non-hypoxic Phase that we have the most robust ability

to interfere with progression to severe disease and death. During this phase, viral replication is robust and our most successful interventions, as predicted, have been targeted antivirals. As of the writing of this article, nirmatrelvir-ritonavir is the small molecule antiviral with a pharmacokinetic enhancer that has shown the greatest reduction in progression to hospitalization and severe disease.[43] Nirmatrelvir is an orally administered main protease (Mpro) inhibitor with pan-human-coronavirus activity. Critical is an assessment of the risk status of an individual so that this therapy can be administered in the first 3-5 days from symptom onset. The administration of early remdesivir (within the first 7 days of symptom onset), a direct acting nucleotide prodrug inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase, has also been demonstrated to have a significant impact on progression.[44] The operational challenge of a 3-day intravenous medication has limited the use of this therapeutic. Monoclonal antibody therapy remains an effective antiviral therapy despite challenges with different variants requiring replacement of original antibodies and cocktails with updated antibodies.[45] As of the writing of this manuscript bebtelovimab remains the only effective monoclonal antibody therapy based on invitro neutralization studies but is consider the third choice based on a lack of efficacy data.

Molnupiravir, a small molecule ribonucleoside prodrug of N-hydroxycytidine that works by triggering an accumulation of deleterious errors into the viral genome has also demonstrated some efficacy for the prevention of progression of COVID-10 to severe or critical disease resulting in hospitalization or death.[46] Advantages of molnupiravir have been the lack of drug-interactions and the lack of a need for adjustment based on renal function.

Critical during this period is also the avoidance of harm through use of agents that increase the risk for progression to severe or critical COVID and death or result in patients not accessing effective therapy. There are also interventions that fail to provide benefit and cause society harms and an increase in antimicrobial resistance such as the unnecessary use of antibacterial agents to treat a viral illness. Antibacterial agents have been extensively studied as early treatment for this viral illness and have failed to show benefit.[47-50] Steroids given during the first week of illness when a patient is in the Early Viral Upper Respiratory Non-hypoxic Phase with oxygen saturations $\geq$94% can be harmful and has been associated with an increased risk of progression to severe and critical COVID-19 resulting in an increased risk for hospital admission, cardiac events, pulmonary embolism and mortality.[51,52]

Several additional small molecule antivirals and monoclonal antibodies are being developed and tested with an appreciation that the efficacy will only be significant if they are administered during the period of viral replication.[53] Research and therapeutic development is ongoing looking at targeting specific viral proteins such as the spike protein, the Nsp12-Nsp7-Nsp8 polymerase complex (RNA-dependent RNA polymerase), the papain-like cysteine protease (PLpro), the 3-Chymotripsin-like protease (3CLpro)-also known as the main protease (Mpro) Nsp13 , the viral proofreading exoribonuclease (Nsp14) and proteins (including many NSPs and Orfs) that may be critical for interaction with host innate cells and reduction of cellular responses.[54,55] Parallel development approaches, with significant overlap, look specifically at disrupting parts of the viral replication cycle such as attachment/receptor binding, entry, uncoating, polyprotein processing, viral RNA synthesis, translation, assembly, viral maturation, exocytosis and virion release.[56] It is anticipated that many more antivirals will become available.

In additional to pharmaceuticals, isolation to prevent ongoing transmission is a critical public health consideration during this phase. The RNA copy number and the amount of culturable virus decreases to below an infectious level by day 10 in most patients with a mild infection. However, the level of infectious virus may remain elevated above infectious levels in patients with severe disease or immune compromise until day 20, viral RNA and viral antigen as detected by rapid antigen testing is still detectable in some individuals over three weeks after initial positive tests or onset of symptoms.[57-60] Some individuals with or without certain treatments may demonstrate a rebound of RNA copy numbers with symptoms and may be experiencing a delayed period of infectiousness.

While most hospitalizations during the early months on the pandemic there has been a shift whereby many patients are being admitted with

an incidental finding of a SARS-CoV-2 positive test or are admitted during this early viral upper respiratory non-hypoxic phase.[61] The location does not impact the logic and timing of what interventions will be helpful and it is important to note that any restrictions on use are associated with limiting use in patients not just in a hospital but admitted due to severe or critical COVID-19 and in the early Inflammatory lower respiratory hypoxic phase.

Nucleic acid amplification tests (NAATs) such as Reverse Transcriptase PCR (RT-PCR) and transcription-mediated amplification (TMA), are the most sensitive detection methods, and can detect low levels of virus RNA with limits of detection (LoD) of approximately 10-1,000 RNA copies/ml or NAAT detectable units/mL (NDU).[62,63] Contact tracing to determine the correlation between infectiousness and Ct (cycle threshold) values or RNA copy numbers is challenging. It is difficult to determine the RNA copy number or Ct value at the time of exposure and transmission.[64] Although RNA and antigen positivity can occur for weeks or even months, the period of virus viability appears to be limited and quantitative RNA detection does not necessarily indicate infectiousness.[65] Detection of sub-genomic RNA, indicative of replicative intermediates of the virus, within the first eight days after onset of symptoms in patients with mild disease, and *in vitro* culture of live virus no later than day nine after symptom onset suggest that the risk of transmission is greatest around symptom onset.[63,64,66] Similar challenges exist for antigen testing which has excellent diagnostic sensitivity and specificity for different variants when used as a diagnostic test but has inconsistent results asking whether a person is likely still infectious or has culturable virus.[67,68] At this stage of the pandemic we have a number of diagnostic tests that are validated as such but no tests with validation for determining infectiousness without a consideration of the time from symptom onset.

Early Inflammatory Lower Respiratory Hypoxic Phase

The Early Inflammatory Lower Respiratory Hypoxic Phase begins during the second week with earlier onset in the elderly and those with comorbidities, and a later onset in younger, healthier individuals.[60,69] The first obvious clinical manifestations of this phase are usually pulmonary, with the onset of hypoxemia, followed by increasing respiratory rate and then increasing hypoxemia, which in many cases can be rapid and require significant supportive care.[70,71] In untreated individuals this can progress to cardiac dysfunction, renal failure, neurological manifestations, and multi-organ dysfunction.[72-75] During this stage dysfunction of the coagulation system may become apparent.[76-79] There is often a rise in inflammatory markers, D-dimers and several cytokines often leading to clinicians and researchers describing this as the period of the cytokine storm.[80] A cytokine recognized to often be elevated during this period, but to a less degree than in acute respiratory syndrome or the cytokine storm associated with chimeric antigen receptor T-cell therapy is interleukin-6 (IL-6).[81,82] A number of efforts to help risk stratify patients at this stage have been employed including many complex scoring systems as well as the simpler neutrophil to lymphocyte ratio (NLR).[83]

It is during this period that corticosteroids have been shown to reduce the risk of progression to critical disease and death.[84] It is critical to point out that the premature use of steroids during the first week of illness when a patient is in the early viral upper respiratory non-hypoxic phase with oxygen saturations $\geq$94% has been associated with significant harm and the absolute reduction in mortality, if given during the Early Inflammatory Lower Respiratory Hypoxic Phase, in the landmark RECOVERY trial was less than 3%.[84] Further investigations into additional or alternative immune modulation have demonstrated mortality reductions with the IL-6 receptor antagonist tocilizumab added to steroids and inhibition of janus kinase with baricitinib when used as an alternative to steroids.[85-87] The addition of further immune modulation may be very time sensitive even within this particular phase as the benefit of adding tocilizumab may only be apparent if given prior to escalation to high flow oxygen therapy or very soon after initiation of mechanical intervention.[88-92] Promising results from novel approaches such as the targeting microtubules with therapeutics such as sabizabulin suggest that we may have additional therapies to add to or replace current immunomodulation.[93]

Early in the pandemic a number of case reports were published alerting clinicians to an increase incidence of both venous and arterial thromboembolic complications in patients with COVID-19.[94-96] A number of studies looking at the

incidence and measures to prevent venous and arterial thromboembolic complications lead to a number of recommendations to treat hospitalized patients with various doses and particular anticoagulants. Current recommendations are for prophylactic intensity anticoagulation in patients with critical illness requiring intensive care unit level support, therapeutic intensity anticoagulation in patients with severe hypoxic COVID-19, and anticoagulation on discharge for only certain higher risk patients.[97-99] Based on the low certainly of evidence in this area, these guidelines are qualified with the statement that "An individualized assessment of the patient's risk or thrombosis and bleeding is important when deciding on anticoagulation."[97-99]

The primary reason for hospitalization during the Early Inflammatory Lower Respiratory Hypoxic Phase is usually for pulmonary support. The need for pulmonary support defines the early inflammatory lower respiratory hypoxic phase. While early in the pandemic there was a practice of early intubation, as the pandemic evolved multiple non-invasive forms of pulmonary support was increasing used, including high flow nasal cannula and prone positioning in attempts to avoid intubation.[100,101]

This topic of avoiding harmful therapies is critical as there are certain therapies that have never been shown to provide benefit in COVID-19 and are only associated with wasted opportunity costs or harm and many therapies that provide benefit during the Early Viral Upper Respiratory Non-hypoxic Phase but provide only minimal benefit, no benefit or can cause harm if given during the Early Inflammatory Lower Respiratory Hypoxic Phase. Remdesivir is an example of a therapeutic agent with great efficacy when given early but with mixed results when given after the period of viral replication and the onset of the Early Inflammatory Lower Respiratory Hypoxic Phase.[102,103] Trials of monoclonal antibodies such as ACTIV-3 were stopped when the DSMB suggested that this therapy was unlikely to help people hospitalized with COVID-19 recover from advanced disease. The list of other agents tried and then abandoned due to no compelling evidence is extensive.[104-106]

Secondary Symptomatic Phase

The Secondary Symptomatic Phase is characterized by a period during when there may be significant inflammation, evidence of increased SARS-VoV-2 viral RNA, secondary bacterial and fungal infections, and thromboembolic complications in patients having undergone treatment as well as those that had limited initial symptoms and no treatment.[107] Diagnosis of the process triggering this secondary symptomatic phase is critical to guiding therapy. It is during this period that there are peak levels of IgG, and many manifestations that are suspected to be secondary to inflammatory and autoimmune phenomena.[108,109] During this phase as well as during earlier phase recognition of a secondary bacterial process is important but also challenging so a number of investigations including certain laboratory parameters such as a low ferritin to procalcitonin ratio have been employed to help in this determination.[110] Late complications during this period are the Multisystem Inflammatory Syndrome in Children (MIS-C) and the Multisystem Inflammatory Syndrome in Adults (MIS-A), vasculitis, Guillain-Barré syndrome, facial palsies, immune mediated thrombocytopenia.[111-115] At this point a careful diagnostic evaluation should be performed and then therapies based on the etiology of the return of persistence of symptoms.

Late Phase

The Late Phase may be a continuation of the acute period for some, a bimodal pattern of disease for other individuals, with improvement followed by worsening or recurrence of symptoms while for some it may be a novel presentation after a minimally or asymptomatic acute experience.[116] There is not always a clear distinction between the acute disease and the late or chronic phase in some patients while in others there can be a period of clinical improvement and in some this period is the first time symptoms are experienced. Since MIS-C and MIS-A typically occur 2-6 weeks after SARS-CoV-2 exposure MIS-C and MIS-A may not present until after 4 weeks during what most would think of as this Late Phase.[111]

In general, the Late Phase is the period of time most associated with the development of Long COVID or post-acute sequelae SARS-CoV-2 infection (PASC). The WHO Clinical Case Definition Working Group on Post-COVID-19 Condition published a Delphi process consensus definition post-COVID-19 condition.[117] This panel arrived at the consensus that "Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months

from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive dysfunction and generally have an impact on daily functioning. Symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms might also fluctuate or relapse over time."[117] Unfortunately at the time of writing of this manuscript the only evidence-based intervention to prevent and treat PASC is COVID-19 vaccination before or after SARS-CoV-2 infection.[17,118-120]

This updated framework which breaks down COVID into the two preclinical periods, the Pre-exposure Period and the Incubation Period, followed by four clinical phases, the Early Viral Upper Respiratory Non-hypoxic Phase, the Early Inflammatory Lower Respiratory Hypoxic Phase, the Secondary Symptomatic Phase and the Late Phase should continue to provide helpful structure to the timing of different therapeutics for patient management as well as for future investigations. This framework is complementary to the stages of different severity described by CDC, NIH, and the WHO but makes it very clear that mild and moderate COVID-19, the Early Viral Upper Respiratory Non-hypoxic Phase has the potential to progress to severe and critical COVID-19, the Early Inflammatory Lower Respiratory Hypoxic Phase).

Conclusion:

An appreciation of the mechanisms underlying the clinical presentations should lead to a better understanding of why timing continues to be so critical in management of COVID-19. This is not a disease with a linear progression where one can wait and see how a person does and then intervene but is rather a disease where a lost opportunity to intervene early in disease will lead to limited options for a patient who has progressed to the hypoxic inflammatory phase.

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