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The Importance of Understanding the Stages of COVID-19 in Treatment and Trials

Daniel O. Griffin[1,2,3], Denise Brennan-Rieder[4], Binh Ngo[5], Pierre Kory[6], Marco Confalonieri[7], Leland Shapiro[8], Jose Iglesias[9], Michael Dube[5], Neha Nanda[5], Gino K. In[5], Daniel Arkfeld[5], Preet Chaudhary[5], Vito M. Campese[5], Diana L. Hanna[5], David Sawcer[5], Glenn Ehresmann[5], David Peng[5], Miroslaw Smorgorzewski[5], April Amstrong[5], Eivind H. Vinjevoll[10], Rajkumar Dasgupta[5], Fred R. Sattler[5], Cristina Mussini[11], Oriol Mitjà[12], Vicente Soriano[13], Nicolas Peschanski[14], Gilles Hayem[15], Maria Carmela Piccirillo[16], António Lobo-Ferreira[17], Iraldo B. Rivero[18], Ivan F. H. Hung[19], Marc Rendell[20], Stephen Ditmore[21], Joseph Varon[22], and Paul Marik[23]*

[1]Department of Medicine, Division of Infectious Diseases, Columbia University, College of Physicians and Surgeons, New York, USA; [2]Research and Development at United Health Group Minnetonka, Minnesota, USA; [3]ProHealth NY Lake Success, New York, USA; [4]CoronaTracker Community Research Group, [5]Keck School of Medicine, University of Southern California, California, USA; [6]Pulmonary and Critical Care Medicine, Aurora St. Luke's Medical Center, Milwaukee, WI, USA; [7]Azienda Ospedaliero-Universitaria di Trieste, Trieste, Italy; [8]Rocky Mountain Regional Veterans Affairs Medical Center in Aurora, CO and University of Colorado Anschutz Medical Campus in Aurora, CO, USA; [9]Jersey Shore University Medical Center, Neptune NJ, Hackensack Meridian School of Medicine at Seton Hall, Hackensack University, NJ, USA; [10]Volda Hospital HMR, Volda, Norway; [11]University of Modena and Reggio Emilia, Modena, Italy; [12]Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [13]UNIR Health Sciences School and Medical Center, Madrid, Spain; [14]University Hospital of Rennes, Rennes, France, [15]Hôpital Paris Saint-Joseph, Paris, France; [16]Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale, Napoli, Italy; [17]Unidade de Investigação Cardiovascular, Faculdade de Medicina da Universidade do Porto, Centro Hospitalar Universitário de São João, Porto, and Hospital Rainha Santa Isabel, Marco de Canaveses, Portugal; [18]Department of Clinical Investigations, Center for Genetic Engineering and Biotechnology, Havana, Cuba; [19]Ivan FN Hung, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong; [20]The Rose Salter Medical Research Foundation, Newport Coast, CA, USA; [21]Parkchester Times, [22]United Memorial Medical Center and United General Hospital, UT Health Science Center at Houston, University of Texas School of Medicine, Houston, Texas, USA, Baylor College of Medicine, UAT, UDEM, UABC, UNE, USON, UPAEP – Mexico, Caribbean Medical University; [23]Eastern Virginia Medical School|, Department of Internal Medicine, Chief, Pulmonary and Critical Care Medicine, Norfolk, VA, USA

Abstract

COVID-19, caused by SARS-CoV-2, continues to be a major health problem since its first description in Wuhan, China, in December 2019. Multiple drugs have been tried to date in the treatment of COVID-19. Critical to treatment of COVID-19 and advancing therapeutics is an appreciation of the multiple stages of this disease and the importance of timing for investigation and use of various agents. We considered articles related to COVID-19 indexed on PubMed published January 1, 2020-November 15, 2020, and considered papers on the medRxiv preprint server. We identified relevant stages of COVID-19 including three periods: pre-exposure, incubation, and 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 should serve as a framework to guide when COVID-19 therapeutics being studied or currently in use is likely to provide benefit rather than harm. ***(AIDS Rev. 2021;22:40-47)***

Corresponding author: Daniel O. Griffin, dgriffin@ProHealthcare.com

Key words

COVID-19. SARS-CoV-2. Phases. Cytokine storm. Antivirals. Immunotherapy.

Correspondence to:
*Daniel O. Griffin
E-mail: dgriffin@ProHealthcare.com

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Introduction

COVID-19 continues to be a major health threat despite the introduction of mitigation strategies, various therapeutics, and vaccines. As we study and recommend therapeutics, we need a common terminology in order to reference the observed stages of COVID, and target interventions to the appropriate phase. Our current therapeutics include: monoclonal antibody therapies, convalescent plasma, the antiviral agent remdesivir, steroids, and anticoagulation. With each of these options, determining the correct timing, phase of disease, and severity of disease is critical to maximizing benefit and reducing harm. Our experience in the treatment of patients with HIV/AIDS taught us this lesson about determining the correct timing and disease severity before treatment. Treatment depends on the phase of disease: in the pre-exposure period, we recommend pre-exposure prophylaxis (PreP) and condoms, with acute exposure use PEP-post-exposure prophylaxis, and in acute infection and chronic infection we use HAART-highly active antiretroviral therapy. With HIV/AIDS, it is also important to determine measurements of viral load and CD4 counts before deciding the timing of intervention. We suggest that a similar paradigm applies to COVID-19.

Methods

We manually searched for articles related to COVID-19 indexed on PubMed published January 1, 2020 through November 15, 2020, and also considered papers on the medRxiv preprint server. Initial search parameters revealed 1175 articles. Articles were included if they provided relevant information and were judged by the authors to be consistent and of adequate quality. Of these, 71 articles were selected and then reviewed by the authors and are referenced in this paper.

Results

Based on our investigations, we arrived at terminology that was broadly descriptive of each phase yet precise and not overly specific to any one organ system. Pulmonologists and critical care specialists might focus on the pulmonary manifestations during the 2nd week after symptom onset after viral replication decreases. Cardiologists might emphasize the cardiac dysfunction of this period, nephrologists the renal manifestations and immunologists the cytokine signature. Rather than selecting one of those options, we elected to use inclusive terminology. As COVID-19 manifestations are identified and the mechanisms of these stages are revealed, it is preferable to have a consensus framework regarding the different processes, symptomatology, complications, and therapeutics relevant in the course of the disease.

We have determined three periods and five phases that comprise the stages of COVID-19. These stages are: the Pre-Exposure Period, the Incubation Period, the Detectable Viral Replication Period, the Viral Symptom Phase, the Early Inflammatory Phase, the Secondary Infection Phase, the Multisystem Inflammatory Phase, and the Tail Phase. The Pre-exposure period ends and the Incubation period start at T_E (Time of exposure); the Detectable Viral Replication Phase starts at T_{DVR} (Time of detectable viral replication). The Viral Symptom Phase starts at symptom onset and shortly after the rise in detectable viral RNA T_S (Time of symptom onset), the Early Inflammatory Phase starts 7-14 days after symptom onset at T_{EI} (Time of early inflammation), and includes the start of a coagulation disturbance whose macrovascular manifestations are not always evident until week three, the Secondary Infection Phase starts at T_{SI} (Time of secondary infection), the multisystem inflammatory phase starts at T_{MI} (Time of multisystem inflammation onset), and the Tail starts at T_T (Time of the tail onset) and may continue for months.

During the Pre-Exposure Period susceptible individuals can employ a variety of measures to minimize their likelihood of exposure to potential infection with SARS-CoV-2, the virus that causes COVID-19. Masks, distancing, ventilation, cleaning, hygiene, minimizing contact with potentially infected individuals, and optimizing management of pre-existing conditions such as diabetes, hypertension, asthma, and COPD are among the measures that are most relevant during this period[1]. This is also the ideal time to employ active immunization (vaccination) and perhaps passive immunization (monoclonal antibodies).

Despite a lack of endorsement of masks early in the COVID-19 pandemic, multiple observational studies indicate that masks are associated with reduction in the relative risk of acquiring infection for multiple pathogens including SARS-CoV-2[2,3]. Governmental and community encouragement of physical distancing in the form of "social distancing" has been associated with a reduction in case numbers and there have been subsequent rises in case counts upon relaxation of

restrictions[4]. Several studies have suggested an increased risk of transmission indoors, particularly in environments with poor ventilation[5].

The Incubation Period begins when an effective exposure results in the initiation of infection. Many individuals who are advised to quarantine for the 14-day period will have had an exposure that is considered significant but will never progress to infection with associated viral replication or symptoms[6]. Although there are nuanced models to stratify risk, a significant exposure which prompts the recommendation for quarantine is an unprotected encounter of more than 15 min, continuous or cumulative, with a proximity of 6 ft or less[7]. The incubation period from exposure to symptoms is now well defined as 2-14 days[8]. If a person reaches day 14 and is not shedding virus, the likelihood of infection has most likely passed. A certain percentage of exposed and infected individuals will shed virus without ever developing symptoms[9-11].

The Detectable Viral Replication phase follows an exposure that results in infection. Viral replication may be detectable as early as 1 day after infection, peaking 3-4 days post-infection[12]. Viral replication in a successful infection likely begins shortly after exposure but is not initially detectable with current technologies. The level of viral RNA copies rises from undetectable to millions in the 1-3 days before development of symptoms and then decreases after the time of symptom onset[13-16].

The RNA copy number decreases to below an infectious level by day 10 in most patients with mild infection. However, it may remain elevated above infectious levels in patients with severe disease or immune compromise until day 20 and viral RNA is still detectable in some individuals over 3 weeks after discharge from the hospital[17-20].

Real-time PCR (RT-PCR) and transcription-mediated amplification (TMA), currently the most sensitive detection methods, 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), depending on the gene and the manufacturer of the assay[21,22]. However, 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[23]. Furthermore, although virus shedding can occur for weeks, the period of virus viability appears to be limited and quantitative RNA detection does not necessarily indicate infectiousness. Detection of sub-genomic RNA, indicative of replicative intermediates of the virus, within the 1st 8 days after onset of symptoms in patients with mild disease, and ***in vitro*** culture of live virus no later than day 9 after symptom onset suggest that the risk of transmission is greatest just before and for several days after symptom onset[22-24].

It is clear that transmission can occur both before symptoms and in asymptomatic individuals as was documented in the Diamond Princess Cruise Ship Cohort and in other follow-up and modeling studies[25].

The Viral Symptom Phase starts after viral RNA levels have peaked and as the viral RNA copy number is decreasing. We define this period as starting at T_S (Time of symptom onset). The symptoms described during this phase range from the less common but highly suggestive loss of taste and smell to a predominantly gastrointestinal presentation. Early descriptions of cough, fever, and myalgia are still common, but a growing list of nonspecific symptoms has clearly established that this is an influenza-like viral illness in its myriad of presentations[26-28]. Certain biomarkers and clinical features including patient age and comorbidities appear to have some predictive value regarding the risk of progression from this phase to severe disease[29-31].

While the onset of viral replication precedes symptoms, it is usually only after symptom onset that most cases of COVID-19 are recognized and treatment can be initiated. It is theorized that this is the critical period to initiate antiviral therapies, such as direct-acting small molecule inhibitors (remdesivir) or monoclonal antibodies[32]. Randomized prospective trials have supported the importance of timing for remdesivir and the monoclonal antibody bamlanivimab (LY-CoV555) demonstrating efficacy if started early and potential harm if treatment is initiated during later phases, such as when patients are requiring mechanical ventilation[33].

The Early Inflammatory Phase which starts at T_{EI} (Time of early inflammation) begins during the 7-14 days after T_S (Time of symptom onset) with earlier onset in the elderly and those with comorbidities, and a later onset in younger, healthier individuals[20,34]. The first obvious clinical manifestations of the early inflammatory phase in most cases are 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[35,36]. In untreated individuals this can progress to cardiac dysfunction, renal failure, neurological

manifestations, and multi-organ dysfunction[37-40]. During this stage, dysfunction of the coagulation system appears to begin[41-44]. There is also a rise in inflammatory markers, D-dimers, and several cytokines. A dominant cytokine during this period may be interleukin-6 (IL-6), however, its levels may be lower than in other syndromes such as ARDS where median IL-6 levels in patients with the hyperinflammatory phenotype of ARDS are 10- to 200-fold higher than levels in patients with severe COVID-19 or in CAR-T patients with CRS[45,46]. Furthermore, in experimental viral infection models, IL-6 is pleiotropic having both pro- and anti-inflammatory effects[47].

This stage was initially described as the "cytokine storm phase" or the "pulmonary phase" and while these descriptions are perhaps accurate regarding the underlying drivers and the obvious clinical manifestations, it is now appreciated that there is significant additional complexity[48,49]. This has led to controversy regarding the term "cytokine storm" and thus it is felt that "early inflammatory phase" is more descriptive and leaves open the ability to advance understanding of this phase. The term early inflammatory phase and the timing of this phase in COVID-19 is also supported by studies demonstrating some modest benefits of steroids use during this phase but not earlier in disease[49,50].

Some of the most prominent clinical manifestations during the early inflammatory phase are those involving the pulmonary system. Many argue that this organ is critical to understanding COVID-19 and observations suggesting improvements in patient outcomes resulting from non-invasive ventilation and positioning have changed the standard of care away from early recommendations of early intubation[51].

Some of the milder pulmonary aspects of COVID-19 may be initially evident during the 1st week of illness with cough while more pronounced pulmonary symptoms are seen in a large number of patients during the early inflammatory phase and may continue to be manifest into later phases of the disease[27,52]. Growing evidence from autopsy and other studies suggests that a majority of COVID-19 patients with pulmonary manifestations develop secondary organizing pneumonia (OP) or its histological variant, acute fibrinous and organizing pneumonia[53-55].

While there is evidence that coagulopathy begins during this phase and anticoagulation is beneficial, the clinical consequences, in the form of major thromboembolic complications, are often not apparent until the 3rd week of illness[42,44]. There is evidence that rise in D-dimer, ventilation perfusion (V/Q) mismatches, and other manifestations are the result of microvascular thrombi triggered by endothelial dysfunction which is driven by the cytokine cascade rather than by direct viral invasion[56,57].

The Secondary Infection Phase starts at T_{SI} (Time of secondary infection) and is characterized by a period during which bacteremia, fungemia, pneumonia, and other secondary bacterial infections occur at an increased incidence. This appears to be a characteristic feature of the disease process and does not only occur in patients having undergone treatment[58]. Not all patients will develop a secondary infection during this phase.

The Multisystem Inflammatory Phase starts at T_{MI} (Time of multisystem inflammation onset) and is characterized by peak levels of IgG, secondary infections, and many manifestations that are suspected to be secondary to autoimmune phenomena[59,60]. This phase gained significant attention when it was described as the Multisystem Inflammatory Syndrome in Children (MIS-C) and the Multisystem Inflammatory Syndrome in Adults (MIS-A)[61,62]. It is now clear that similar manifestations occur in children and adults. During this stage processes such as vasculitis, Guillain-Barré syndrome, facial palsies, immune mediated thrombocytopenia, and other manifestations can occur co-temporally with the rise in IgG[63-65].

The post-acute Tail Phase does not so much start as continue when a patient passes through the acute period, yet has residual symptoms. In certain circumstances, patients experience a bimodal pattern of disease, with improvement followed by worsening or recurrence of symptoms[66]. For understanding when certain therapeutics might be efficacious it is useful to define this period as starting at T_T (Time of the tail onset). During this phase, individuals have both subjective as well as objective manifestations ranging from fatigue to documented cardiac and pulmonary dysfunction[67,68]. There is still a lack of consensus regarding the terminology best used to refer to patients that suffer past the initial 4 weeks and terms such as long hauler COVID, long COVID, and long-term COVID (LTC) are used in different countries by different physicians and patients.

Discussion

While some infectious disease specialists have developed significant experience treating patients with COVID-19, many therapies continue to be used without

evidence of benefit and without regard to timing, potentially causing harm. Consensus regarding the terminology and phases of COVID-19 is critical for understanding the appropriate timing for the study and delivery of therapeutics.

It is possible and likely that some of the failures in randomized controlled trials seen to date may be due to timing of treatments. The context of disease phases may explain the failure of remdesivir or monoclonal antibody therapies when given late in disease[69].

The Pre-Exposure Period represents the target for vaccination (active and passive) and the ideal time for study of prophylactic medications with very low risk of adverse effects. Available evidence would suggest that this is perhaps the time that vitamin D, zinc, targeting ideal body weight, smoking cessation, and other routine health measures might have a role. It is during the Incubation Period that starts at T_E (Time of exposure) that the risk of developing disease is increased and a targeted approach blocking viral replication and cellular entry can be considered.

The Detectable Viral Replication Phase is the time in which antivirals, monoclonal antibodies, and therapies that augment innate immune responses such as interferons would have the highest potential for benefit versus harm (Fig. 1). The Viral Symptom Phase occurs very soon after viral RNA is detectable. For most individuals, this will be the time at which their illness comes to clinical attention. The population in this phase will be predominantly an outpatient population, and studying therapeutics in this group will potentially prevent hospitalizations and viral transmission, having a significant impact on resource utilization. It is also critical during this period to have clear criteria identifying infectiousness for both public health considerations and at the individual level to determine when a patient can safely return to work and other social settings. An appreciation of the RNA level at which a person is infectious is critical for public health testing as the focus is different from clinical testing. Testing for infectiousness needs to take into account not only the accuracy of diagnosis at an individual level but also focus on identifying infectious individuals who can spread disease in schools or other places where humans congregate.

The initial clinical manifestations of the Early Inflammatory Phase are pulmonary compromise with hypoxemia, followed by impacts on the cardiac, renal, and other organ systems. Hospitalization is most likely to occur in this phase (Fig. 2). Even in severe cases, the viral RNA copy number is already decreasing at a rapid rate in most individuals at T_{EI}. Therapeutics that target viral replication and augment the innate immune response such as interferons have a decreasing likelihood of benefit at this later stage of disease.

As there is growing evidence that the manifestations evident during this phase are driven by host immune responses rather than ongoing viral replication or viral virulence factors, there is support for trials and research exploring the role of different immunomodulatory therapies at this stage.

At the outset of the pandemic, we lacked a robust infrastructure for establishing and running trials in the outpatient setting. It is critical to study therapeutics at the time when they are likely to make a difference, and therefore new relationships with urgent care centers and outpatient practices are a high priority. Our consensus framework should help guide the timing of various therapeutics and the patient populations most likely to benefit.

The disturbances in the coagulation system also appear to begin during the early inflammatory phase in the 2nd week of illness, but the macrovascular manifestations may not be evident until week three of illness. It is clear from the October 2020 call to action from the American Society of Hematology Guidelines panel that high-quality evidence to direct the selection and dosing of anticoagulation is still not available for patients with mild disease who never require hospitalization, patients with severe disease during their hospitalization time and for the period of increased risk that lasts for months in both of these populations[70].

During the Secondary Infection Phase, bacteremia, fungemia, pneumonia, and other secondary bacterial infections occur at an increased incidence. This phase is also characterized by ongoing immune dysfunction which is poorly understood and occurs due to COVID-19 and not due to any specific therapeutics. Many patients are exposed to unnecessary antibiotics early on in the disease process, but it is only during this phase that antibiotics are appropriate and beneficial for most patients. As the pandemic continues, the challenges of growing rates of antimicrobial resistance will become more manifest if inappropriate antibiotic use continues.

The Multisystem Inflammatory Phase is characterized by manifestations which may be secondary to autoimmune phenomena. Better understanding and the introduction of improved therapeutics may not only improve outcomes for patients with COVD-19, but may also translate to other diseases that for years have been suspected of being post-infectious.

The Tail Phase is now appreciated to be a common feature of COVID-19. Growing numbers of individuals are reporting suffering from this aspect of COVID-19

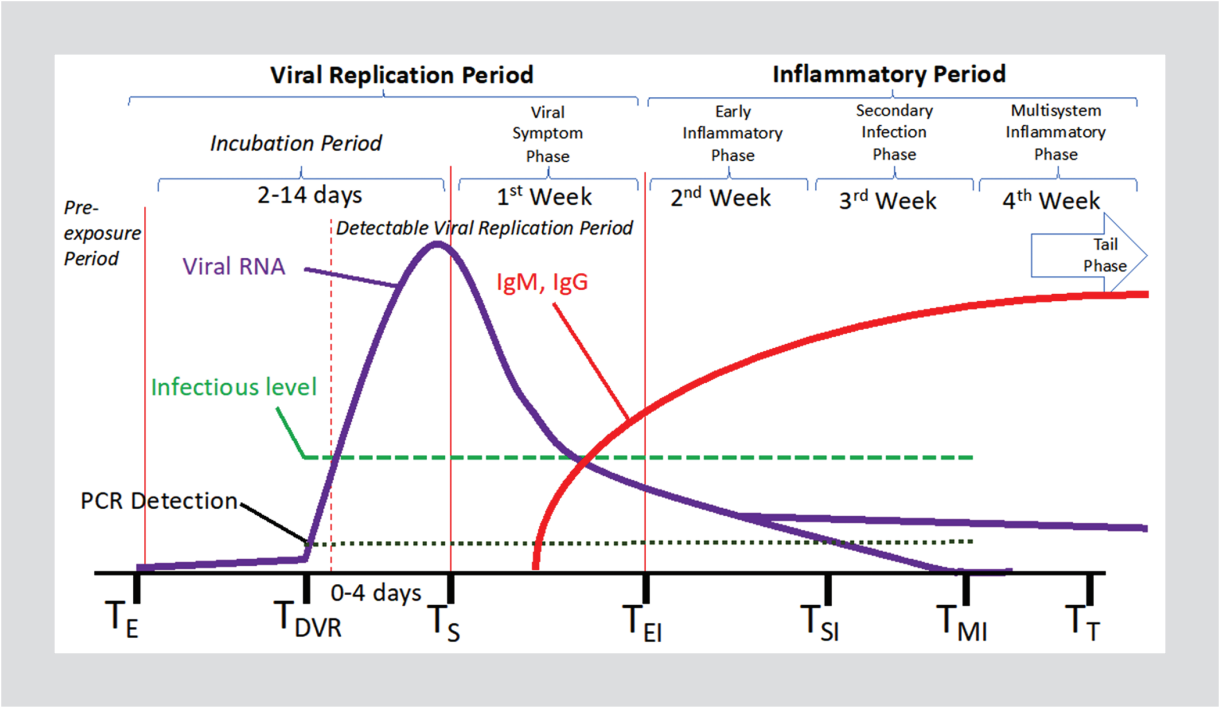

Figure 1. *High viral RNA levels precede the inflammatory phase and are decreasing at the time of hospital admission and need for ICU level care.*

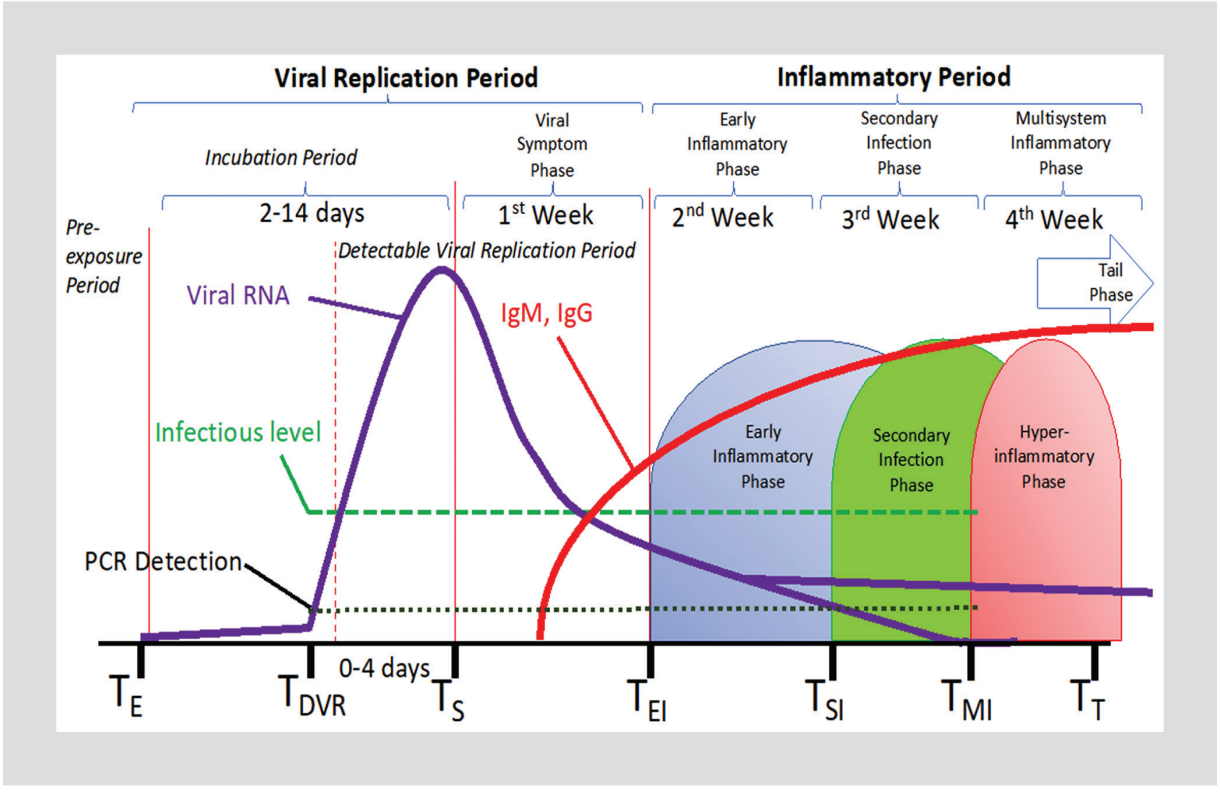

Figure 3. *COVID-19 progresses through various stages with certain degree overlap but with distinct mechanisms targeting each stage. Dotted lines from left to right represent the Early Inflammatory Phase (blue), the Secondary Infection Phase (green), and the Hyperinflammatory Phase (red continuous line).*

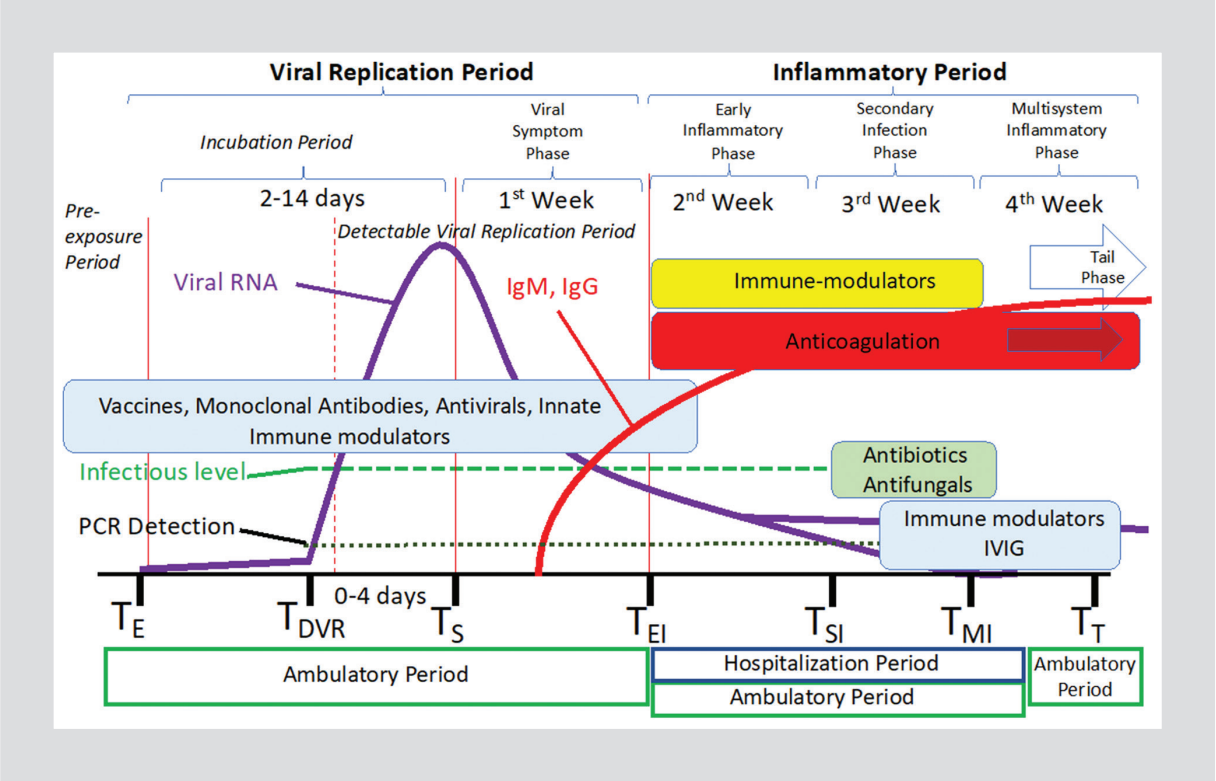

Figure 3. *Most appropriate phase for testing and use of various classes of therapeutics T_E (Time of exposure), T_{DVR} (Time of detectable viral replication), T_S (Time of symptom onset), T_{EI} (Time of early inflammation), T_{SI} (Time of secondary infection), T_{HI} (Time of multisystem inflammation), and T_T (Time of the tail onset).*

and support groups have formed for "long haulers." The mechanisms driving this phase are poorly understood and investigation has been limited[71].

As we learn more about the post-exertional fatigue seen in this phase it appears to be distinct from that described in chronic fatigue syndrome (CFS) or what is now known as myalgic encephalitis (ME). Understanding the underlying mechanism(s) of this phase and developing therapeutics is critical to helping these individuals return to their productive roles in society. With these phases defined and their mechanisms starting to be better understood, the timing of potential benefit can hopefully be identified. (Fig. 3)

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