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A Review of Persistent Post-COVID Syndrome (PPCS)

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Abstract

Persistent post-COVID syndrome, also referred to as *long COVID*, is a pathologic entity, which involves persistent physical, medical, and cognitive sequelae following COVID-19, including persistent immunosuppression as well as pulmonary, cardiac, and vascular fibrosis. Pathologic fibrosis of organs and vasculature leads to increased mortality and severely worsened quality of life. Inhibiting transforming growth factor beta (TGF-β), an immuno- and a fibrosis modulator, may attenuate these post-COVID sequelae. Current preclinical and clinical efforts are centered on the mechanisms and manifestations of COVID-19 and its presymptomatic and prodromal periods; by comparison, the postdrome, which occurs in the aftermath of COVID-19, which we refer to as persistent post-COVID-syndrome, has received little attention. Potential long-term effects from post-COVID syndrome will assume increasing importance as a surge of treated patients are discharged from the hospital, placing a burden on healthcare systems, patients' families, and society in general to care for these medically devastated COVID-19 survivors. This review explores underlying mechanisms and possible manifestations of persistent post-COVID syndrome, and presents a framework of strategies for the diagnosis and management of patients with suspected or confirmed persistent post-COVID syndrome.

Keywords SARS-CoV-2 · COVID-19 · Immunology · TGF-β

Introduction

Winston Churchill, the eminently aphoristic and epigrammatic Prime Minister of Great Britain from 1941 to 1945, once wrote: "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning." The SARS-CoV-2 pandemic is a story in three parts: prologue or onset, middle chapters, and epilogue or resolution, of which only the prologue and some of the middle chapters have been written, marking the end of the beginning but also hopefully the beginning of the end as the containment and mitigation measures to limit the spread of the disease finally begin to take effect [1].

The assumption is that COVID-19 ends with the resolution of symptoms and the avoidance of mortality. Consequently, the main focus is (appropriately) on early recognition and treatment. Therapeutic management focuses on resuscitation and immediate treatment with antivirals, immune modulators, and cytokine-targeted therapies to dampen the overly exuberant immune response, i.e., "cytokine storm" [2] responsible for multi-organ dysfunction syndrome (MODS). Clinically symptomatic patients are the visible part of the metaphoric COVID-19 iceberg; however, early anecdotal evidence of post-COVID morbidity [3] and mortality [4], the submerged part of the metaphoric iceberg, suggests an urgent need for and focus on specialized aftercare, especially as a surge of patients are declared "recovered" and discharged from ICUs.

By analogy with post-sepsis syndrome [5] and post-ICU syndrome [6], emerging pathological entities characterized by a clinically significant deterioration of quality of life (QOL) and increased risk of indolent death associated with a constellation of effects that persist long after the resolution of infectious symptoms, we have coined the umbrella term "persistent post-COVID syndrome" (PPCS) to describe

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the morbid post-ICU course of COVID survivors. Also, by analogy with post-sepsis syndrome, which occurs in approximately 50% of sepsis survivors and has been labeled a "hidden public health disaster" [7], these long-term PPCS effects may occur on a scale sufficient to overwhelm existing health care capacity. While several strategies to optimize management of the acute COVID-19 episode are under evaluation, limited attention has been given to the appropriate management and prevention of potential long-term PPCS sequelae, which is perhaps related to the remoteness of symptoms from the incident infection and/or the current focus on "one clinical catastrophe at a time" and "first things first." A potential unifying hypothesis to account for longstanding illness, examined in more detail below, is overexpression of transforming growth factor beta (TGF-β), which leads to a protracted state of immunosuppression and fibrosis.

This article briefly addresses (1) a possible TGF-β-driven mechanism of persistent post-COVID syndrome, (2) a summary of clinical manifestations of PPCS, and (3) potential strategies for the diagnosis and management of PPCS.

Post-COVID Mechanisms

Following trauma or a severe primary infectious disease like COVID-19, in which a systemic inflammatory response syndrome or SIRS is predominant, an overwhelming and long-lasting counterbalancing compensatory anti-inflammatory response syndrome (CARS) occurs that leads to postinfectious/posttraumatic immunosuppression [8]. The purpose of the CARS response, a mirror-imaged counter-regulation to SIRS or systemic inflammatory response syndrome, is to dampen the proinflammatory state, prevent maladaptive multiple-organ dysfunction [9], and govern the return to immunologic homeostasis or normalcy [10].

Multiple simultaneously interacting and opposing factors are involved, orchestrating a fine-tuned balance of pro- and anti-inflammatory responses, i.e., SIRS and CARS, that ultimately determines the outcome in COVID-19. Excessive inflammatory responses are a function of (1) viral exposure or inoculum, (2) the presence/absence of comorbidities, and (3) the state of immunocompetence, and are characterized by excessive release of inflammatory cytokines such as interleukins 1, 6, 8, 17, and 1β, monocyte chemoattractant protein-1, and tissue necrosis factor α [11] collectively known as "cytokine storm" [12]. Unabated, this process results in the development of acute lung injury (ALI), acute respiratory distress syndrome (ARDS), coagulopathy, hypotension, hypoperfusion, organ failure (also known as multiple-organ failure (MOF) or multiple-organ dysfunction syndrome (MODS)), and death, as shown in Fig. 1 [13].

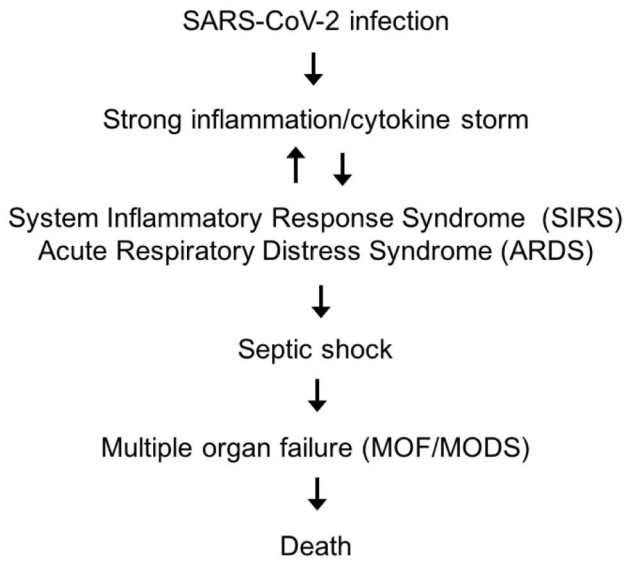

Fig. 1 The COVID-19 cascade leading to mortality

If, on the other hand, the inflammatory response is repressed too far in the direction of CARS, then the patient, having managed to "weather" the initial hyperinflammatory cytokine storm and the progression to ARDS, may enter a stage of protracted immunosuppression [14, 15] known as PICS for persistent inflammation, immunosuppression, and catabolism syndrome that is seen post-sepsis and which is one of the hypothesized causes of persistent post-COVID syndrome (PPCS), as shown in Fig. 2.

In support of this hypothesis, post-septic patients are prone to latent virus reactivation [16] and multiple news sources have reported on relapse or reactivation of SARS-CoV-2 in recovered COVID-19 patients [17, 18]. Likewise, as in sepsis, COVID-19 patients are at risk for the development of secondary bacterial and fungal infections [19], highlighting the immune suppression and dysregulation that is present (Fig. 3).

In addition to the loss of immune competence, post-COVID patients are also vulnerable to the development of pulmonary fibrosis [20], which is commonly seen in follow-up imaging of recovered patients and which is different than interstitial pulmonary fibrosis (IPF) [21]. However, the true extent to which post-ARDS fibrosis represents a problem is not well defined since the other effects of dyspnea, fatigue, and weakness seem to be out of proportion to the degree of ongoing lung damage and the degree of gas exchange impairment (Fig. 4).

Transforming growth factor beta (TGF-β) is a multifunctional cytokine with profibrogenic, anti-inflammatory, and immunosuppressive effects that are elevated during and after sepsis as well as during and after COVID-19 [22], presumably to counteract the

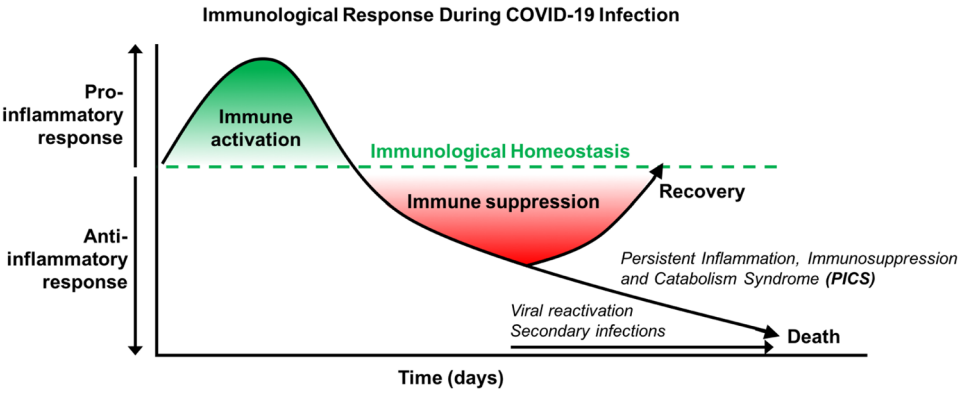

Fig. 2 Simplified net immunological response in COVID-19 by analogy with sepsis. Immunologic response in COVID-19 over time: initially, the proinflammatory response predominates. Anti-inflammatory cytokines are expressed to dampen the cytokine storm. With chronic immunosuppression, persistent inflammation immunosuppression and catabolism syndrome (PICS) dominates. Early deaths may be caused by cytokine storm while later deaths, which occur during the anti-inflammatory phase, may be caused by secondary infections

hyperinflammatory response. Histologic changes from the lungs of COVID-19 patients demonstrate fibroblastic proliferations and interstitial fibrosis, suggestive of TGF-β involvement [23]. Thus, as a potent inducer of fibrosis and immunosuppression, TGF-β signaling, which is mediated by Smad proteins or MAP kinases and Akt [24], potentially represents an attractive target for therapeutic intervention.

Post-COVID Manifestations

Post-COVID sequelae vary from patient to patient, and a consensus regarding the characterization of possible symptoms has not been reached [25]. At the time of publishing, large-scale clinical studies regarding post-COVID sequelae are not readily available. In Table 1, we

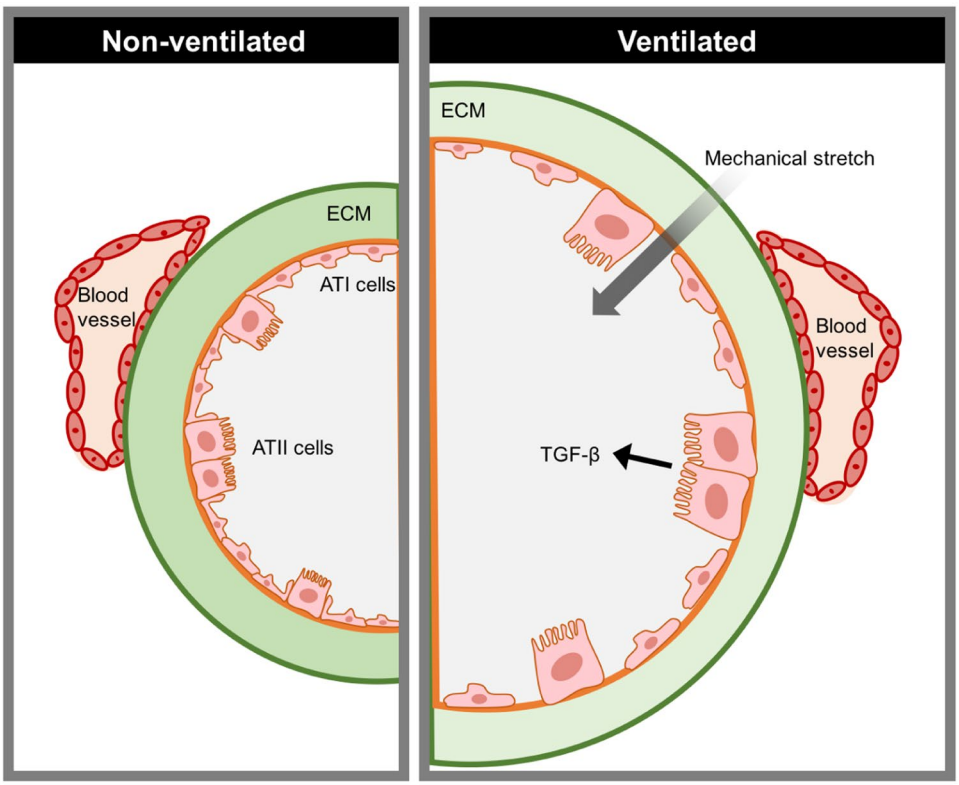

Fig. 3 Mechanical stretch from ventilation releases mediators such as TGF-β that leads to fibrosis. ECM: extracellular matrix; AT1 and AT2 alveolar pneumocytes type 1 and 2; TGF-β: transforming growth factor beta

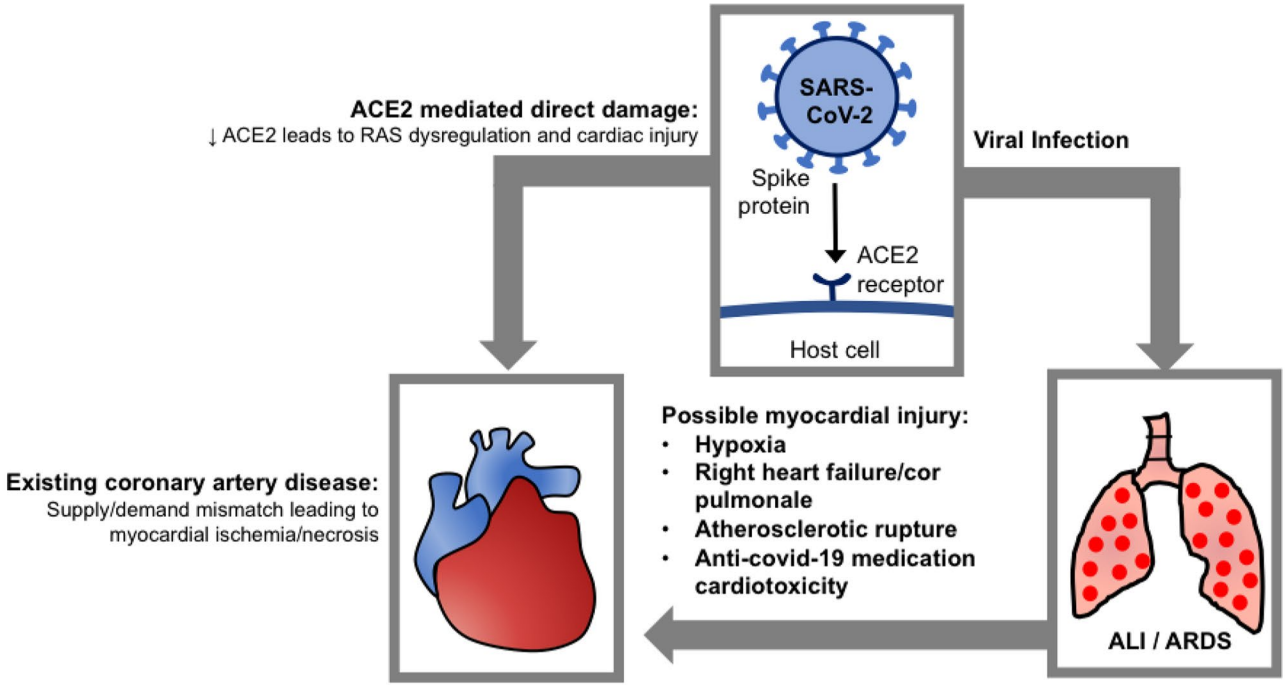

Fig. 4 Potential mechanisms of COVID-19-induced cardiac injury. ALI/ARDS: acute lung injury/adult respiratory distress syndrome; RAS: renin-angiotensin system; ACE: angiotensin-converting enzyme 2

suggest a framework to aid in identifying and diagnosing post-COVID manifestations. This framework includes four screening categories: (1) Laboratory investigation, (2) radiologic pathology, (3) deterioration in functional status, and (4) subjective symptomatic and quality-of-life parameters. In the following, a selection of post-COVID manifestations are explored.

Pulmonary Fibrosis and Dysfunction

While the majority of COVID-19 cases are mild or asymptomatic, approximately 5–8% of infected patients develop adult respiratory distress syndrome or ARDS, which is characterized by hypoxemia, bilateral pulmonary infiltrates secondary to non-cardiogenic pulmonary edema, and decreased lung compliance, often requiring mechanical ventilation [26, 27]. The pathologic evolution of ARDS is thought to involve three overlapping phases: exudative, proliferative, and fibrotic [28]. In the exudative phase, release of proinflammatory cytokines such as IL-1β, TNF, and IL-6, influx of neutrophils, and endothelial-epithelial barrier disruption occur, which leads to alveolar flooding and respiratory distress [29]. The exudative phase is followed by a fibroproliferative phase, in which fibrocytes, fibroblasts, and myofibroblasts accumulate in the alveolar compartment, leading to excessive deposition of matrix components including fibronectin, collagen I, and collagen III [30].

Table 1 Framework to aid in the screening and diagnosis of persistent post-COVID sequelae

1. Laboratory investigation
Confirmed active or past COVID-19 infection through throat swab RT-PCR and/or antibody testing*
Abnormal laboratory findings compared with baseline**
2. Radiologic pathology
Pulmonary pathology on CT/radiologic imaging compared with baseline**
3. Deterioration of functional status
Deterioration in functional status compared with baseline**
4. Subjective symptomatic and quality-of-life parameters
New or worsening symptoms longer than 2 weeks past baseline**
Duration of symptoms or re-emergence of symptoms longer than 2 weeks past baseline**

*Negative throat swab RT-PCR and/or antibody test does not conclusively rule out past or ongoing COVID-19 infection. **Baseline defined as timepoint prior to initial COVID-19 infection

One of the mechanisms that contribute to the development of a fibroproliferative response in ARDS is mechanical ventilation since shear forces not only induce secretion of transforming growth factor β1 but also activate collagen synthesis and inhibit collagenase production [31].

A subset of ARDS survivors and, hence, also, by extension, COVID-19 patients progress to pulmonary fibrosis, of which exercise-induced breathlessness and chronic dry cough are the prominent symptoms and for which management is largely supportive consisting of supplemental oxygen, pulmonary rehabilitation, and vaccination against *Streptococcus pneumoniae* and influenza [32]. Two FDA-approved medications, nintedanib and pirfenidone, are non-curative but have been demonstrated to slow the progression of pulmonary fibrosis [33]. These patients, whose mortality risk is elevated, may continue to present with exercise limitations and reduced quality of life for up to 5 years post-ARDS [34].

Cardiac Fibrosis and Dysfunction

COVID-19 patients commonly present with signs of myocardial injury including heart failure and myocarditis and/or exacerbation of existing cardiovascular disease as determined by elevated levels of troponin T (TnT) and brain natriuretic peptide (BNP) [35]. Potential mechanisms of injury include the following:

- increased pulmonary vascular resistance with subsequent pulmonary hypertension and right heart failure
- overstimulation of the renin-angiotensin system (RAS), which mediates deleterious effects on the cardiovascular system including secondary hyperaldosteronism, leading to hypokalemia and cardiac arrhythmias [36]
- atherosclerotic plaque rupture via the action of pro-inflammatory cytokines, precipitating infarction, especially in the context of pre-existing coronary artery diseases [37]
- ACE-2-mediated viral invasion of cardiomyocytes, resulting in myocarditis
- myocardial oxygen supply/demand mismatch from the combination of decreased venous return and severe hypoxemia due to ARDS, leading to myocardial ischemia/necrosis
- possible cardiotoxicity of potential anti-COVID agents including the macrolide antibiotic, azithromycin, associated with a prolonged QT interval [38], chloroquine/hydroxychloroquine, which may produce conduction defects in the heart, tocilizumab, which increases cholesterol levels [39], and lopinavir/ritonavir, the protease inhibitors that may prolong PR and QT intervals and also inhibit CYP3A4 activity, which influences the metabolism of other cardiac medications including statins [40].

The common denominator of myocardial injury is a remodeling process that includes hypertrophy and fibrosis of the left ventricular wall, leading to reduced contractility and impaired global function [41], of which TGF-β, as the main profibrotic cytokine, is a major player. While it is perhaps too early to predict long-term cardiac consequences of COVID-19, extrapolation is possible with SARS-CoV-1 patients, given the genetic similarities between SARS-CoV-1 and SARS-CoV-2, that at 12-years of follow-up demonstrated cardiovascular abnormalities in 40% [42].

Neurological Fibrosis and Dysfunction

Infection with SARS-CoV-2 commonly leads to respiratory symptoms typical of a viral pneumonia, including fever, cough, dyspnea, and sore throat but also, interestingly, anosmia and dysgeusia [43], which suggests that the virus is neurotropic. In a retrospective case series of 214 patients in Wuhan, China, a high incidence of neurologic symptoms was seen. Seventy-eight (36.4%) patients had central nervous system (CNS) (24.8%), peripheral nervous system (PNS) (8.9%), or skeletal muscle symptoms (10.7%). The two most common CNS symptoms were dizziness (16.8%) and headache (13.1%). Acute cerebrovascular disease, ataxia, epilepsy, and impaired consciousness were also reported [44].

Tissue fibrosis is a common response to damage in most organs of the body except the brain because fibrogenic cells are restricted to particular niches [45]. However, with disruption of the blood brain barrier due to cytokine storm, for example, or direct viral injury to nervous tissue, scar formation is induced.

Neurologic and psychiatric sequelae are commonly seen in sepsis survivors [46, 47]. Likewise, neuropsychiatric symptoms have also been reported with after SARS-CoV-2 infection [48]. These symptoms include depression, anxiety, and psychosis [49].

Since multiple neurological disorders including AIDS dementia complex, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis, anxiety, depression, and schizophrenia [50] are linked to the deregulation of the TGF-β signaling pathway, this cytokine is a potential therapeutic target for COVID-19-induced neuropsychiatric symptoms.

COVID-19-Associated Coagulopathy

Some patients with severe COVID-19 infection develop a DIC-like coagulopathy with fulminant activation of coagulation and consumption of coagulation factors. This is characterized by delayed clotting times (PT and aPTT), low platelets, and decreased fibrinogen (< 1.0 g/L) due to their consumption. Thrombotic complications include

pulmonary embolism and strokes, which suggest the need for pharmacological thrombosis prophylaxis especially in ICU patients [51].

Thrombotic "after-effects" include the potential for recurrence, long-term anticoagulation with Coumadin or enoxaparin, which increases the risk of hemorrhage, physical impairments from cerebral vascular accident (CVA) [52], myocardial infarction (MI) or pulmonary embolism, and alterations of behavior and emotion.

Table 3 Clinical studies of TGF-β inhibitors in cancer for potential repurposing in PPCS

Agents	Target	Phase
Trabedersen (AP12009)	TGF-β2 mRNA	2b
Belagenpneumatucel–L (Lucanix)	TGF-β2	3 (failed)
Fresolimumab (GC1008)	Pan TGF-β	2
Galunisertib (LY2157299)	TβRI	2
Tasisulam (LY573636)	TGF-β	2
BETA PRIME (AdAPT-001)	TGF-β 1 and 3	1

Management

Management strategies for the treatment of post-COVID sequelae will vary greatly depending on the symptomatic profile and needs of each individual patient. Management strategies should account for prior pre-existing medical conditions and care teams should provide regular follow-up for each patient until symptoms subside and for some time thereafter. A framework of general recommendations for the management of patients with suspected or confirmed PPCS is presented in Table 2. In the following, we explore potential treatment strategies for specific post-COVID manifestations.

By analogy with sepsis, which COVID-19-induced ARDS parallels, hyperinflammation during SARS-CoV-2 infection is followed by a prolonged immunoparalytic and profibrotic state that drives heightened vulnerability to secondary infections and organ dysfunction even after so-called recovery from the disease (Fig. 2). On this basis, immunodulatory therapies are seemingly warranted, to prevent or reverse the anti-inflammatory phenotype, although many of these immunodulatory therapies (e.g., GM-CSF, pooled intravenous immunoglobulins (IVIG), IFNγ, interleukin-7, PD-L1 inhibitors, and IL-3) have been tried during sepsis, with mostly mixed results, possibly due to the complex temporal fluctuations of pro- and anti-inflammatory cytokines in sepsis [53].

However, in post-sepsis syndrome and, by extension, PPCS, persistent inflammation, immunosuppression, and catabolism or PICS predominates, which resembles the malignant phenotype, hence the rationale to investigate immunomodulatory therapies such as checkpoint inhibitors, TGF-β inhibitors, hematopoietic growth factors, cytokines, and chemokines specifically in this post-infectious setting, rather than during ongoing sepsis per se, when inflammation fluctuates dynamically. In particular, for PPCS and for post-sepsis/post-ICU syndromes, TGF-β inhibitors may hold promise as agents that neutralize or reverse immune suppression as well as fibrosis.

Several potentially repurposable TGF-β inhibitors are under evaluation in the clinic for the treatment of cancer. These include Trabedersen (AP12009, Antisense Pharma), an antisense oligonucleotide, Belagenpneumatucel-L (Lucanix, NovaRx), a TGF-β2, antisense allogenic tumor cell vaccine, galunisertib monohydrate (LY2157299, Eli Lilly), a small-molecule inhibitor of TβRI, vactosertib (EW-7197 or TEW-7197), a novel small-molecule inhibitor of ALK5 that inhibits TGF-β1-induced Smad/TGFβ signaling, fresolimumab (GC1008, Genzyme/Sanofi), a fully human monoclonal antibody blocking pan-TGF-β (TGF-β1, TGF-β2, and TGF-β3), tasisulam (LY573636), a small-molecule inhibitor of TGF-β, and BETA PRIME (AdAPT-001, EpicentRx), a modified replicating oncolytic adenovirus that encodes the TGF-β type II receptor to trap or neutralize TGF-β [54]. Table 3 summarizes a number of these clinical TGF-β inhibitors.

Standard of care for many acute events includes not only acute management but also mitigates the risk of subsequent complications in scenarios where the risks and appropriate interventions are widely recognized. Examples include treating with antiplatelet therapy (such as Aggrenox) after stroke, anticoagulation which is increasingly in the form of direct oral anticoagulants (such as rivaroxaban or apixaban) after orthopedic surgery,

Table 2 Recommendations for the management of patients with suspected or confirmed persistent post-COVID-19 syndrome (PPCS)

1. Physician examination of patient with mapping of current symptomatic status or medical concerns
2. Establish COVID-19 exposure status and potential disease history through oral history and possible clinical testing
3. Screen for possible non-COVID-19 co-morbidities or chronic medical conditions
4. Administer appropriate medical treatments for acute symptoms or established underlying chronic conditions
5. Educate patient in the possible manifestations of persistent post-COVID-19 also known as *long COVID-19* sequelae
6. Continue regular patient follow-up and encourage patient to seek medical care at onset of worsening symptoms

and post-myocardial infarction regimens including statins, anti-platelet agents, ACE inhibitors, and beta blockers. While post-ARDS complications have begun to be recognized, the surge of COVID-19 is poised to bring PPCS and post-ARDS syndrome to the forefront and open the question of how it should be handled when there is no current standard of care.

Conclusion

At the forefront of clinical care for acute COVID-19 are multiple guidelines, recommendations, and best practices that have been promulgated and prioritized for prevention and management; however, presumably because the focus is on the immediate, day-to-day "anti-COVID fight" rather than on a potential future one, no guidelines are currently available for postinfectious care or recovery and there is a notable dearth of information on and strategies about how to assess and manage post-COVID patients.

The purpose of this review is to make the case and to raise awareness (and the alarm) for persistent post-COVID syndrome (PPCS), a newly coined umbrella term, by analogy to post-sepsis/post-ICU syndrome that covers a loose confederation of heterogeneous symptoms for which no pathognomonic laboratory test exists, making it easy to overlook or ignore. However, to overlook or ignore the hidden "iceberg" of PPCS, which may be unique or a version of post-sepsis/post-ICU is to possibly replace or supplant one epidemic with another, as evidenced by the rising tide of physical and psychological disabilities that have been described in post-COVID patients [55–57] and which have the potential to re-inundate an already overburdened health care system.

Nevertheless, evidence of a causal association between COVID-19 diagnosis and subsequent morbidity is difficult to establish, especially since chronic illness and persistent post-COVID syndrome (PPCS) may share common risk factors and antecedents, such as older age, diabetes, smoking, malnutrition or obesity, immunosuppression, and hypertension, which reflect a broad vulnerability to these pathologies. Other factors, which may increase diagnostic and management difficulties include.

- the temporal separation between the acute and chronic symptoms
- a lack of awareness of post-COVID and post-ICU pathology, potentially resulting in a failure to "connect the dots" with regard to the multi-system signs and symptoms
- the chicken-and-egg question about whether and to what extent critical illness per se is responsible for and causally related to prolonged post-COVID illness, or whether and to what extent pre-existing comorbidities and pre-COVID clinical trajectories influence the post-COVID burden and are responsible for pushing frail patients with low resiliency past a tipping point.

Finally, it is probably unrealistic to expect a "magic bullet" treatment for PPCS that will completely "roll back" the symptoms; however, since the central issues for PPCS are potentially immune paresis and, hence, susceptibility to secondary infections as well as fibrotic remodeling in the lungs, heart, and brain that develops as the end result of a chronic inflammatory process, then immunomodulatory therapy, and particularly inhibition of TGF-β, stands at the intersection between inflammation, immunosuppression, and fibrosis and may serve as a mechanistic lynchpin linking post-infectious immunoparalysis with fibrosis to facilitate the design of new targeted strategies for the prevention of these devastating sequelae of COVID-19.

One of the first American battle cries was, "The redcoats are coming!". The most recent may be "re-COVID is coming" due to seasonal recurrence of the SARS-CoV-2 virus and along with it, according to the premise of this review, persistent post-COVID syndrome.

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Declarations

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