

# Le condizioni post COVID

Prof. Francesco Menichetti

Presidente,

Gruppo Italiano per la Stewardship Antimicrobica

GISA

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# Ringraziamenti



# Definizione

- Con il termine "condizioni post-COVID" il **CDC** indica l'ampia gamma di conseguenze sulla salute presenti **quattro o più settimane dopo l'infezione da SARS-CoV2.**
- Le condizioni post-COVID comprendono uno **spettro di conseguenze fisiche, sociali e psicologiche, nonché limitazioni funzionali**, che impattano sul benessere e la qualità della vita del paziente.
- Le condizioni post-COVID sono indicate con molteplici nomi, tra cui:
- ***Long COVID , COVID-19 post-acuto, Effetti a lungo termine del COVID, **Sindrome da COVID post-acuta (PACS)**, COVID cronico, COVID di lunga durata, Sequele tardive, Sequele post-acute dell'infezione da SARS-CoV-2***

# A clinical case definition of post-COVID-19 condition by a Delphi consensus

## Panel: A definition of the post-COVID-19 condition

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 (other symptoms are listed in the appendix [p 4] and published literature<sup>14</sup>), and generally have an impact on everyday 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.

A separate definition might be applicable for children.

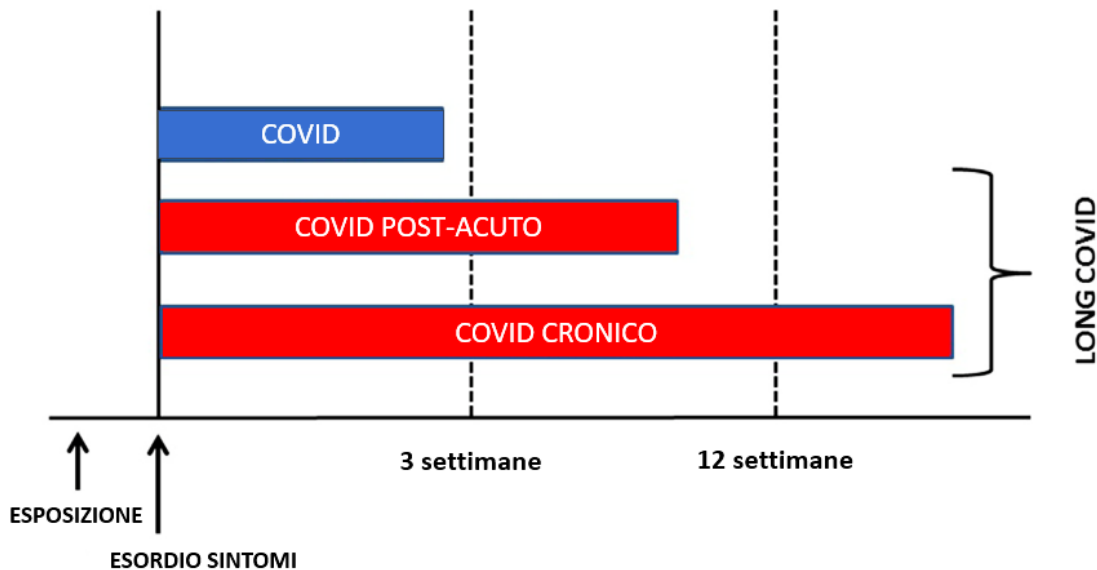


Fig.1: classificazione del long COVID

# Prevalenza

- La prevalenza delle PACS è difficile da stimare, con ampie variazioni (5-30%).

*Open Forum Infectious Diseases*

MAJOR ARTICLE



OXFORD

## Systematic Review of the Prevalence of Long COVID

Mirembe Woodrow,<sup>1,✉</sup> Charles Carey,<sup>2,✉</sup> Nida Ziauddeen,<sup>1,3</sup> Rebecca Thomas,<sup>4</sup> Athena Akrami,<sup>5,6</sup> Vittoria Lutje,<sup>7</sup> Darren C. Greenwood,<sup>8,a,✉</sup> and Nisreen A. Alwan<sup>1,3,9,a</sup>

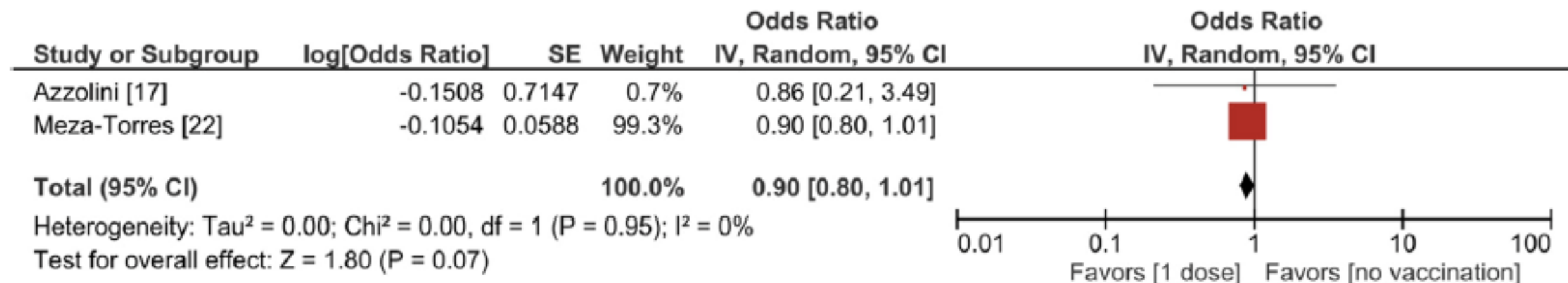
- PACS associate ad una ridotta capacità di svolgere le attività quotidiane.
- **1.2–1.9% (almeno 3-5 milioni)** degli adulti USA vive con PACS da almeno 1 mese con limitazione delle attività quotidiane

# Protective effect of COVID-19 vaccination against long COVID syndrome: A systematic review and meta-analysis

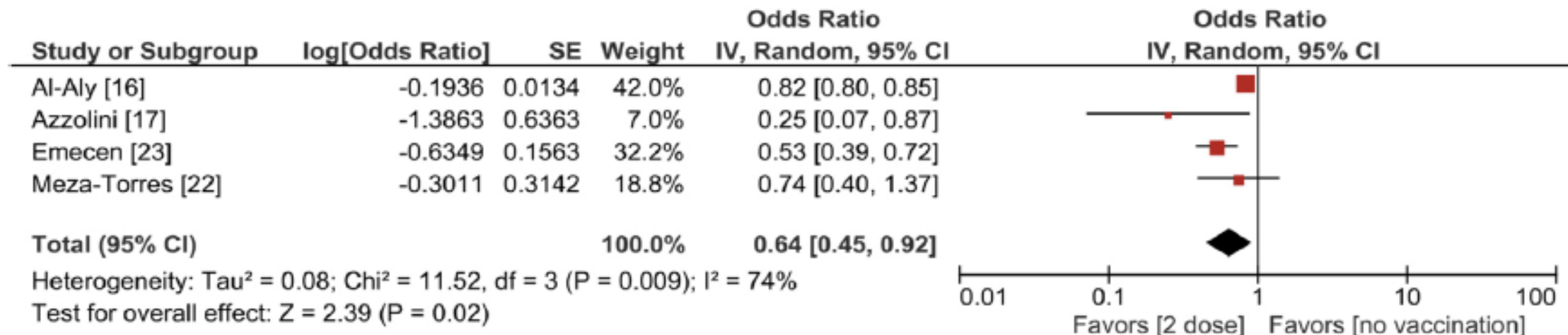


Atsuyuki Watanabe<sup>a</sup>, Masao Iwagami<sup>b,c</sup>, Jun Yasuhara<sup>d</sup>, Hisato Takagi<sup>e</sup>, Toshiki Kuno<sup>f,\*</sup>

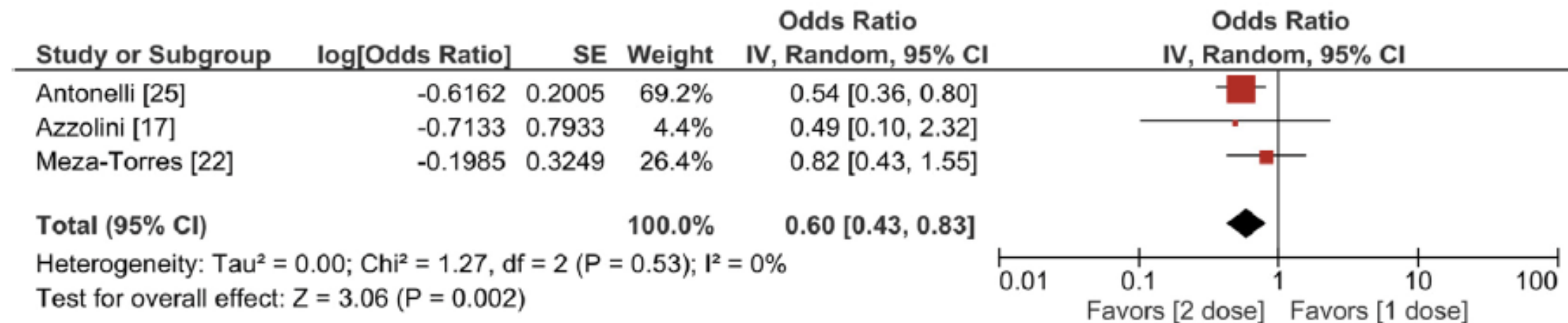
## c) one-dose vaccination vs. no vaccination



a) two-dose vaccination vs. no vaccination



b) two-dose vaccination vs. one-dose vaccination

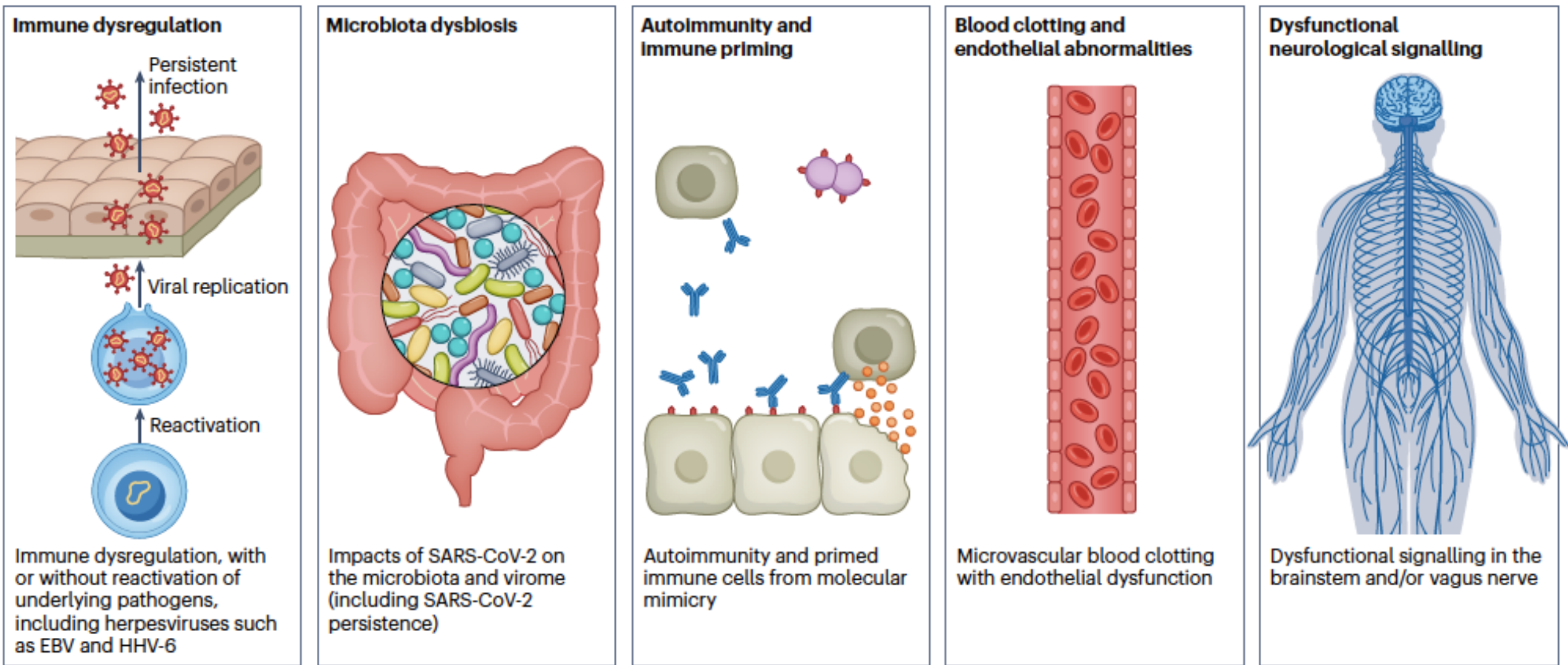


# **Ipotesi patogenetiche**

Le condizioni post-COVID sono attribuibili a diversi processi fisiopatologici:

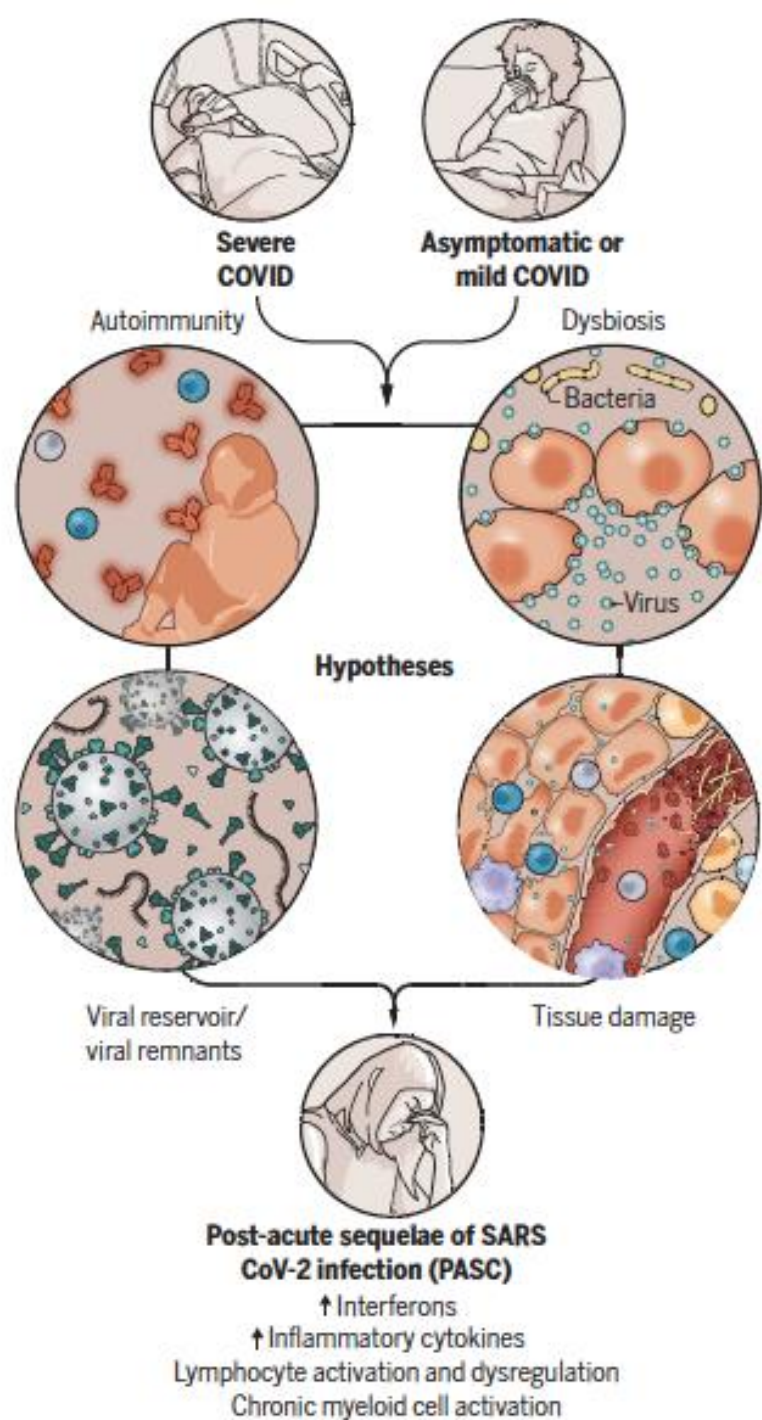
- ***Disregolazione immunitaria con o senza riattivazione virale***
- ***Disbiosi del microbiota***
- ***Autoimmunità***
- ***Ipercoagulabilità e danno endoteliale (danno tissutale)***
- ***Segnali neurologici disfunzionali***





**Fig. 3 | Hypothesized mechanisms of long COVID pathogenesis.** There are several hypothesized mechanisms for long COVID pathogenesis, including immune dysregulation, microbiota disruption, autoimmunity, clotting

and endothelial abnormality, and dysfunctional neurological signalling. EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



## and immunopathology of COVID-19

<sup>2\*</sup>, Federica Sallusto<sup>3,4\*</sup>, Akiko Iwasaki<sup>5,6\*</sup>

**Fig. 2. Immunology of PASC.** A fraction of COVID-19 patients with either severe or mild COVID-19 develop a variety of new, recurring, or ongoing symptoms and clinical findings 4 or more weeks after infection. Analyses of immune responses in people with PASC reveal key inflammatory cytokines and cellular activation phenotypes that are significantly elevated over nonPASC convalescent controls. Further studies are needed to identify the drivers of PASC pathophysiology.

# Presentazione delle condizioni post-COVID

- Diversi modelli di insorgenza PACS, tra cui:
- **sintomi e condizioni persistenti che iniziano al momento della malattia acuta COVID-19**
- **segni, sintomi o condizioni di nuova insorgenza** a seguito di malattia asintomatica o di un periodo di miglioramento o remissione dei sintomi acuti
- **evoluzione dei sintomi e delle condizioni** che includono alcuni sintomi persistenti (ad es. mancanza di respiro) con **l'aggiunta di nuovi sintomi** o condizioni nel tempo (ad es. difficoltà cognitive)
- **peggioramento di sintomi o condizioni preesistenti**

# Sintomi più comuni

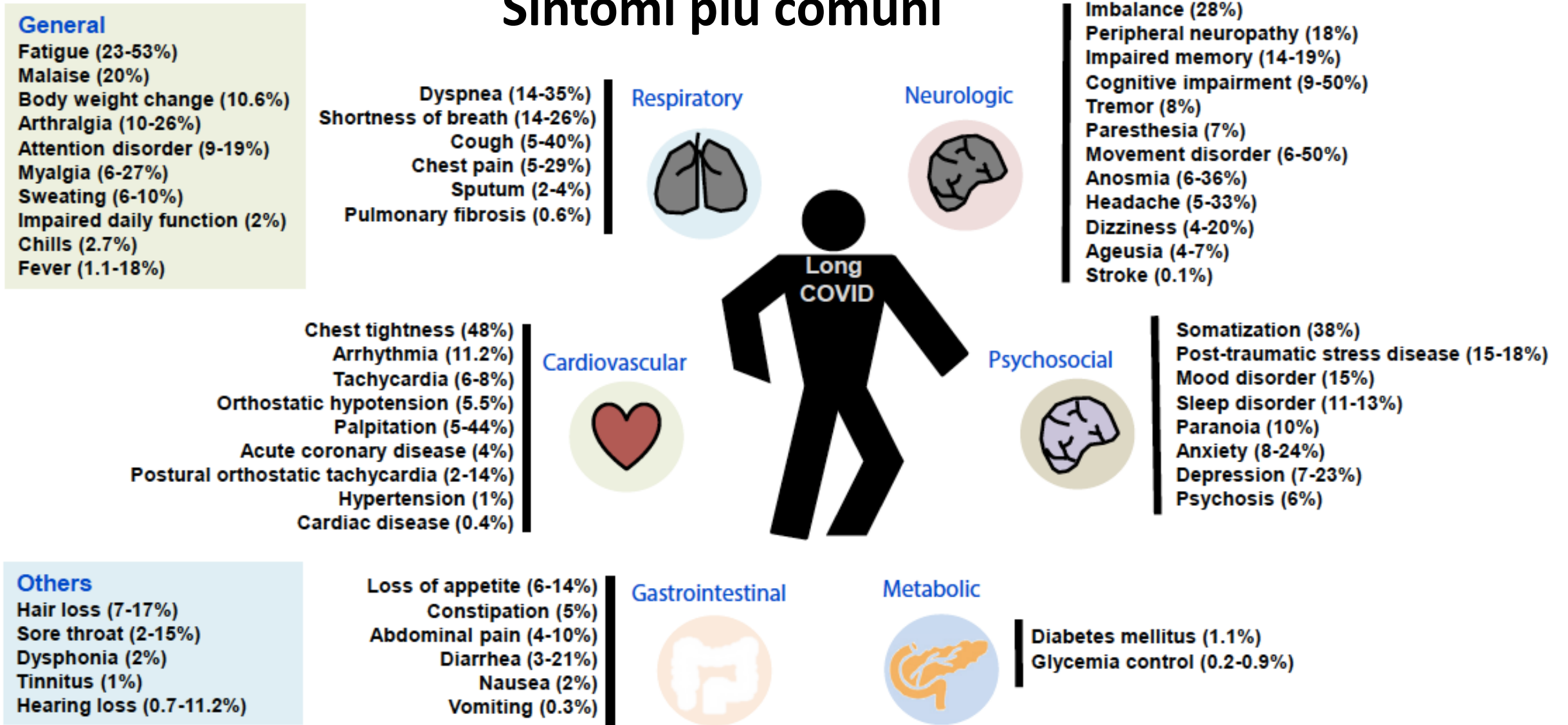
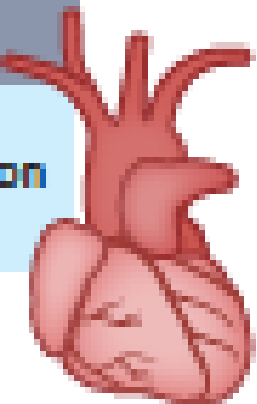
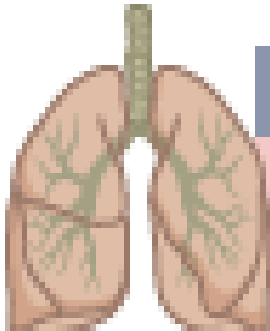


Figure 1. Clinical manifestations of long coronavirus disease (COVID).<sup>12,22,23</sup>

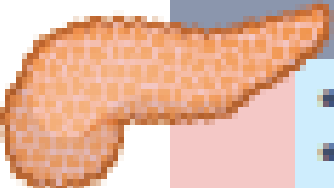
Symptoms
Pathology



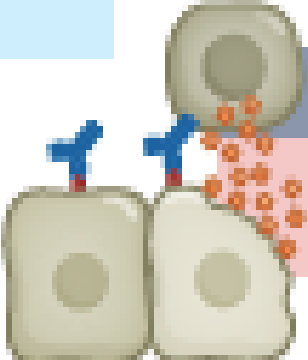
Heart	
<ul style="list-style-type: none"> <li>• Chest pain</li> <li>• Palpitations</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiac impairment</li> <li>• Myocardial inflammation</li> <li>• POTS</li> </ul>



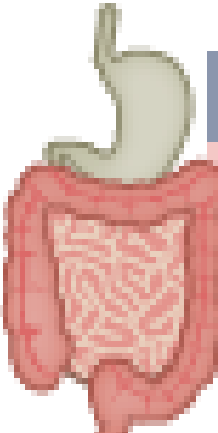
Lungs	
<ul style="list-style-type: none"> <li>• Cough</li> <li>• Dyspnoea</li> </ul>	<ul style="list-style-type: none"> <li>• Abnormal gas exchange</li> </ul>



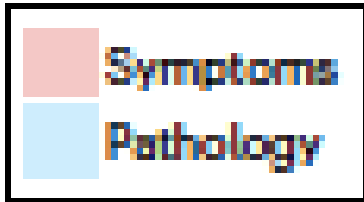
Pancreas	
<ul style="list-style-type: none"> <li>• Diabetes</li> <li>• Pancreas injury</li> </ul>	



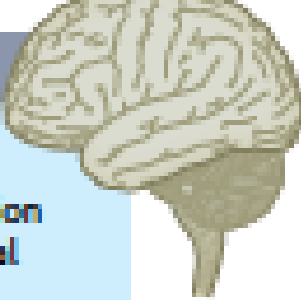
Immune system	
<ul style="list-style-type: none"> <li>• Autoimmunity</li> <li>• MCAS</li> </ul>	



Gastrointestinal tract	
<ul style="list-style-type: none"> <li>• Abdominal pain</li> <li>• Nausea</li> </ul>	<ul style="list-style-type: none"> <li>• Gut dysbiosis</li> <li>• Viral persistence and viral reservoir</li> </ul>



**Neurological system**




<ul style="list-style-type: none"> <li>• Cognitive impairment</li> <li>• Fatigue</li> <li>• Disordered sleep</li> <li>• Memory loss</li> <li>• Tinnitus</li> </ul>	<ul style="list-style-type: none"> <li>• Dysautonomia</li> <li>• ME/CFS</li> <li>• Neuroinflammation</li> <li>• Reduced cerebral blood flow</li> <li>• Small fibre neuropathy</li> </ul>
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**Kidneys, spleen and liver**



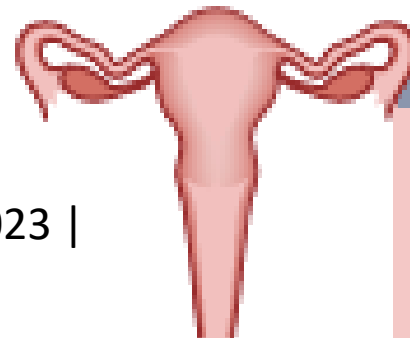
<ul style="list-style-type: none"> <li>• Organ injury</li> </ul>
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**Blood vessels**



<ul style="list-style-type: none"> <li>• Fatigue</li> </ul>	<ul style="list-style-type: none"> <li>• Coagulopathy</li> <li>• Deep vein thrombosis</li> <li>• Endothelial dysfunction</li> <li>• Microangiopathy</li> <li>• Microclots</li> <li>• Pulmonary embolism</li> <li>• Stroke</li> </ul>
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**Reproductive system**



<ul style="list-style-type: none"> <li>• Erectile dysfunction</li> <li>• Increased severity and number of premenstrual symptoms</li> <li>• Irregular menstruation</li> </ul>	<ul style="list-style-type: none"> <li>• Reduced sperm count</li> </ul>
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**Tabella 1.** Categorie della sindrome post-COVID.

<b>Sindrome Post COVID</b>	<b>Aspetti clinici principali</b>	<b>Note</b>
Sindrome da fatica post-COVID	Astenia profonda	Escludere : anemia, ipotiroidismo, squilibri idroelettrolitici.
Sindrome cardio-respiratoria post-COVID	Tosse, febbre, dispnea, dolore toracico.	Improvviso peggioramento della dispnea: pneumotorace, embolia polmonare, malattia coronarica o scompenso cardiaco
Sindrome neuro-psichiatrica post-COVID	Cefalea, anosmia, difficoltà neurocognitive, insonnia, depressione e altre patologie psichiatriche.	Improvvisa comparsa di sintomi neurologici: vasculite, trombosi o demielinizzazione. Valutare in modo appropriato le condizioni psicologiche
Sindrome gastro-intestinale post-COVID	Dolore addominale, diarrea, stipsi, vomito.	Può essere conseguenza della malattia. Diversi farmaci utilizzati durante le fasi acute possono dare sintomi gastrointestinali, soprattutto il lopinavir/ritonavir.
Sindrome epato-biliare post-COVID	Nausea, ittero, alterata funzionalità epatica.	Farmaci quali remdesivir, favipiravir, lopinavir/ritonavir e tocilizumab possono causare alterazione della funzionalità epatica.
Sindrome muscolo-scheletrica post-COVID	Mialgie, artralgie e debolezza muscolare.	Possono dipendere dalla malattia, dall'ospedalizzazione prolungata in terapia intensiva, dalle complicanze neurologiche, dagli squilibri idroelettrolitici e dalle miopatie. L'artralgia infiammatoria deve essere differenziata da altre cause quali Artrite Reumatoide e LES.
Sindrome tromboembolica post-COVID	Dispnea in caso di tromboembolia polmonare, dolore toracico in infarto miocardico acuto e debolezza muscolare e deficit neurologici in caso di ictus.	La diagnosi precoce e il suo trattamento sono salvavita. Usare PDT classici
Sindrome da infiammazione multisistemica o autoimmune post-COVID	Febbre, sintomi gastrointestinali, rash, dolore toracico, palpitazioni.	Livelli elevati di markers infiammatori.
Sindrome genito-urinaria post-COVID	Proteinuria, ematuria, danno renale.	Determinato da disfunzione endoteliale, coagulopatia, attivazione del complemento, danno virale diretto sul rene, sepsi, disfunzione multiorgano.
Sindrome dermatologica post-COVID	Lesioni vescicolari, maculopapulari o orticarioidi o geloni a livello delle estremità (piede da COVID).	

# Accertamenti diagnostici

- **Rx torace, PFR, ECG o ecocardio**, per problemi respiratori o cardiaci
- Se Rx torace normale e normale saturazione di ossigeno, la **TC del torace** potrebbe non aggiungere molto
- l'**angioTC** polmonare può avere una resa inferiore nel workup di embolia polmonare nei pazienti senza un **D-dimero elevato** e sintomi compatibili.
- **RMN cerebrale** potrebbe non risultare patologica in assenza di deficit neurologici focali nei pazienti con sintomi di nebbia cerebrale.
- Ulteriore cautela deve essere adottata nel prescrivere **l'imaging nei bambini** senza un alto indice di sospetto di patologia.
- Studi di imaging più specializzati (ad esempio, **risonanza magnetica cardiaca**) dovrebbero essere subordinati alla consultazione specialistica.



Table 1b. Specialized diagnostic laboratory testing to consider for patients with post-COVID conditions

Category	Laboratory Tests
Rheumatological conditions	Antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide, anti-cardiolipin, and creatine phosphokinase
Coagulation disorders	D-dimer, fibrinogen
Myocardial injury	Troponin
Differentiate symptoms of cardiac versus pulmonary origin	B-type natriuretic peptide

## Sindromi cliniche specifiche

- I pazienti con PASC possono condividere alcuni sintomi di altre condizioni:
- **Encefalomielite mialgica/sindrome da stanchezza cronica (ME/CFS)**
- **Fibromialgia (FM)**
- **Sindrome post-trattamento della malattia di Lyme (PTLDS)**
- **Disautonomia (POTS)**
- **Sindrome da attivazione dei mastociti (MCAS)**

# Encefalomielite Mialgica/Sindrome della Fatica Cronica

La diagnosi richiede la presenza dei seguenti tre sintomi

1. **Riduzione sostanziale o alterazione delle capacità occupazionali, educazionali, sociali, o personali** che persista per più di 6 mesi e sia accompagnata da astenia, spesso profonda, di nuova o recente insorgenza (non preesistente), non sia il risultato di sforzo eccessivo continuo, e non sia alleviata efficacemente dal riposo
2. **Malessere post-sforzo,\* e**
3. **Sonno non ristoratore \***

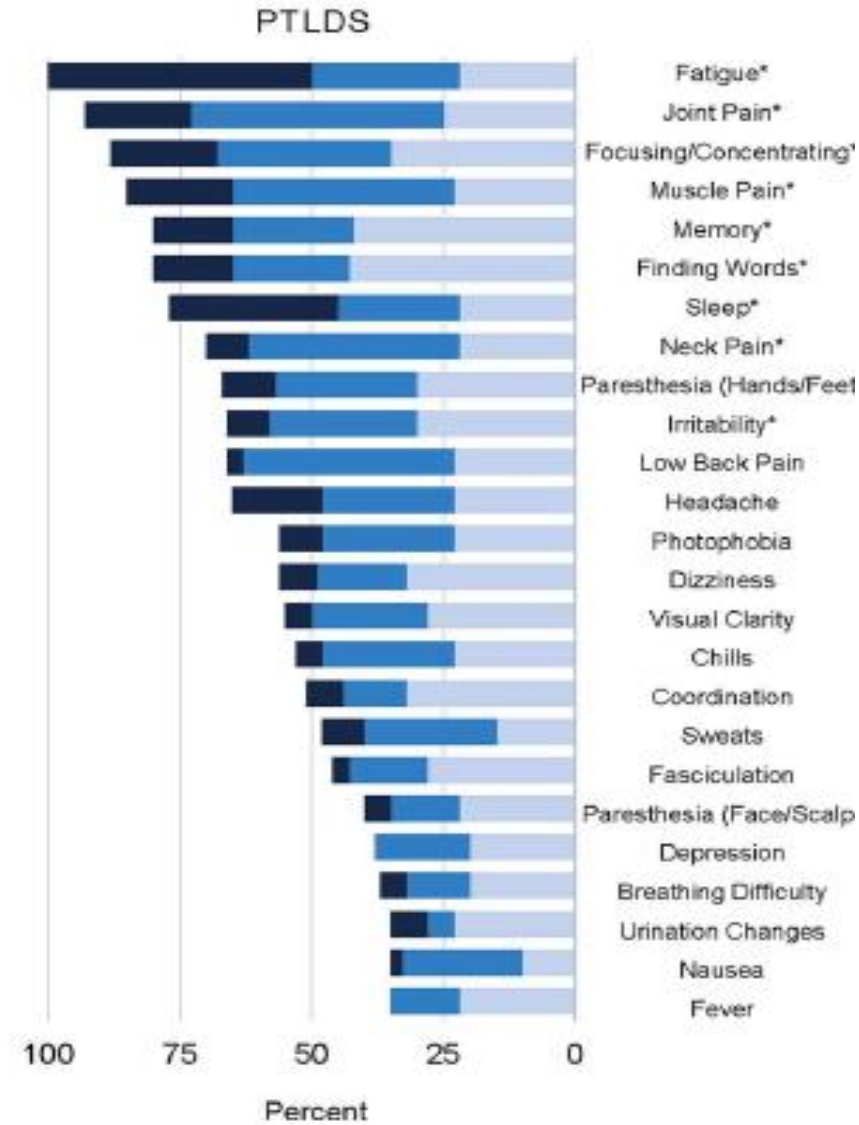
**Concomitante presenza di almeno uno dei due disturbi seguenti:**

1. **Alterazione cognitiva\* o**
  2. **Intolleranza ortostatica**
- *La frequenza e la severità dei sintomi deve essere valutata. La diagnosi di ME/CFS deve essere messa in discussione se i pazienti non soffrono di tali disturbi per almeno la metà del tempo con intensità moderata, sostanziale, o severa*

# Fibromialgia: classificazione e valutazione

- La **diagnosi** è clinica ed utilizza i criteri dell'American College of Rheumatology (ACR) 2010 modificati nel 2011 e 2016.
- **I criteri NON prevedono la palpazione dei tender points.** I pazienti sono invece valutati con il widespread pain index—che suddivide il corpo in 19 regioni ed assegna punteggio a quelle riferite come dolorose—e con uno score di severità dei sintomi che valuta l'entità dell'astenia, del sonno non ristoratore, e dei sintomi cognitivi.
- **Il widespread pain index ed il symptom severity scores sono stati combinati in un singolo questionario con uno score massimo di 31 e possono essere compilati direttamente dal paziente.**
- Uno score da 12 a 13 si è dimostrato efficace nel distinguere coloro che corrispondevano ai criteri ACR 2010 dagli altri

# Post-Treatment Lyme Disease

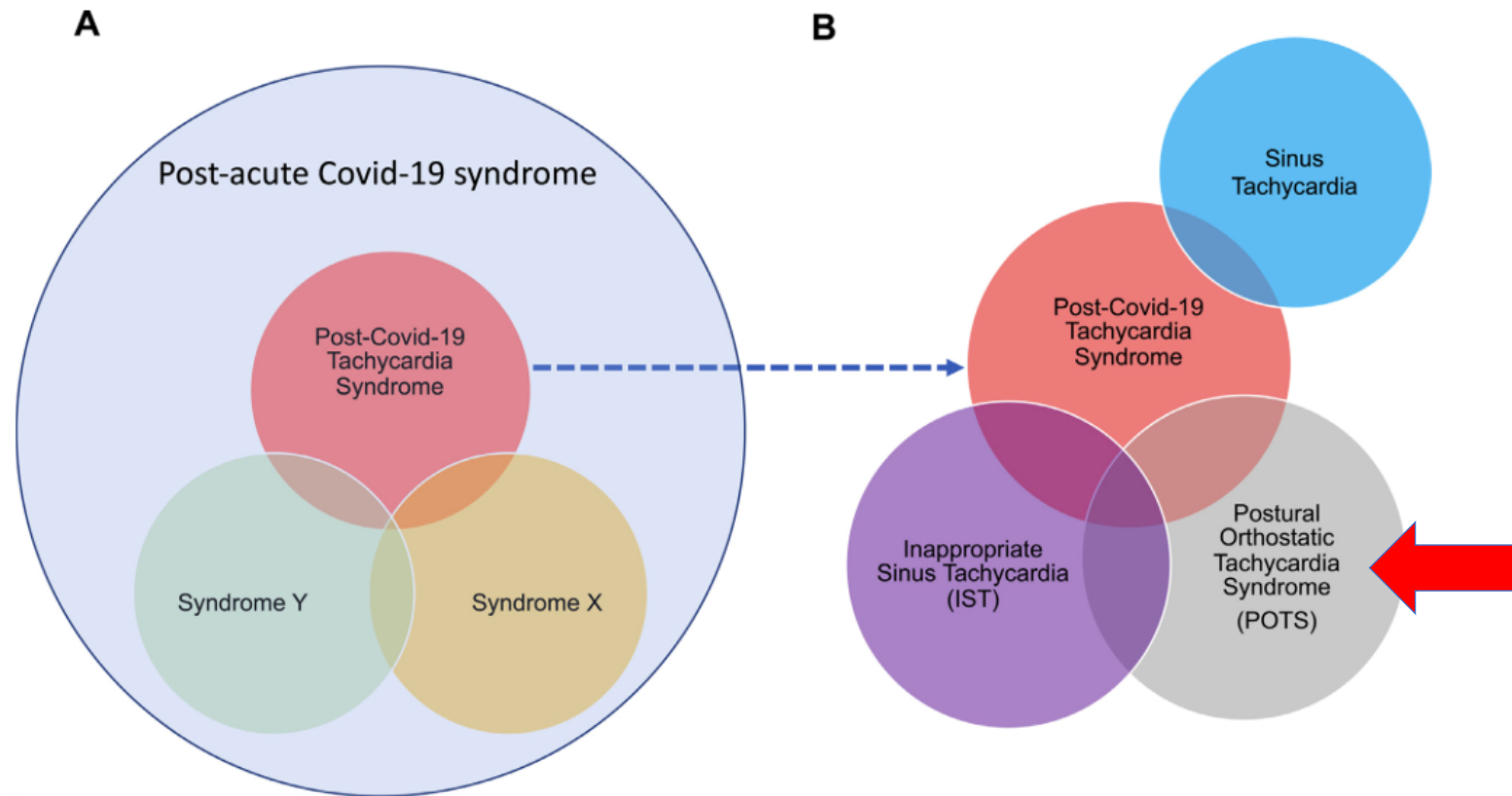


*Rebman AW and Aucott JN (2020)  
 Post-treatment Lyme Disease as a  
 Model for Persistent Symptoms in  
 Lyme Disease. Front. Med. 7:57.  
 doi: 10.3389/fmed.2020.00057*

# Post-COVID-19 Tachycardia Syndrome: A Distinct Phenotype of Post-Acute COVID-19 Syndrome

## CLINICAL SIGNIFICANCE

- Post-acute COVID-19 syndrome is a novel clinical syndrome with symptoms beyond 4-12 weeks after a SARS-CoV-2 infection
- Tachycardia is commonly reported in these patients and may be considered a distinct phenotype
- Putative mechanism for tachycardia in this setting include dysautonomia
- Post-acute COVID-19 syndrome patients reporting palpitations should be subjected to basic cardiovascular evaluation (including head-up tilt testing if concomitant orthostatic intolerance)
- Treatment options include cardiovascular drugs and structured rehabilitation program



**Figure 1** Potential distinctions and overlaps between post-COVID tachycardia syndrome and other sub-syndromes in post-acute COVID-19 syndrome. COVID = coronavirus disease.

# Long-COVID POTS

- La diagnosi di POTS richiede una **eccessiva tachicardia ortostatica** (incremento della FC > 30 bpm negli adulti [> 40 bpm nei pazienti dai 12 ai 19 anni] entro 10 minuti dall'assunzione della posizione eretta) **in assenza di ipotensione ortostatica**, con associati sintomi di intolleranza ortostatica, per almeno 3 mesi.
- Se si associano fiato corto, palpitazioni, dolore toracico, astenia, dolore, alterazioni cognitive, disturbi del sonno, intolleranza ortostatica, neuropatia periferica, disturbi addominali, nausea, diarrea, dolori articolari e muscolari, sintomi di ansia o depressione, eruzioni cutanee, mal di gola, cefalea, otalgia e tinnito:
- **possono suggerire la diagnosi di sindrome della tachicardia posturale (POTS) post-COVID-19.**

# Sindrome da attivazione delle mastocellule (MCAS)

- La MACS è una malattia infiammatoria multisistemica causata da iperattività delle mastocellule e dal rilascio di citochine infiammatorie
- **I sintomi della MCAS si sovrappongono ampiamente a quelli descritti nella PACS (post-acute COVID syndrome), con dolore toracico, palpitazioni e dispnea.**
- *Alcuni ricercatori hanno avanzato l'ipotesi che la prolungata sintomatologia del COVID possa essere causata da una anormale iperattivazione dei mastociti in pazienti affetti da una sottostante MCAS primitiva.*
- I mastociti esprimono anche ACE2 rendendole suscettibili all'attacco diretto del SARS-CoV-2.



# Mechanisms of long COVID and potential therapeutic agents

Conditions	Drugs	Mechanism of action	Note
<i>Chronic inflammation and endothelial dysfunction</i>	Sulodexide	Restore the endothelial glycocalix	Improve endothelial function, attenuate thrombosis and inflammation, alleviate chest pain and palpitations Reduce palpitations (hypotension)
	LD beta-blockers Ivabradine	Decrease stroke volume Increase stroke volume	
<i>Activation of the coagulation system</i>	apixaban & atorvastatin combo	Anticoagulation, pleiotropic effect on the endothelium	Thrombosis, neurologic healing, *fatigue & anosmia
	omega-3 fish oil		
<i>Chronic inflammation and pulmonary fibrosis</i>	pirfenidone, corticosteroids, montelukast, colchicine, human serum albumin	Collagen inhibition	Respiratory function, dyspnea

# Mechanisms of long COVID and potential therapeutic agents

Conditions	Drugs	Mechanism of action	Note
<i>Long COVID and the neurological and olfactory systems</i>	Atorvastatin Vortioxetine Fampridine RUCONEST IVIG. PEA-LUT, nasal sprays w/ ivermectin, retinoic acid	Statin Antidepressant Multiple sclerosis Hereditary Angioedema  Nutritional supplement	Brain fog  Olfactory dysfunction, anosmia
<i>Nutraceuticals and supplements</i>	Vitamin C, Vitam D, soy, taurine, L-arginine	Oxidative stress & immune dysregulation	Fatigue, lung fibrosis
<i>Gut dysbiosis</i>	probiotics		Fatigue
<i>Novel therapies</i>	mesenchymal stem cells, MSCs	immunomodulators	Symptoms of PASC

## Review Article

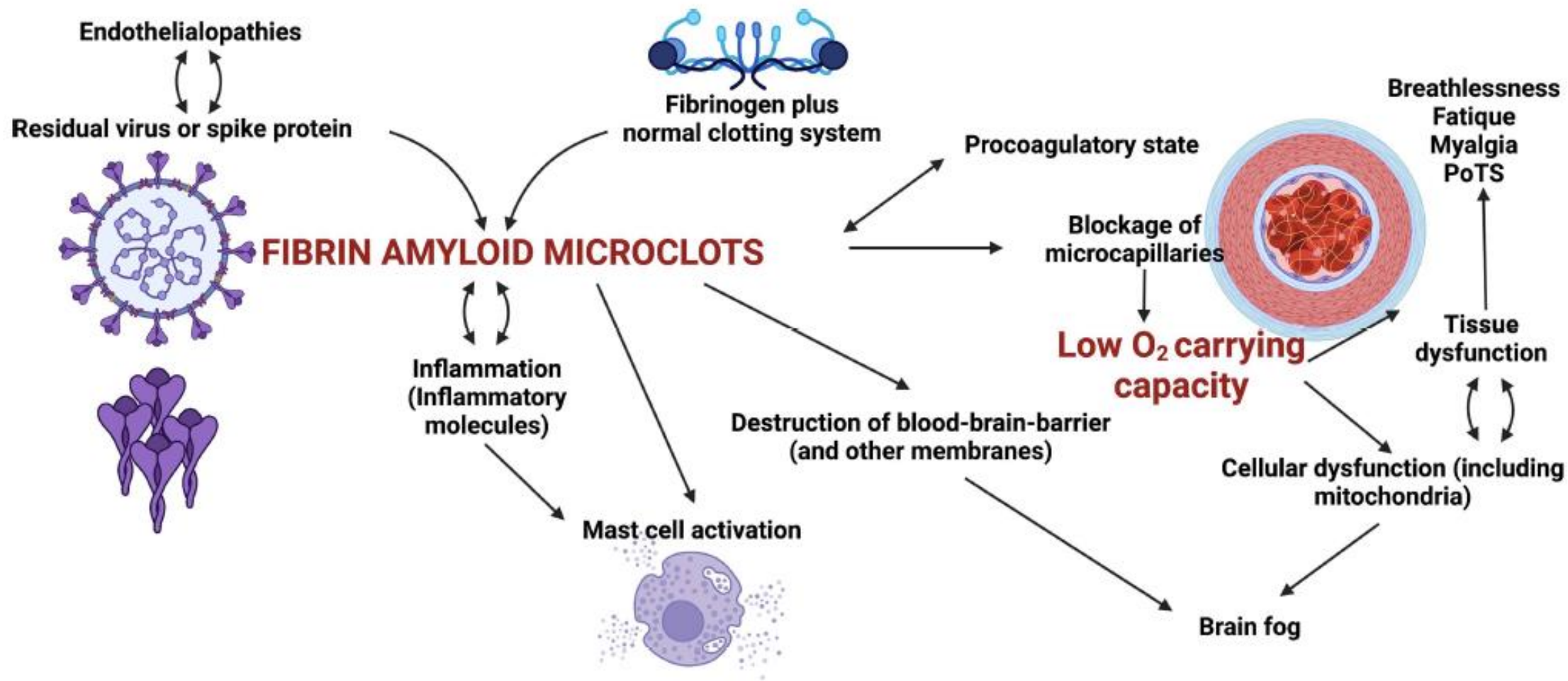
# A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications

✉ Douglas B. Kell<sup>1,2,3</sup>, Gert Jacobus Laubscher<sup>4</sup> and ✉ Etheresia Pretorius<sup>3</sup>

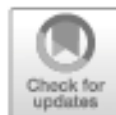
## Conclusions

Here we have argued, and focus on the fact, that Long COVID is characterized by the presence of persistent fibrin amyloid microclots that might block capillaries and inhibit the transport of O<sub>2</sub> to tissues, entrapping numerous inflammatory molecules, including those that prevent clot breakdown (as we have indeed recently shown) (Figure 10).

In addition to microclot formation, significant platelet dysfunction and a systemic endotheliitis drive systemic cellular hypoxia. These pathologies can explain most, if not all, of the lingering symptoms to which individuals with long COVID refer. We have noted that amyloid microclots, platelet hyperactivation and endothelial dysfunction, might form a suitable set of foci for the clinical treatment of the symptoms of long COVID [231]. Therefore, if fibrinaloid microclots are largely responsible for the symptoms of Long COVID, their removal is to be seen as paramount for relieving these symptoms and allowing the body to repair itself.



**Figure 10. Some of the sequelae of fibrinaloid microclot formation in the symptomology of Long COVID. Many others, such as a role for auto-antibodies, are not shown.**



## Chronic post-COVID-19 syndrome and chronic fatigue syndrome: Is there a role for extracorporeal apheresis?

### Abstract

As millions of patients have been infected by SARS-CoV-2 virus a vast number of individuals complain about continuing breathlessness and fatigue even months after the onset of the disease. This overwhelming phenomenon has not been well defined and has been called “post-COVID syndrome” or “long-COVID” [1]. There are striking similarities to myalgic encephalomyelitis also called chronic fatigue syndrome linked to a viral and autoimmune pathogenesis. In both disorders neurotransmitter receptor antibodies against  $\beta$ -adrenergic and muscarinic receptors may play a key role. We found similar elevation of these autoantibodies in both patient groups. Extracorporeal apheresis using a special filter seems to be effective in reducing these antibodies in a significant way clearly improving the debilitating symptoms of patients with chronic fatigue syndrome. Therefore, such a form of neuropheresis may provide a promising therapeutic option for patients with post-COVID-19 syndrome. This method will also be effective when other hitherto unknown antibodies and inflammatory mediators are involved.

## BMJ INVESTIGATION

# Long covid patients travel abroad for expensive and experimental “blood washing”

Patients with long covid are travelling to private clinics in Cyprus, Germany, and Switzerland for blood filtering apheresis and anticoagulation drugs. Experts question whether these invasive treatments should be offered without sufficient evidence. **Madlen Davies** reports

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## Long covid and apheresis: a miracle cure sold on a hypothesis of hope

Kamran Abbasi *editor in chief*

Cite this as: *BMJ* 2022;378:o1733

<http://dx.doi.org/10.1136/bmj.o1733>

Published: 14 July 2022

There are no trials, only hypotheses. There is no research evidence of benefit, only anecdotal reports and the blind faith of vulnerable people seeking a miracle cure. We all need hope, but hope can sometimes be a dangerous thing.



*Perspective*

# **The Potential Role of Hypothalamic Phospholipid Liposomes in the Supportive Therapy of Some Manifestations of Post-COVID-19 Condition: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Brain Fog**

Francesco Menichetti

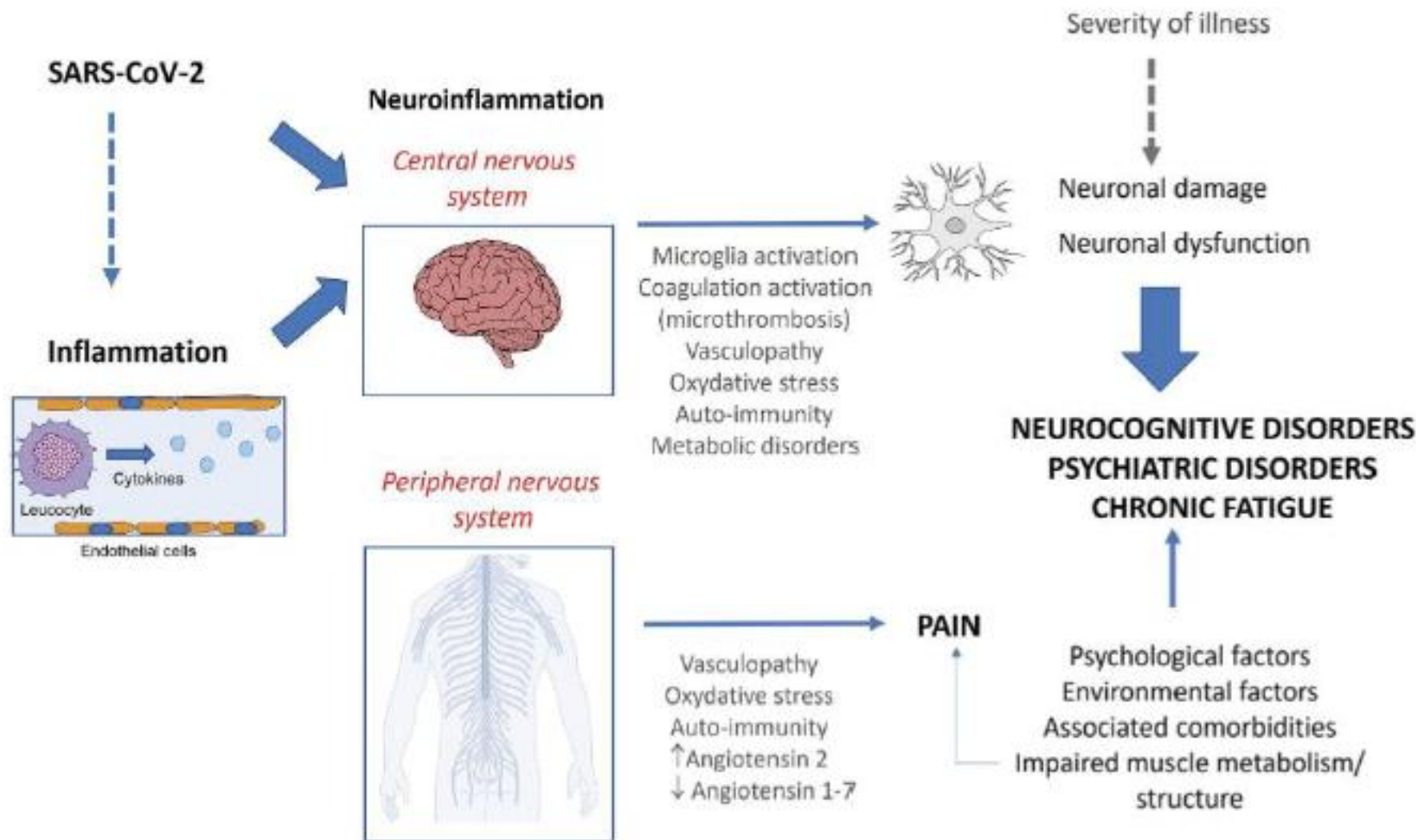


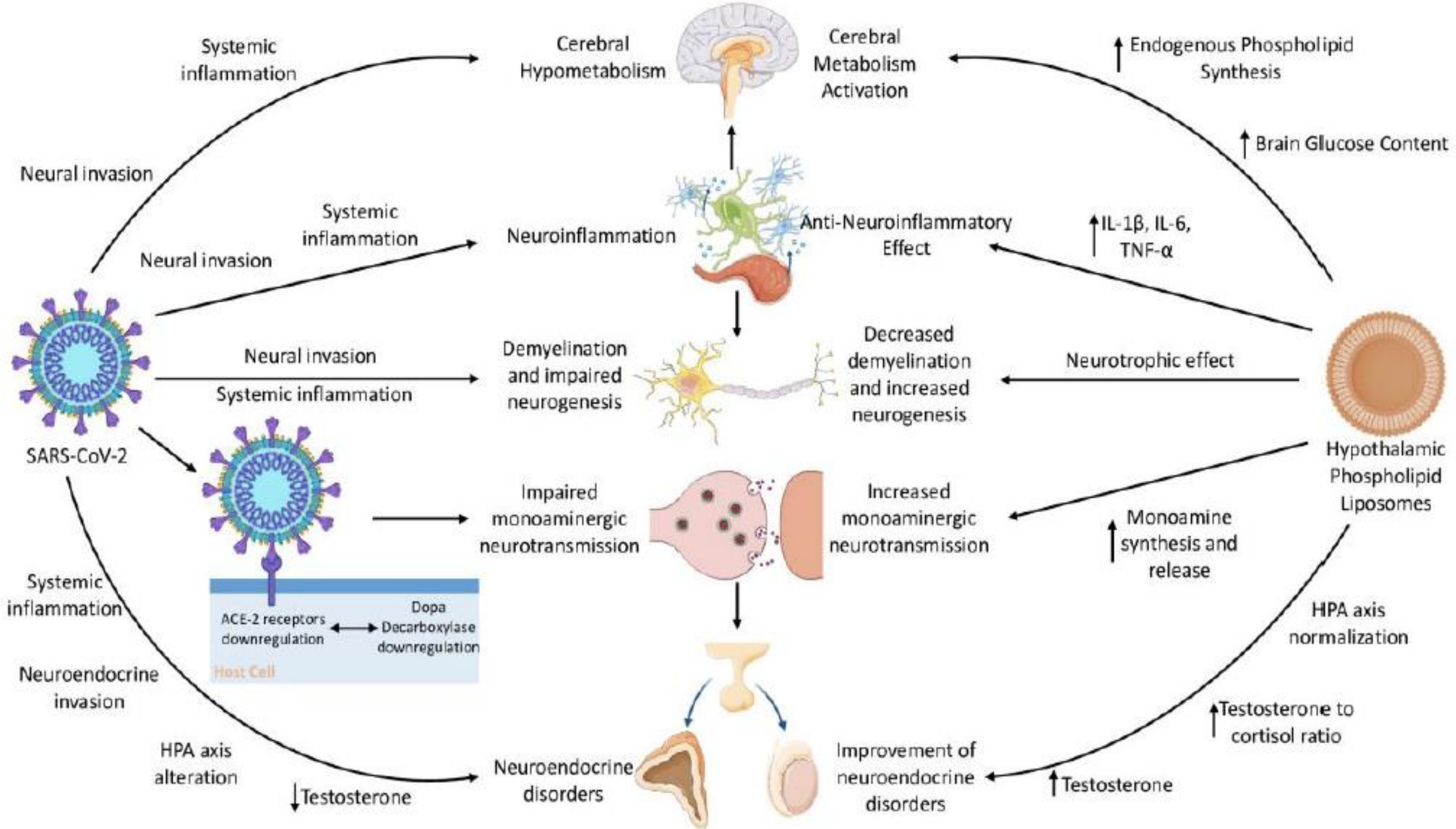
Figure 1. Putative pathophysiological mechanisms involved in Post-COVID-19 condition [23].



**Table 2.** Post-COVID-19 condition's pathophysiology and clinical manifestations matched to the relevant hypothalamic phospholipid liposomes' mechanism of action and clinical evidence (ACE2—Angiotensin I Converting Enzyme 2; IL-1 $\beta$ —Interleukin 1 $\beta$ ; IL-6—Interleukin 6; TNF- $\alpha$ —Tumor Necrosis Factor  $\alpha$ ; PE—Phosphatidylethanolamine; PC—Phosphatidylcholine; PS—Phosphatidylserine).

Post-COVID-19 Condition	Hypothalamic Phospholipid Liposomes
Pathophysiology	Mechanism of Action
Hypometabolic activity in certain brain areas [72]	Activation of cerebral metabolism (i.e., increased brain glucose content and phospholipid synthesis) [47]
ACE2–Dopa Decarboxylase co-expression, which leads to impaired monoaminergic neurotransmission [49]	Increased catecholamine turnover and release, stimulation of tyrosine hydroxylase and dopamine-dependent adenylyl cyclase, modification of monoaminergic receptor adaptation [47,48]
Neuroinflammation from CSF cytokine elevation (e.g., IL-1 $\beta$ , IL-6) and microglial reactivity [23,62,64]	Antagonizing effect on proinflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ) in different brain areas [47]
Demyelination and impaired neurogenesis [27,64]	Neurotrophic effect, increase in neurogenesis and dendritogenesis, as well as antagonizing effect of PE, PC, and PS on demyelination [48,66,67]
Low testosterone [74,77]	PS increases plasma levels of testosterone compared to placebo and the testosterone to cortisol ratio in an exercise-related context [78,79]

Post-COVID-19 Condition	Hypothalamic Phospholipid Liposomes
Clinical Manifestations	Clinical Evidence
Fatigue	Improvement of asthenia [83,84]
Brain fog	<p>PS:</p> <ul style="list-style-type: none"> <li>Improves age-associated cognitive decline, especially memory, with no adverse effects [86].</li> <li>May reduce the risk of dementia and cognitive dysfunction in the elderly [87].</li> <li>Improved the memory of a small group of patients with Alzheimer's disease [88].</li> </ul>
Anxiety and depression	Improvement in the symptomatology of anxiety and depression as monotherapy or add-on to antidepressants [47,48]
Orthostatic intolerance	Antagonizing effect on hypotension and reflex tachycardia caused by trazodone [83]
Male sexual health problem	Phospholipids (PC in particular) improve erectile dysfunction and loss of libido [80]



## The Race to Understand Post-COVID-19 Conditions

Paul G. Auwaerter, MD

For more than a decade after the 1918 influenza pandemic, a mysterious Parkinson-like syndrome with sleep disturbance, hypomimia, and a high mortality rate developed in thousands of people across the globe. In 1920 the U.S. Surgeon General declared that the syndrome, popularly termed “encephalitis lethargica,” was caused by influenza. However, opinions varied, mainly as cases of encephalitis lethargica frequently differed from respiratory infections thought to represent influenza (1). More than a century later, questions remain regarding the cause, transmission, and availability of effective treatments, and lastly, will it happen again?

produce such problems as fatigue and pain. Perhaps there are common mechanisms, whether an aberrant response to viral infection or loss of a job?

Many postinfectious disorders have defied detailed scientific understanding or precise diagnosis, causing contention among clinicians, researchers, and patients. Some, such as the common cold due to rhinovirus infection, appear to have little effect on health. In contrast, others, such as primary Epstein-Barr virus infection and *Coxiella burnetii* (Q fever), precipitate a postinfectious syndrome infection in 11% to 12% of patients (8). Both infectious mononucleosis and Lyme disease may cause persistent symptoms after the resolution

# Conclusioni

- Long Covid: sequele post-infettive a medio lungo termine
- Patogenesi non chiara, variegata, complessa
- Pletora di sintomi multi-organo, sindromi specifiche
- Attenzione alla diagnosi differenziale
- Difficoltà nel management dei singoli pazienti
- Spazio eccessivo per ipotesi immaginifiche e terapie improbabili
- Necessità di EBM: studi osservazionali di coorte, basic science



**G.I.S.A.**<sup>APS</sup>

GRUPPO ITALIANO PER LA STEWARDSHIP ANTIMICROBICA

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