What we do and do not know in Long COVID: Treatments for a Path to Recovery

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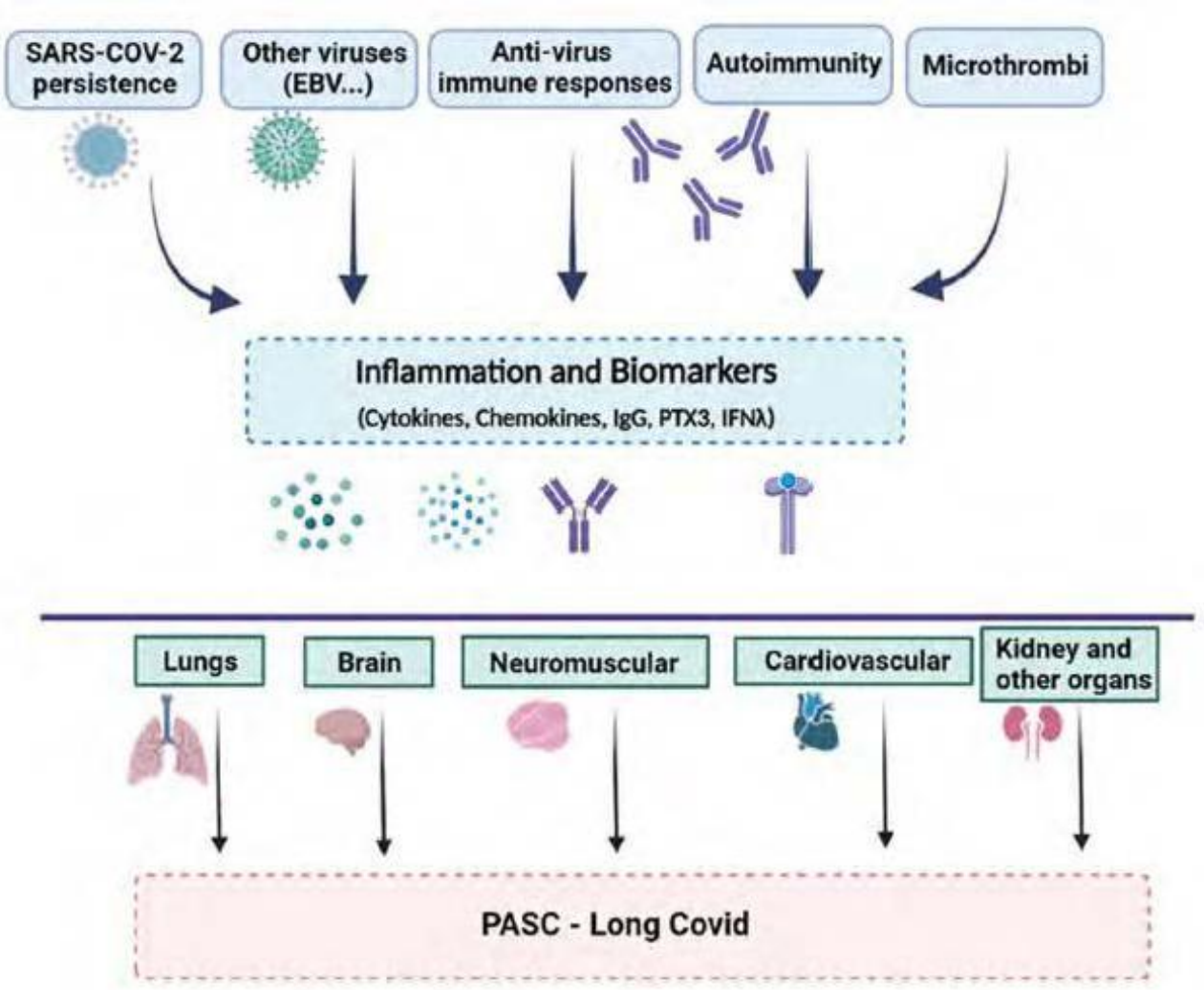
Pathogenesis and Targets of PASC



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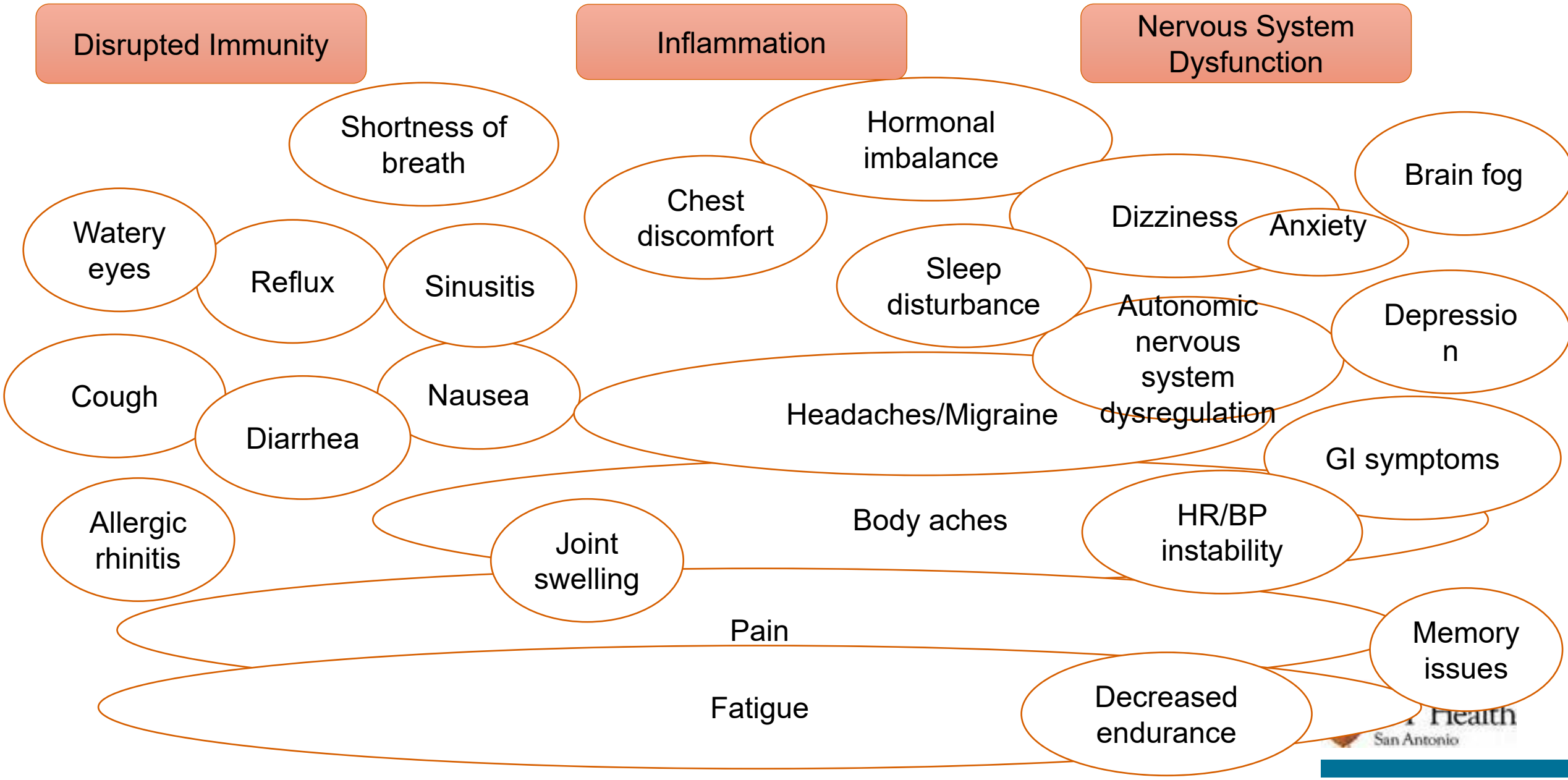
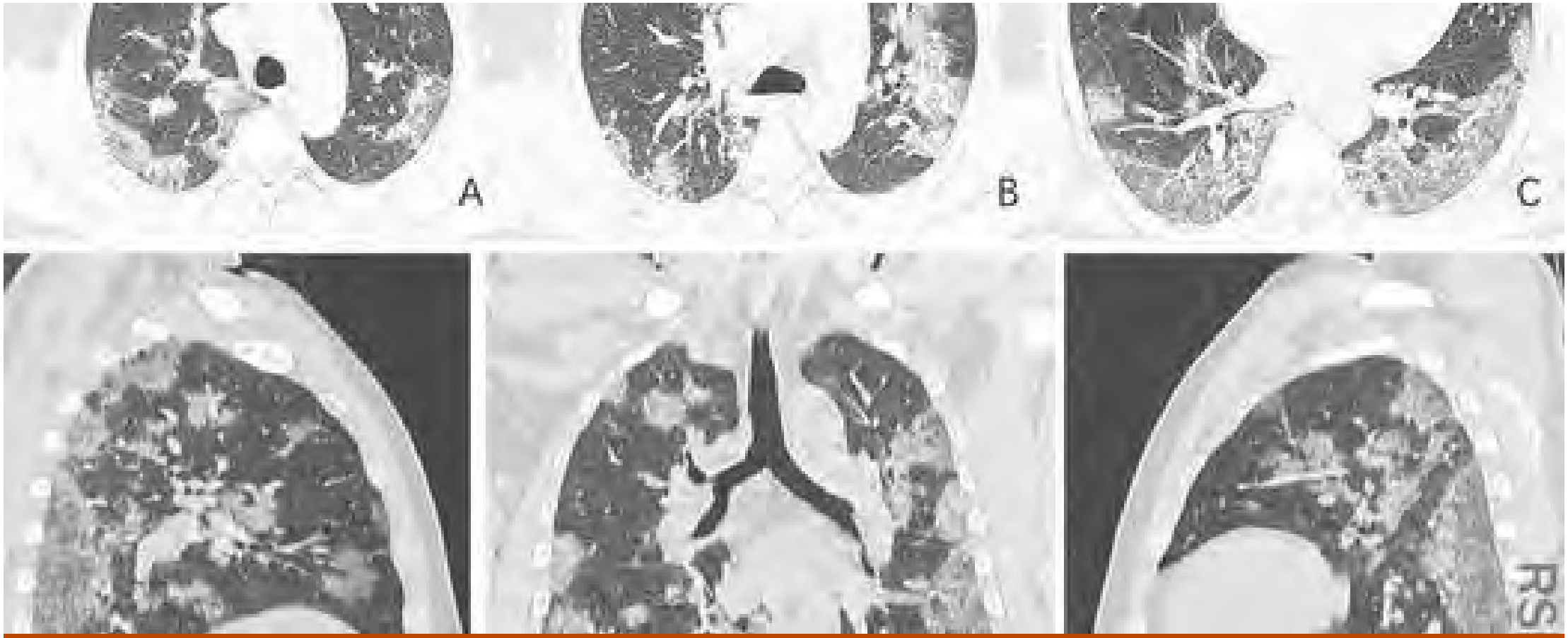
Post-Acute Sequelae of COVID (PASC) Symptoms





What we know for treatments?

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Long COVID: Mechanisms
Possible therapeutic strategies

Mechanism	Treatment
Acute viral infection with irreversible tissue damage	Prevention Anti-virals Post-acute vaccine Anti-inflammatory drugs Rehabilitation

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Taylor & Francis

Disability and Rehabilitation

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/idre20

Inpatient rehabilitation can improve functional outcomes of post-intensive care unit COVID-19 patients—a prospective study

Margarida Rodrigues, Ana João Costa, Rui Santos, Pedro Diogo, Eugénio Gonçalves, Denise Barroso, Miguel P. Almeida, Inês Machado Vaz & Ana Lima

Inpatient Rehab

Prospective
N = 42
Avg 32 days of inpatient rehab

IMPLICATIONS FOR REHABILITATION

- Post-ICU COVID-19 survivors present multiple sequelae and disabilities.
- An intensive and interdisciplinary inpatient rehabilitation results in significant improvement in limb and respiratory muscle strength, cough effectiveness, fatigue, balance, exercise capacity, and ability to perform activities of daily living.
- Timely referral from the acute care setting to rehabilitation services is crucial to minimize the functional impact of severe multisystemic disease and prolonged hospitalization.

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Journal of the Intensive Care Society

J Intensive Care Soc. 2022 Aug; 23(3): 264–27
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The Post-ICU presentation screen
intensive care survivors part II: Cl
national Post-Intensive care Rehal

Zudin Puthucheary,[1,2] Craig Brown,[3] Evelyn C
Nirandeep Rehill,[10] Hugh Montgomery,[11] Leann

J Intensive Care Soc

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J Korean Med Sci. 2022 Aug 29; 37(34): e262.
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PMCID: PMC9424699
PMID: 36038958

J Korean Med Sci

Comprehensive Rehabilitation in Severely Ill Inpatients With COVID-19: A Cohort Study in a Tertiary Hospital

Hyeonseong Woo,[1] Sanghee Lee,[1] Hyun Sung Lee,[1] Hyun Jun Chae,[1] Jongtak Jung,[2] Myung Jin Song,[2] Sung Yoon Lim,[2] Yeon Joo Lee,[2] Young-Jae Cho,[2] Eu Suk Kim,[2] Hong Bin Kim,[2] Jae-Young Lim,[1] Kyoung-Ho Song,[2] and Jaewon Beom[1]

- Prospective service e
acute hospitals in Eng
- A greater proportion of COVID-19 patients were referred for inpatient rehabilitation (13% vs. 7%) and community-based rehabilitation (36% vs.15%).
- No differences are seen in the rehabilitation needs of patients with and without COVID-19 infection.

n =37

Comprehensive rehabilitation management effectively improved muscle mass, muscle strength, and physical performance.

Dose-response relationship of rehabilitation and functional improvement emphasizes the importance of intensive post-acute inpatient rehabilitation in COVID-19 survivors.

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Outpatient Long COVID Rehabilitation:

Progressive autonomic reconditioning recommended

Breathing exercises: Helps increase vagal tone

Avoid Post exertional malaise

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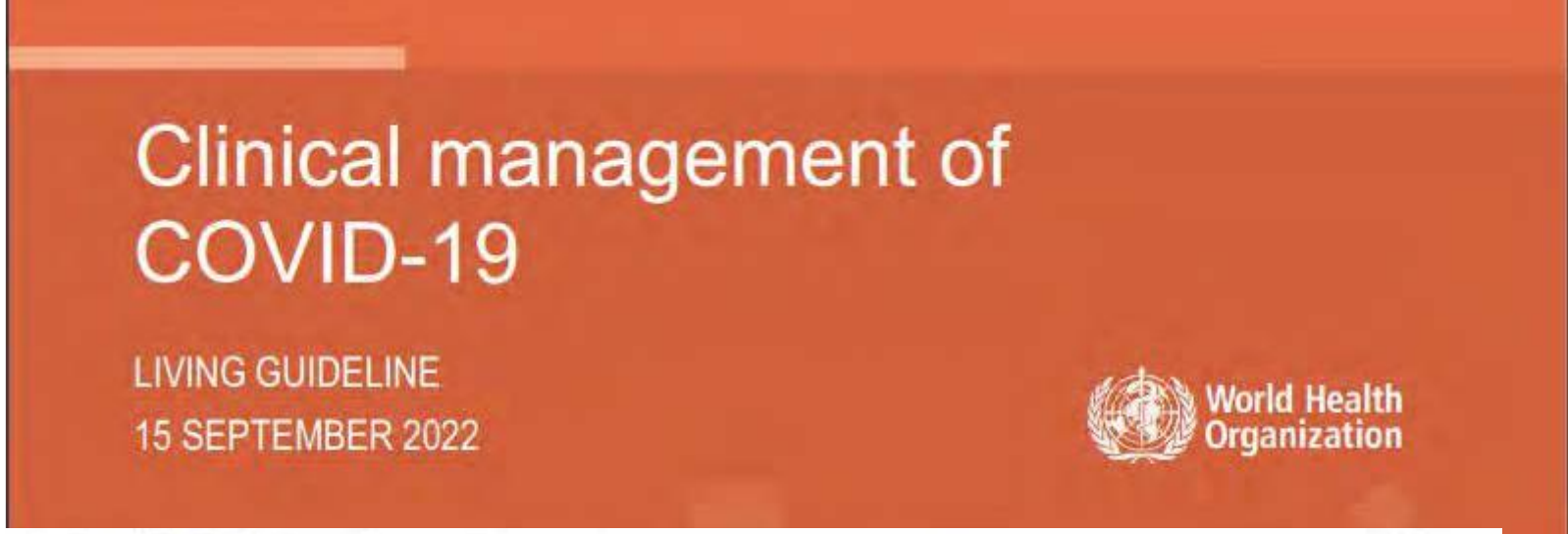
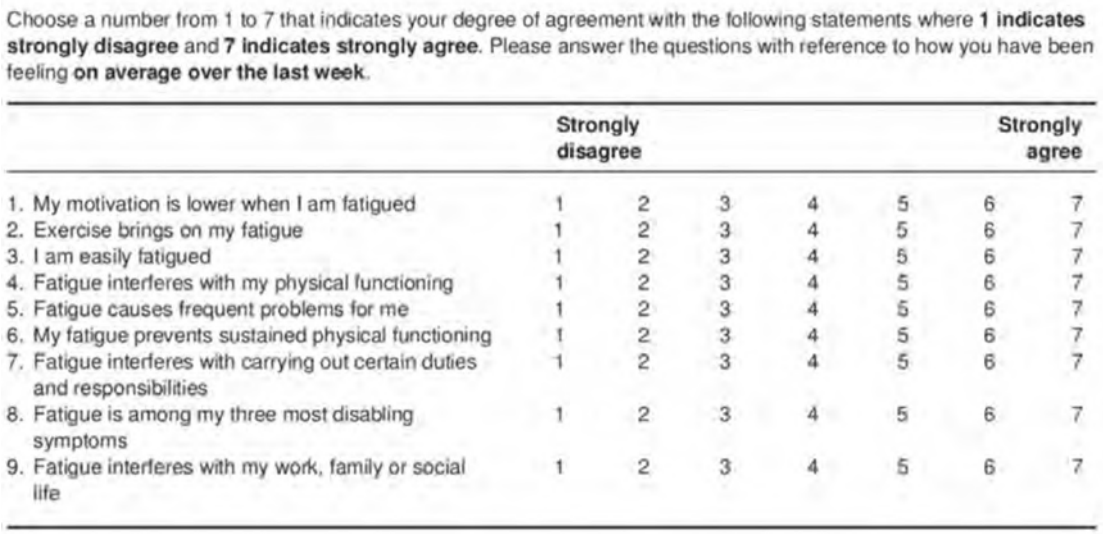
- Components and functions of rehab care
  - Multidisciplinary
  - Continuity & coordination of care
  - People-centered & shared decision-making
- Red flags for safe rehabilitation
  - Exertional desaturation & cardiac impairment should be ruled out before physical exercise
- Post-exertional symptom exacerbation
  - Assess PESE
  - Pacing/energy conservation
  - Graded exercise should NOT be offered
- Orthostatic intolerance
  - Screen
  - Self-management skills
- Return to everyday activities and work
  - Energy conservation, assist products
  - Prolonged & flexible phased RTW



Use validated measurements

Fatigue Severity Scale



Choose a number from 1 to 7 that indicates your degree of agreement with the following statements where **1 indicates strongly disagree** and **7 indicates strongly agree**. Please answer the questions with reference to how you have been feeling **on average over the last week**.

	Strongly disagree						Strongly agree
1. My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2. Exercise brings on my fatigue	1	2	3	4	5	6	7
3. I am easily fatigued	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family or social life	1	2	3	4	5	6	7

- Neuro-QoL scale
- Health-related QoL
- Compass-31
- DePaul Symptom Questionnaire or DSQ-SF or DSQ-PEM

Symptom measurement can be the difference between getting disability coverage or being declined

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Know/teach triggers

- Physical or cognitive exertion
- Stress
- Dehydration
- Weather changes
- Consuming large meals
- Alcohol consumption
- Premenstrual period

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Support For Disability & Work Accommodations

Likely the 2nd most important thing we can do!

- All patients need to time to recover
- Relapses are common
- Working, stress, pushing themselves too hard is the most common trigger for relapses and PEM
- Facilitating respite and / or reasonable reentry back to work is enormously beneficial for quality-of-life faster recovery

Accommodations & Disability for Fatigue & Brain Fog

Possible Disability Accommodations:

Limited hours

Frequent breaks

Avoid standing

Parking close to entry

Adjust work activities

Limit tasks with divided attention

Optimize range of movements

Limit environments with multiple sensory inputs

Return home if breathing rate is increased for more than a few minutes?

For Disability Applications, Document:

Activity levels pre/post infection

Symptoms that are remitting and relapsing

Specific work activities will result in physical and mental fatigue

Environmental settings that result in sensory overload (markets, etc)

Work-ups that rule out other associated causes including pre-existing conditions

Long COVID: Mechanisms
Possible therapeutic strategies

Mechanism	Treatment
Persistent viral infection and ongoing tissue harm	Anti-virals (Paxlovid, molnupiravir, remdesivir) Virus monoclonal antibodies (ex. Evusheld) Therapeutic vaccine

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PASC And COVID Vaccines

Preliminary patient led observational study showed 56.7% of those who had PASC who were vaccinated showed overall improvement in PASC symptoms while 18.7% deteriorated and 24.6% were unchanged. (Strain et al. Lancet reg Health Eur. 2022;12:100265)

A study of 906 participants showed that the odds of experiencing symptoms more that 28 days post-vaccination, were halved by two vaccinations (Antonelli et al. Lancet infectious Diseases. 2022;22:43-55)

Study in Italy during the omicron wave indicated strong protection against PASC after breakthrough infection if vaccinated with mRNA vaccines. (Azzolini Et al. JAMA 2022;328)

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Long COVID: Mechanisms
Possible therapeutic strategies

Mechanism	Treatment
Inflammation • Direct: SARS-CoV-2 • Indirect: EBV/CMV reactivation, dysbiosis	Anti-inflammatories: steroids, colchicine, antihistamines, JAK/STAT inhibitors, mAbs (anti-INF, anti-IL-6, anti-IL1β, anti-TNFα), IVIg, etc Viral reactivation: EBV, CMV Dysbiosis: Microbiome

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Long COVID:
Mechanism & Possible Therapeutic Strategies

Pathogenesis	Potential Treatment
Autoimmune/Autoantibodies	IVIg, B cell-directed therapies

Currently 75 Clinical Trials for Long COVID in ClinicalTrials.gov

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Long COVID:
Therapeutic Strategies for Autoimmunity

Monoclonal Antibody to IL-6

Anakirnra – IL-1 receptor antagonist

Infliximab – monoclonal anti-TNF-α

Abatacept – inhibits T-lymphocyte activation

JAK inhibitor DMARDs

Naltrexone

Systemic steroids

IVIg

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Low Dose Naltrexone in ME/CFS

Table 1. Mechanisms of action and clinical use in regard to different doses of naltrexone used.

Dose Range	Dose Specific Mechanism of Action	Clinical Use
Standard (50–100 mg)	Opioid receptor antagonism	Alcohol and opiate abuse
Low-dose (1–5 mg)	Toll-like receptor 4 antagonism, opioid growth factor antagonism	Fibromyalgia, multiple sclerosis, Crohn's disease, cancer, Hailey-Hailey disease, complex-regional pain syndrome
Very low-dose (0.001–1 mg)	Possibly same as low-dose	Had use in metadone detoxification taper
Ultra low-dose (<0.001 mg)	Binding to high affinity filamin-A (FLNA) site and reducingμ-opioid receptor associated Gs-coupling	Potentiating opioid analgesia

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LDN in PASC

Table 3
Incidence of reported symptoms at baseline and at 2 month

Symptoms	Baseline n (%)	2 month follow up n(%)	
Total	36	36	
Fatigue	33(91.7)	27(75)	
Fevers	6(16.7)	2(5.6)	
Sore throat	13(36.1)	8(22.2)	
Anosmia/dysgeusia	16(44.4)	11(30.6)	.171
Hair loss	11(30.6)	9(25)	.65
Tinnitus	17(47.2)	12(33.3)	.2
Chest pain/tightness	20(55.6)	12(33.3)	.047
Palpitations	22(61.1)	16(44.4)	.132
Cough	19(37.3)	5(13.9)	.016
Shortness of breath	25(69.4)	19(52.8)	.09
Headache	27(75)	24(63.9)	.314
Dizziness	17(47.2)	14(38.9)	.618
Brain fog	27(75)	20(55.6)	.072
Sleep disturbance	26(72.2)	16(44.4)	.058
Dysthesia	20(55.6)	13(36.1)	.056
Abdominal discomfort/ bloating	17(47.2)	14(38.9)	.449
Nausea/Vomiting	12(33.3)	6(16.7)	.083
Diarrhoea	14(38.9)	9(25)	.166
Joint pain	26(72.2)	13(36.1)	.008
Myalgia	20(55.6)	14(38.9)	.163
Low mood	28(77.8)	17(47.2)	.003
Anxiety	20(55.6)	16(44.4)	.337
Personality change	9(25)	0(0)	.001

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Safety and efficacy of low dose naltrexone in a long covid cohort; an interventional pre-post study

Brendan O'Kelly [a,b,*], Louise Vidal [b], Tina McHugh [b], James Woo [a], Gordana Avramovic [b], John S. Lambert [a,b]

[a] Infectious Diseases Department, Mater Misericordiae University Hospital, Dublin 7, Ireland
[b] School of Medicine, University College Dublin, Dublin 4, Ireland

O'Kelly, B et al. Brain, Behavior, & Immunity-Health 24 (2022)

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Long COVID: Mechanisms
Possible therapeutic strategies

Mechanism	Treatment
Microvascular disease Persistent microclots Endothelial dysfunction	Anticoagulants, thrombolytics, dialysis Rivaroxaban, Triple therapy (clopidogrel, ASA, apixaban) EECP
Mitochondrial dysfunction	AXA1125, mito-directed therapies

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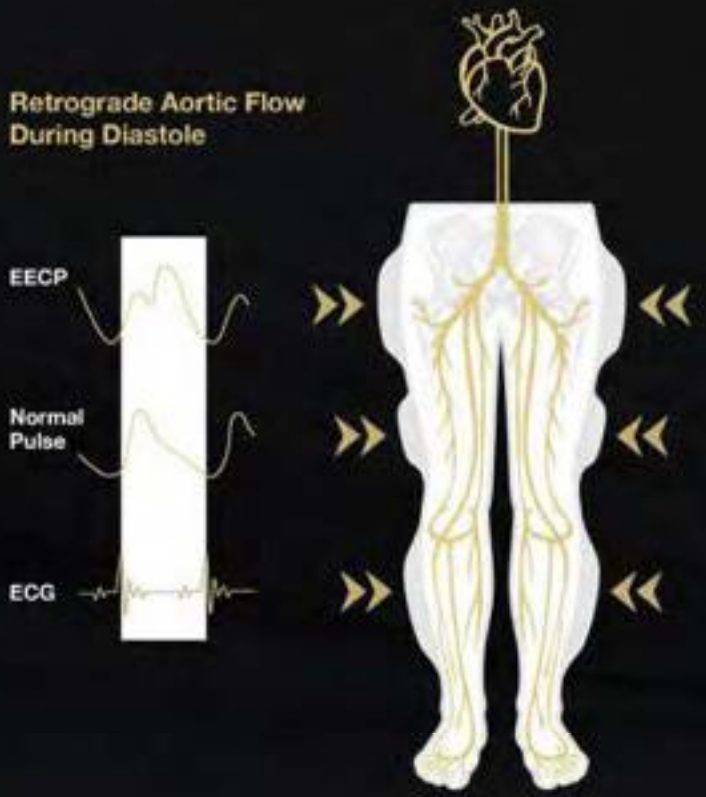
EECP

Mechanism of Action

Mechanical Force



Physiologic / Biochemical Changes

PHYSIOLOGIC / HEMODYNAMIC

- ↑ Diastolic Augmentation
- ↑ Systolic Unloading
- ↑ Shear Stress
- ↑ Endothelial Progenitor Cells

BIOCHEMICAL / NEUROHOMONAL

- ↓ BNP, ANP, Angiotensin II
- ↓ Inf. Cytokines (TNF-a, MCP-1)
- ↑ Growth Factors (VEGF, HGF)

Cardiac / Systemic Benefits

CARDIAC

- ↓ Ischemia
- ↑ Coronary Blood Flow / Perfusion
- ↑ CO / Cardiac Efficiency
- ↑ Angiogenesis & Collateralization

SYSTEMIC

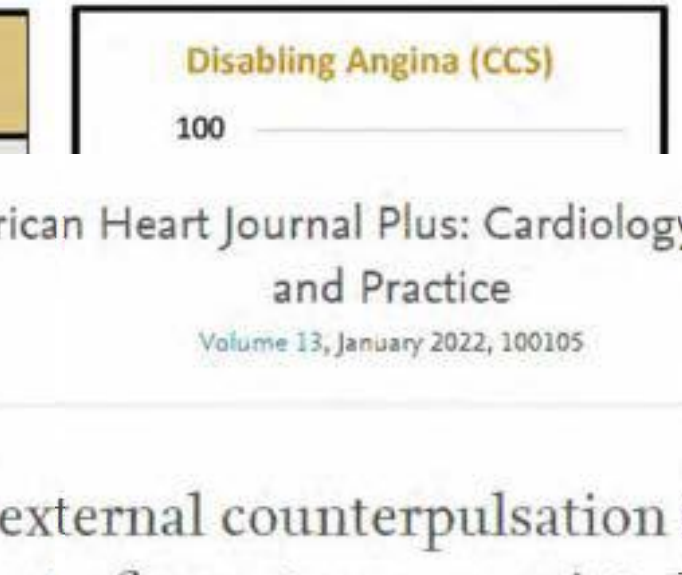
- ↓ Endothelial Dysfunction
- ↑ Vascular Tone & Stiffness
- ↑ Perfusion to Vital Organs

EECP Improves Long COVID Related Clinical Markers

EECP **improved validated markers** of fatigue, brain fog, shortness of breath, chest pain and function capacity (n=50)

Degree of Benefit after EECP (Summary)

Endpoint	Change from Baseline	*P*-Value
PROMIS Fatigue	-5.9 ± 3.8	
DASI	19.8 ± 15.5	
SAQ-7 Summary	25.9 ± 19.9	
6MWT (feet)	163.3 ± 207.5	



ELSEVIER
American Heart Journal Plus: Cardiology Research and Practice
Volume 13, January 2022, 100105
AHJO

Short Communication

Enhanced external counterpulsation for management of symptoms associated with long COVID

Mohanakrishnan Sathyamoorthy [a], Monica Verduzco-Gutierrez [b], Swathi Varanasi [c], Robyn Ward [d], John Spertus [e], Sachin Shah [c, f]

AMERICAN COLLEGE of CARDIOLOGY

Presented at ACC CV Summit Feb 14, 2022

@MVGutierrezMD

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Post-COVID Rehab

Community-based approach

Early and often

Inpatient Rehab

Home-based Rehab

Respiratory Rehab / Breathing Program

Autonomic Reconditioning

Mobility and Functional Rehab

Education

Mental health services

Would good enough be good enough for you?

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