Glutathione + cyclodextrin vs COVID-19

An Osteopathic approach to addressing the challenges of treating severe and post-COVID-19 illness

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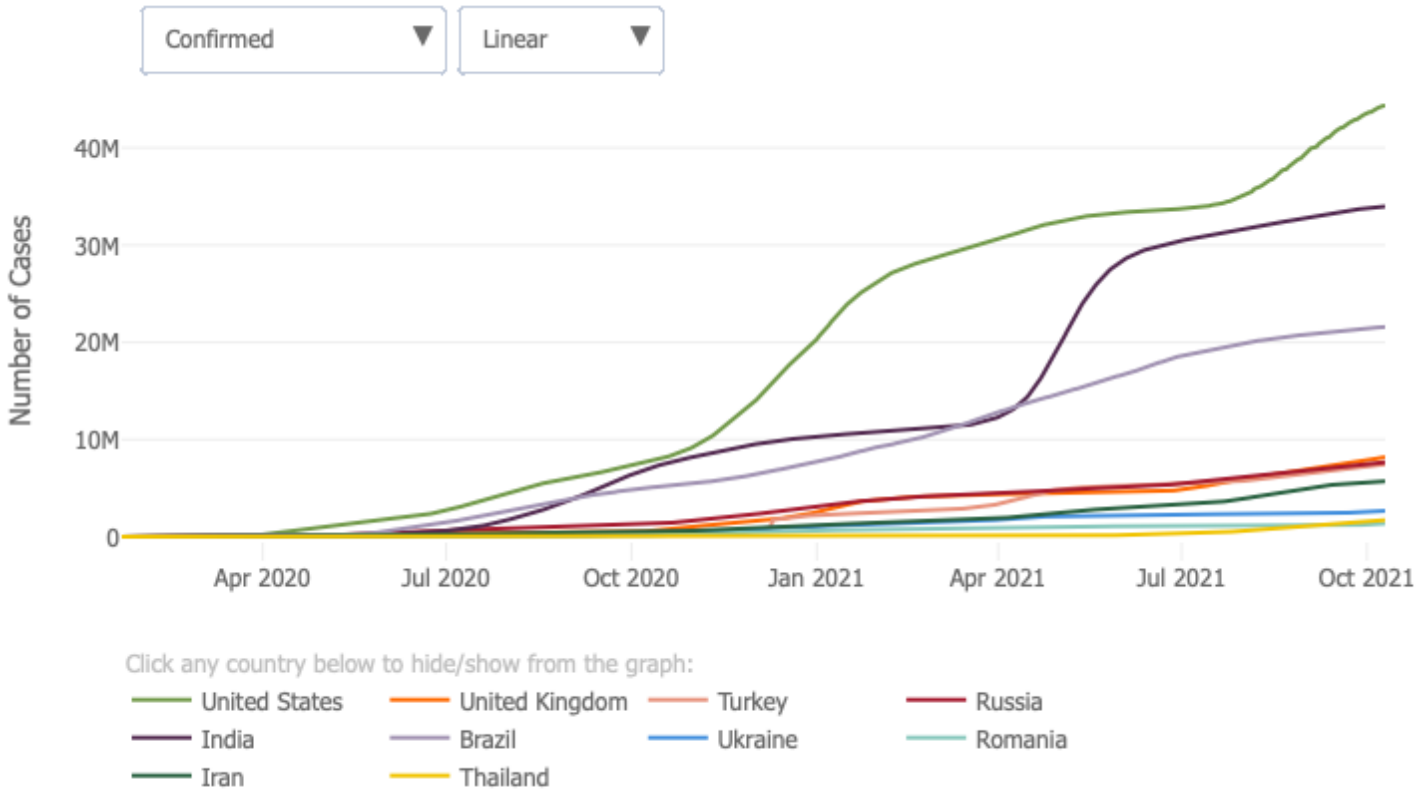
COVID-19 pandemic

- December, 2019: WHO new corona virus in Wuhan, China

- January, 2022
  - Cases
    - 377 million worldwide
    - 76 million in US
  - Deaths:
    - 5.7 million worldwide
    - 910K in US

who.int
Worldometers.info

Cumulative COVID-19 cases



Johns Hopkins coronavirus resource center

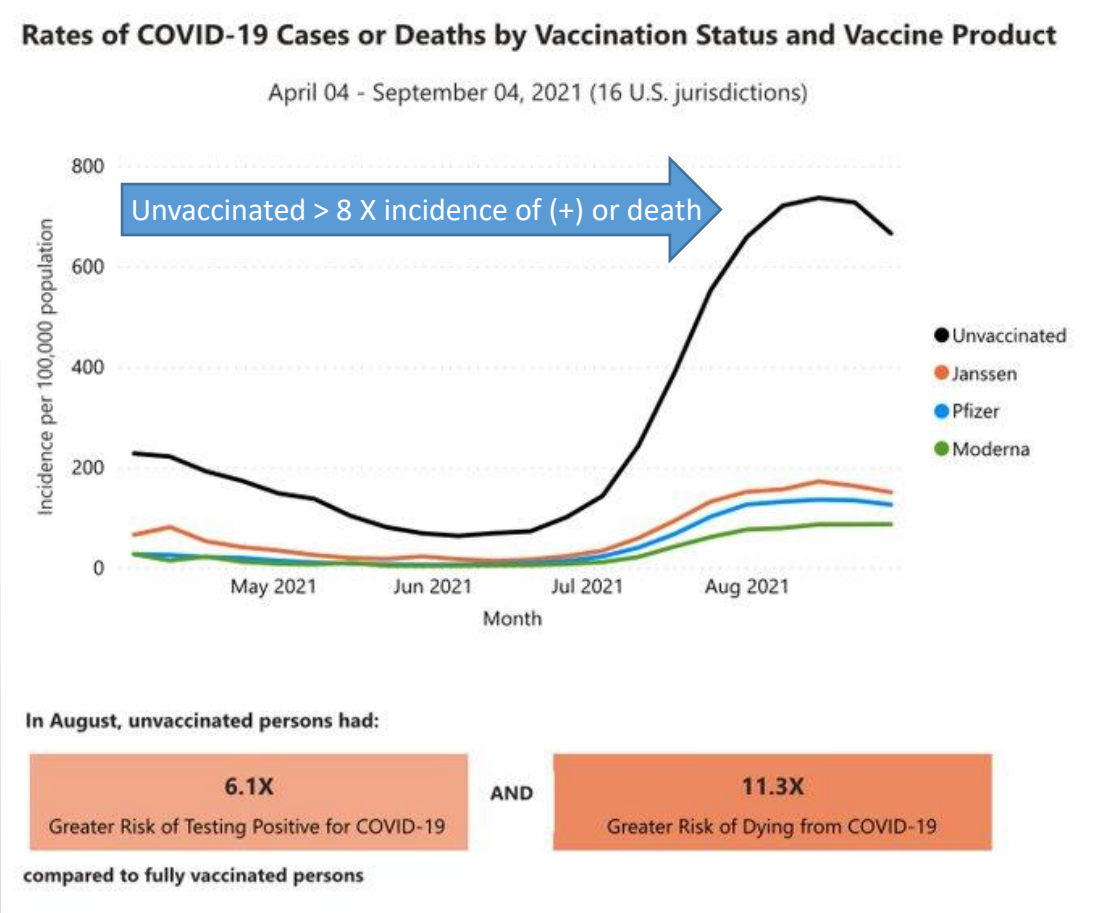
Current therapeutic strategies

- Prevent/minimize infection
  - Vaccines
- Reduce viral load
  - Neutralizing antibodies
  - Antivirals
- Treat the severe illness
  - Corticosteroids?
- Prevent or mitigate post-COVID, ”long-haulers”, symptoms
  - ???

COVID-19 treatment successes

- Vaccines

Vaccine efficacy:
Death rates with and without vaccination



Covid.cdc.gov, 2021

COVID-19 treatment successes

- Antivirals
  - Remdesivir
    - Impairs RNA replication (mutagenic), (teratogenic?)
    - Intravenous
  - Molnupiravir
    - Inpairs RNA replication (mutagenic), (teratogenic?)
    - Oral
  - Paxlovid
    - Protease inhibition
    - Oral
- Antibodies
  - Monoclonal
  - Polyclonal

COVID-19 treatment challanges

- Acute, severe illness
  - Dexamethasone: Immunosupression
    - Beyond reversibility (sepsis, multi-organ failure) →supportive care
    - “too much - too late”

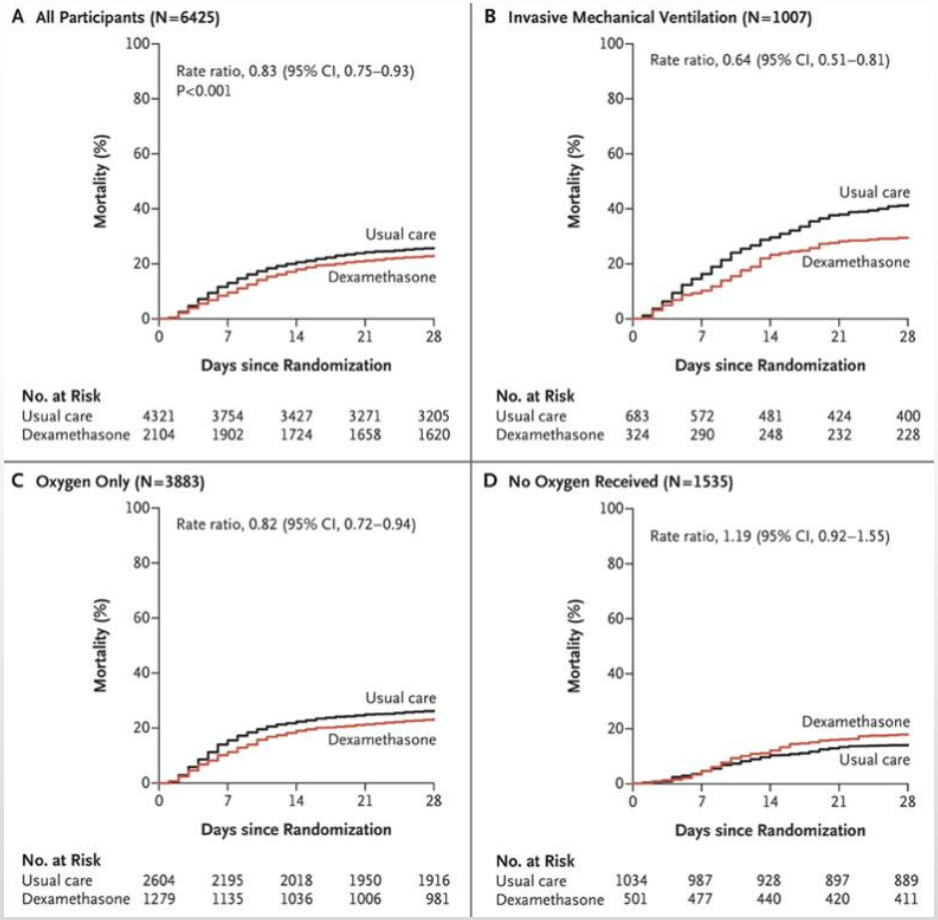
- Post-Covid syndrome
  - Growing population
  - Supportive care

Recovery study:
dexamethasone in hospitalized patients

- N=6425 Usual care=4321 Dexamethasone =2103
- Dexamethasone 6mg daily up to 10 days (mean 7 days)
- Primary outcome: mortality at 28 days
- Secondary outcome: discharged at 28 days

NEJM: Feb 2021

RECOVERY study outcomes
Kaplan-Meier

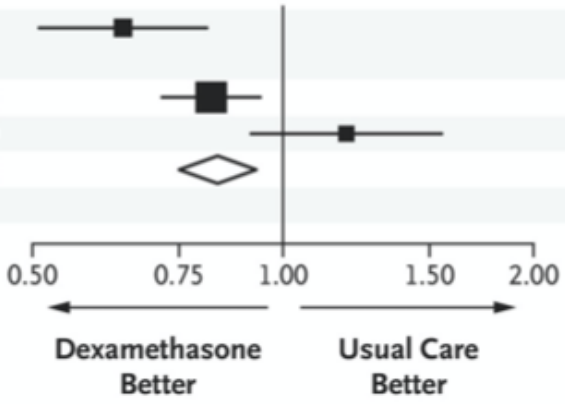


RECOVERY study outcomes

Odds ratio (mortality)

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.92–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.6



Recovery study:
secondary outcome

HOSPITAL DISCHARGE	% discharged at 28 days	Median time to discharge
Usual care	63.6%	13 days
Dexamethasone	67.3%	12 days

NEJM: Feb 2021

The COVID STEROID 2 Randomized Trial
Dexamethasone 6mg vs 12mg/day x 10 days

- Primary outcome:
  - Days alive without life support after 28 days in adults with COVID-19 and severe hypoxemia
  - Outcome: no statistical difference in median days alive and not in ICU (intubated, vasopressors, dialysis)
    - 6mg: 20.5 days
    - 12mg: 22.0 days
  - Good news: still alive and not in ICU after 3 weeks
  - Bad news: still hospitalized after 3 weeks. (Equally effective or equally ineffective???)

- Secondary outcome:
  - 90-day mortality
    - Mortality with 6mg: 90-day (37.7%)
    - Mortality with 12mg: 90-day (32%)
  - Good news: > 60% alive after 90 days
  - Bad news:
    - > 60% still hospitalized after 90 days due to complications of the COVID-19 illness
    - 4% with invasive necrotizing fungal infection due to immunosupression

- Can we do better?
  - Prevention with early treatment of CSS before irreversible damage occurs
  - Avoid immunosuppression.
  - Modulate, not suppress immune response (= adaptive immune response)`

(JAMA online October 21, 2021)

COVID-19 treatment challenges

- How can we do better?
- Treatment alternatives?
- Understanding the disease process
  - Significance of oxidative stress from excessive reactive oxygen species (ROS)

SPI-DEX

spironolactone + dexamethasone

- Presumptive mechanism
  - Spironolactone:
    - Inhibit mineralo-corticoid receptor, ATP stimulated, lysosome exocytosis
    - Suppress aldosterone stimulation of reactive oxygen species (ROS) production?
  - Low-dose dexamethasone: Cortisol suppression; not immunosupression

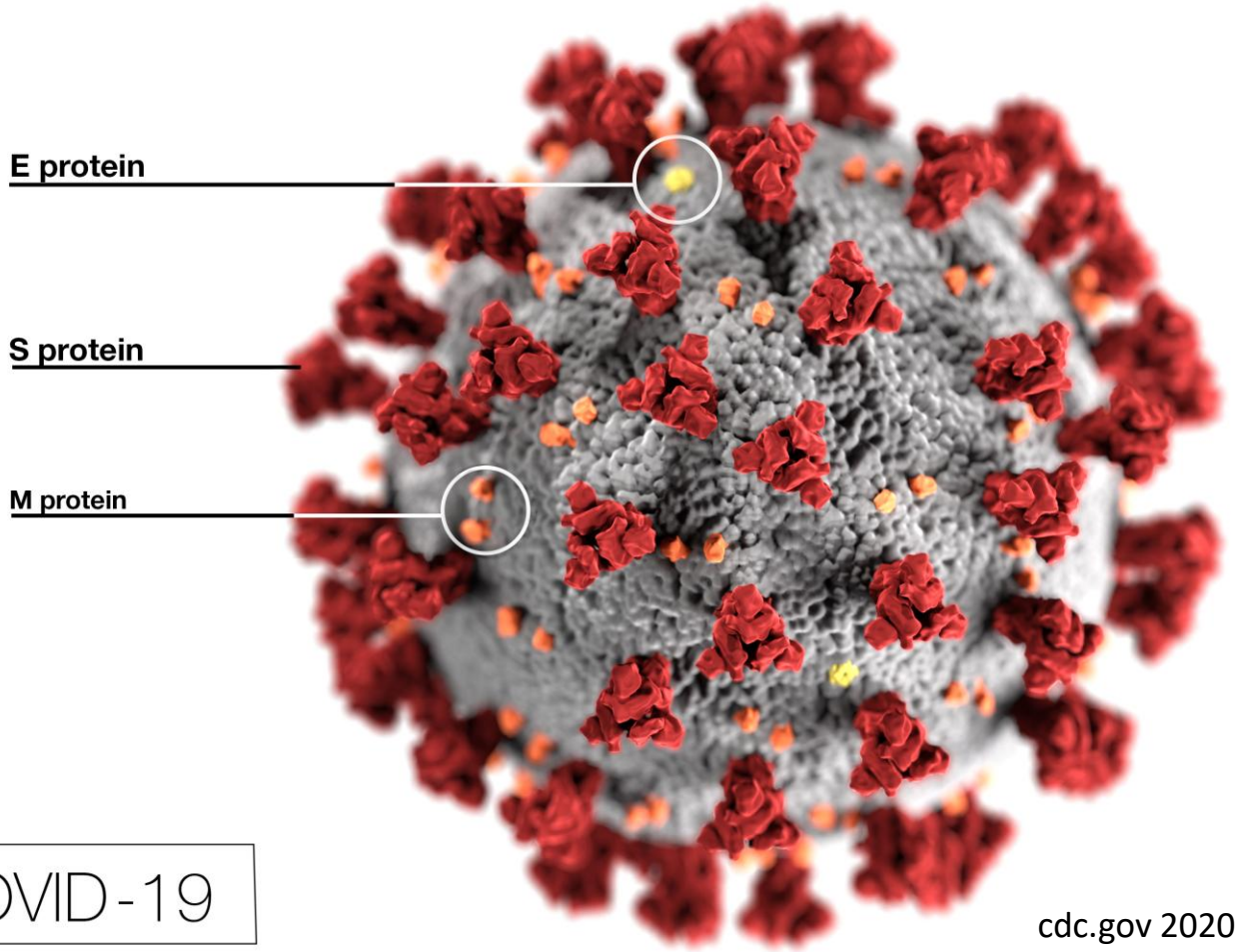
- Study population n=80: hospitalized with moderate-severe SARS-CoV-2 pneumonia
  - N=40: dexamethasone po 16mg/day x 10 days (Hi-dex)
  - N=40: dexamethasone 4mg/day + spironolactone po 100mg/day x 10 days (Spi-dex)

- Results: at 5 days
  - More patients discharged on Spi-Dex
  - Radiological evidence of pneumonia
    - 24/40 on Hi-Dex, 15/40 on Spi-Dex
    - Radiological deterioration: 5/40 on Hi-Dex, 0/40 on Spi-Dex

C Edwards. *Frontiers in Endocrinology*, 2021

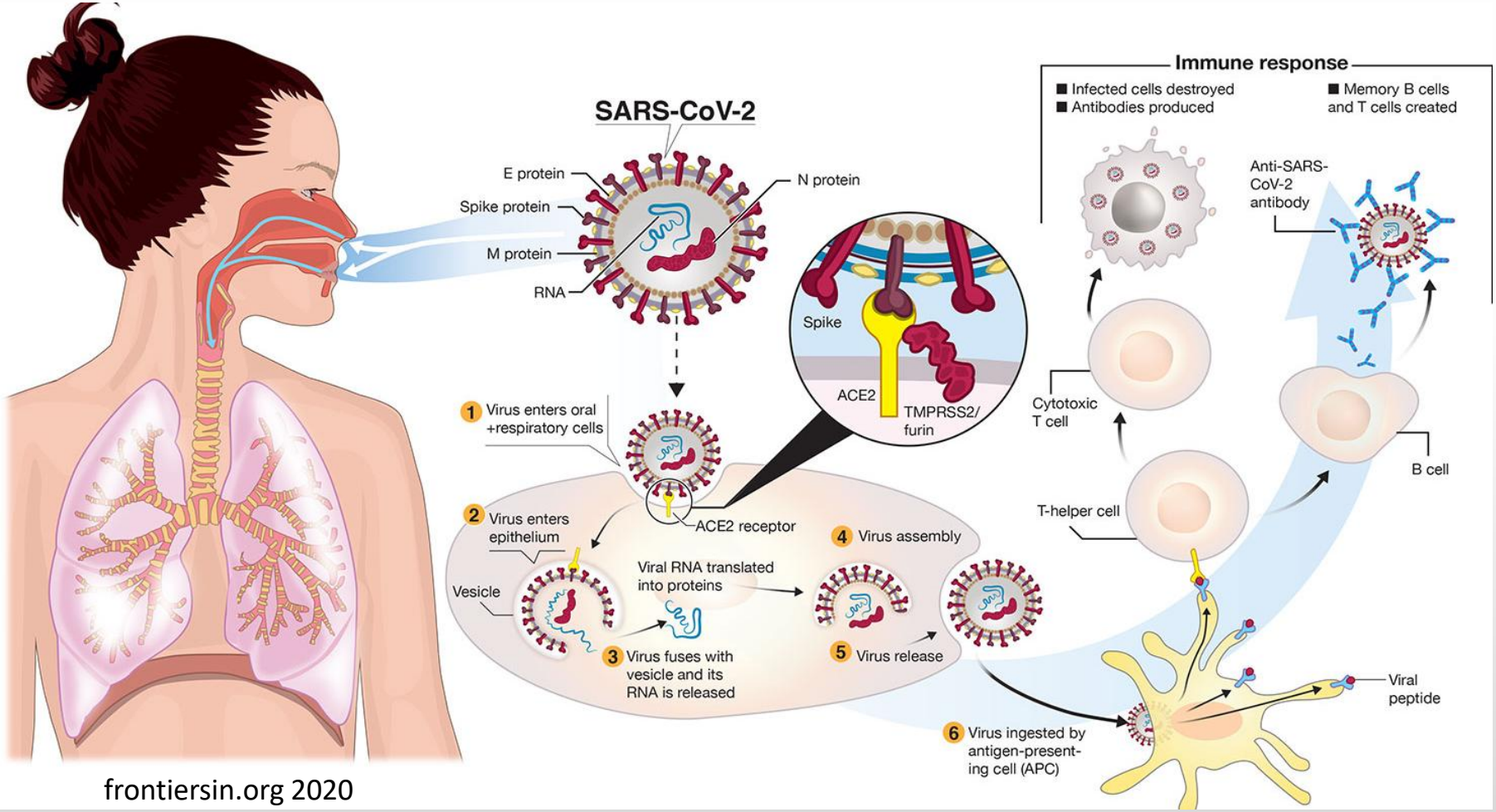
COVID-19 illness

SARS-CoV-2 virus



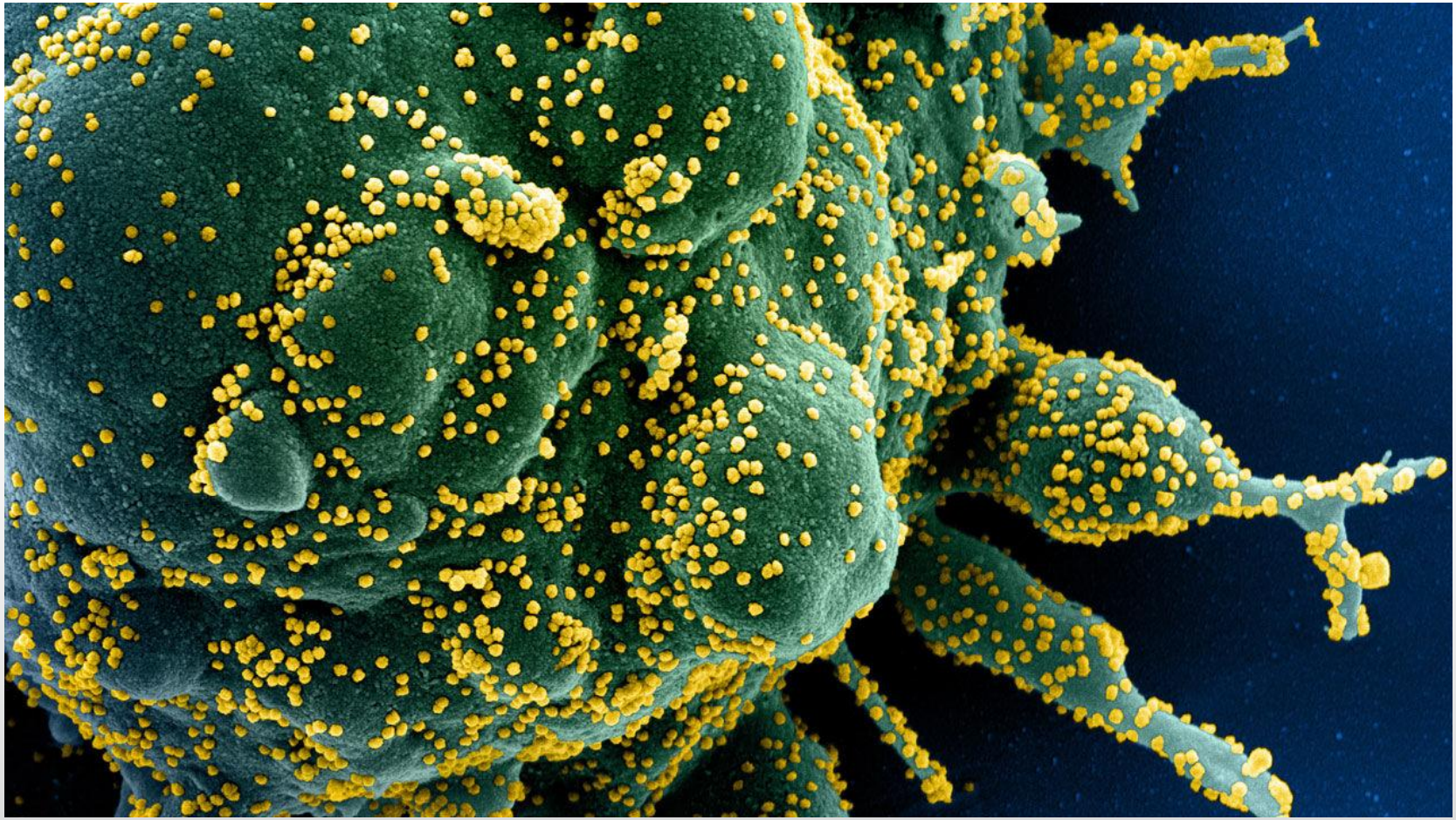
cdc.gov 2020

SARS-CoV-2 virus infection



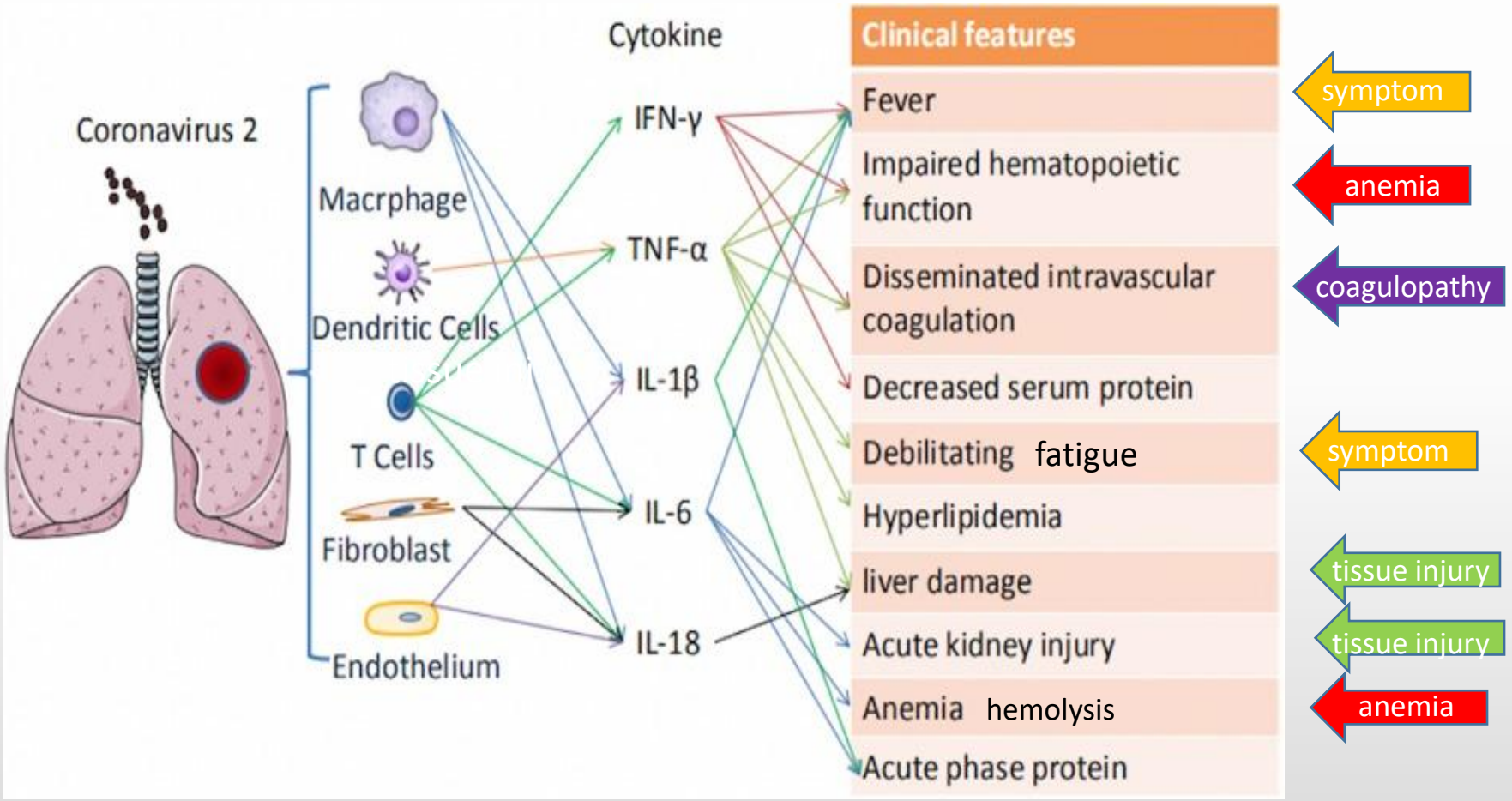
frontiersin.org 2020

SARS-CoV-2 viremia



sciencemag.org 2020

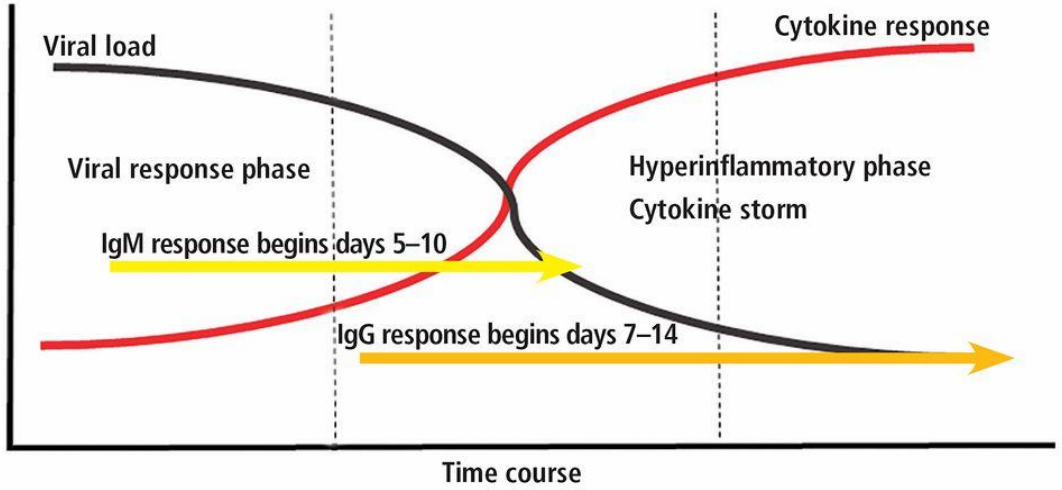
Hyperimmune cytokine response



Sciencedirect.com, 2020

Inflammatory response

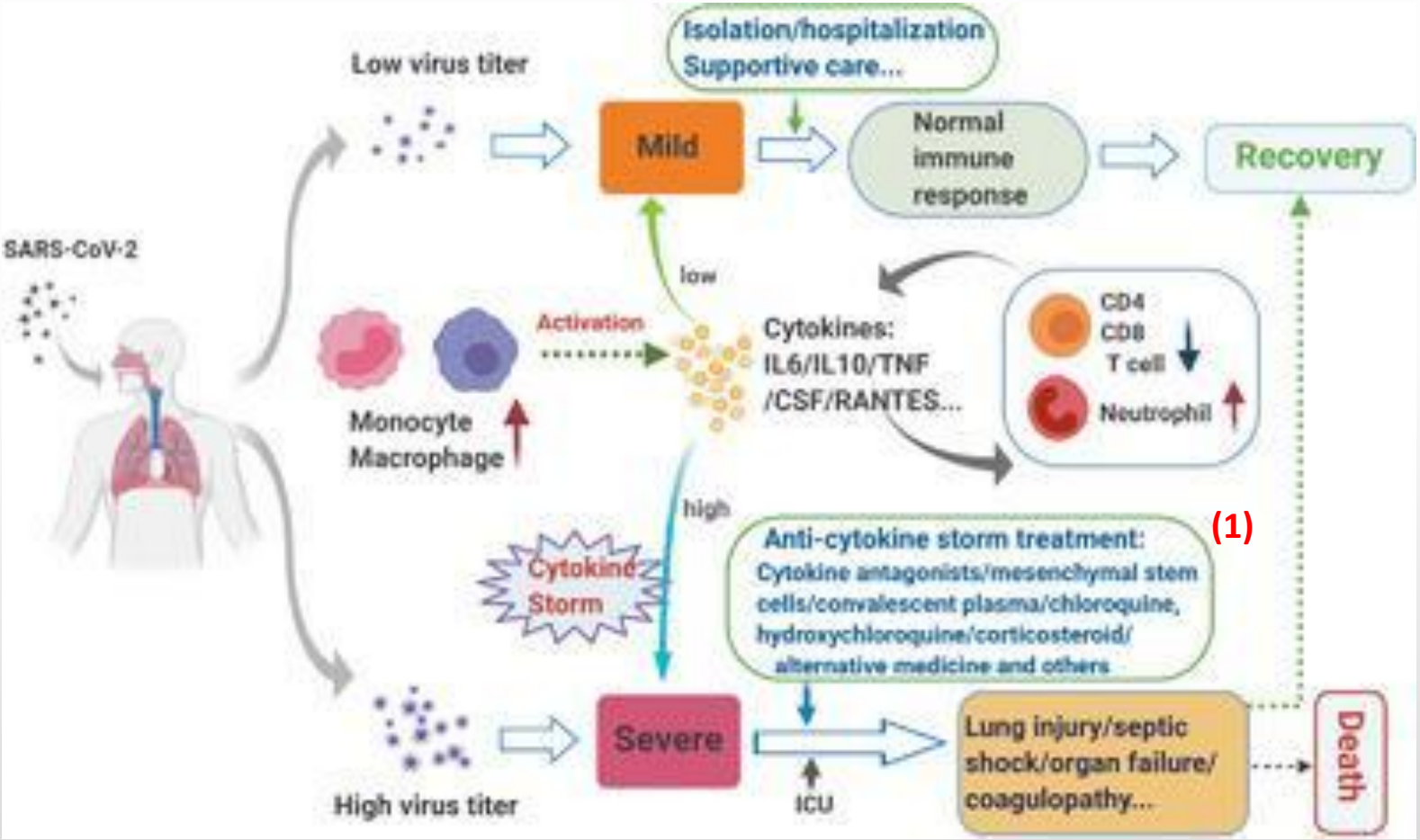
	Stage 1 Asymptomatic	Stage 2 Nonsevere symptomatic	Stage 3 Severe respiratory-inflammatory
Immune response over time: **Self-limiting in 80%** **Severe in 15%–20%** **Fatal in 1%–2%**	**Innate immune activation** Viral engagement of PAMPs Low type 1 IFN	**Adaptive immune activation** Generation of specific antibodies and T-cell response Release of DAMPs	**Cytokine release syndrome** IL-1, IL-6, TNF, GM-CSF, IFN-gamma, others Coagulopathy Complement



DAMPs= damage-associated molecular patterns; GM-CSF = granulocyte macrophage colony-stimulating factor; IFN = interferon; IgM = immunoglobulin M; IL-1 = interleukin 1; IL-6 = interleukin 6; PAMPs = pathogen-associated molecular patterns; TNF = tumor necrosis factor

Cleveland Clinic Journal of Medicine 2020

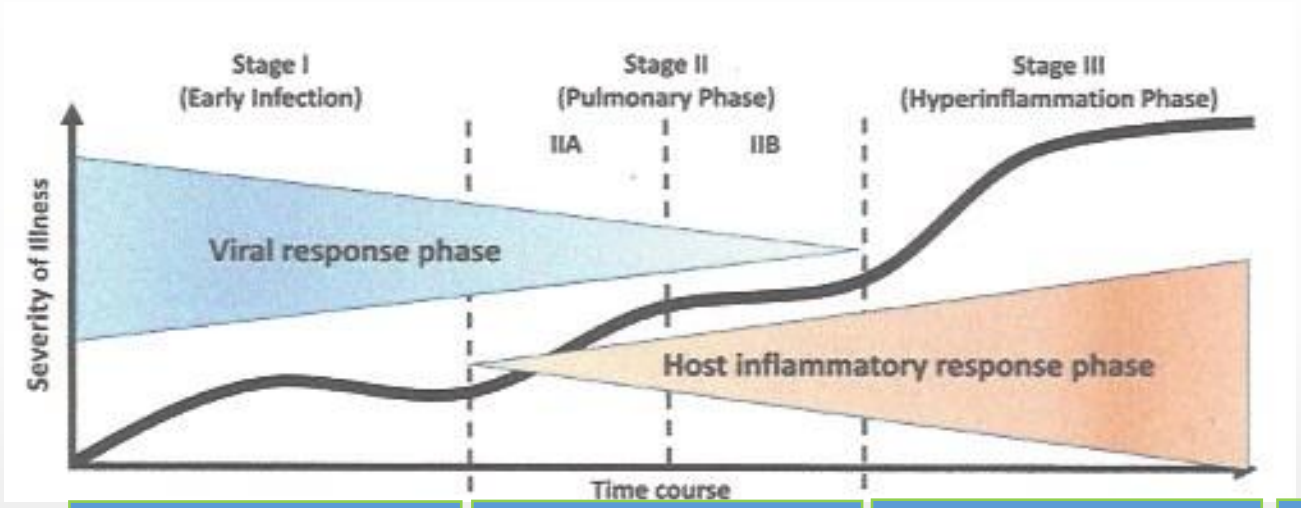
Determinants of clinical course



jib.onlinelibrary.wiley.com 2020

(1) S Alam, *Frontiers in Pharmacology*, 2021

Stages of COVID illness:
Respiratory criteria



Early mild symptoms:
- Cough
- Fever

Shortness of breath

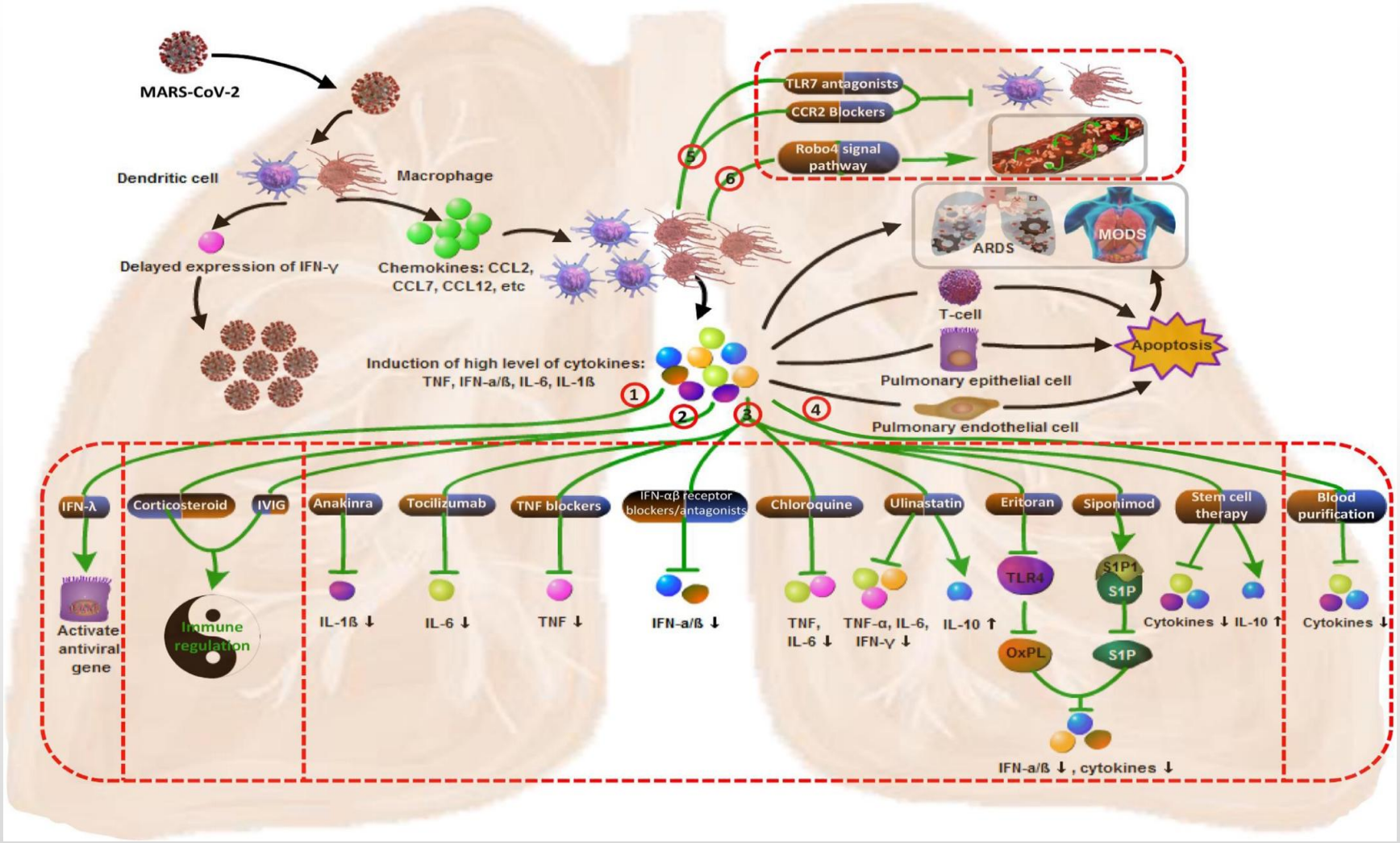
Without hypoxia | With hypoxia

Cytokine storm
- SIRS

- Multi-organ failure
- ARDS
- Sepsis

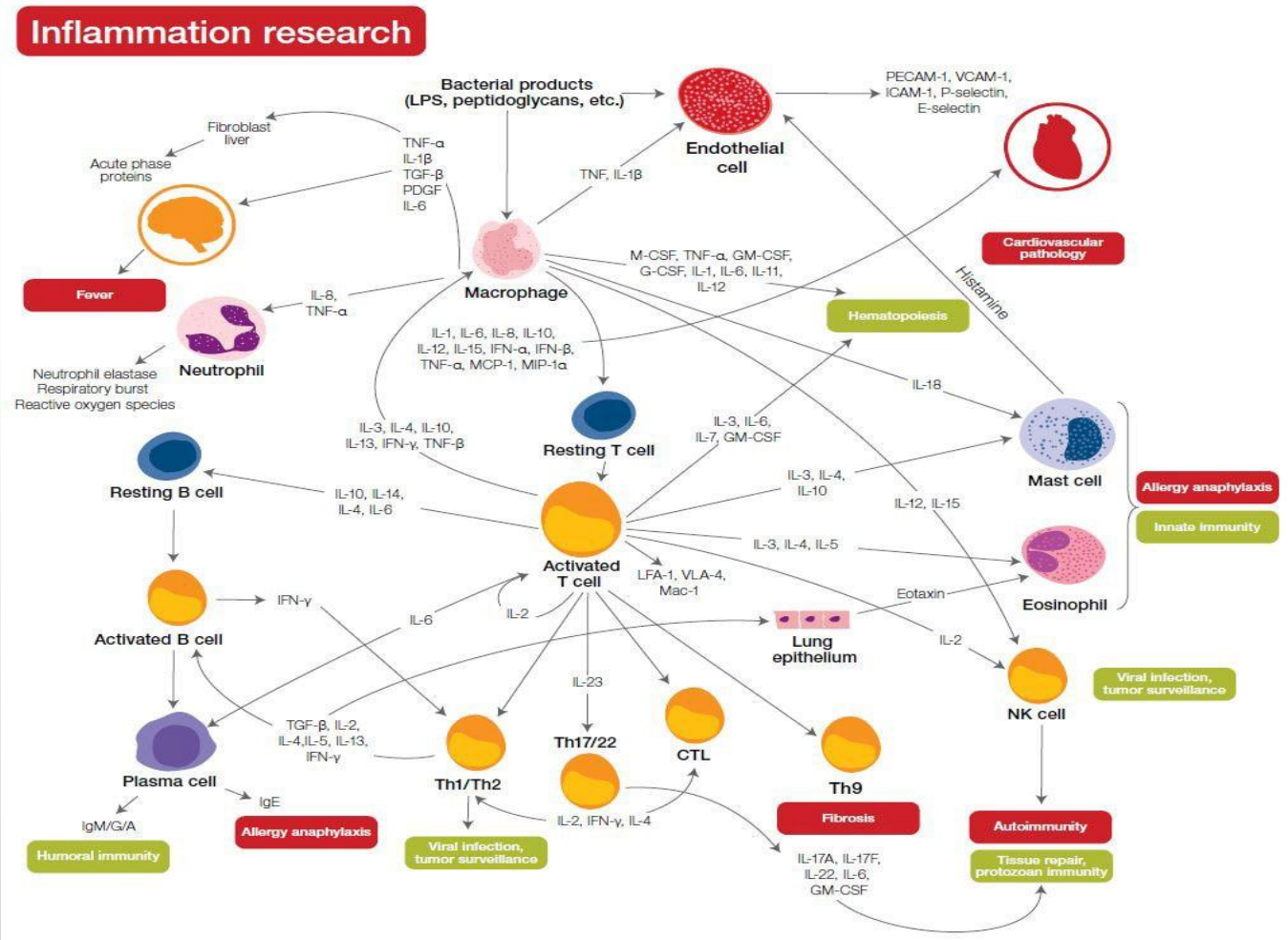
J. Heart and Lung Transpl. May, 2020

Early therapeutic targets



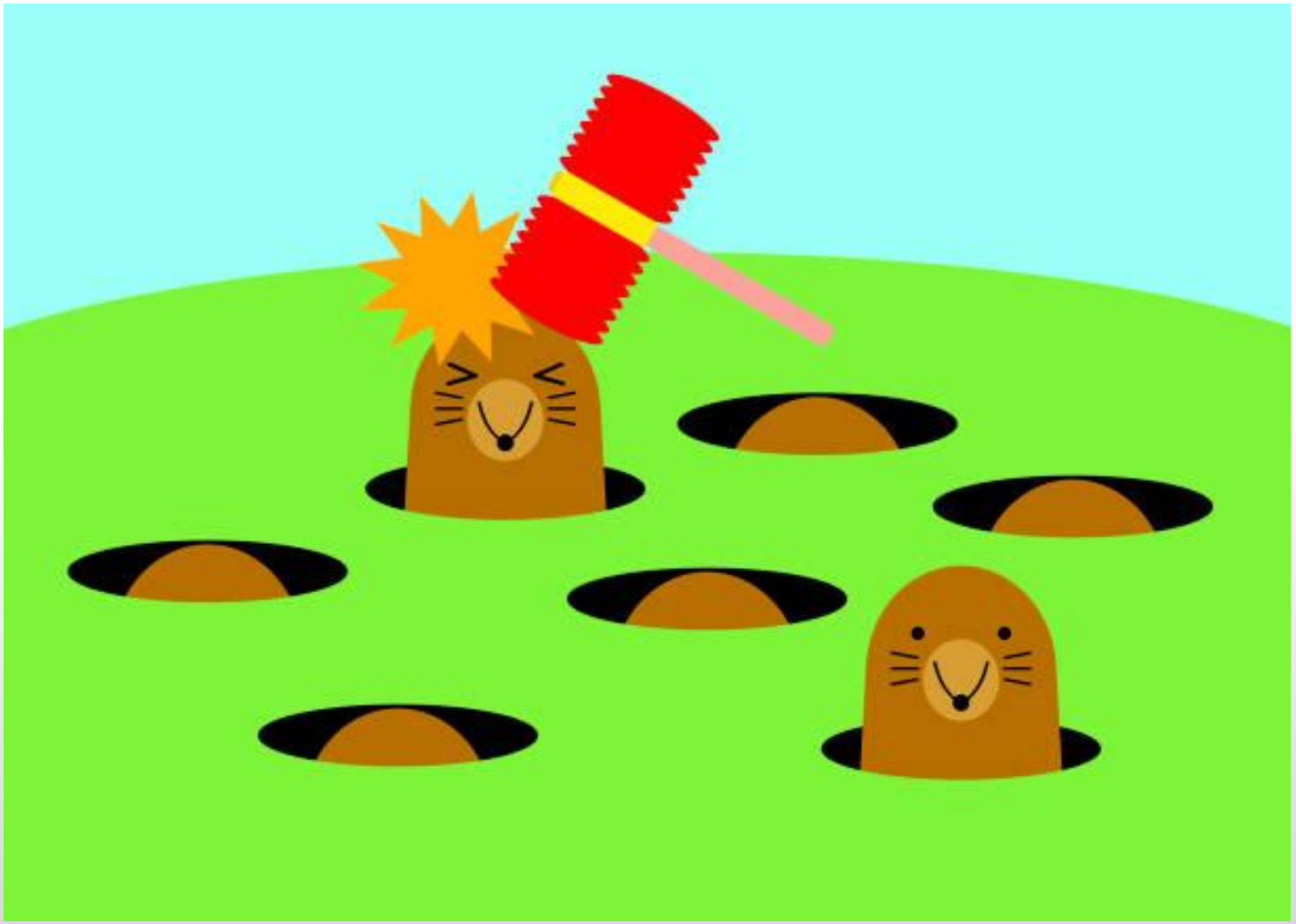
Q Ye, *Journal of Infection* 2020

Inflammatory response:
complex, dynamic, interwoven



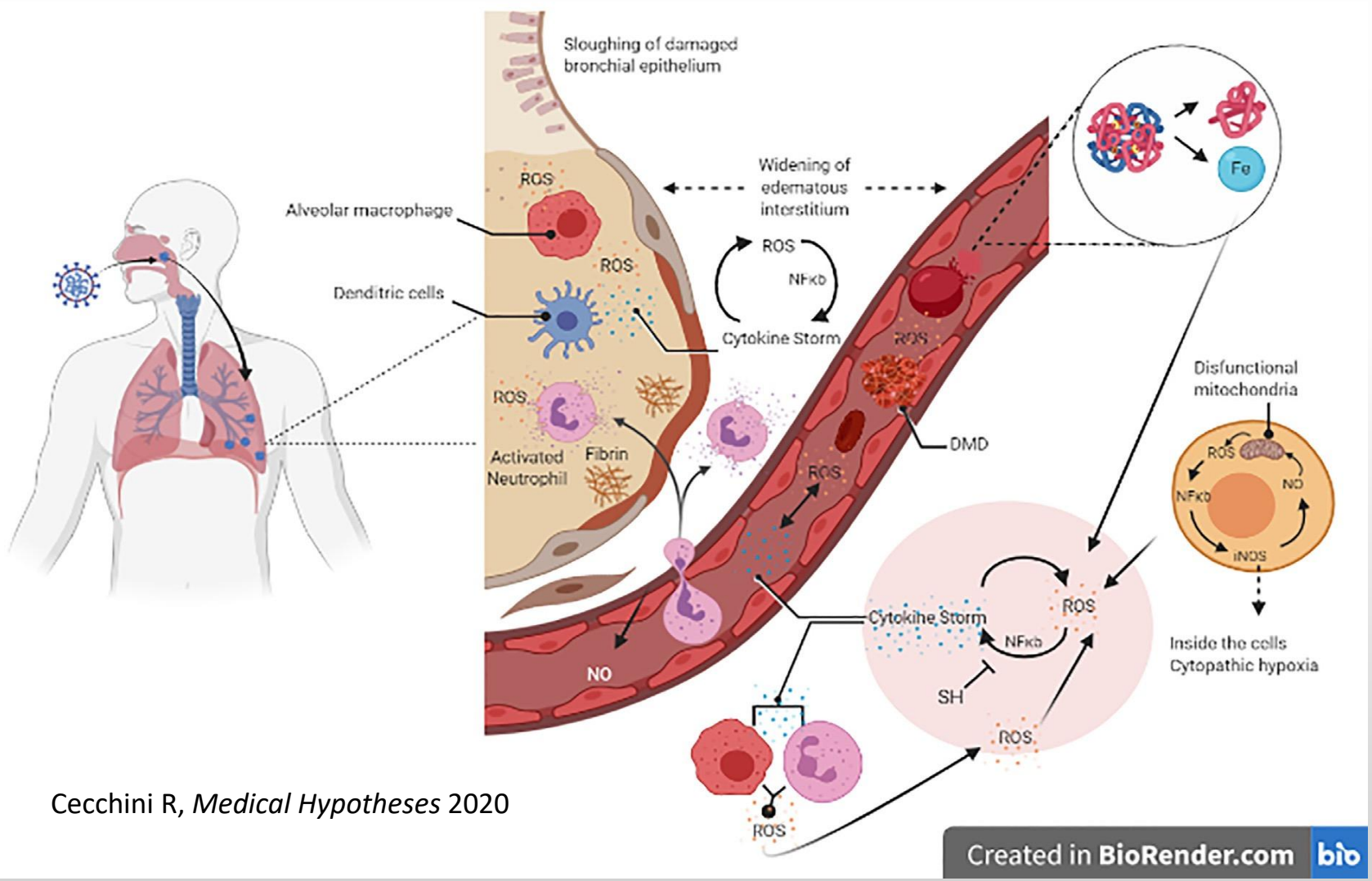
thermofisher.com, 2020

Whack-A-Mole



Addressing the cytokine storm:

Targeting reactive oxygen species (ROS) → oxidative stress



Cecchini R, *Medical Hypotheses* 2020

Consequences of the Cytokine Storm: (direct and indirect)

- Increased ROS → nuclear factor κB →cytokine cascade →ROS →CSS
- Direct tissue injury →
  - Parenchymal: (alveolitis) → ARDS
  - Endothelial: (vasculitis)
- Coagulopathy →
  - Micro: disseminated intravascular coagulation (DIC)
  - Macro: pulmonary embolism (PE)
- Anemia →
  - Hemolysis
  - Impaired hematopoesis
- Hypoxia (tissue injury + coagulopathy + anemia)→
  - Systemic
  - Mitochondrial[(1)]
- Multiorgan dysfunction/failure[(1)], sepsis

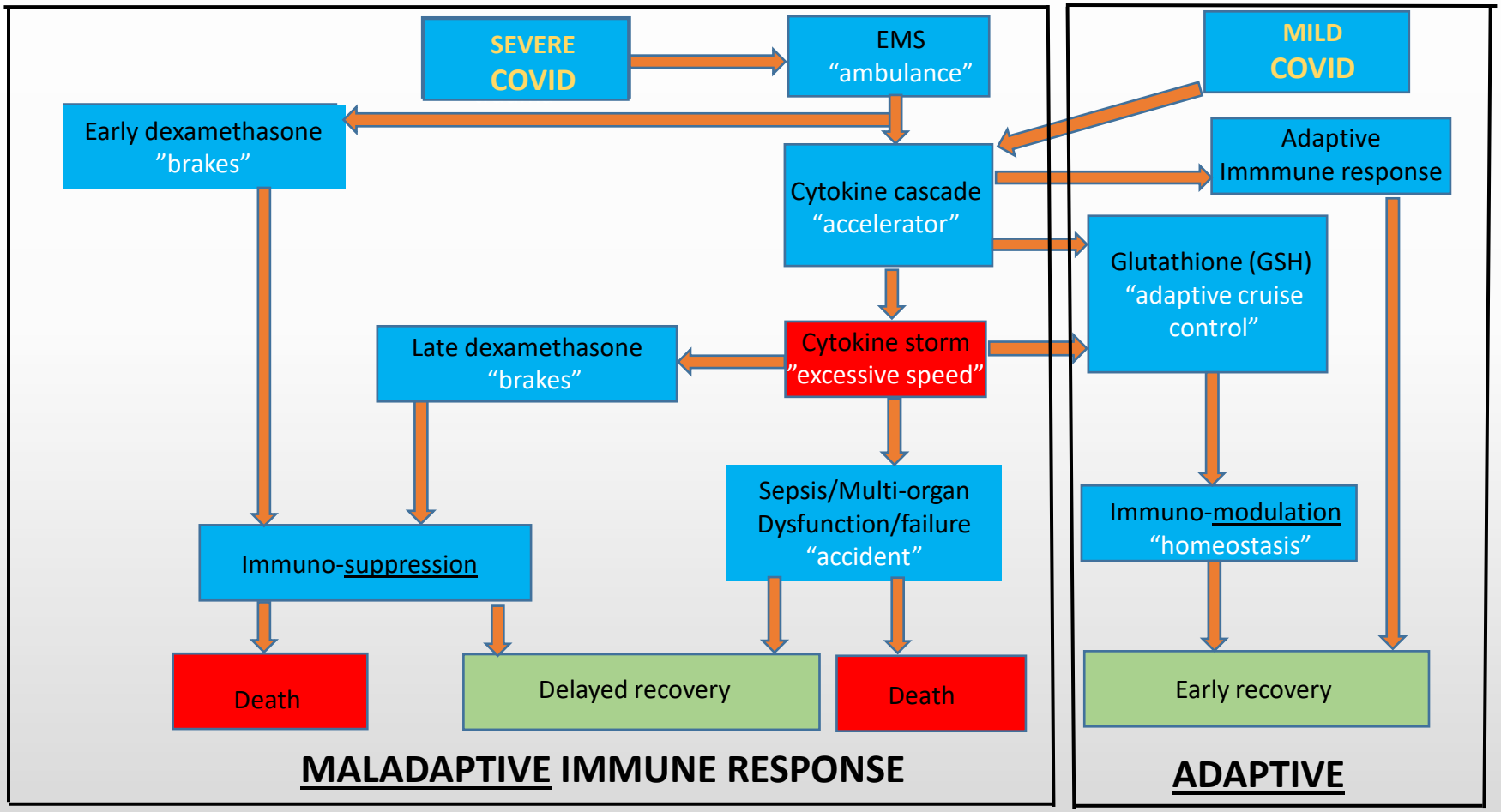
[(1)] A Kozlov, *Annals of Intensive Care*, 2011

Cecchini R, *Medical Hypotheses*, 2020
Guloyan V, *Antioxidants*, 2020
Polonikov A, *ACS Infectious Diseases*, 2020

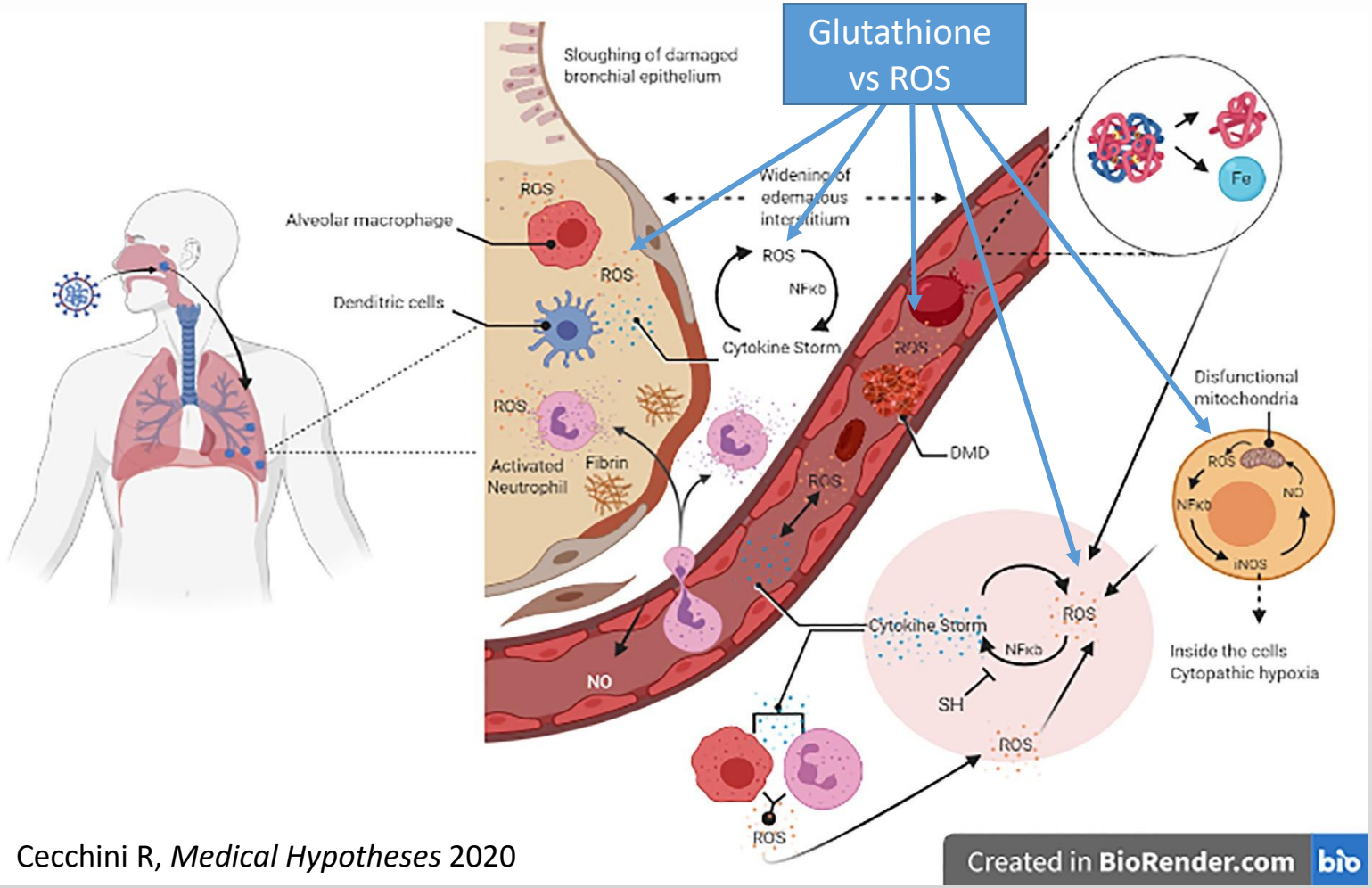
Glutathione (GSH) vs ROS/OS

- Our body's "master anti-oxidant" →reduces ROS
  - Tempers the cytokine response
    - Cytokine cascade →
      - "Accelerator"
    - Immuno-suppression (dexamethasone)
      - "Brakes"
    - Immuno-modulation (GSH)- "Goldilocks concept" (adaptive physiology/homeostasis that allows the body to heal itself)
      - "Governor, adaptive cruise control"
    - Cytokine storm → Multi-organ failure
      - "Accident"

Dexamethasone vs GSH and the COVID “trauma victim"

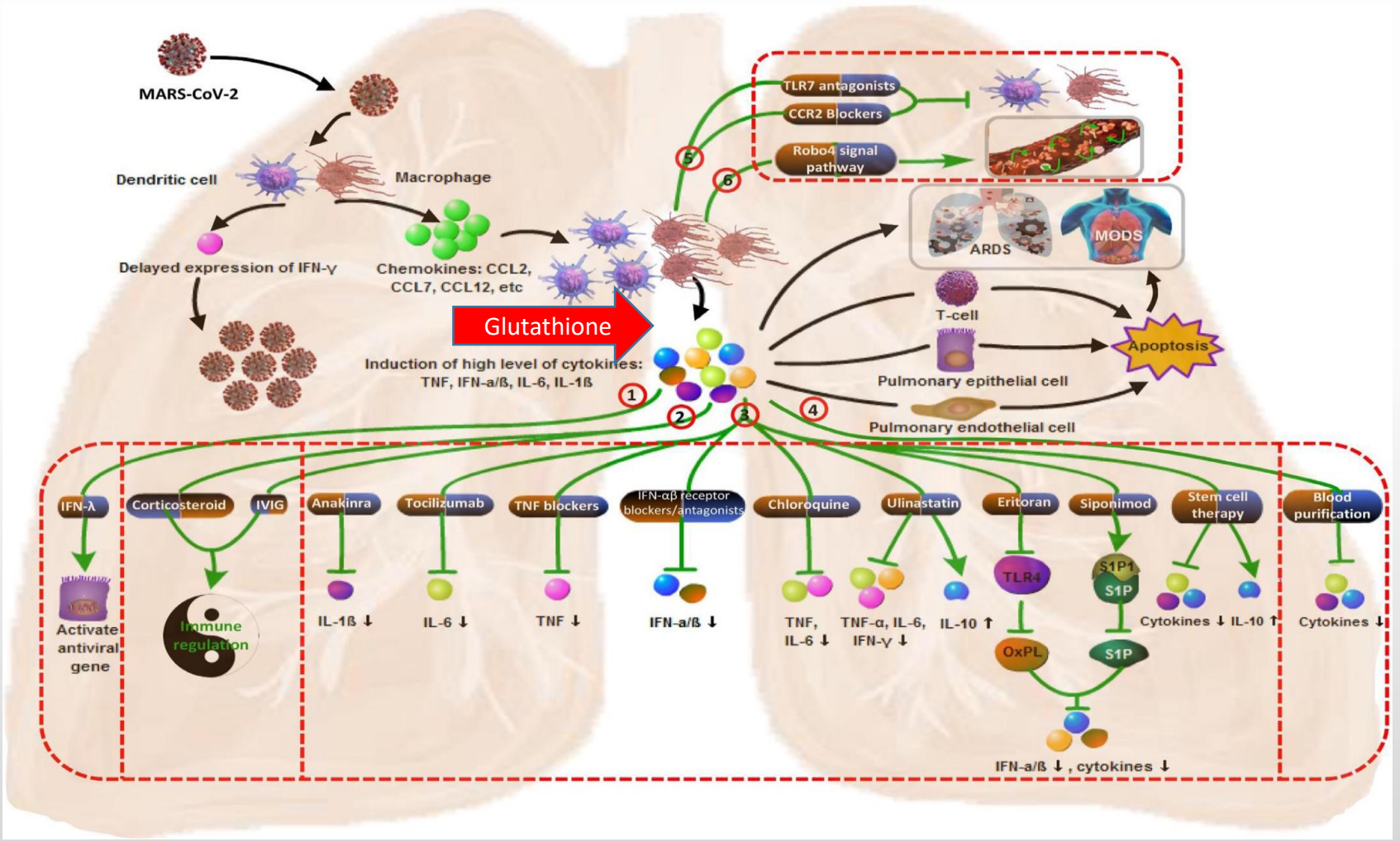


ROS and cytokine storm: a unifying concept



Cecchini R, *Medical Hypotheses* 2020

Potential therapeutic targets



Q Ye, *Journal of Infection* 2020

Delivery barriers to effective glutathione treatment:
bioavailability/therapeutic efficacy

- Oral – GI degradation
- Intravenous
  - Expensive and limited availability
  - Technical limitation of IV administration
  - Serum vs RBC levels? **(1)**
    - Serum half-life < 25 minutes through urinary excretion
- Transdermal liquid **(2)**
  - Bypasses GI degradation
  - Ease of use (neonates to elderly)
  - Cellular delivery (RBCs)
  - How??

(1) S Aebi, *Eur J Clin Invest*, 1991
(2) N Patel, Auro Pharmaceuticals

Cyclodextrin

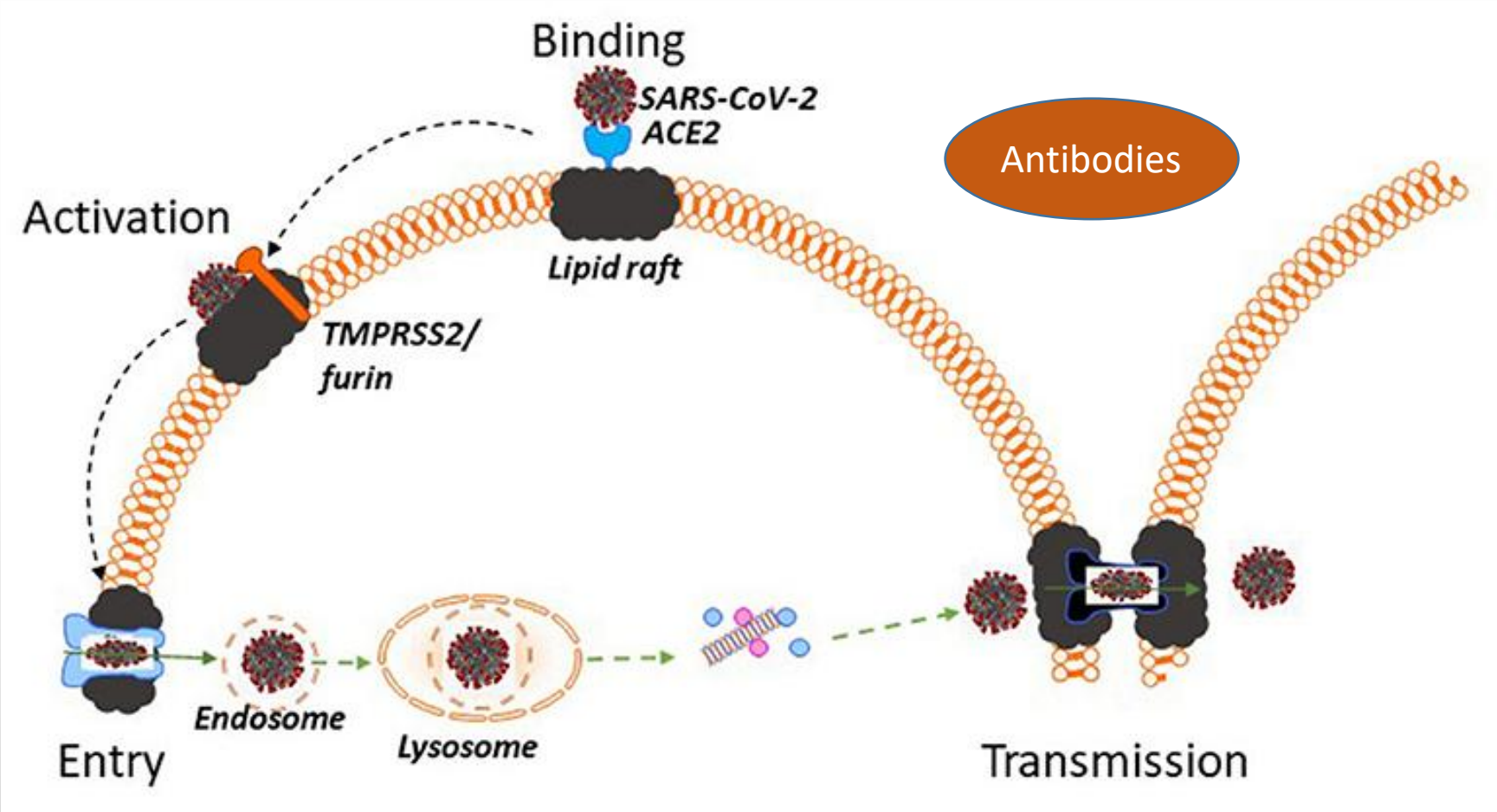
- Cyclic (oligosaccharide) sugar molecule

- Delivery vehicle for glutathione through nano-technology
  - Transdermal absorption through water channels
  - Serum and tissue levels (facilitated transport vs passive diffusion)

- Intrinsically antiviral: destruction of lipid rafts*
  - Impede viral binding to ACE 2 receptors on host cell
  - Impede viral entry by endocytosis into host cell
    - Cholesterol sequestration of cell membrane lipid raft
  - Impede cell-to-cell transmission – direct viral transfer (ie. delta variant)

- D Sviridov, *Frontiers in Immunology*, 2020
- I Ripa, *Frontiers in Immunology*, 2021

Lipid rafts in SARS-CoV-2 pathogenesis

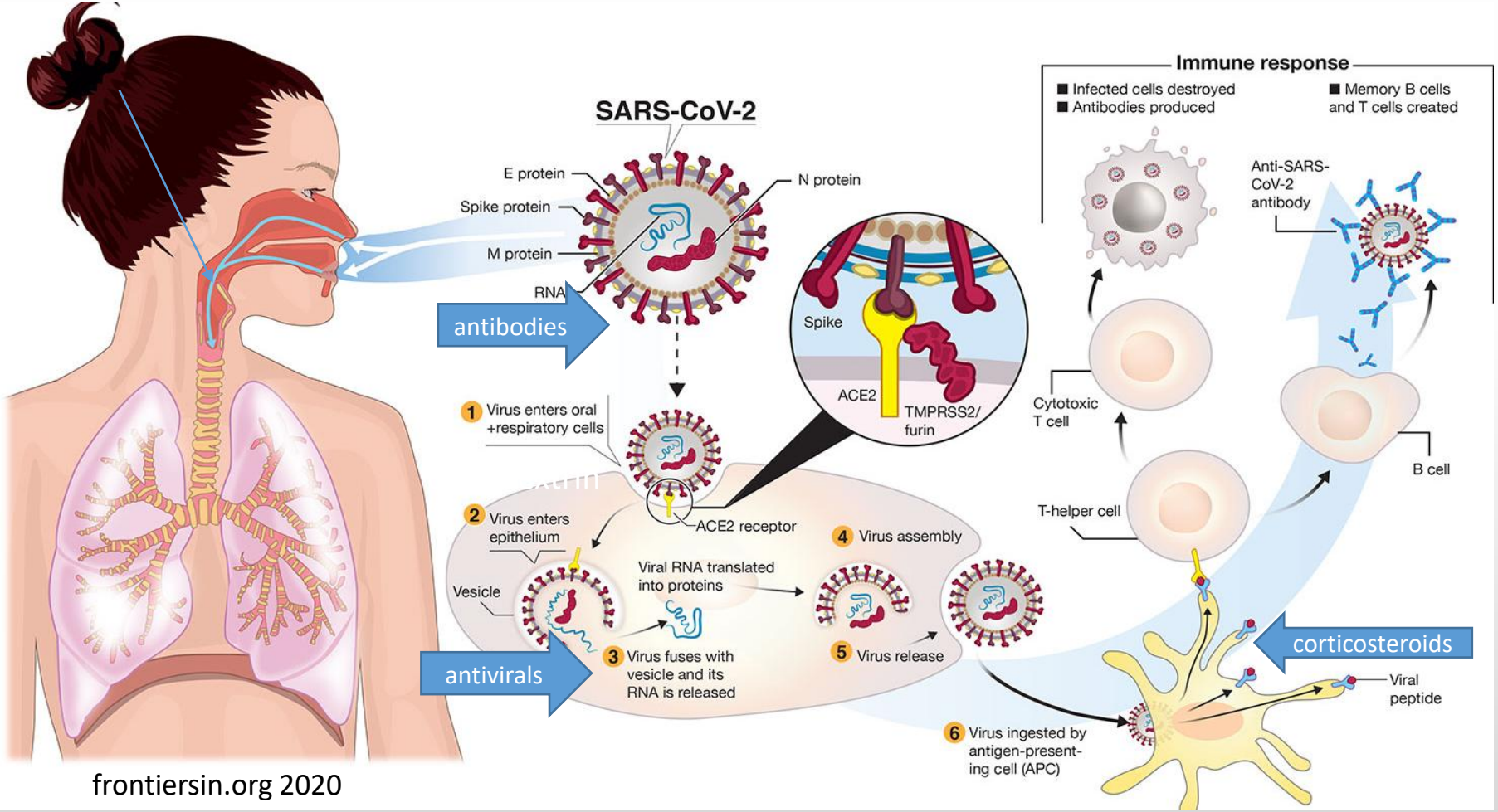


D Sviridov, Frontiers in Immunology, 2020

Organs with high density of ACE-2 receptors

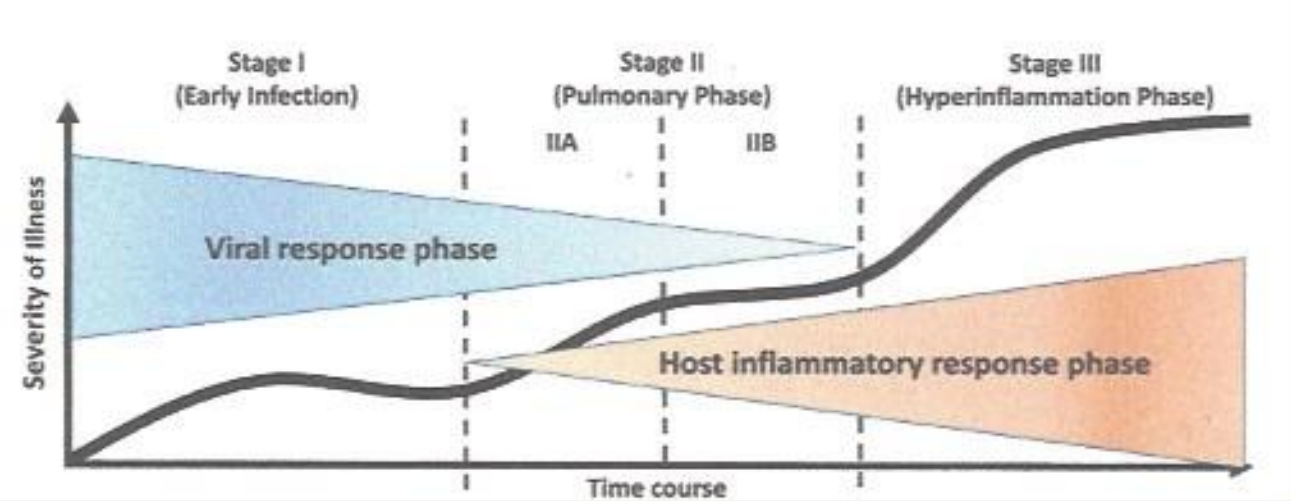
- Nasopharynx
  - Anosmia
  - Sore throat
- Brain
  - Headache
- Lungs
  - Cough
  - Shortness of breath/hypoxia
- Gastrointestinal tract
  - Diarrhea, nausea, vomiting
- Heart, kidney, liver
  - Elevated troponin, BNP
  - Low eGFR
  - Elevated transaminase
- Vasculature
  - Endothelium: vasculitis with elevated hsCRP
  - Blood: micro/macro thrombosis with elevated D-dimer

Current COVID-19 treatments



frontiersin.org 2020

Therapeutic options - 2021



Stage IV and Post-COVID

Vaccine	Monoclonal ab IV Molnupiravir po Paxlovid po	Remdesivir IV Monoclonal ab IV	Dexamethasone IV/po	Support

Glutathione + cyclodextrin = Glutaryl™

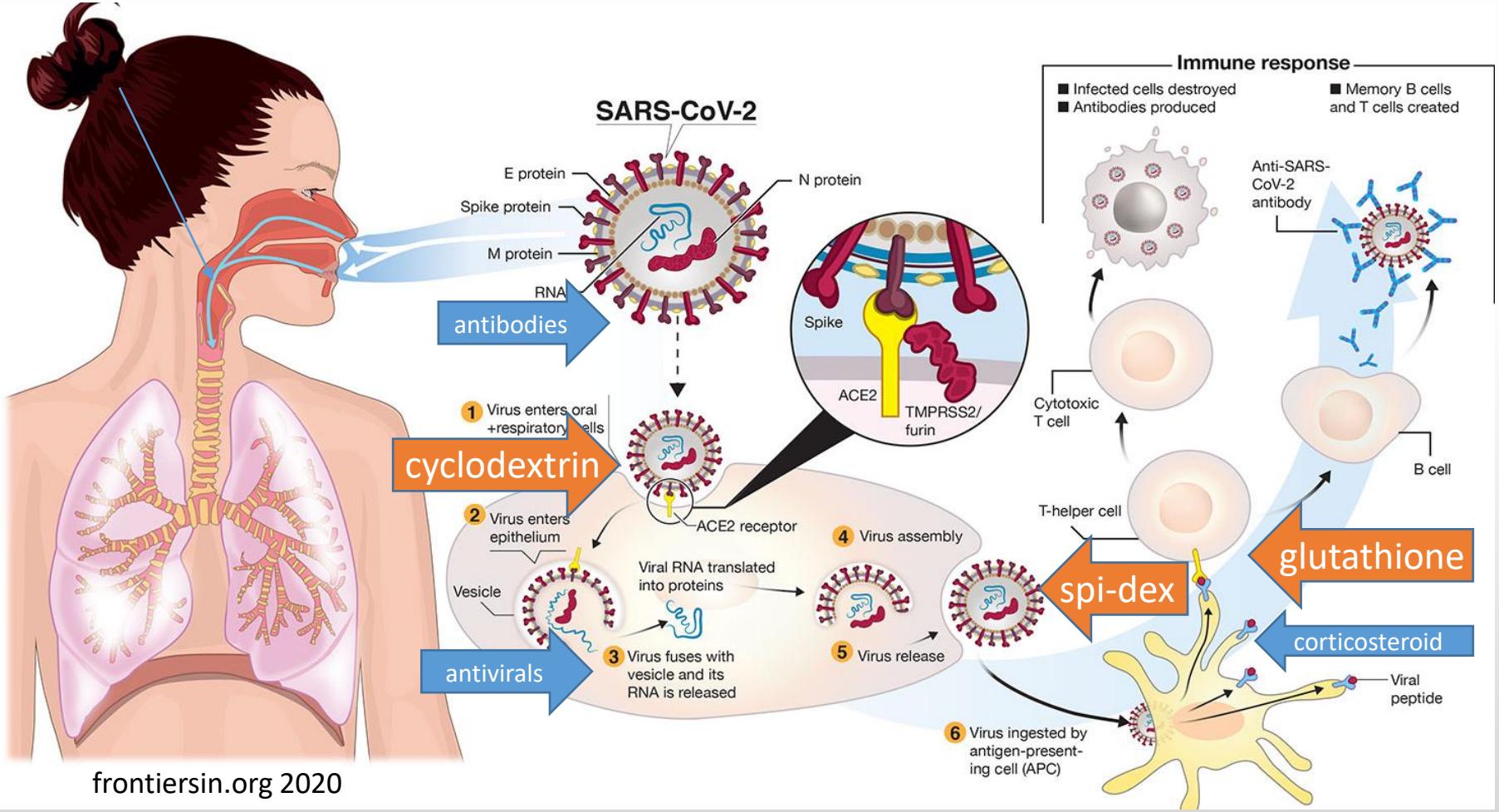
- Glutathione (GSH)
  - Our body's primary anti-oxidant – vs ROS
- Cyclodextrin
  - Cyclic sugar molecule – GSH transport, antiviral
- Vitamin C
  - Assists in restoration of endogenous GSH from GSSG
  - Product stabilizer
- All ingredients have "Generally Regarded As Safe" – (GRAS status) by the FDA → OTC

Patel, Auro Pharmaceuticals, Inc

The role of a transdermal therapeutic agent vs. COVID-19 illness

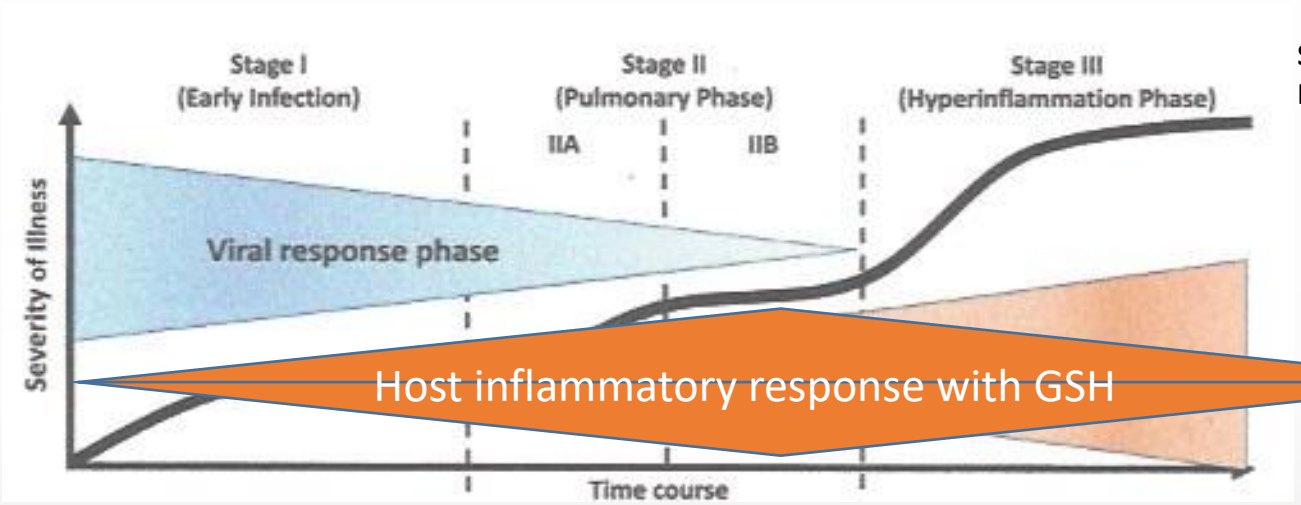
- A single topical agent that simultaneously:
  - Impedes viral entry
  - Tempers the cytokine cascade (adaptive physiologic response)
- Reduces the viral load and shortens duration of COVID-19 symptoms
- Is stable at room temperature
- Repurposed OTC product
- Is non-toxic

Complementary treatments vs COVID-19 illness - 2022



frontiersin.org 2020

Therapeutic options - 2022



Stage IV and Post-COVID

Vaccine

Monoclonal ab IV Molnupiravir po Remdesivir IV Paxlovid po	Remdesivir IV Monoclonal ab IV	Dexamethasone IV Spi-Dex	Support

cyclodextrin

Glutathione (GSH)

H. Siddiqi T. Lee J. Beigel W. Fischer P. Horby

Post-covid syndrome

- What is it?
- How common is it?
- What is its health and socio-economic impact?
- Can we treat it?

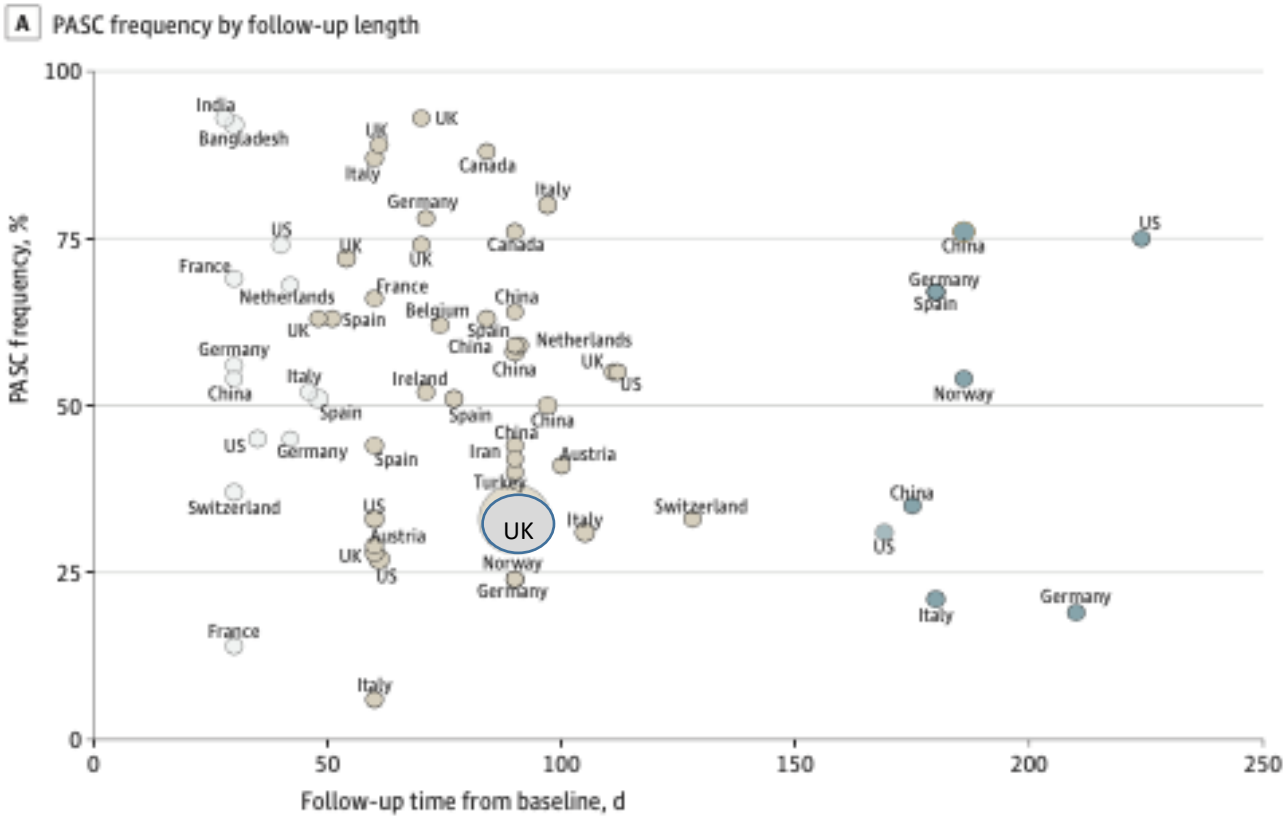
Post-covid syndrome

- AKA
  - Post-acute sequelae of SARS-CoV-2 (PASC)
  - “Long-haulers”, “long-COVID”
- Cause? (1)
- Resolution
  - Good news: eventual spontaneous resolution of symptoms
  - Bad news: may take > 6 months to recover
- Health/socio-economic impact
  - Incidence does not correlate to disease severity (ie. Respiratory criteria)
  - Occurs after acute, mild-moderate, and asymptomatic illness = millions
    - Meta-analysis: 80% of COVID-19 patients had at least one symptom after 14-110 days (2)
    - Fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), dyspnea (24%) (2)
    - Prospective study: 11% could not fully participate in everyday and work life 7 months after disease onset (3)
  - Impairs function, livelihood, and sense of well-being =/> 6 months
- Current treatment: supportive care

(1) A Proal, *Frontiers in Microbiology*, 2021
(2) S Lopez-Leon, *Scientific Reports*, 2021
(3) M Augustin, *Lancet*, 2021

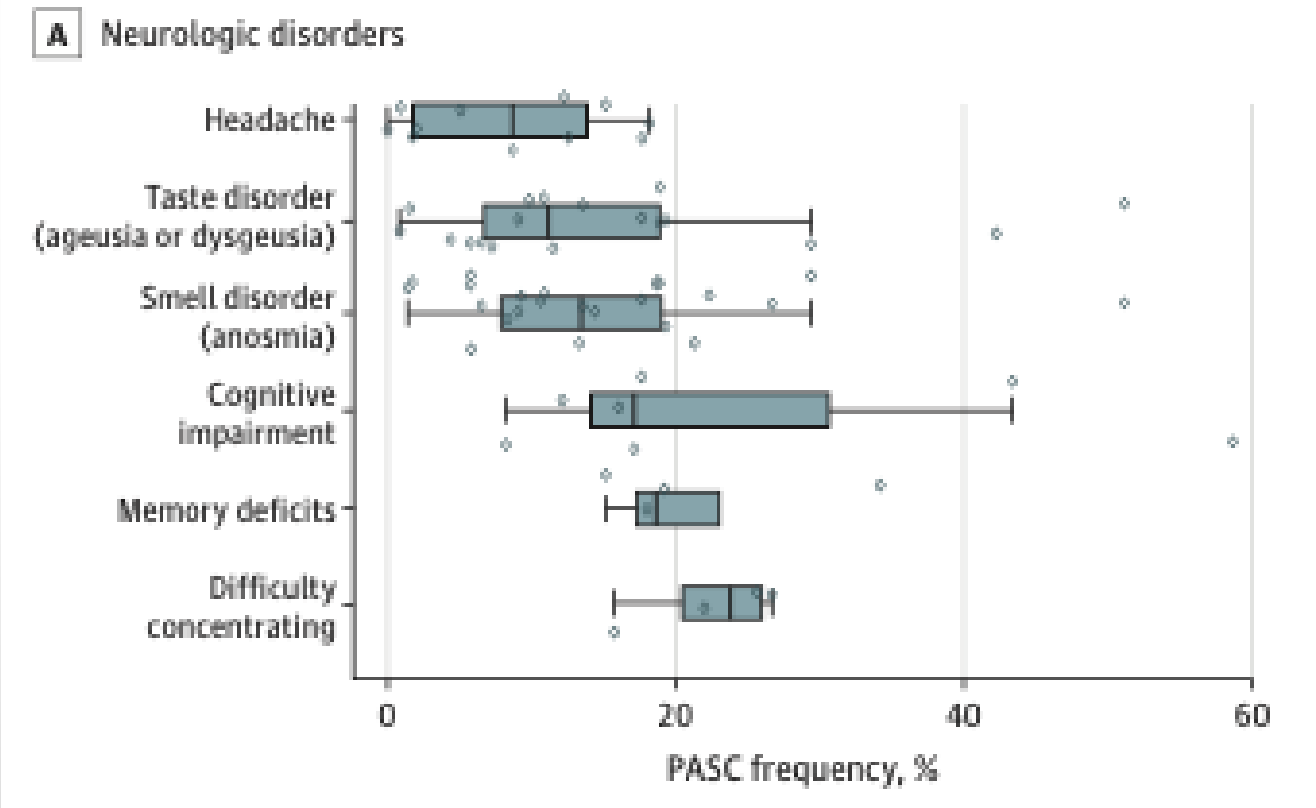
Summary of Studies on PASC
(57 studies, 250,000 survivors)

Figure 1. Studies Included Studying Postacute Sequelae of COVID-19 (PASC)



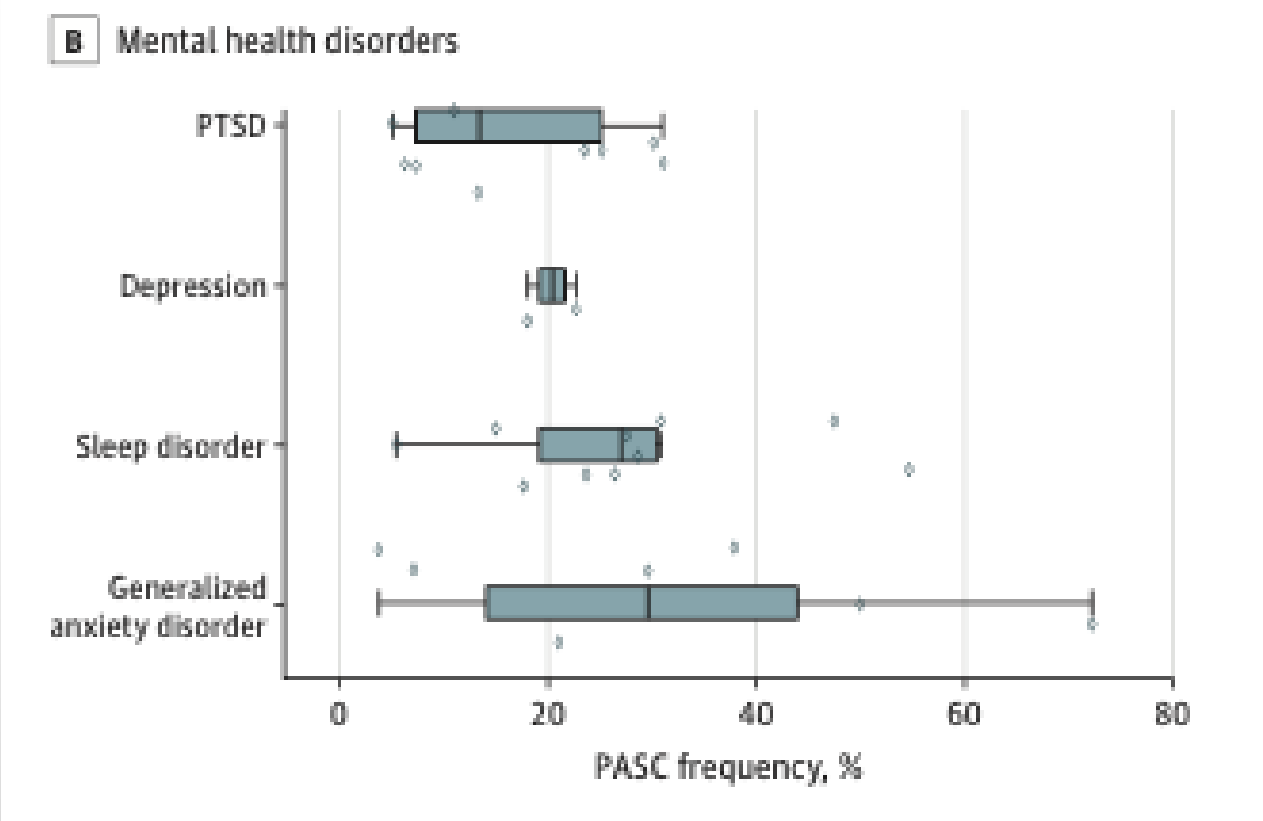
D Groff, *JAMA Network Open*, 2021

PASC: Neurologic disorders



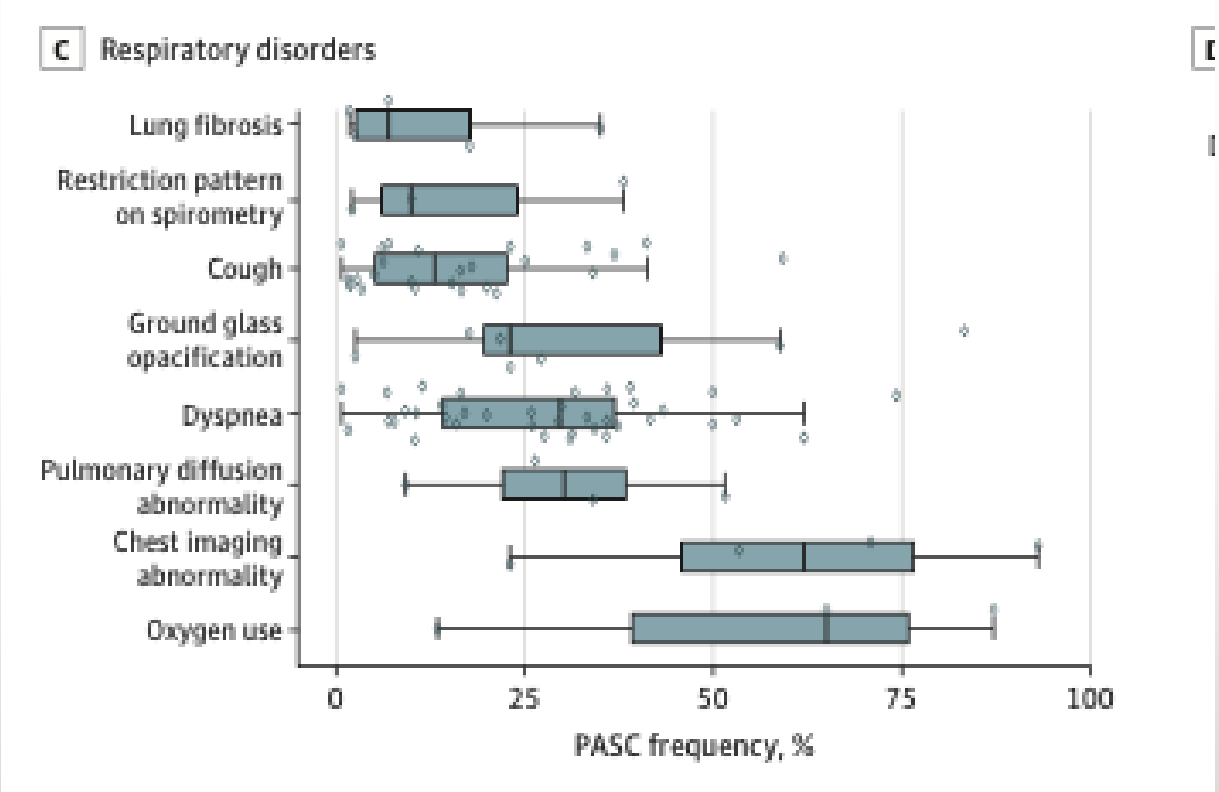
D Groff, *JAMA Network Open*, 2021

PASC: Mental health disorders



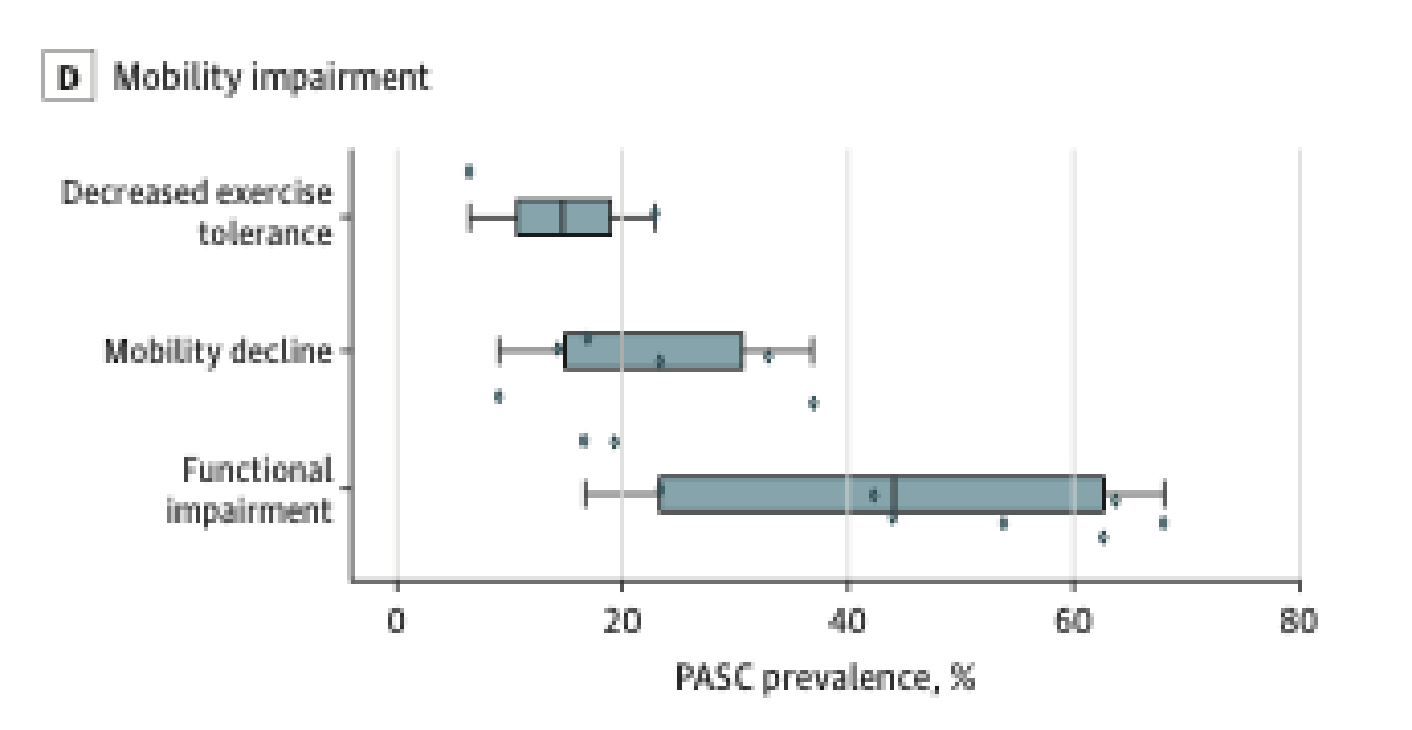
D Groff, *JAMA Network Open*, 2021

PASC: Respiratory disorders



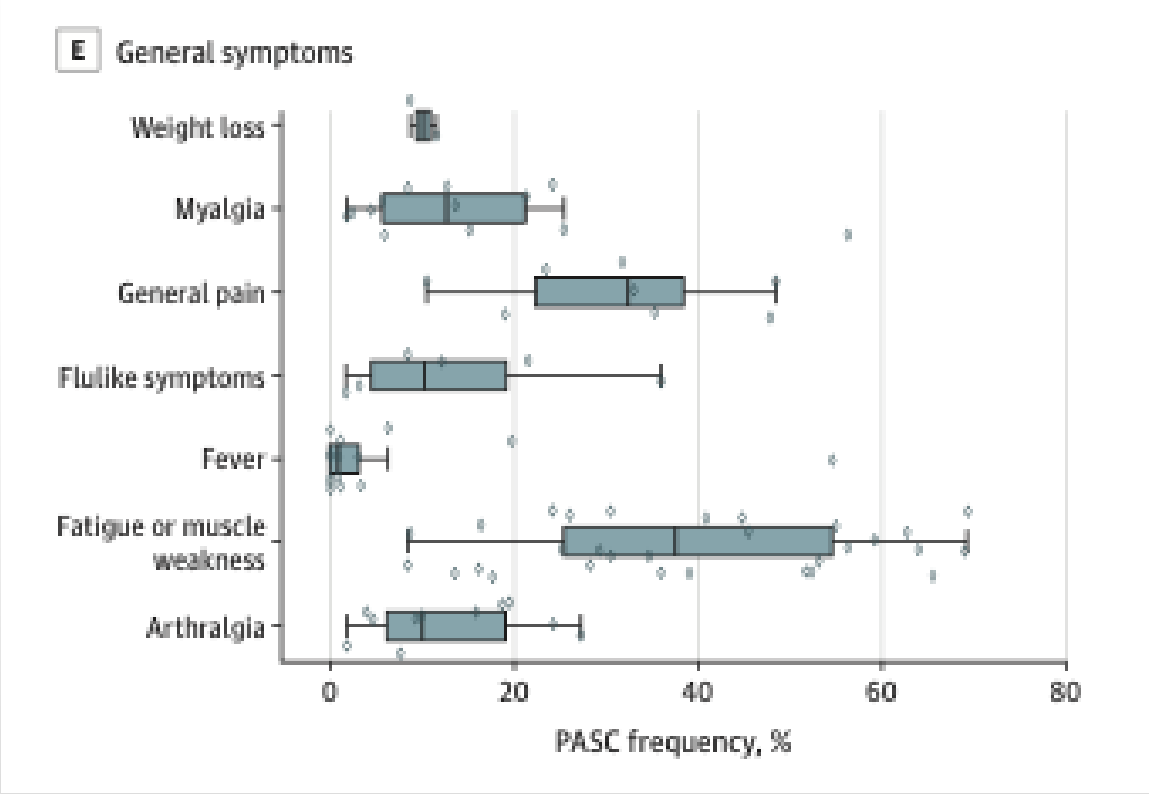
D Groff, *JAMA Network Open*, 2021

PASC: Mobility impairment



D Groff, *JAMA Network Open*, 2021

PASC: General symptoms



D Groff, *JAMA Network Open*, 2021

Post-COVID conditions (CDC)

- Dyspnea or increased respiratory effort
- Fatigue
- Post-exertional malaise and/or poor endurance (PEM)
- "Brain fog", or cognitive impairment
- Cough
- Chest pain
- Headache
- Palpitations and/or tachycardia
- Arthralgia
- Myalgia
- Paresthesia
- Abdominal pain
- Diarrhea
- Insomnia and other sleep difficulties
- Fever
- Lightheadedness
- Impaired daily function and mobility
- Pain
- Rash
- Mood changes
- Anosmia or dysgeusia
- Menstrual cycle irregularities

* Post-exertional malaise (PEM) is the worsening of symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks

Post-covid syndrome:
multi-organ, multi-layered

- Residual symptoms lasting 1 to >6 months
  - Nasopharynx
    - Change in smell or taste
  - Brain
    - Headache
    - Depression: direct tissue injury, immunologic, stress, social isolation
    - Poor concentration “brain fog”
  - Lungs
    - Cough or shortness of breath
  - GI
    - Diarrhea
  - Heart:
    - Multisystem inflammatory syndrome in children (MIS-C)
    - MIS-A (adults)
  - Kidneys
    - CKD
  - Functional?
    - Fatigue
    - PTSD

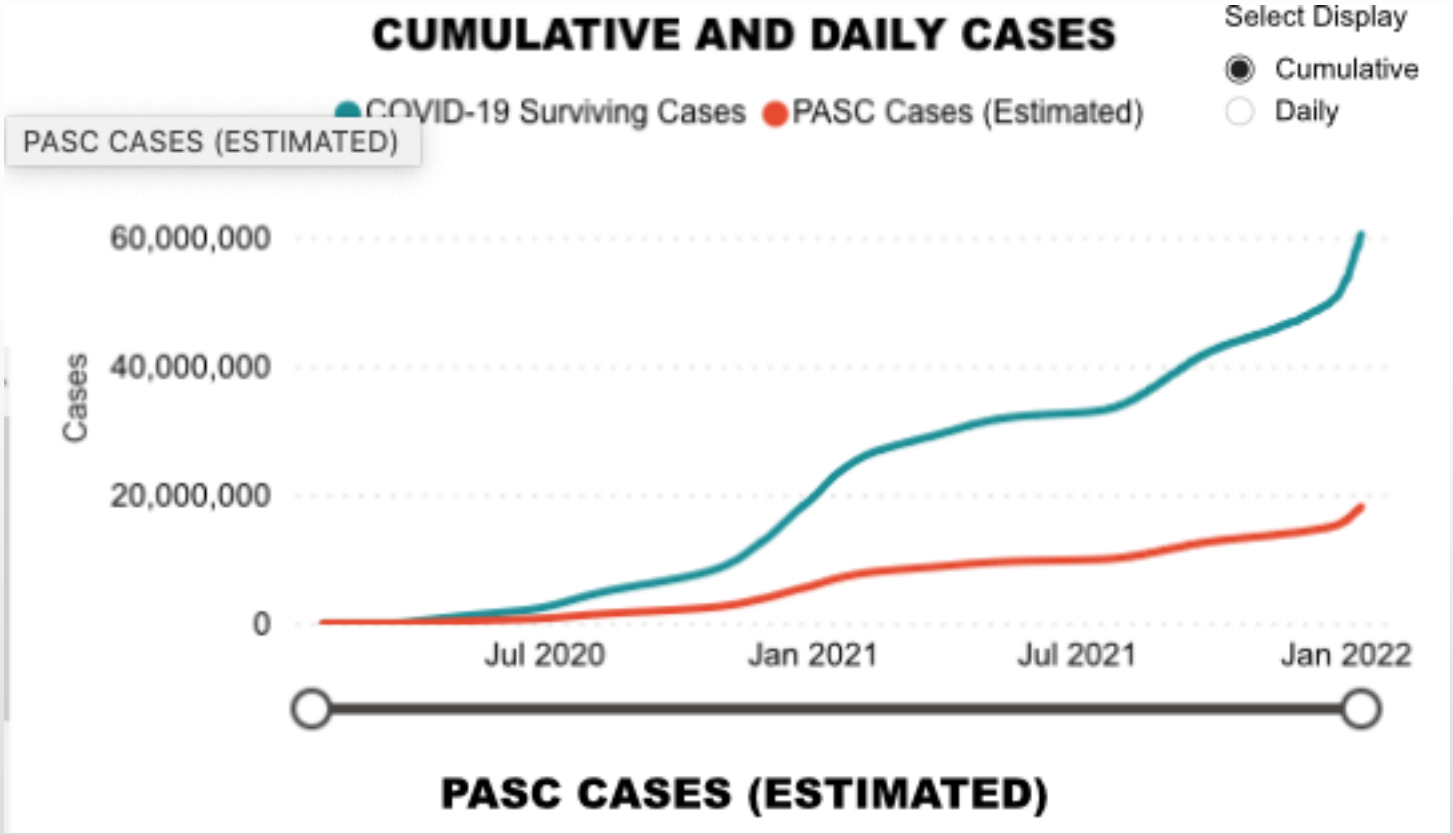
Potential asymptomatic population with post-COVID syndrome

- Meta-analysis of percentage of asymptomatic COVID-19 (+) individuals[(1)]
  - Pooled patients: 40.5%
  - Pregnant women: 54.1%
  - Air or cruise passengers: 52.9%
  - Nursing home residents or staff: 47.5%

- Percentage of COVID (+) patients with symptoms 30 days after diagnosis[(2)]
  - Hosptitalized: 50%
  - Symptomatic: 27.5%
  - Asymptomatic: 19%
  - 40.5% x 19% x 76 million = 6 million asymptomatic patients have developed post-COVID
  - Estimated total cases = >16 million [(3)]

[(1)] Q Ma, *JAMA Network Open*, 2021
[(2)] FAIR Health, *White paper on Long-Haul COVID, 2021*
[(3)] American Academy of Physical Medicine & Rehab, 2022

PASC dashboard



American Academy of Physical Medicine & Rehab, 2022

Post-COVID subtypes

	Type 1	Type 2	Type 3A	Type 3B	Type 4A	Type 4B	Type 5
Initial symptoms	Variable	**Mild**	**Mild**	**Mild**	**None**	**None**	**None**
Duration of PASC symptoms	Variable	>6 weeks	3-6 months	**>6 months**	Variable	Variable	N/A
	Re: severity, organ damage, co-morbidities						Death <12 mo.
Period of quiescence	No	No	**Yes**	**Yes**	No	No	N/A
Delayed onset of symptoms					**Yes** 1-3 mo.	Yes >3 **mo**.	Yes

Type 1: Duration related to severity of illness or co-morbidities
Type 2: Duration >6 weeks with no delay of onset after mild illness
Type 3: Duration of 3-6 months after symptom-free period after mild illness
Type 4: Duration variable after no initial symptoms and onset delay of 1-3 months
Type 5: Initially with no or few symptoms but with sudden death <12 months

R. Becker, University of Cincinnati Med Ctr, 2021

Presumptive causes of sub-types?

- Type 1: variable after tissue injury →repair, recovery, rehabilitation
- Type 2: prolonged cytokine stimulation?
  - Residual cellular hyperimmune state
- Type 3: incomplete clearance of immune stimulant?
  - Residual virus in GI tract?
  - NIH Recover study
- Type 4: what triggers the delayed symptoms??
  - Persistence of virus with eventual escape from adaptive immunity??
- Type 5:
  - Arrhythmia?
  - Unmasking of subclinical or accelerating underlying co-morbidity?

- Current treatment at U/Cincinnati Post-Covid clinic
  - Cardiac rehab
  - Pulmonary rehab
  - Physical therapy
  - Multi-disciplinary subspecialty supportive care

Post-covid syndrome:
complex, puzzling

- Causes?
  - Structural (tissue injury)? Function? Both?
  - Cytokine dysregulation?:
    - Persistent (persistent viruses)? Delayed reactivation (loss of adaptive immunity)?
    - Preventable? Treatable?

- Relationship to severity of illness?? Note:
  - Acute (pulmonary) staging criteria: Hypoxemia
  - Delayed multisystem inflammatory syndrome (MIS): hsCRP, ferritin, D-dimer, cardiac enzymes, BNP, liver enzymes, creatinine

- Treatable??? Therapeutic intervention with cyclodextrin/GSH?
  - Early treatment: prevention of CSS with viral eradication?
  - Convalescent regulation of persistent/reactivated cytokine response? Both??
  - Fatigue: Mitochondrial GSH depletion [(2)]??

H Maltezou, *Vaccines*, 2021
[(2)] K Filler, Science Direct, 2014

Duration of SARS-CoV-2 viral RNA shedding:
a meta-analysis

Location	Mean duration (days)	Maximum duration (days)
Upper respiratory tract	17.0	83
Lower respiratory tract	14.6	59
Stool	17.2	126
Serum	16.6	60

M Cevik, *Lancet.com/microbe*, 2021

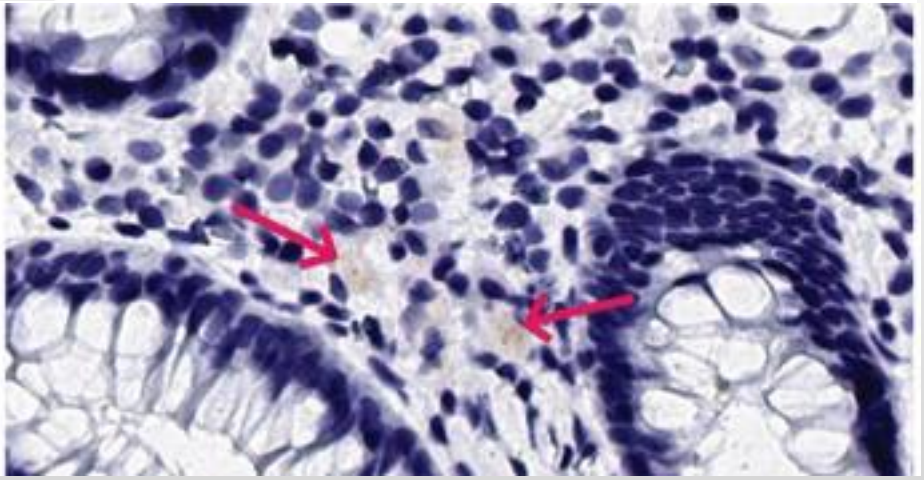
Persistent COVID-19 virions

CASE REPORT

OPEN

Persistent SARS-CoV-2 Nucleocapsid Protein Presence in the Intestinal Epithelium of a Pediatric Patient 3 Months After Acute Infection

Dalia Arostegui, MD, Kenny Castro, MD, Steven Schwarz, MD, Katherine Vaidy, MD, Simon Rabinowitz, MD, and Thomas Wallach, MD



J of Pediatric Gastroenterology and Nutrition, 2022

Future GSH + cyclodextrin treatment studies vs COVID-19: confirm its efficacy

- Avoid hospitalization:
  - Add to vaccine, antiviral, monoclonal antibody
  - "What works, what's available, what's acceptable"
- Treatment of hospitalized individuals
  - On admission: Decrease hospital stay
    - Prevent progression to mechanical ventilation
    - Add to monoclonal antibody, antiviral
  - ICU transfer: Decrease mortality
    - Early, alternative treatment to dexamethasone?
    - Administer with Spi-Dex?
- Prevent and/or treat post-COVID symptoms
  - Early intervention → prevent or shorten duration?
  - Convalescent treatment? Both??
  - Fatigue resolution (mitochondrial function?)

Studies with GSH + cyclodextrin:
Beyond COVID

- Viral illnesses: inhibition of viremia (cyclodextrin), oxidative stress (GSH)
  - Hemorrhagic: Hanta, Ebola, Dengue (I Messaoudi) (J Choi) (I Ripa)
  - Respiratory: RSV, influenza (Y Hosakote) (Y Gu)
  - Encephalitis: West Nile, Eastern equine (T Valyl-Nagy) (J Echevarria) (I Ripa)
  - Myocarditis: Coxsackie (C Tschope) (I Ripa), post-vaccine MIS-C?
  - Cutaneous: Herpes (vet), zoster, HPV: (DNA viruses) (I Ripa) (S Hambleton)
- Kawasaki syndrome, MIS-C/A (S Paglialunga) (C Sharma)
- Autism: oxidative stress and low GSH (G Bjorklund)
- Chronic-fatigue syndrome/myalgic encephalomyelitis (A Komaroff) (B Paul) (K Filler)
- Multiple sclerosis – (EBV) (K Bjornevik)
- Sickle-cell disease (R Queiroz) (O Ifeanyi) (O Ilesanmi)
- Non-alcoholic steato-hepatitis (NASH) (M Masarone)
- Acetaminophen toxicity (NAC vs GSH)
- Oncology
  - Graft-vs-host (GVH) disease (S Kumar)
  - Anthracycline myocarditis (M Volkova)

2022 treatment strategy vs COVID-19

- Prevent hospitalization (Primary care)
  - Vaccines, Paxlovid®, glutathione/cyclodextrin
- Early discharge/avoid ICU (Hospitalist)
  - Monoclonal antibodies, Spi-Dex, glutathione/cyclodextrin
- Save lives (Hospitalist/intensivist)
  - Spi-Dex, glutathione/cyclodextrin
- Prevent/treat post-COVID syndrome (Primary care)
  - Vaccines, Paxlovid®, glutathione/cyclodextrin
- End the pandemic (Everyone)
  - All of the above – thorough screening, contact-tracing + early treatment

- Restore normalcy: (-) masks, (+) hugs

Questions?

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