Chronic and Acute COVID-19: The Biologic Underpinnings and the Functional Medicine Approach

• Joel M. Evans, MD
• Chief of Medical Affairs, Institute for Functional Medicine, Federal Way, WA
• Co-Director, Institute for Functional Medicine Course on COVID-19
• Director, The Center for Functional Medicine, Stamford, CT
What is Functional Medicine?
Functional Medicine utilizes an individualized, patient-centered, science-based approach that identifies the underlying causes of disease and promotes optimal wellness.
The Functional Medicine Model

...utilizes a detailed understanding of each patient’s genetic, biochemical, and lifestyle factors and leverages that data to direct personalized treatment plans that lead to improved patient outcomes.

The Functional Medicine Model

...utilizes a detailed understanding of each patient’s genetic, biochemical, and lifestyle factors and leverages that data to direct personalized treatment plans that lead to improved patient outcomes.

Why is Understanding genetics important?

• It will allow testing to identify at risk individuals.
• It allows us to understand underlying mechanisms of disease in order to design:
  — Medications
  — Lifestyle interventions (all are important)
    • For you, this IHS audience: EFA’s, Glycocalyx, NO, NAC, Curcumin, Vit D
Genes, COVID-19 and phenotype

The genetic landscape seems to play a pivotal role in COVID-19 dynamics.

We need to embrace and evaluate patients’ genome analyses to provide severe disease high-risk identification and personalize COVID-19 treatment.
The quest to find genes that drive severe COVID
There are genes strongly associated with developing COVID-19 and becoming gravely ill.

People with a SNP on chromosome 3 are 2x as likely to be hospitalized with COVID-19.

These tests aren’t yet reliable, but they could be motivation for higher-risk people to get vaccinated.

Integrated network analysis reveals new genes suggesting COVID-19 chronic effects and treatment

We identified a new set of genes associated with SARS-CoV-2 host response.

Functional analysis reveals possible long-term systemic effects of the infection, such as vascular remodeling and fibrosis.

Finally, we identified potentially relevant drugs to improve the host response to the virus.
**Figure 3** Pathway enrichment for each biological system (in vitro and in vivo), ...
The Latest in Genomics: Structural Variations

• Genomic approaches have been used to identify disease susceptibility and severity in COVID-19.

• GWAS: to understand risk factors at the population level. This provides insights into the pathophysiology.

• Genome sequencing: to identify rare variants in known genes whose biological functions suggest plausible models by which they may function as severe risk factors.

• Structural Variations are defined as genetic variants involving larger regions of an individual genome.

• As these remain difficult to detect, SVs have not yet been investigated with respect to their relationship with COVID-19.

More than 34% of all known disease-causing variations are larger than a single base pair change, i.e., single nucleotide variation (SNVs or SNPs).

Several studies have demonstrated the importance of large SVs in the characterization of human immunity profiles.

Optical genome mapping identifies rare structural variations as predisposition factors associated with severe COVID-19

• The latest (February 2022)
• Genome mapping on 52 severely ill COVID-19 patients.
• 7 SVs involving genes implicated key host-viral interaction pathways: innate immunity, Type I Interferon, the inflammatory response, as well as viral replication and spread in 9/52 patients (17%).

Why is Understanding genetics important?

• It will allow testing to identify at risk individuals.
• It allows us to understand underlying mechanisms of disease in order to design:
  – Medications
  – Lifestyle interventions (all are important)
    • For you, this IHS audience: EFA’s, Glycocalyx, NO, NAC, Curcumin, Vit D
  – Vaccines
A multi-valent vaccine in development is based on genetics

• Long-term immunity to coronaviruses likely stems from T cell activity.
• This study selected SARS-CoV-2-derived T cell epitopes in HLA-genotyped individuals with different ethnicities.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8261158/
A multi-valent vaccine in development is based on genetics

- Nine peptides derived from the four major structural proteins of SARS-CoV-2 were included in a peptide vaccine candidate to mimic the T cell responses observed in natural COVID-19 infection.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8261158/
A multi-valent vaccine in development is based on genetics

• Computational extrapolation suggests that PolyPEPI-SCoV-2 vaccination will likely elicit multi-antigenic T cell responses in 98% of individuals, independent of ethnicity.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8261158/
The Functional Medicine Model

...utilizes a detailed understanding of each patient’s genetic, biochemical, and lifestyle factors and leverages that data to direct personalized treatment plans that lead to improved patient outcomes.
Biochemistry

• The role of co-morbidities (from CDC) and Biochemistry
  – Cancer
  – Chronic kidney disease
  – COPD (chronic obstructive pulmonary disease)
  – Immunocompromised state from solid organ transplant
  – Obesity (BMI >30)
  – Serious heart conditions (heart failure, coronary artery disease, cardiomyopathies)
  – Sickle cell disease
  – Type 2 diabetes mellitus

Long Covid has Similar Biochemistry

Risk factors for long COVID: analyses of 10 longitudinal studies and electronic health records in the UK

Poor pre-pandemic mental health (1.46x)
Poor general health (1.62x)
Asthma (1.32x)
Overweight or obesity (1.25x)

All Associated with higher risk of long COVID.

https://www.medrxiv.org/content/10.1101/2021.06.24.21259277v2.full-text Preprint July 10, 2021
Biochemistry

• The following biochemical imbalances, seen in these chronic diseases, must inform our clinical decisions for prevention and treatment for both acute and chronic Covid-19.
  – Mitochondrial function and oxidative stress
  – Hyperglycemia
  – Inflammation
  – Immune system function
The Functional Medicine Model

...utilizes a detailed understanding of each patient’s genetic, biochemical, and lifestyle factors and leverages that data to direct personalized treatment plans that lead to improved patient outcomes.
Lifestyle Factors That Matter for both Acute and Chronic Covid-19.

- Non-restorative sleep
- Sedentarism
- Obesity
- Gut Health
- SDH

- Nutrition
- Stress
- Loneliness and isolation
- Smoking
- Implicit Bias
Lifestyle Factors That Matter for both Acute and Chronic Covid-19 are also associated with:

- Mitochondrial function and oxidative stress
- Hyperglycemia
- Inflammation
- Immune system function
Therefore, genetics, overall health, biochemical imbalances and lifestyle are all interrelated when it comes to Acute and Chronic Covid.
The Functional Medicine Model

...utilizes a detailed understanding of each patient’s genetic, biochemical, and lifestyle factors and leverages that data to direct personalized treatment plans that lead to improved patient outcomes.
Pre-emptive improvement of biochemical imbalances (inflammation, oxidative stress, mitochondrial function, immune function) and lifestyle factors have plausible utility in favorably modulating the resistance to infection, and the clinical course of Acute and Chronic COVID-19.
Acute COVID-19:

What we know now: Prevention
Make people healthier

Modifiable Risk Factors for SARS-CoV-2
Michelle Simon, PhD, ND; Joseph Pizzorno, ND, Editor in Chief; Joseph Katzinger, ND
Integrative Medicine • Vol. 20, No. 5 • October 2021
## Table. Potential Risk Reduction from Modifiable Factors

<table>
<thead>
<tr>
<th>Modifiable Factor</th>
<th>Infection</th>
<th></th>
<th>Severe Disease</th>
<th></th>
<th>Death</th>
<th></th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>% Protection</td>
<td>OR</td>
<td>% Protection</td>
<td>OR</td>
<td>% Protection</td>
<td>Reference</td>
</tr>
<tr>
<td>None of the 4 major US cardiometabolic risk factors (total obesity [body mass index ≥ 30 kg/m²], diabetes mellitus, hypertension, and heart failure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>O’Hearn et al (2021)</td>
</tr>
<tr>
<td>Normal weight (OR for obesity)</td>
<td>2.73a</td>
<td>63%</td>
<td>3.81</td>
<td>74%</td>
<td>1.61</td>
<td>38%</td>
<td>Cai et al (2021)</td>
</tr>
<tr>
<td>Normal blood sugar (OR for diabetes or elevated FBG levels)</td>
<td>1.55</td>
<td>35%</td>
<td>3.21</td>
<td>69%</td>
<td></td>
<td></td>
<td>Shauly-Aharonov et al (2021); Gregory et al (2021)</td>
</tr>
<tr>
<td>Healthy Vitamin D (OR for low levels)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>De Smet et al (2021)</td>
</tr>
<tr>
<td>Healthy ω-3 fatty acid levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Zapata et al (2021)</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kim et al (2021)</td>
</tr>
<tr>
<td>Pescatarian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kim et al (2021)</td>
</tr>
<tr>
<td><strong>NOT</strong> high protein (a high protein diet was associated with elevated risk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kim et al (2021)</td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
<td>0.27</td>
<td>73%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pal et al (2021)</td>
</tr>
<tr>
<td>Quercetin supplementation (not blinded or controlled)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Di Pierro et al (2021)</td>
</tr>
</tbody>
</table>

*aThe odds ratio shown is comparing obesity with non-obesity

b(1 – 1/OR) × 100
Risk Reduction - Summary

<table>
<thead>
<tr>
<th>Health Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of DM, HTN, Obesity, CHF¹</td>
</tr>
<tr>
<td>Normal body weight²</td>
</tr>
<tr>
<td>Normal blood sugar³</td>
</tr>
<tr>
<td>Vitamin C⁴</td>
</tr>
<tr>
<td>Vitamin D⁵</td>
</tr>
<tr>
<td>Omega-3 fatty acids⁶</td>
</tr>
<tr>
<td>Curcumin⁷</td>
</tr>
<tr>
<td>Quercetin⁸</td>
</tr>
<tr>
<td>Diet⁹</td>
</tr>
</tbody>
</table>

See References: Risk Reduction with Health Factors


Acute COVID-19:
What we know now: Treatment
Vitamin D
• Hypothesis (May 2020):
• Perspective: improving vitamin D status in the management of COVID-19
  – Lung inflammation and fibrosis occur due to the release of pro-inflammatory cytokines, interleukin (IL)-1B and IL-18 by activated macrophages and type 1 T helper (Th1) immune cells
  – Vitamin D has immunomodulatory, anti-inflammatory, antifibrotic and antioxidant actions. Expression of inflammatory cytokine [e.g., IL-1α, IL-1β, tumor necrosis factor-α] was inhibited by vitamin D and insufficiency was associated with overexpression of Th1 cytokines

» https://www.nature.com/articles/s41430-020-0661-0?fbclid=IwAR3yo41dvfU1HWVX_Y6z7iXFN3X2C06A5glfC4LcNmXzCA48A7ViMAf7N8
• Study (May 2021)
• **Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease**
  – VD group received Pulse D therapy (targeted daily supplementation of 60,000 IUs of vitamin D for 8 or 10 days
  – Vitamin D level has increased from $16 \pm 6$ ng/ml to $89 \pm 32$ ng/ml after Pulse D therapy in VD group
  – Therapeutic improvement in vitamin D to 80–100 ng/ml has significantly reduced the inflammatory markers associated with COVID-19 without any side effects.

» https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8138022/
The Latest on Vit D

• Pre-infection 25-hydroxyvitamin D3 levels and association with severity of COVID-19 illness

• In hospitalized patients, those with vitamin D <20 ng/mL were 14 times more likely to have severe or critical disease than patients with levels ≥40 ng/mL

– PLOS ONE February 3, 2022
– https://doi.org/10.1371/journal.pone.0263069
Quercetin
### Quercetin and Resistance to COVID-19

<table>
<thead>
<tr>
<th>Quercetin</th>
<th>Infect</th>
<th>Severe</th>
<th>LongC</th>
<th>Death</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 mg liposomal</td>
<td>0.32</td>
<td></td>
<td>0 vs 3</td>
<td></td>
<td>Not blinded or formal control, Prospective</td>
</tr>
</tbody>
</table>

Study Design

30 day, prospective study
152 COVID-19 outpatients
Half standard of care only
Half standard of care plus quercetin
500 mg bid liposomal quercetin
400 mg total quercetin/day
Open label
This is a Preliminary Study

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
</table>
| Dr. Di Pierro respected scientist  
- Expert in natural products research  
- >50 articles in PubMed  
- 2020 AIC speaker | Not published in major journal  
- Di Pierro member of Scientific Board of Pharmextracta  
- Open label  
- The control group had more co-morbidities  
  - Sub analysis still showed major benefit |

## Outcomes: All Patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>Intervention</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td>28.9%</td>
<td>9.2%</td>
<td>0.002</td>
</tr>
<tr>
<td>Days of hospitalization</td>
<td>6.77</td>
<td>1.57</td>
<td>0.001</td>
</tr>
<tr>
<td>Needed O₂</td>
<td>19.7%</td>
<td>1.3%</td>
<td>0.01</td>
</tr>
<tr>
<td>Admitted to ICU</td>
<td>10.5%</td>
<td>0.0%</td>
<td>0.02</td>
</tr>
<tr>
<td>Deaths</td>
<td>3.0%</td>
<td>0.0%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

No reported serious adverse events
Outcomes: Only Those with No Co-Morbidities

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>Intervention</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td>22.4%</td>
<td>8.5%</td>
<td>0.08</td>
</tr>
<tr>
<td>Days of hospitalization</td>
<td>5.14</td>
<td>1.25</td>
<td>0.01</td>
</tr>
<tr>
<td>Needed O₂</td>
<td>12.9%</td>
<td>0</td>
<td>0.005</td>
</tr>
<tr>
<td>Admitted to ICU</td>
<td>6.5%</td>
<td>0</td>
<td>0.05</td>
</tr>
<tr>
<td>Deaths</td>
<td>6.5%</td>
<td>0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Di Pierro, et al. Possible Therapeutic Effects of Adjuvant Quercetin Supplementation Against Early-Stage COVID-19 Infection: A Prospective, Randomized, Controlled, and Open-Label Study Int J Gen Med 2021:14 2359–2366
Clinical Takeaways

Preliminary study

Quercetin shown to be safe in many studies

Liposomal quercetin is a logical adjunct to standard of care

Recommendations:

1. All patients should be advised to consume foods rich in flavonoids
2. All patients at risk should be prescribed 500 mg/d of liposomal quercetin
Pre-exposure: What to address

- **Reduce Viral Exposure Load**
  - Mask
  - Wash Hands
  - Distancing
  - Eye protection? “Essential workers protocol”
  - Per CDC guidelines

- **Comorbidities**
  - Obesity

- **Lifestyle Factors**
  - Sleep
  - Exercise
  - Nutrition
  - Stress
  - Relationships

- **Gut Health**
  - Individualize
  - Comorbidities

- **Inflammation**
  - Oxidative stress
  - Mitochondropathy
  - Hyperglycemia
  - Furin*

- **Immune System**
  - EGCG*
  - Curcumin
  - Astragalus
  - Quercetin
  - Resveratrol
  - NAC* / GSH
  - Berberine*
  - Andrographis*
  - Melatonin

- **Environmental Factors**
  - *Elevated Furin:
    - Hypertension
    - Diabetes
    - CVD
    - Hyperinsulinemia
    - Hypertriglyceridemia
    - Obesity
    - Autoimmunity
    - Dementia
Pre-exposure: What to address

Reduce Viral Exposure Load
- Mask
- Wash Hands
- Distancing
- Eye protection? “Essential workers protocol”
- Per CDC guidelines

Comorbidities Obesity
- Lifestyle Factors
  - Sleep
  - Exercise
  - Nutrition
  - Stress
  - Relationships

Immune System
- Inflammation
  - Oxidative stress
  - Mitochondropathy
  - Hyperglycemia
  - Furin*

- Lifestyle Factors
- Gut Health
- Consider low dose:
  - EGCG*
  - Curcumin
  - Astragalus
  - Quercetin
  - Resveratrol
  - NAC*/GSH
  - Berberine*
  - Andrographis*

- Mucosal
  - Consider low dose:
    - Vit A,C,D,E,B6,B12
    - Folate, Fe, Zn, Cu, Se
  - Consider:
    - LD heparin nasal spr.

- Innate
  - Consider low dose:
    - Vit A,C,D, NAC, EGCG
    - Astragalus, Quercetin, Resveratrol,
    - Mushrooms, B glucans, Elderberry, Echinacea

Individualize Comorbidities
**Pre-exposure: What to address**

**Reduce Viral Exposure Load**
- Mask
- Wash Hands
- Distancing
- Eye protection?
  - “Essential workers protocol”

**Comorbidities Obesity**
- Lifestyle Factors
  - Sleep
  - Exercise
  - Nutrition
  - Stress
  - Relationships

**Inflammation**
- Oxidative stress
- Mitochondropathy
- Hyperglycemia
- Furin*

**Immune System Resistance Resilience**
- Mucosal
  - Consider low dose:
    - Vit A,C,D,E,B6,B12
    - Folate, Fe, Zn, Cu, Se
  - Consider:
    - Strep. salivarius
    - LD heparin nasal spr.

**Environment**
- Consider adding:
  - Melatonin
  - Elderberry
  - Leeks & lectins
  - Nettles (tea/sup)

**Lifestyle Factors**
- See Unit 11
- See “Intro to FM”

**Gut Health**
- EGCG*
- Curcumin
- Astragalus
- Quercetin
- Resveratrol
- NAC* / GSH
- Berberine*
- Andrographis*
- Melatonin

**If not already taking, strongly consider these:**
- Vit A,C,D, NAC, EGCG
- Astragalus, Quercetin, Resveratrol, *Mushrooms, B glucans, Elderberry, Echinacea*
Post-exposure: Not symptomatic

If not already taking, consider adding:

- Melatonin
- Elderberry
- Resveratrol
- Curcumin
- Quercetin
- EGCG
- Leeks
- Nettles

If already taking, increase to high dose range
Post-exposure:

Discontinue Echinacea

If not already taking, add;
If already taking, increase to high dose range:

Resveratrol
Curcumin

Quercetin
EGCG

Leeks – Nettles

Add melatonin: If already taking, increase to 10 – 20 mg qhs
### Dosing Recommendations

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zinc</strong> (acetate, citrate, picolinate, or glycinate orally, Zinc gluconate as lozenge)</td>
<td>30-60 mg daily, in divided doses</td>
</tr>
<tr>
<td><strong>Elderberry</strong> (17% anthocyanosides)</td>
<td>500 mg po qd (up to 12 weeks)</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td>5,000 IU po qd</td>
</tr>
<tr>
<td><strong>Vitamin A</strong></td>
<td>Up to 10,000-25,000 IU/d</td>
</tr>
<tr>
<td><strong>Vitamin C</strong></td>
<td>1-3 grams po qd</td>
</tr>
<tr>
<td><strong>N-acetylcysteine</strong></td>
<td>1-3 grams po qd</td>
</tr>
<tr>
<td><strong>Quercetin</strong></td>
<td>Regular: 1 gm po bid; phytosome: 500 mg, bid (up to 12 weeks)</td>
</tr>
<tr>
<td><strong>Epigallocatechin gallate (EGCG)</strong></td>
<td>4 cups green tea daily or 225 mg po qd</td>
</tr>
<tr>
<td><strong>Curcumin</strong></td>
<td>500-1,000 mg po bid (of absorption-enhanced curcumin)</td>
</tr>
<tr>
<td><strong>Melatonin</strong></td>
<td>5-20 mg qd</td>
</tr>
<tr>
<td><strong>Resveratrol</strong></td>
<td>100-150 mg po qd</td>
</tr>
</tbody>
</table>
Key Clinical Takeaways for Mitigating SARS-CoV-2 Infection

This free resource details the specific interventions that you can put into practice right now at this stage of the pandemic to mitigate COVID-19 risk for all your patients.

Available now at https://ifm.org/covid
Long Covid
Chronic Covid
Post Acute Sequelae of SARS-C0V-2
PASC
PASC: The Basics

- The NIH published “Trying to Make Sense of Long Covid Syndrome” on **January 19, 2021**¹ (11 months after recognizing acute COVID-19)

- Definition: collection of symptoms during or following a **confirmed or suspected** case of COVID-19 and which continue for **more than 28 days**²

---


PASC: The Basics

- 3700 international patients, mostly white females between 30 and 60 living in U.S.
- >50% never SOUGHT hospital care, only 8% admitted
- Approximately 60% had symptoms > 6 months


PASC: The Basics

• Most common symptoms: fatigue, post-exertional malaise, cognitive dysfunction.

• Triggers were exercise, mental activity or stress (remember this for therapeutics…go gently)


PASC: The Basics

• A study in Lancet in January 2021 showed that 6 months after symptom onset, more than 75% of hospitalized patients in Wuhan reported at least one symptom.

• Fatigue, muscle weakness, sleep difficulties, anxiety, and depression were common.

PASC: The Basics

• >50% had significant persistent lung abnormalities, more common in those who’d been more severely ill.¹

• Pre-print study from the UK:
  – 70% of hospitalized did not feel fully recovered at 6 months²

---

Symptoms and Functional Impairment Assessed 8 Months After Mild COVID-19 Among Health Care Workers

- Approximately 80% of all hospitalized patients with COVID-19 report persistent symptoms after several months.
- 26% reported at least 1 moderate to severe symptom lasting for at least 2 months.
- 15% at least 1 moderate to severe symptom lasting for at least 8 months.
- The most common moderate to severe symptoms lasting for at least 2 months were anosmia, fatigue, loss of taste on the tongue, and dyspnea.

Should we be surprised?

“It is more typical than not that a virus infection leads to long-lasting symptoms in some fraction of individuals”

Akiko Iwasaki, PhD
Professor of Immunology
Yale School of Medicine

https://www.vox.com/22369734/long-hauler-covid-vaccine
Immune Health is critical

• National Institute for Health Research in U.K.
• 207 people + test compared with 45 healthy people
• Those with no symptoms or a mild case
  – Mounted a robust immune response
  – Produced T cells, B cells and antibodies in larger numbers
  – Rapidly returned to normal.
• There was no evidence in these patients of widespread inflammation that can lead to damage in multiple organs.

• National Institute for Health Research in U.K.
• 207 people + test compared with 45 healthy people
• Those hospitalised had an impaired (delayed) immune response, which led to:
  – Weakened attempt to fight the virus
  – Widespread inflammation from the time of symptom onset.
  – This suggests those who develop severe disease have an abnormal inflammatory immune response even at the time of diagnosis
  – This is exactly what we see in those with chronic disease, biochemical imbalances or sub-optimal lifestyle factors (JME)
The Immune Signature

• Evidence of inflammation (in severe cases) suggests immunopathology may be inevitable in some individuals, or that preventative intervention might be needed before symptom onset.

Severe COVID19 Infection: Common Immunologic Findings

- Impaired interferon signature (Type I & III)
- Neutrophilia – active deployment in large numbers
- Aberrant activation of monocytes/macrophages
- **T cell depletion** (esp CD4+ and CD8+)
- **Depletion of NKT cells**
- **T cell exhaustion** (positive for markers PD-1, Tim-3)
- **Elevated pro-inflammatory cytokines** and other mediators (bradykinin)

PASC: The Immune Signature

• Immune recovery is complex, with signatures characteristic of increased oxidative phosphorylation and reactive-oxygen species-associated inflammation.

• "These late immunometabolic inflammatory changes and unresolved immune cell defects, if persistent, may contribute to "long COVID".

• This supports the FM approach just described to PREVENT long COVID (JME)

PASC: The Immune Signature

• Defective immune recovery might drive ongoing disease and contribute to long-term disease sequelae (“long COVID”).
• This supports the FM approach just described (JME)

PASC: The Circulation

• The persistent alterations of erythrocytes and neutrophils could be connected with long-term symptoms

• 70% described chronic headache or neurological symptoms, 54% had concentration disorders, and 62% circulatory problems such as cold sweat and tachycardia.

• We hypothesize that the persisting changes of blood cell physical phenotypes could contribute to the long-term impairment of circulation and oxygen delivery linked with COVID-19.
Reason for Concern:

• COVID Symptoms, Symptom Clusters, and Predictors for Becoming a Long-Hauler: Looking for Clarity in the Haze of the Pandemic
  
  — Previous variants are associated with long-hauler syndrome in up to about one third of infections, regardless of the degree of severity of illness.
  
  — ‘Long-haulers represent a very significant public health concern, and there are no guidelines to address their diagnosis and management’.

https://doi.org/10.1101/2021.03.03.21252086
Reason for Concern:

• Even asymptomatic infections are associated with long-haulers symptoms in up to 19% of infections with prior variants.
  – A Detailed Study of Patients with Long-Haul COVID
  – An Analysis of Private Healthcare Claims (1.9 million)
    • FAIR Health, a national, independent nonprofit organization dedicated to bringing transparency to healthcare costs and health insurance information
Reason for Optimism: Vaccines

• Previous variants have shown protection against long-hauler syndrome if vaccinated, by about 50%
  • https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00460-6/fulltext
• By 7 - 10 fold in another study.
  • https://www.medrxiv.org/content/10.1101/2021.11.17.21263608v1
• A third study failed to show any protective impact from prior vaccination.
  • https://www.medrxiv.org/content/10.1101/2021.10.26.21265508v1
Reason for Optimism: Vaccines

• A small study confirms the common report that patients who experience long Covid symptoms may experience improvement with subsequent vaccination.
  • https://doi.org/10.1101/2021.03.11.21253225
  – Is this due to persistent infection, persistent viral particles or other effects of immune system stimulation?
• Therefore, the FM approach to PASC involves:
  – Reducing (resolving) Inflammation
  – Optimizing mitochondrial efficiency
  – Reducing ROS
  – Normalizing Immune Signatures
  – Improving cell membrane and microvascular health
  – Ensuring Gut Health
    • Directly related to immune health and treats immune signature issues, local and systemic inflammation.
    • Improves absorption of nutrients
    • Many long haulers have GI Sx
• Address each patient’s unique vulnerabilities:
  – Co-Morbidities
  – Immune Health
  – Biochemical Imbalances
  – Lifestyle Factors
• Consider dietary, lifestyle, pharmaceutical, nutraceutical and botanical interventions where appropriate.
• Do all of this in a way that is culturally appropriate and free of implicit bias.
Conclusions

• Literature documenting the impact of lifestyle, inflammation, poor nutrition, oxidative stress, mitochondrial function, gut dysfunction, nutrient insufficiency and immune health and acute and chronic COVID 19 is clear.

—See IFM materials on COVID-19.

www.ifm.org/covid
Highlights of The IFM Supplement Protocol:

• Vit D titrate to normal levels
• NAC: 600-900 mg/d
• Curcumin: 500-1000 mg bid
• Fish Oil: 1000 mg of EPA/DHA
• Melatonin: 5-20 mg qhs (titrate to sleep)
• Antioxidant Support
• Gut Support with gut healing nutrients, prebiotics, probiotics
• Mushrooms
• B Vitamins
• Multi Vitamin
Addressing Mitochondrial Function

• Reduce ROS by reducing formation by improving health, reducing stress and increasing elimination with antioxidants.
• Modulate nitric oxide levels with arginine, citrulline, beets, pomegranate, dark leafy greens
• Address metabolomics like blood sugar
• Specific nutrients like glutathione, fish oil, ALA, carnitine
We don’t yet know about Omicron and PASC but there is reason to believe it will be less frequent and less severe
The Latest IFM Update
Title
COVID-19 Ongoing Updates: Latest information on Omicron, testing, infectiousness, and more.

Description
The Institute for Functional Medicine (IFM) is proud to present this COVID update, providing the functional medicine community with the latest research and clinical experience regarding COVID-19. In this video recording, IFM Chief of Medical Affairs Dr. Joel Evans and IFM COVID-19 task force member Dr. Gary Goldman will provide an update on the latest information on SARS-CoV-2 and COVID-19. Today’s topics include the Omicron subvariant, the evolving infectiousness timeline, and the latest information on testing and vaccination.

To access, go to ifm.org/COVID and click on the link that says “watch latest webinar,” which is just underneath the heading: Free COVID-19 Webinar Series.
IFM.ORG/COVID
http://ifm.org/IHS
The FM Approach isn’t just about supplements or the bottom of the matrix...
Physiology and Function: Organizing the Patient’s Clinical Imbalances

- Assimilation (e.g., Digestion, Absorption, Microbiota/GI, Respiration)
- Defense & Repair (e.g., Immune, Inflammation, Infection/Microbiota)
- Energy (e.g., Energy Regulation, Mitochondrial Function)
- Structural Integrity (e.g., from Subcellular Membranes to Musculoskeletal Structure)
- Communication (e.g., Endocrine, Neurotransmitters, Immune messengers)
- Social (e.g., Meaning & Purpose, Relationships)
- Spiritual (e.g., Emotional Regulation, Grief, Sadness, Anger, etc.)
- Mental (e.g., Cognitive Function, Perceptual Patterns)
- Emotional (e.g., Emotional Regulation, Grief, Sadness, Anger, etc.)
- Biotransformation & Elimination (e.g., Toxicity, Detoxification)
- Transport (e.g., Cardiovascular, Lymphatic System)

Modifiable Personal Lifestyle Factors
- Sleep & Relaxation
- Exercise & Movement
- Nutrition
- Stress
- Relationships

Retelling the Patient’s Story
- Antecedents (Predisposing Factors—Genetic/Environmental)
- Triggering Events (Activators)
- Mediators/Perpetuators (Contributors)

© Copyright 2011 Institute for Functional Medicine
Illness and Spiritual Beliefs

Clinician as Healer
Disclaimer:

This is **One** Way
This happens to be **MY** Way
This is **NOT** the only way
There are **Many** other ways
There are **Many** paths to the same destination
All faiths and many belief systems describe a “non-physical” part of our selves...
If you are an atheist or agnostic:

Pascal’s Wager

Blaise Pascal, 17th Century French Mathematician and Philosopher
All faiths give us guidelines on how to behave while the non-physical soul inhabits a physical body.
• **Christianity**
  – Doctrine of Justification by Faith
  – 10 Commandments

• **Judaism**
  – 613 Commandments

• **Islam**
  – Sunna (Rules of Life)

• **Hinduism**
  – Dharma

• **Buddhism**
  – Dhamma
It is my belief that addressing and acknowledging this concept helps us

physically

and emotionally

Especially during this pandemic!
So Who Are We?

A non-denominational answer
Who we really are...

A combination of Soul and Personality

Soul:
Aspect of infinite consciousness, the spiritual self, the eternal part of you. It is complete and whole.
Who we really are...

A combination of Soul and Personality

Personality:
The role that your spiritual self assumes your life. This includes your temperament, gifts, and shortcomings.
We can also look at this as:
The Soul is the higher self

Personality is the lower self
This is consistent with major religions:

- **Christianity:**
  - Higher self
  - Lower self described as “temptations of the world”

- **Judaism**
  - Higher Self is “Yetzer Ha Tov”
  - Lower Self is “Yetzer Ha Rah”

- **Islam**
  - 5 selves, including a Lower Self (an-nafs al-ammarah) and a perfected “Higher” self (an-nafs al-kamilah)

- **Hinduism and Buddhism**
  - Higher and Lower Self
It is the **personality** that makes us suffer through wishing that things would be different then they are.
Spiritual Path

We must fully accept our current situation (responsibilities and experiences) as a starting point, and not overly ruminate over them.

• We then accept our duties (job, family responsibilities) before we progress further. We must master the chores and unpleasantness of our life (cooking, cleaning, work, etc.) without drama.

• “When doing the dishes, do the dishes.”
Right Thought, Right Mind, Right Action

What we think determines what we feel.

What we feel determines how we act.

How we act determines whether we grow our higher or lower self, thus determining our progress on the spiritual path.
“The bio-psycho-social (BPS) model of healthcare (must) be reaffirmed and an “S” be added for spiritual, recognizing that our patients have needs in all four of these domains.

Biomedical Reductionism Falls Short
An editorial by George Lundberg, M.D. (former editor of JAMA)
Medpage Today, March 22, 2011
Lies, cruelty and hate are emotions that hurt us spiritually and physically.

– Spiritually by preventing or slowing our spiritual growth (higher self).
– Physically by putting us into the stress response (sympathetic dominant state).
• **Stress** is an epigenetic modification.

• **Meditation and prayer** are epigenetic modifications.

• **Right thought, right mind, right action** are epigenetic modifications.
What we think and feel determines what molecules are released into our bodies.

The molecules in our bodies determine what we think and feel.
So it is a complicated web:

What we think and feel:
– Accelerates or impedes the rate of our spiritual growth.
– Determines the predominant state of our nervous system (sympathetic or parasympathetic).
– Determines the molecules traveling throughout our body.
– Is determined by our spiritual belief system.
A world view that helps us cope with the pandemic, societal division and disparities and severe weather.

Does NOT mean abandoning the task of trying to be a better citizen, working on your health and “accepting” whatever happens.

It means claiming one’s role as the steward of one’s thoughts, feelings, actions and health.
• Our spiritual belief systems influence and shape our responses to the stresses of life.

• Our spiritual belief systems influence our emotional state.

• Our spiritual belief systems influence our nervous system.

• Our spiritual belief systems help determine the molecules traveling throughout our body.
This is bi-directional:

• **The mind affects the body.**
  – Stress, anger, jealousy, etc. have harmful effects on the body (pro-inflammatory).
  – Peace, love, and contentment have beneficial effects on the body.
  – Helping to change the way we think improves our health.

• **The body affects the mind**
  – Chronic pain can lead to **depression and anxiety**.
  – Physical exercise can lead to **endorphin release**.
  – Lifestyle change improves **mood**.
Therefore, spirituality gives a perspective that improves the mind and the body in these stressful times.
If I Dared to Dream....

How I see the future of Integrated Medicine after the Pandemic
Create more “Integrated” practitioners:

– Integrative Medicine CANNOT be optimally practiced by a practitioner that is not integrated.
– Multiple Modality Medicine (MMM) CAN EASILY be practiced by a practitioner that is not integrated.
  • Green Pharmacy, referrals to other modalities
An “Integrated" practitioner focuses on:

• Physical Health
• Emotional Balance
• Mental Clarity
• Spiritual Growth
• Physical Health
  – *We* must do all *we* can do to achieve optimal health.
  • Lifestyle Change
  • Multiple Modality Medicine
  – Share what we learned with our patients in order to help
• Emotional Balance
  — We must do all we can do to balance ourselves emotionally.
  • Resolve our conflicts.
  • Bring our lives into balance.
  — Advise our patients to do the same and share how we did it.
• Mental Clarity
  – **We** must do all **we** can do to achieve mental clarity.
    • Keep focused and avoid drama.
    • Meditate in any way that works.
  – Advise our patients to do the same and share how we did it
Spiritual Growth

- **We** must do all **we** can to achieve spiritual growth...find a world view that resonates.

- It will inform and infuse everything we do.

- Advise our patients to do the same and share how we did it.
The pandemic is making our patients feel older and unhappy

• **How the COVID-19 pandemic might age us**
  – *Nature*, Jan 19, 2022
  – “As the COVID-19 pandemic continues, we might feel we’re ageing faster than before.”
  – Infectious disease, loneliness and stress can affect cellular ageing, making us less healthy and shortening lifespans.

• **Integrative Medicine** knows how to address these concerns. **Integrated physicians** will know how to address these concerns even better.
Let’s all become Integrated Physicians, not just Integrative Physicians

Our patients need this from us and they will benefit.

We will benefit.

Let’s all support each other on this path. It's not easy to do this alone.
Thank You

Amy Mack
Jim Gordon (cmbm.org)
Jeff Bland
Diversified
Integrative Practitioners Everywhere