COVID-19 and Immune Response Considerations from Co-morbid Psychiatric Diagnosis, Early Stress, Low Social Support, and Age

Presented by: Karen Lewicki, MD, JD for White River VA Mental Health and Behavioral Sciences Grand Rounds April 3, 2020
Contact: karen.lewicki@va.gov
No conflicts to declare
Learning Objectives

1. Name several presentations of Covid-19 including digestive, cardiac, and neurological
2. Review the mechanisms of innate and adaptive immune responses to virus
3. Understand what is meant by the “Conserved Transcriptional Response to Adversity” whereby the central nervous and immune systems work together to anticipate pathogenic threats
4. Identify mechanisms through which inflammation becomes dysregulated in some identifiable patient groups
5. Name potential avenues of treatment focused on ameliorating dysregulated immune responses
Coronaviruses are positive-stranded RNA viruses in an envelope made of two proteins, M (membrane) and S (spike). There have been two previous zoonotic coronaviruses, SARS-CoV (11% fatality) and MERS-CoV (34% fatality). These viruses cause transient respiratory or GI illness, although SARS also had neurologic manifestations.
Commonly reported symptoms of COVID-19

<table>
<thead>
<tr>
<th>Symptom</th>
<th>%</th>
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<tbody>
<tr>
<td>Fever</td>
<td>87.9</td>
</tr>
<tr>
<td>Dry cough</td>
<td>67.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38.1</td>
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<tr>
<td>Sputum production</td>
<td>33.4</td>
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<tr>
<td>Shortness of breath</td>
<td>18.6</td>
</tr>
<tr>
<td>Muscle pain or joint pain</td>
<td>14.8</td>
</tr>
<tr>
<td>Sore throat</td>
<td>13.9</td>
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<tr>
<td>Headache</td>
<td>13.6</td>
</tr>
<tr>
<td>Chills</td>
<td>11.4</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>5.0</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>4.8</td>
</tr>
</tbody>
</table>
| Diarrhea                      | 3.7-31 |\(^{[31]}\)
| Haemoptysis                   | 0.9 |
| Conjunctival congestion       | 0.8 |
Although respiratory symptoms continue to make the common and expected presentation of Covid-19, other presentations have been reported. In addition to anecdotal reports of coagulopathy, significant cardiac and neurologic symptoms and presentations have been recorded:
1. COVID-19 case reports suggest that there is increased myocardial injury (as evidenced by elevated high-sensitivity troponin I) in one study where 4 patients out of 41 required intensive care unit (ICU) care and another study (n = 138 patients) reported that 7.2% had acute cardiac injury, 8.7% had shock, and 16.7% had cardiac arrhythmias — most patients required ICU.

2. SARS virus is associated in one study (n = 121) with hypotension, bradycardia, tachycardia, cardiomegaly, and arrhythmia (mostly transient); cardiac arrest and death in another study (n = 15); and subclinical diastolic impairment with systolic involvement on echocardiography (reversible on clinical recovery) in a third report (n = 46).

3. Angiotensin-converting enzyme 2 (ACE2) is expressed in the heart and SARS-CoV-2 virus binds to cells expressing receptors, particularly ACE2.
COVID-19: Neurologists in Italy to Colleagues in US: Look for Poorly-Defined Neurologic Conditions in Patients with the Coronavirus

By Jamie Talan
March 27, 2020
The CDC has identified several conditions that put people at high risk for severe illness:
Based upon available information to date, those at high-risk for severe illness from COVID-19 include:

- **People aged 65 years and older**
- People who live in a nursing home or long-term care facility
- Other high-risk conditions could include:
  - People with chronic lung disease or moderate to severe asthma
  - People who have serious heart conditions
  - People who are immunocompromised including cancer treatment
  - People of any age with severe obesity (body mass index [BMI] ≥40) or certain underlying medical conditions, particularly if not well controlled, such as those with diabetes, renal failure, or liver disease might also be at risk
This presentation will largely consider how a person’s physical response to their social environment can increase their risk of contracting Covid-19 and experiencing a more severe course. In particular, we will be looking at the action of non-conscious, evolutionarily conserved responses, such as altered transcription of immune response genes, which has been the work of researchers including Steve Cole, Michael Irwin, and George Slavich.

First, however, we will review how viral infections work:
Anti-viral defense - a brief review

Toll-like receptors on macrophages and dendritic cells recognize viral patterns.

TLR4 - viral components on the infected cell surface

TLR3, 7, 8, 9 - viral nucleic acids on endosomal membranes

Ligand recognition leads to activation of Type 1 Interferons - so named because they interfere with viral replication

Interferon inducible genes go on to: induce maturation of dendritic cells, enhance antibody responses in B cells, and mediate induction of CD8+ T cell responses
Innate immune system action initiates action against pathogens, followed by action of the adaptive system

Natural Killer (NK) cells of the innate system recognize and destroy cells that are not displaying the normal volume of MHC I complexes.

Dendritic cells of the innate system activate “helper” T cells, which in turn release signalling molecules called cytokines which further activate both the innate and adaptive systems.
Is immune function or viral susceptibility altered in the context of psychiatric disease?
PTSD nearly doubles infection risk

Date: October 15, 2019
Source: Boston University School of Medicine
Summary: A new study is the first to examine the relationship between post-traumatic stress disorder (PTSD) and dozens of infection types in a nationwide cohort. Researchers found that PTSD affects infection risks for men and women differently, having, for example, more of an effect on a woman’s risk of urinary tract infection and a man’s risk of skin infection.

However there has been a general awareness for decades that “stress” can alter immune function - this NEJM study is nearly 30 years old:

**ORIGINAL ARTICLE**

**Psychological Stress and Susceptibility to the Common Cold**

Sheldon Cohen, Ph.D., David A.J. Tyrrell, M.D., and Andrew P. Smith, Ph.D.

**CONCLUSIONS.**

Psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness, and this risk was attributable to increased rates of infection rather than to an increased frequency of symptoms after infection. (N Engl J Med 1991; 325:606–12.)
The question has not been whether stress can make you sick, so much as what kind of stress, and how.
How stress influences disease: Study reveals inflammation as the culprit

Date: April 2, 2012
Source: Carnegie Mellon University
Summary: Stress wrecks havoc on the mind and body. Until now, it has not been clear exactly how stress influences disease and health. Now researchers have found that chronic psychological stress is associated with the body losing its ability to regulate the inflammatory response. The research shows for the first time that the effects of psychological stress on the body’s ability to regulate inflammation can promote the development and progression of disease.

What kind of stress?
Social Safety Theory: A Biologically Based Evolutionary Perspective on Life Stress, Health, and Behavior

Annual Review of Clinical Psychology
Vol. 16: (Volume publication date May 2020)
Review in Advance first posted online on March 6, 2020. (Changes may still occur before final publication.)
https://doi.org/10.1146/annurev-clinpsy-032816-045159

George M. Slavich
Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, California 90095-7076, USA;
email: gslavich@mednet.ucla.edu
Multiple lines of research over the last two decades have indicated that across species of social mammals, the central nervous systems function cooperatively to track an individual’s quality of social safety and connection.
Connected and isolated social mammals face different risks and have different needs

**Connected:**

- More likely to encounter viruses from nearby conspecifics, thus greater need of active anti-viral gene programs
- Less anticipation of physical fighting, thus less active anti-coagulation
- Able to rely on nearby others to sense danger, thus sleep more deeply

**Isolated:**

- Lower virus exposure from conspecifics, thus less active anti-viral gene programs
- As in many mammal groups a fight precedes expulsion more active coagulation factors
- Lighter sleep
- Overall increase of background inflammation
Although glucocorticoids act in the short term to decrease inflammatory signalling, over time receptor responsiveness decreases.

At the same time, sympathetic responses drive increased inflammatory gene activity.
A second figure from this paper.

A key idea here is that transcriptional alterations are driven by **subjective perception** of social connection, as well as by immune system detection of damage and pathogen associated patterns.
The work of Jos Brosschot on cardiovascular responses to social stress converges with Steven Cole’s concept of the CTRA, or Conserved Transcriptional Response to Adversity.
Ever at the ready for events that never happen.

Brosschot JF.

Author information

Abstract
Stress, whether daily stress, work stress or traumatic stress, is unhealthy. This lecture covers three recent theoretical approaches in explaining the mechanisms underlying the influence of psychological stress on somatic health. It is argued that stress research should focus less on stressors themselves and put more emphasis on prolonged stress responses. Three mechanisms are identified that cause this unhealthy prolonged stress response: first, the partly-proven mechanism of perseverative cognition; second, the mechanism of unconscious stress, which is currently being explored; and third, the notion of the stress response being a default response that is inhibited only when safety is perceived. All three mechanisms are deeply rooted in millions of years of our evolution. Although the dangers of the past have virtually disappeared, many of us remain ever at the ready for events that never happen.

KEYWORDS: Perseverative cognition; default stress response; generalized unsafety; loneliness; perceived safety; unconscious stress
Brosschot’s acronym for his concept is GUTS
Decreased social connection, increased social isolation, and loneliness, are seen with many psychiatric disorders

Stigma of psychiatric diagnosis can drive perception of rejection

With some disorders, like depression, perception of social isolation, guilt and other feelings driving self-isolation, are parts of the disorder

With PTSD, lack of social support is a risk factor for and driver of symptoms

Increased risk of metabolic syndrome and diabetes seen in many psychiatric disorders is both a sign that CTRA/GUTS processes are at work and indicate patients are at increased risk of severe course of Covid-19 infection
Adverse Childhood Experiences are likely also to drive processes associated with CTRA/GUTS

The 10 questions of Dr. Felitti and Dr. Anda’s ACE questionnaire speak to experiences in which a child has difficulty receiving social support - either because of active aggression or abuse (physical, emotional, sexual) - or because the parents are unable to provide social support due to absence, incarceration, drug use etc.
Adverse Childhood Experience (ACE) Questionnaire
Finding your ACE Score ra hbe 10 24 06

While you were growing up, during your first 18 years of life:

1. Did a parent or other adult in the household often …
   Swear at you, insult you, put you down, or humiliate you?
   or
   Act in a way that made you afraid that you might be physically hurt?
   Yes  No  If yes enter 1 ________

2. Did a parent or other adult in the household often …
   Push, grab, slap, or throw something at you?
   or
   Ever hit you so hard that you had marks or were injured?
   Yes  No  If yes enter 1 ________

3. Did an adult or person at least 5 years older than you ever…
   Touch or fondle you or have you touch their body in a sexual way?
   or
   Try to or actually have oral, anal, or vaginal sex with you?
   Yes  No  If yes enter 1 ________

4. Did you often feel that …
   No one in your family loved you or thought you were important or special?
   or
   Your family didn’t look out for each other, feel close to each other, or support each other?
   Yes  No  If yes enter 1 ________
When frequent or significant social rejection is experienced during development, the formation of the nervous and immune systems is affected. Development in a socially hostile or neglectful environment can lead to more robust connection between the nervous and immune systems and overall increased inflammatory responses, which is a likely cause of the increased burden of both autoimmune and inflammatory disease seen in patients with high ACE scores (4 or greater).
Health risks associated with ACE scores:

At or over 2: Doubles risk of autoimmune disease

At or over 4: Increased risk for diabetes, stroke, COPD and emphysema

At or over 6: Premature mortality up to 20 years, not explained by health behaviors

At or over 7: Triple lifetime odds of lung cancer

3.5x odds of ischemic heart disease
Emotional responses and reaction styles also seem to have a direct connection to immune system function.
Inflammation, Self-Regulation, and Health: An Immunologic Model of Self-Regulatory Failure.

Shields GS\(^1\), Moons WG\(^2\), Slavich GM\(^3\).

Author information
1 Department of Psychology, University of California, Davis.
2 Moons Analytics, San Diego, CA.
3 Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles.

Abstract
Self-regulation is a fundamental human process that refers to multiple complex methods by which individuals pursue goals in the face of distractions. Whereas superior self-regulation predicts better academic achievement, relationship quality, financial and career success, and lifespan health, poor self-regulation increases a person's risk for negative outcomes in each of these domains and can ultimately presage early mortality. Given its centrality to understanding the human condition, a large body of research has examined cognitive, emotional, and behavioral aspects of self-regulation. In contrast, relatively little attention has been paid to specific biologic processes that may underlie self-regulation. We address this latter issue in the present review by examining the growing body of research showing that components of the immune system involved in inflammation can alter neural, cognitive, and motivational processes that lead to impaired self-regulation and poor health. Based on these findings, we propose an integrated, multilevel model that describes how inflammation may cause widespread biobehavioral alterations that promote self-regulatory failure. This immunologic model of self-regulatory failure has implications for understanding how biological and behavioral factors interact to influence self-regulation. The model also suggests new ways of reducing disease risk and enhancing human potential by targeting inflammatory processes that affect self-regulation.
Figure from Inflammation, Self-regulation, and Health, previous
Reduced Helper T cell and Natural Killer cell activity is observed in the context of impaired self-regulation.
Antigen-presenting cell (dendritic cell)

Helper T cells release cytokines that activate much of the adaptive and nonadaptive immune system during infection.

(a) CD4

Activated T_H cell

MHC II

Antigen

T cell receptor

Cytokines

(b) CD8

Activated T_C cell

MHC I

Infected cell

Antigens

T cell receptor

Granizes

Perforins

Cytotoxic T cells destroy infected cells by releasing enzymes that rupture cell membranes.
CDC guidelines for risk include moderate to severe asthma as a condition. It is worth being mindful of the role which subjective experiences of stress and early experiences contribute to this disease process.

Evidence establishing a link between prenatal and early life stress and asthma development

Maria José Rosa, DrPH, Alison Lee, MD, MS, and Rosalind J. Wright, MD, MPH
Why do older people appear to be at greater risk?

- Tissues and systems are more worn (cardiovascular)
- Immunosenescence

Notably, persistent social threat and loneliness appear to drive accelerated cellular aging and a more reactive, inflammatory-signal driven immune response
Thus although psychiatric patients are not identified by the CDC as belonging in a high risk category, it falls to us as clinicians who know our patient’s histories - of early experience, of current social connection or disconnection - to estimate how the above characterized processes affect their risk.
Based upon available information to date, those at high-risk for severe illness from COVID-19 include:

- **People aged 65 years and older**
- People who live in a nursing home or long-term care facility
- Other high-risk conditions could include:
  - People with chronic lung disease or moderate to severe asthma
  - People who have serious heart conditions
  - People who are *immunocompromised* including cancer treatment *
  - People of any age with severe obesity (body mass index [BMI] ≥40) or certain underlying medical conditions, particularly if not well controlled, such as those with diabetes, renal failure, or liver disease might also be at risk

* or altered immune function due to CTRA-type transcriptional responses, especially if gauged by early developmental onset (ACE 4 or higher) or co-occurring inflammatory disorder
That was an exploration of factors potentially increasing Covid-19 infection risk or severity

Can understanding of how social connection impacts immune response point to ways to fight disease?
Ways to “boost” the immune system:

1. Limit alcohol

2. Exercise

   The signalling molecule IL-6 may be an inflammatory or anti-inflammatory messenger depending on context - exercise appears to promote its anti-inflammatory signalling action.
As described here:
Ways to “boost” the immune system:

1. Limit alcohol

2. Exercise

3. Sleep
Promotion of good sleep hygiene is always indicated, but melatonin has been investigated as a possible immune modulator in the context of viral infection, starting with Ebola.

COVID-19: Melatonin as a potential adjuvant treatment

Rui Zhang, Xuebin Wang, Leng Ni, Xiao Di, Baitao Ma, Shuai Niu, Changwei Liu, Russel J. Reiter

https://doi.org/10.1016/j.lfs.2020.117583
Ways to “boost” the immune system:

1. Limit alcohol
2. Exercise
3. Sleep
4. Social connection
From Zoom to Netflix group watching apps, there are myriad ways for people to maintain social connection during the pandemic.

There are also ways for people to try to access the benefits of social connection during isolation, however, and these include the writing interventions pioneered by James Pennebaker, Expressive Writing.

A common format of an expressive writing intervention is to direct a participant to identify a signal event they experienced, often a secret or a thing they have not talked about with others, and to direct them to write their “deepest thoughts and feelings” about it for a time-limited period of 30 minutes on 3 separate occasions. Participants are told their writing will be read. Immune system benefits have commonly been observed in research on this intervention. Notably discussion of the writing does not appear to be necessary for benefit; it seems necessary only that the writer knows that what they have written will be read.
Numerous studies have been done on the effects of Expressive Writing.

Effect of written emotional expression on immune function in patients with human immunodeficiency virus infection: a randomized trial.

Petrie KJ¹, Fontanilla I, Thomas MG, Booth RJ, Pennebaker JW.

Abstract

OBJECTIVES: To determine whether writing about emotional topics compared with writing about neutral topics could affect CD4+ lymphocyte count and human immunodeficiency virus (HIV) viral load among HIV-infected patients.

METHODS: Thirty-seven HIV-infected patients were randomly allocated to 2 writing conditions focusing on emotional or control topics. Participants wrote for 4 days, 30 minutes per day. The CD4+ lymphocyte count and HIV viral load were measured at baseline and at 2 weeks, 3 months, and 6 months after writing.

RESULTS: The emotional writing participants rated their essays as more personal, valuable, and emotional than those in the control condition. Relative to the drop in HIV viral load, CD4+ lymphocyte counts increased after the intervention for participants in the emotional writing condition compared with control writing participants.

CONCLUSIONS: The results are consistent with those of previous studies using emotional writing in other patient groups. Based on the self-reports of the value of writing and the preliminary laboratory findings, the results suggest that emotional writing may provide benefit for patients with HIV infection.
Immune benefits of other meditative practices also being explored
Experimental trials:

- Melatonin
- Vitamin C
- Tocilizumab, Baricitinib, Ruxolitinib, Fedratinib
Conclusion:

Converging lines of research show that social mammals have evolutionarily-driven biological responses to the perception of social disconnection.

These responses typically involve increases in systemic inflammation and immune response changes with overall poorer anti-viral responses.

When stress responses to social threat continue over time, the result can look like responses associated with greater age.

For these reasons, patients with early adversity and psychiatric histories may be at greater risk of contracting Covid-19, and experiencing a more severe course.

We can use our awareness of this biology to identify and protect vulnerable patients.

We can use it to aid everyone.

Thank you!