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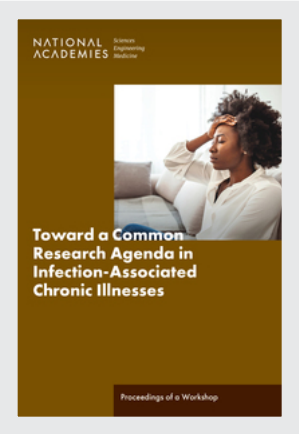

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Toward a Common Research Agenda in Infection-Associated Chronic Illnesses

Claire Biffl, Elizabeth Ashby, Julie Liao, Megan Snair, *Rapporteurs*

Forum on Microbial Threats

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Forum on Neuroscience and Nervous Systems Disorders

Board on Health Sciences Policy

Health and Medicine Division

Proceedings of a Workshop

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TOWARD A COMMON RESEARCH AGENDA IN INFECTION-ASSOCIATED CHRONIC ILLNESSES: A WORKSHOP TO EXAMINE COMMON, OVERLAPPING CLINICAL AND BIOLOGICAL FACTORS WORKSHOP PLANNING COMMITTEE[1]

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **DIANE E. GRIFFIN,** Johns Hopkins University. was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

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Boxes and Figures

BOXES

FIGURES

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Acronyms and Abbreviations

AFM	acute flaccid myelitis
AI	artificial intelligence
ATP	adenosine triphosphate
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebral spinal fluid
EBV	Epstein-Barr virus
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GI	gastrointestinal
HIV	human immunodeficiency virus
IFN-alpha	interferon alpha
IVIG	intravenous immunoglobulin
LIINC	Long-term Impact of Infection with Novel Coronavirus study

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ME/CFS	myalgic encephalitis/chronic fatigue syndrome
MIS-C	multisystem inflammatory syndrome in children
ML	machine learning
MRI	magnetic resonance imaging
MS	multiple sclerosis
NIH	National Institutes of Health
PASC	postacute sequelae of COVID-19
PCR	polymerase chain reaction
PK	pharmacokinetics
POTS	postural orthostatic tachycardia syndrome
PTLDS	posttreatment Lyme disease syndrome
RCT	randomized controlled trial
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCFA	short-chain fatty acids

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1

Introduction[1]

Infection-associated chronic illness is used in this workshop as an umbrella term for several diseases that share overlapping symptoms. Examples include long COVID (also referred to as postacute sequelae of COVID-19 or PASC), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), persistent or posttreatment Lyme disease syndrome (PTLDS). and multiple sclerosis (MS).[2]

Many infection-associated chronic illnesses have been underresearched, underfunded, and met with skepticism. However, since 2020, the onset, scale, and timing of long COVID has brought these issues to the forefront and underscored an increasing recognition of chronic illnesses that appear to arise from infectious diseases, according to Tim Coetzee, National Multiple Sclerosis Society. This growing public health problem often includes a patient history of acute infection followed by long-lasting and often debilitating symptoms including severe fatigue, cognitive impairment, and multiorgan dysfunction. Lyle Petersen, director of the Division of Vector-Borne Diseases at the U.S. Centers for Disease Control and Prevention, noted

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[2] Throughout this workshop proceedings, speakers and workshop attendees use the term "chronic illness" as a general term that refers to the infection-associated chronic illnesses as explained in this paragraph.

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that while elucidating the mechanisms underlying the development and persistence of these chronic illnesses remains an area of active research, the major proposed pathology mechanisms appear to be similar across chronic illnesses associated with different infectious etiologies (see Figure 1-1).

In addition to debilitating physical effect on patients, chronic illnesses present broader societal effects. For example, between 31 and 70 percent of COVID patients remain absent from work after the acute phase of the disease (Nittas et al., 2021), and it is estimated that long COVID may be responsible for 1.6 million fewer full-time workers in the U.S. labor market (Bach, 2022a). Annual economic burdens of other chronic conditions, such as post-treatment Lyme disease syndrome and ME/CFS are estimated to exceed $1 billion and $2 billion in the United States, respectively (Hook et al., 2022; Jason et al., 2008).

In addition to the commonality in chronic symptoms among long COVID, PTLDS, ME/CFS, MS, and other illnesses, there are also similarities in the leading hypotheses for their mechanism of disease—including pathogen or antigen persistence, immune response dysregulation, altered neurologic function, or altered microbiome composition and activity, among others. Given this potential overlap, researchers studying different infection-associated chronic illnesses face common challenges in identifying disease biomarkers and developing diagnostics and therapeutic options. Recognizing the commonalities across the symptoms and research challenges, several speakers including Harlan Krumholz (Yale School of Medicine) and David Putrino (Mount Sinai Health System) described the need for a holistic understanding of infection-associated chronic illnesses that includes moving beyond condition-specific silos to advance research

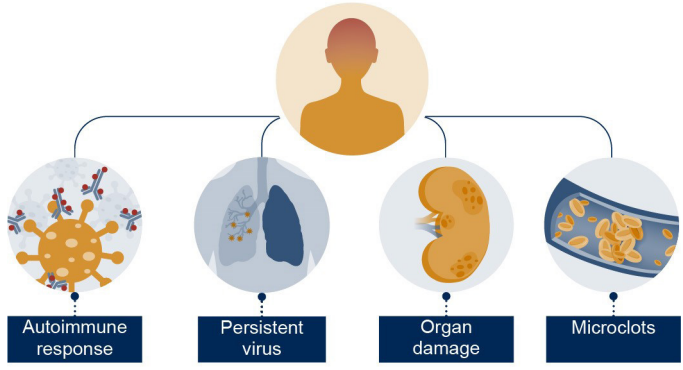

FIGURE 1-1 Potential mechanisms for infection-associated chronic illnesses.
SOURCE: Presentation by Hilary Marston, June 30, 2023 (GAO, 2022).

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more comprehensively, translating to improved options for patients across multiple conditions.

To address these challenges and advance current knowledge, the Forum on Microbial Threats and the Forum on Neuroscience and Nervous System Disorders held a public workshop, Toward a Common Research Agenda in Infection-Associated Chronic Illnesses: A Workshop to Examine Common, Overlapping Clinical and Biological Factors. The workshop sought to explore the current understanding of, and future research opportunities for, infection-associated chronic illnesses. Discussions were designed to consider the latest research and knowledge gaps in the following areas:

- Overlapping clinical and biological factors underlying infection-associated chronic illnesses
- Current practice and novel technologies to develop urgently needed diagnostic tests for different stages of illness and the potential underlying infectious agent
- Identification of therapeutic targets and strategies to prevent or impede chronic illness progression
- Coordination and collaboration among various stakeholders and practitioners that will increase research and enhance care across different patient populations

While some speakers and discussions presented in the workshop focused only on singular diseases, many aspects of the population profiles, symptomology, or biomarkers and therapeutic targets are likely salient across diseases and may apply to several different conditions. The scope of the workshop is defined in the Statement of Task (Appendix B), and the complete workshop agenda is included (Appendix C).

ORGANIZATION OF THE WORKSHOP

The workshop was held virtually and in person June 29–30, 2023, at the National Academies of Sciences, Engineering, and Medicine in Washington, DC. The first day focused on the mechanisms underlying infection-associated chronic illnesses. These sessions included various historical and stakeholder perspectives, discussions of host- and pathogen-mediated factors that influence development of conditions, and research priorities in diagnosis. Day two focused on clinical advancements and collaboration, featuring discussions on patient-driven research, innovation and infrastructure in research, and opportunities in therapeutics development. The workshop closed with final remarks on challenges and opportunities in developing a shared research agenda.

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ORGANIZATION OF THE PROCEEDINGS

This proceedings document is organized into seven chapters. Following the introduction, Chapter 2 presents an overview of infection-associated chronic illnesses, and Chapter 3 describes common mechanistic factors of these illnesses. Chapter 4 explores future opportunities and research priorities for diagnostics, with Chapter 5 focusing on opportunities for therapeutics. Chapter 6 continues the discussion on advancing research through patient-driven efforts and the innovation and infrastructure needed. Finally, Chapter 7 considers challenges and opportunities in a shared research agenda. Suggestions for future research efforts and potential next steps by individual speakers are outlined in a box at the end of Chapter 7.

This proceedings document has been prepared by the workshop rapporteur as a factual summary of presentations and discussions at the workshop. The planning committee's role was limited to planning and convening the workshop. The views contained in the proceedings are those of individual workshop participants and do not necessarily represent the views of all workshop participants, the planning committee, or the National Academies.

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2

Overview of Infection-Associated Chronic Illnesses

Key Points from Individual Speakers and Participants[1]

- There is overlap between postinfectious syndromes and chronic viral infections, and the scientific field is now beginning to appreciate the potential for this persistence of acute infections resulting in documented clinical morbidity. (Henrich, Komaroff)
- Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and long COVID share a similar set of symptoms and underlying pathophysiology. Ongoing symptoms may be attributable in part to an evolutionary protection mechanism known as the sickness behavior response. (Komaroff)
- A coordination partnership in research can have numerous benefits, making studies more efficient and relevant, connecting researchers with patients, improving equity, and accelerating discovery. (Krumholz)
- The time of illness needs to be accounted for, as conditions can look immunologically different at different time points. Research on these conditions should also involve several com-

continued

[1] This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

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parator groups, including patients with diagnoses ranging from ME/CFS to Lyme disease to dysautonomia. (Davis)
- There is an opportunity to use rigor and knowledge to help serve people living with these conditions while the answers in research are still in development. This should include public education for providers, medical students, and the media on the legitimacy of these conditions. (O'Rourke)
- To advance progress in infection-associated chronic illness, patients need to be centered in research efforts, listened to, made active participants, and have their conditions and challenges more visible in the public agenda and arena. (Obregón)

This chapter summarizes speaker talks that provided background information on the overlap between the underlying biological abnormalities in patients and shared pathophysiology across conditions. Speakers in this session shared perspectives from different stakeholders affected by these diseases, while providing suggestions on what is needed to advance the knowledge generation in this area and help patients.

SPONSOR REMARKS

The workshop was supported in part by the Division of Vector-Borne Diseases and the Division of High-Consequence Pathogens and Pathology of the Centers for Disease Control and Prevention (CDC) and the Steven & Alexandra Cohen Foundation. Speakers affiliated with each sponsor shared their perspectives as part of setting the context for the workshop. Lyle Petersen, director of the Division of Vector-Borne Diseases, CDC, shared his personal experience from being infected with West Nile virus several years prior. He found he was not getting better following the acute infection and that it took him nearly 6 months to fully recover. During this time, he was unable to work a full day and often struggled to even walk up short sets of stairs despite having previously run several marathons. Petersen noted that the causes of many of the chronic illnesses following infection are unknown.

Other knowledge gaps across diseases include the pathogenic mechanisms of why these symptoms occur, and how to help patients improve, Petersen said; however, the broad reach of the COVID pandemic and the large number of people suffering from long COVID has reenergized efforts to address these gaps in knowledge. Speaking on behalf of CDC, Petersen said that it is critical to better understand the epidemiology and pathogenesis of these chronic symptoms and identify more effective approaches to manage, treat, and potentially cure these debilitating illnesses. Mul-

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tiple treatment trials over the past decades have failed to resolve chronic symptoms that stem from various infectious disease triggers, he said, so it is necessary to continue active research that can advance treatments for symptoms and improve diagnostic capabilities.

Ben Nemser, chief program officer at the Steven & Alexandra Cohen Foundation, underscored that while most people survive and recover from initial infection by a pathogen, a substantial portion cannot regain their full health. Millions of Americans face debilitating symptoms of infection-associated chronic illnesses every day, Nemser said, placing untold strain on their families and communities. He shared his hope to collectively forge a legacy of scientific achievement where people can not only survive these infections but thrive afterwards in recovery.

COMMON GROUND ACROSS INFECTION-ASSOCIATED CHRONIC ILLNESSES

Tim Henrich, University of California, San Francisco, reviewed the common ground observed across disease conditions, with a specific focus on pathogen persistence, immune dysregulation, and ongoing inflammation following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other infection-associated chronic illnesses. He pointed out that in early 2020, when the emergence of a novel coronavirus in China may have appeared to pose little risk to the United States. However, researchers at University of California, San Francisco, suspecting there may be longer-term effects outside the usual acute viral infection symptoms, began studying the long-term immunological effect of COVID-19 infections even before there were any documented cases in the area. Over time, more news stories emerged of people who recovered from COVID-19 but were still unable to return to normal activities in their life. Eventually these patients adopted the name of *long COVID* or *long haulers*, as their symptoms persisted for months to years.

Persistent symptoms are not unique to long COVID, Henrich continued. Many RNA viruses have now been found to result in chronic sequelae, including Ebola virus, respiratory syncytial virus, Zika virus, West Nile virus, and others. For example, Henrich said, Ebola is known as a severe acute infection that can have extremely high mortality . But even for those who recover from the acute infection, many suffer from tiredness, headaches, muscle and joint pain, weight gain, and other symptoms for months afterward (CDC, 2023a). Studies have found increased levels of biomarkers showing inflammation, intestinal tissue damage, and T and B cell activation and exhaustion in these patients up to 2 years after making a full recovery from the acute infection (Wiedemann et al., 2020). An additional study demonstrated that some people who recovered from Ebola can continue to carry the virus after initial convalescence and again exhibit symptoms

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of acute disease without evidence of reexposure to the virus from other sources. This has even resulted in instances of a person becoming sick again months after initial recovery and then transmitting the virus to another individual (Mbala-Kingebeni et al., 2021).

While Ebola spread has been more geographically confined, Henrich said, there are many other viruses widely distributed around the world that are responsible for a large burden of chronic viral infection in humans. For example, even though people can now be on fully suppressive antiretroviral therapy for human immunodeficiency virus (HIV), there can still be persistent infection by the virus, leading to depletion of the gut microbiota and alteration of the gut mucosa regardless of the antiviral treatment, he explained. This can lead to persistent inflammation, immune activation, immune exhaustion, and even immune senescence.

If there is a similar inflammatory biomarker profile across diseases, one could argue that multiple exposures to these pathogens could have an additive effect, he said. For example, if someone is already living with HIV and becomes infected with COVID, they may be at greater risk of acquiring long COVID. Recent studies provided evidence supporting this hypothesis. One study found that people living with HIV are 1.75 times as likely to have persistent COVID-19 symptoms compared to people who are HIV negative (Kingery et al., 2022). Another small case control study found that people living with HIV were four times as likely to have long COVID (Peluso et al., 2022).

Looking beyond HIV, Henrich also highlighted the role that Epstein-Barr virus (EBV) plays in chronic infections, in addition to the serious illness that it can cause in acute stages of infection. He pointed to a large study that tracked 10 million active military individuals over several years and found that the risk of being diagnosed with multiple sclerosis (MS) increased 32-fold after EBV infection, but not after cytomegalovirus (CMV) infection (Bjornevik et al., 2022). Further analysis of this data by Horwitz et al. (2022) did reveal elevated levels of MS diagnosis associated with CMV, though the risk was not as high compared with that associated with EBV. So while there is clearly a viral trigger, Henrich noted, it seems there are often environmental conditions, which can include the factors from the physical environment or host immune responses, that can increase the risk of the chronic sequelae. There are also clear overlaps and triggers between infections, with some evidence showing reactivation of EBV following acute COVID-19 infection: 67 percent of people with long COVID had evidence of EBV reactivation during acute SARS-CoV-2 infection, compared to just 10 percent of those who fully recovered from COVID infection without suffering from chronic symptoms (Gold et al., 2021).

There is clear overlap between postinfectious syndromes and chronic viral infections, said Henrich, and the scientific community is beginning to

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appreciate the potential for acute infections to persist and potentially lead to documented clinical morbidity. Reactivation of existing chronic viral infections in the setting of another acute microbial illness may also play a role, he added. The majority of these pathogens and infections are localized to the affected tissues, so researchers and clinicians need to account for tissue-specific alterations in addition to biomarkers in the peripheral blood. Finally, he said, researchers need to keep in mind that patients may have new immune or inflammatory baseline set points as a result of COVID-19 that need to be accounted for in prospective research and clinical diagnostics. There may be additional longer-term effect of COVID-19 on human health, but the severity of this remains to be seen.

A HISTORICAL PERSPECTIVE

Anthony Komaroff, Harvard Medical School and Brigham and Women's Hospital, reviewed the similarity of symptoms suffered by people with postinfection syndromes and the emerging evidence around a shared underlying pathophysiology—especially for ME/CFS and long COVID. As Henrich mentioned, viruses, bacteria, and other microbial pathogens can produce lingering symptoms after acute infection. In a systematic review of 21 studies, these lingering symptoms were rigorously characterized in patients with ME/CFS and long COVID and concluded that most of the symptoms are shared between both conditions (Wong and Weitzer, 2021). However, said Komaroff, the question remains of whether either syndrome has underlying objective biological abnormalities.

Komaroff went on to share additional evidence from a comparison of underlying pathophysiology between the two conditions and discussed the findings of significant overlap between ME/CFS and long COVID related to the nervous system, metabolism, cardiovascular and pulmonary systems, and gut microbiome (Komaroff and Lipkin, 2023). Regarding the gut microbiome, there is now established evidence of low-grade chronic gut inflammation attributed in part to reduced numbers of symbiotic bacteria producing anti-inflammatory molecules such as butyrate and acetate, which also correlated strongly with the severity of fatigue (Guo et al., 2023). This inflammation allows bacterial products and organisms to "leak" into systemic circulation, possibly causing systemic inflammation and can secondarily lead to neuroinflammation. This has been replicated in multiple cohorts of people with ME/CFS, he added.

Another remaining question is what triggers the pathophysiology of both syndromes. In both cases there is evidence of mitochondrial dysfunction, oxidative stress, cellular aging, and chronic inflammation. This becomes a vicious cycle, he explained, as one initial abnormality can lead to a series of abnormalities even if the triggering events are different (see Figure 2-1).

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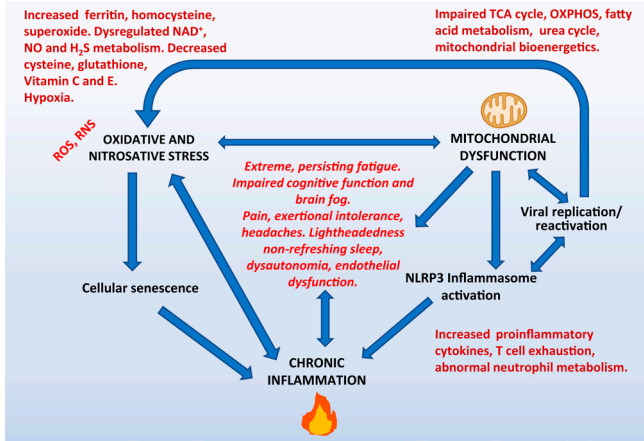

FIGURE 2-1 Relationship between abnormalities.
NOTE: Nicotinamide adenine dinucleotide (NAD+); nitric oxide (NO); hydrogen sulfide (H2S); reactive oxygen species (ROS); reactive nitrogen species (RNS); tricarboxylic acid (TCA); oxidative phosphorylation (OXPHOS); NOD-like receptor protein-3 (NLRP3).
SOURCE: Anthony Komaroff presentation, June 29, 2023; Paul et al., 2021.

To understand how this pathophysiology leads to the symptoms of ME/CFS and long COVID, Komaroff shared the sickness behavior hypothesis, which can be difficult to characterize in humans but is well documented in other animals. Sickness symptoms are a hardwired protective response that lead to behavioral changes such as less physical and mental activity, less eating and digestion, less energy consuming behaviors overall—all to preserve adenosine triphosphate (ATP) to fight the infection. Usually this is transient for an infection like the flu because the infection is promptly eradicated, said Komaroff, but this response seems to persist for chronic conditions such as long COVID and ME/CFS. This could be because the inflammation persists, or because a protective response that is meant to be temporary gets "stuck" because the neurochemical mechanism meant to turn it off becomes defective. Symptoms are experienced in the brain. If sickness behavior has been preserved by evolution, that behavior is likely orchestrated by a group of neurons dedicated to that task. This was hypothetical until the last 3 years, he noted, when a series of publications in *Nature* identified a cluster of neurons located in the hypothalamus and the brain stem of mice that orchestrates this sickness behavior (Bains and Sharkey, 2022; Hrvatin et al., 2020; Ilanges et al., 2022; Takahashi et al., 2020). Anything that causes inflammation in the brain can trigger these neurons, whether it is reactivation of latent viruses, systemic inflammation, or a proinflammatory gut microbiome.

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Effects on Society

Taking a broader look at the effects on society in the United States, Komaroff shared the disease burden of ME/CFS and long COVID in both prevalence and cost. As many as 2.5 million people may be living with ME/CFS, with direct and indirect costs totaling $17–24 billion per year (IOM, 2015). An estimated 16 million people are experiencing long COVID illnesses nationwide (Bach, 2022b), which will cost the country $544 billion each year, totaling $2.7 trillion over the next 5 years (Cutler and Summers, 2020).

These two examples of postinfection illnesses share a similar set of symptoms, and it has now been well documented that they also share underlying pathophysiology, Komaroff stated. What is still unknown is whether the same underlying pathophysiology for ME/CFS and long COVID is also shared by other postinfection syndromes. In both ME/CFS and long COVID, he posited, the symptoms may be due in large part to the expression of an ancient, evolutionarily preserved, orchestrated response meant to be protective—the sickness behavior response—the final common pathway that involves activation of neurons dedicated to generating sickness symptoms. An understanding of this underlying biology will ultimately lead to good diagnostic tests and effective treatments, he concluded.

STAKEHOLDER PERSPECTIVES

Several stakeholders provided their perspectives on research and lived experience of infection-associated chronic illnesses, including scientists, community-based researchers, and personal accounts from patients living with infection-associated chronic illnesses.

Research to Better Understand Long COVID

Joseph Breen, National Institutes of Health (NIH), described his team's efforts as part of the Researching COVID to Enhance Recovery (RECOVER) program at NIH, and how it might interface with the efforts to address infection-associated chronic illnesses more broadly.[2] The goal of the program is to understand, predict, treat, and prevent postacute sequelae of COVID, he explained, including long COVID and multisystem inflammatory syndrome in children (MIS-C). This program is guided by a principle of patient-centered research on a national scale and aims to cover

[2] For more on the RECOVER study at NIH, see: https://recovercovid.org/ (accessed July 19, 2023).

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large swaths of the United States population to include people typically underrepresented in research.

RECOVER is using platform protocols to understand what is happening in communities while also trying to adapt to the numerous changes that have happened throughout the last few years of the pandemic, shared Breen. The initiative so far has enrolled more than 20,000 adults and children in research cohorts and incorporated 60 million electronic health records (EHRs), he noted. The eventual goal is to try and merge the data from EHRs with data from RECOVER's observational cohort studies across the country, he explained. In 2020–2021 alone, there were 42 different studies directed towards understanding the mechanisms of the various pathologies of long COVID symptoms. Another goal at the initiative is to leverage these findings from the large RECOVER cohort to benefit not only the long COVID patient community but also patients with overlapping symptoms such as people suffering from ME/CFS, posttreatment Lyme disease syndrome, or other similar conditions.

Community-Based Participatory Research

Harlan Krumholz, Yale School of Medicine, discussed the beginning of his work in community-based participatory research approximately 15 years ago. Krumholz stated that he initially struggled with the concept, which diverges from the traditional research model in which researchers alone determine the terms of studies and do not prioritize partnerships with patients. However, he realized that there were many areas for improvement within the traditional model, as patients were often alienated, recruitment was slow, and many participants dropped out of studies. Additionally, implementation and dissemination of study outcomes were typically neglected, lessening the effect of these findings. Over time, community members and patients became his teachers as they worked together to utilize the wisdom of people living with these symptoms.

His team at Yale began a study called LISTEN for people living with long COVID and vaccine-related injuries, with the hypothesis that insights from this study could benefit people living with other postinfectious conditions.[3] His team studied social media, read stories, held patient-led meetings and town halls, recognized the gaps in knowledge, worked across traditional boundaries, and used new methods and tools. The idea, he said, was to disrupt norms and reject the status quo to embrace interdisciplinarity.

If democratizing research is about representation, Krumholz asked, who is really speaking for the patients and patient researchers? He outlined

[3] For more on the LISTEN study, see https://medicine.yale.edu/ycci/listen-study/ (accessed July 19, 2023).

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some of the challenges they encountered related to cognitive biases and encouraging academic and clinical researchers to think more creatively. Crowdsourcing can also lead to so many ideas that it is difficult to sort through in a systematic and actionable way. While bringing in patients to the research process can encourage more out-of-the-box thinking, they may lack the scientific knowledge to balance new ideas with technical feasibility. Conversely, communication and coordination are skills that are not well taught in traditional research, he noted.

There are ample rewards for the partnership between researchers and study participants, as studies can be more efficient and relevant by tapping into both groups' expertise. The connection between researchers and participants can become quite strong, which fuels momentum and creates a positive process and competitive advantage for researchers. In the LISTEN study, Krumholz said, his team would have never thought of certain questions to ask in surveys without first talking to the patients with lived experiences. Krumholz shared that using this model builds platforms and processes that allow researchers and patients to move together and advance as a team, promote acceptance, improve equity, and accelerate discovery. He also argued that models must be propelled by high quality science and can be applied to many areas beyond long COVID where people are motivated to find answers.

Considering Critical Research Needs

Hannah Davis, Patient-Led Research Collaborative, introduced herself as a long COVID patient also diagnosed with ME/CFS, dysautonomia, cognitive impairment, and blood clots from COVID. Her organization was borne out of the Body Politic support group in April 2020, she explained, when multiple advocates for chronic illness conditions reached out to support each other and efforts began to build upon the knowledge from existing patients and researchers.

Currently, approximately 1 in 18 American adults are living with long COVID, she said (Ford et al., 2023). Long COVID not only overlaps with biological symptoms from other conditions, the infectious origins of these chronic illnesses can also interact. Many patients with long COVID have reactivated latent viruses, she explained, and the reactivation of EBV in the acute phase of COVID-19 infection has been hypothesized to be involved in ME/CFS development as well. Some infections' initial onset may progress from the initial immune overactivation to immune system exhaustion over the years, she said. Therefore, research efforts need to account for time of illness and be aware that conditions such as ME/CFS can look immunologically different at different time points; there is also a need for standardizing and unifying outcome measures across research trials for bet-

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ter learning, said Davis. She also called for research on these conditions to involve several comparator groups, including patients with diagnoses ranging from ME/CFS to post-treatment Lyme disease syndrome to dysautonomia, among others. Davis stated that there is a need for dynamic, strategic designs of multiarm trials where therapeutic agents can be quickly added or removed depending on discovery or performance, as patients cannot afford to wait years for treatments that do not show a clear benefit.

Almost every infection-associated chronic illness has faced major stigmatization, Davis highlighted, and the field needs a massive increase of medical provider and researcher education. Finally, with a note on equity, she called for any research agenda to prioritize the most affected populations, including low-income workers, Black and Latino populations, and transgender individuals. Research should involve people with lived experience of long COVID, said Davis, and improved funding opportunities for disabled and chronically ill researchers is necessary.

Designing a Long Overdue Paradigm Shift

Meghan O'Rourke, Yale University, opened her remarks by stating that while some people spend their 20s and 30s dreaming about buying a home or planning their wedding, she spent hers dreaming about this conference. Elaborating on her personal journey through chronic illness, she explained how her family spent a celebratory weekend in Connecticut after her college graduation. Shortly after that, she started experiencing symptoms such as debilitating fatigue, night sweats, and cognitive problems. Despite many doctors and clinic visits, no one thought she was actually sick, and she was routinely told her symptoms were caused by anxiety. She expressed feeling stuck by the limitations imposed on her by illness, despite having a wonderful partner and a dream job at the time. Eventually, nearly 10 years later, she finally received a diagnosis of Lyme disease, along with other coinfections. She shared that while the suffering and physical pain was extreme, the hardest thing to bear was the invisibility of the illness. Living with a stigmatized or dismissed illness is very difficult, O'Rourke shared, noting that she recently heard from someone with a similar chronic illness who could not even go to the emergency room for help due to a lack of understanding and belief of these conditions.

O'Rourke shared that the long time frame of her own illness has helped her remain aware of new and changing science and findings, become more comfortable with uncertainty, and identify her own cognitive biases and areas of entrenched thinking. She outlined the critical need for science to study symptom manifestations as overlapping conditions and not individual illnesses, the need to break down silos to accelerate progress, and the need to turn knowledge into action for many patients that are still suffering. In

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conclusion, she shared three key questions to consider when advancing research in this area:

1. How will any research help patients?
2. How can change happen faster so that new information reaches frontline doctors promptly?
3. How can new doctors be trained to understand the long-term sequelae of infections and understand the reality of infection-associated chronic illnesses?

She concluded by invoking a broad idea from historian Thomas Kuhn. He argued that paradigm shifts in medicine do not happen by slow and steady incremental change. They happen when a change in perception allows us to see anew what was already there, O'Rourke said, and that happens when people new to the field come in with fresh eyes and ask questions. She was hopeful that the attention and interest of long COVID can help propel the advancement of research into Lyme disease and other tickborne illnesses, and the paradigm shift could result in building a deeper scientific understanding of all chronic illness triggered by infection.

DISCUSSION

Rafael Obregón, UNICEF, moderated a discussion with the session's panelists that centered around the value of additional research in determining whether the similar underlying biology (immune, neurologic, metabolic, cardiovascular and pulmonary, and microbiome-based) that is being identified in long COVID and ME/CFS should also be examined in other post-acute infection syndromes. Henrich agreed that the immune system and overall host response is critical, and that many are now studying this with the goal of understanding the immune response associated with these chronic illnesses, and whether there are therapeutics opportunities through modifying these immune responses. In addition, children clearly have a different immune response compared to adults, he said, and there is a need to look more carefully at age and sex differences in the immune response.

O'Rourke added that, in her experience, each successive insult to her immune system from additional infections felt like she was "slowly wading into deeper water." She agreed there is a critical need to understand more about the immune system. But importantly, she remarked, in an age when medicine is based on evidence: what can be done for people who live at the edge of medical knowledge? How can scientific rigor and knowledge be translated to help people living with these conditions while the answers being researched are still in development? While we wait for science to uncover the answers, she said, there are many people whose experience and symptoms are reflexively rejected by those around them. She advocated for

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the research field to develop ways to support public education for doctors, medical students, and the media to understand that while there may not be a clear understanding of the mechanisms yet, these conditions, symptoms, and complaints are legitimate, and those living with these challenges should have their lived experiences supported.

In discussing the confounding effects of overlapping biomarkers and illnesses, Henrich said that COVID-19 has brought recognition and legitimacy to these persistent chronic conditions and shone a new light on all of these overlaps. On the clinical side, he added, "We've also learned that if you don't understand something, that doesn't mean the patient isn't right." He agreed there is a need to better understand what is happening instead of just dismissing patients' symptoms as fabricated or exaggerated.

Komaroff introduced a note of caution: while multiple biological correlates have been identified in these syndromes, correlation and causation are not the same. He noted that some of the underlying biological abnormalities may, in fact, help cause the symptoms while others may just be epiphenomena. He called for more efforts to follow patients longitudinally and have them remain in close contact with researchers on good and bad days in order to identify biomarkers that change when symptoms worsen compared to baseline, which may help point to causation. This kind of study looking at illness cycles can be very instructive.

Krumholz added that every day people are going in to see their doctors and being dismissed. The critical output of this meeting is legitimizing these symptoms and conditions, he said. He called for accelerating research through the knowledge pipeline and streamlining innovation across the full spectrum of these chronic illnesses, while pointing to the fundamental need for more resources. When thinking about pandemic preparedness, he continued, prevention and response is important, but this long tail of recovery around the world demands a plan to augment efforts and get more answers, and more attention and investments, commensurate with the size of the problem. Davis and O'Rourke agreed, with Davis commenting there should be a $3 billion annual commitment to infectious-onset illness, to include public education campaigns so people realize their risks, even if they have recovered from a prior infection.

Obregón summarized the comments and emphasized the need of placing people at the center of these efforts, listening to patients, treating patients as participants rather than subjects, and making these conditions and challenges more visible by bringing them to the public agenda and arena. Collectively, there is a chance to make a difference, he concluded.

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3

Common Mechanistic Factors of Infection-Associated Chronic Illnesses

Key Points from Individual Speakers and Participants[1]

- Latent viral infections interact in complex ways in those who get sick with other infections, but this is still not well understood. Additionally, there is growing evidence that these infections associate with long COVID. (Peluso)
- Data support that early in acute COVID-19 infection there is a viremic phase where tissues throughout the body become seeded with the virus that then replicate and evolve in the different anatomic compartments of the body. (Chertow)
- The SARS-CoV-2 viral RNA can persist in multiple anatomic compartments for an extended interval, and in multiple cell types, and in various phases of COVID-19 illness. (Chertow)
- In animal model studies, Lyme disease bacteria can persist following conventional single antibiotic treatments, and combination treatments were more effective in clearing infection in some models. (Embers)
- The brain can choose to shut down certain activities when ill, leading to fatigue, slowed cognitive processing, and lack of motivation. There is a role in this space for more psychiatric research and the education of physicians and researchers across different fields to integrate their expertise. (Miller)

[1] This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

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With the surge in research in this area since 2020, much of which attributed to the high prevalence of long COVID, it is increasingly recognized that there are many common symptoms and potential mechanisms linking different types of infection-associated chronic illnesses. Consequently, attention has turned to learning more about the common factors that may exist across multiple conditions. This chapter begins with discussion of host-mediated factors of illnesses, such as immune dysfunction, autonomic dysfunction, neuroinflammation, and the microbiome. It then reviews pathogen-mediated factors and the role of pathogen persistence, including lessons from research with Epstein-Barr virus (EBV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and animal studies.

HOST-MEDIATED FACTORS

Speakers in this section presented their research on mechanisms behind the cause and symptoms of infection-associated chronic illnesses that are affected by host-mediated factors, such as immune dysregulation and autoimmunity, reactivation of—or interactions with—latent viruses, dysfunction of the autonomic nervous system, and neuroinflammation.

Immune Dysfunction

Carmen Scheibenbogen, Charité University, presented on immune dysregulation and autoimmunity from her work based on long COVID and myalgic encephalitis/chronic fatigue syndrome (ME/CFS). Presenting an overview of post-COVID conditions, she acknowledged the increased incidence of well-defined diseases such as new onset diabetes, autoimmunity, and cardiovascular conditions, but she focused on long COVID symptoms (e.g., fatigue, exertion intolerance, cognitive symptoms, and pain) as a major problem in younger patients. Echoing comments from Anthony Komaroff, Harvard Medical School, on the overlap between diseases, she found through a prospective observational study that about 50 percent of long COVID patients fit the diagnostic criteria for ME/CFS (Kedor et al., 2022). ME/CFS is a complex illness that has been neglected and poorly studied over the past few decades, Scheibenbogen said, noting that patients often report aggravated symptoms following everyday activities. There is significant overlap between symptoms experienced by long COVID and ME/CFS patients.[2] One potential common mechanism behind these symptoms may be viral persistence or reactivation of latent viruses from an earlier infection (e.g., EBV) that lead to inflammation and autoimmunity,

[2] For a comparison of common symptoms reported by patients with ME/CFS and long COVID, see Figure 2-2.

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which eventually results in endothelial disease, hypoperfusion, or microclots (Davis et al., 2023).

Scheibenbogen also shared evidence for the role of autoimmunity in infection-triggered ME/CFS and post-COVID conditions. In patients who develop these chronic illnesses, there is often family history and/or comorbidity of autoimmune disease, coinfection with EBV, qualitative alterations in the memory B cell population (such as B cell receptor skewing), other autoimmune risk factors, or correlation of autoantibody levels with symptom severity. For example, levels of autoantibodies to the autonomic nervous system correlate with symptom severity and level of fatigue in patients with infection-triggered ME/CFS (Freitag et al., 2021), as well as patients who fit the diagnostic criteria for both long COVID and ME/CFS (Sotzny et al., 2022). However, correlation was not seen in ME/CFS patients without a known infection trigger or in post-COVID patients who did not fit the criteria for ME/CFS. In summary, Scheibenbogen showed that a subset of long COVID patients have ME/CFS, and there is evidence for autoantibodies as a mediating factor of long COVID and ME/CFS, so studies to examine treatments that target autoantibodies are needed.

Latent Viruses as Drivers of Chronic Illness

Michael Peluso, University of California, San Francisco (UCSF), reviewed the Long-term Impact of Infection with Novel Coronavirus (LIINC) study conducted at UCSF, which has enrolled more than 800 participants and banked more than 50,000 biospecimens. Acknowledging that there are many proposed mechanisms of long COVID, as other speakers have noted, Peluso presented data on the role of viral reactivation with a focus on EBV (see Figure 3-1).

While most infections are successfully cleared, some infectious agents can establish latency or persist in the human body. This is often associated with herpesviruses, said Peluso, including EBV and cytomegalovirus (CMV). EBV is a ubiquitous herpesvirus that can infect B cells and establish latency in memory B cells, where it associates with the host genome and relies on normal host cell division to passively propagate into new cells. But under certain conditions, EBV can reactivate and enter a lytic cycle, where the virus expresses all its genes to produce infectious viral particles, leading to cell death and viral propagation. The immune response to EBV is complex, but Peluso highlighted that antibody levels can be measured as a proxy for viral activity, with some antibodies persisting over time and others peaking and waning after a period of months.

EBV has been implicated in a variety of conditions, often autoimmune diseases, but most associations are correlations and not causational. One recent finding is the association between EBV and the increased risk of

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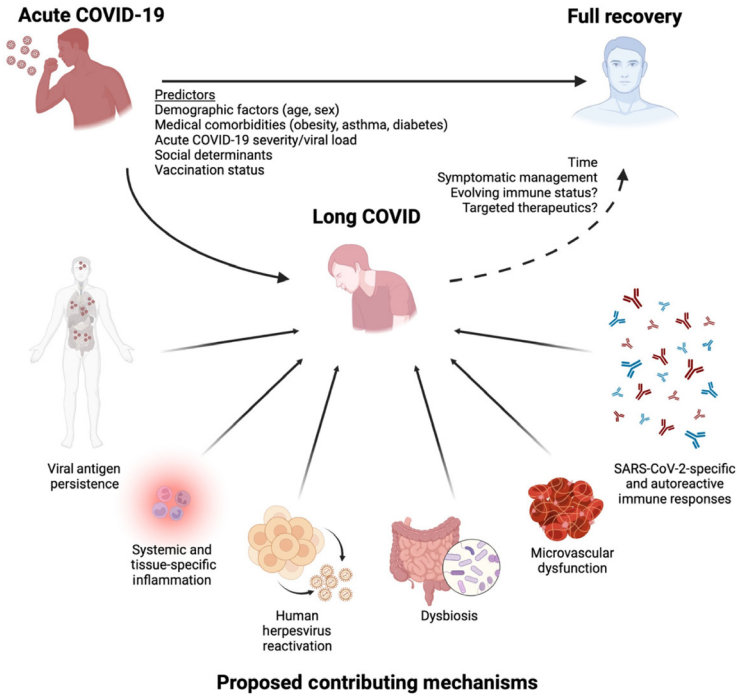

FIGURE 3-1 Proposed mechanisms of long COVID.
NOTES: Figure 3-1 was originally published in *Trends in Immunology* in 2022. A modified version was included in Peluso's presentation.
SOURCE: Michael Peluso presentation, June 29, 2023; Peluso and Deeks, 2022.

developing multiple sclerosis (MS), Peluso stated.[3] Other herpesviruses have been frequently associated with ME/CFS, but the current evidence in literature is insufficient to firmly establish if EBV infection is associated with developing ME/CFS, or if the chronic illness is creating an environment where EBV can reactivate. Though some benefits of antiviral treatment against EBV were shown for people who were suffering from ME/CFS and have high viral loads, there are a limited number of these studies, Peluso explained. Based on this prior knowledge from ME/CFS, he investigated whether EBV is associated with developing long COVID. Indeed, higher EBV titers were associated with more symptomatic long COVID phenotypes (Gold et al., 2021), and EBV viremia during early infection was associated with subsequent development of long COVID symptoms (Su et al., 2022).

[3] See Bjornevik et al. (2022). https://www.science.org/doi/10.1126/science.abj8222 (accessed January 19, 2024).

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With these two studies in mind, Peluso examined chronic viral coinfections and their effect on the likelihood of developing long COVID through the LIINC study. Initial serologic evidence suggested that patients with recent EBV reactivation had 2.5 times higher odds of reporting long COVID fatigue, and those with evidence of elevated serologic responses to EBV had two times higher odds of experiencing neurologic symptoms of long COVID such as brain fog (Peluso et al., 2023a). While the initial data did not show a clear relationship with cardiopulmonary or gastrointestinal symptoms, a follow-up study did demonstrate a strong association between EBV reactivation, cardiopulmonary symptoms, and abnormal performance on exercise testing (Durstenfeld et al., 2023).

Cytomegalovirus, a herpesvirus similar to EBV, infects 60 percent of adults in high income countries; it can also cause a mononucleosis-like illness and can reactivate in immunocompromised hosts. Initial observations found that CMV seropositivity was associated with nearly two times higher odds of hospitalization during acute COVID-19 infection (Peluso et al., 2023b). However, in the study on chronic viral infections and the differential likelihood of long COVID, Peluso and colleagues found that CMV seropositivity was associated with decreased odds of having long COVID. This was an unexpected finding that was opposite of their data on EBV, but it was consistent with previously reported results that CMV-infected young adults mounted better immune responses to the flu vaccine (Furman et al., 2015). There is a protective correlation between CMV and MS, with one study reporting 30 percent decreased odds of developing MS for CMV-seropositive individuals (Grut et al., 2021).

Peluso posited that one explanation could be that EBV acts via the inflammatory and autoimmune pathways and is compartmentalized differently than CMV in the immune system (Peluso et al., 2023a). Another potential explanation could point to the immunoregulatory effects that CMV exerts on its host that alter immune responses that would otherwise drive development of long COVID. These different effects from EBV and CMV on acute COVID-19 infection are outlined in Figure 3-2.

Going forward, Peluso plans to further explore the role of CMV and EBV in long COVID through characterizing tissue samples in the LIINC biobank, examining linkages between EBV and autoimmunity, and testing if EBV antiviral treatment provides clinical benefit. It is also unclear if there is active viral replication in patients with long COVID, so an opportunity for future research could include probing tissue samples to understand this possible mechanism. There are also knowledge gaps in understanding whether other types of EBV treatment (e.g., host-targeted therapeutics) will have any clinical benefit compared with traditional antiviral drugs. Finally, he reiterated that there is growing evidence linking these latent viral infections with long COVID, and that research advancements for long COVID

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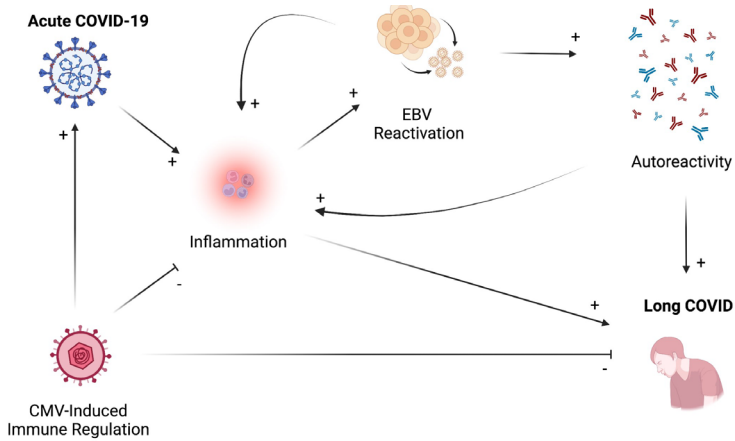

FIGURE 3-2 Differential effects of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) in long COVID.
SOURCE: Michael Peluso presentation, June 29, 2023, created with BioRender.com.

may help determine the role that these viruses play in other infection-associated chronic illnesses.

Autonomic Dysfunction

Satish Raj, University of Calgary, spoke about the cardiovascular aspects of autonomic dysfunction and its downstream effects, including postural orthostatic tachycardia syndrome (POTS) and orthostatic intolerance. One early observation in the emergence of long COVID was the common presentation of tachycardia in patients, he said. Raj observed that many symptoms experienced by patients with long COVID were historically seen in patients with POTS.[4]

Reviewing POTS in more detail, Raj said it is a clinical syndrome that is diagnosed based on abnormal physiology, particularly excessive orthostatic tachycardia,[5] but patients also experience symptoms that get worse

[4] The Canadian Cardiovascular Society released a position paper on the need to define the ecosystem of orthostatic intolerance beyond just POTS, see: https://doi.org/10.1016/j.cjca.2019.12.024 (accessed December 10, 2023). Challenges remain in diagnosing conditions featuring orthostatic intolerance, as patients experiencing different ranges of symptoms may receive differing diagnoses. Further, the range of symptoms associated with ME/CFS overlaps with other diagnoses.

[5] Excessive orthostatic tachycardia is characterized by an increase in heart rate of greater than 30 beats per minute in adults when transitioning from lying down to standing up. The diagnosis of POTS requires an exaggerated increase in heart rate over the course of 10 minutes upright compared to supine values. The heart rate increment must be at least 30 beats per

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positionally and last for more than 3 to 6 months. POTS may be the most well-known orthostatic intolerance condition, he noted, but there are other similar disorders. For example, patients with inappropriate sinus tachycardia have abnormally high heart rates all the time, even while lying down. There are also several different types of orthostatic hypotension (drop in blood pressure related to position) disorders, all of which occur within a short time of standing, he explained. Raj and colleagues looked for autonomic abnormalities in patients with long COVID and found that nearly 75 percent of patients had some symptom in common with POTS, 30 percent of patients met the diagnostic criteria for POTS, and most met the criteria for at least one cardiovascular autonomic abnormalities (Hira et al., 2023).

These results also revealed a sex difference in both symptom presentation and in frequency of the specific disorders. Overall, more female patients were found to have symptoms and accounted for the majority of POTS patients in the study, though there was no significant difference in initial presentation of orthostatic hypotension (Hira et al., 2023). In summary, Raj found that these autonomic hemodynamic disorders were common in patients with long COVID and cautioned that these disorders are often overlooked in routine care if care providers do not specifically look for the associated symptoms.

Treatment options for POTS often target the hallmark symptom of excessive tachycardia, and can be categorized into pharmacological and nonpharmacological treatment approaches. Pharmacological treatments include medications to reduce heart rate or regulate blood pressure, such as propranolol, ivabradine, pyridostigmine, and desmopressin. Nonpharmaceutical approaches can include increased dietary salt intake, diet changes, compression garments, and exercise as tolerated. A recent study found that a high salt diet increased blood volume, decreased norepinephrine levels, and decreased the patient's heart rate (Garland et al., 2021). Compression garments were also recently found to decrease heart rate and partially alleviate other symptoms (Bourne et al., 2021).Raj emphasized that the primary motivation for patients to seek care is their quality of life. Raj reiterated it is important to keep in mind that these chronic disorders are associated with significant disability, and while a cure is not readily available right now, there are some interventions that can provide some relief to patients.

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minute for adults (20 years of age and older), or at least 40 beats per minute for adolescents (12-19 years of age) in the absence of orthostatic hypotension during the first 3 minutes upright. The diagnosis also requires the presence of chronic orthostatic symptoms such as fatigue, lightheadedness, blurry vision, weakness, cognitive difficulties, and nausea. See https://link.springer.com/article/10.1007/s10286-011-0119-5 (accessed November 21, 2023).

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Common Underlying Mechanisms of Chronic Illnesses

Mitchell Miglis, Stanford University, spoke about the overlap between numerous autonomic disorders such as POTS, ME/CFS, and long COVID. Long COVID symptoms, including fatigue, brain fog, nausea, gastrointestinal issues, insomnia, anxiety, allergy issues, and others are familiar to patients with other autonomic disorders. Involvement of autonomic dysfunction in ME/CFS has been long known, with reduced cerebral blood flow and hypocapnia detected in ME/CFS patients upon orthostatic challenge (van Campen et al., 2020). While POTS is the most commonly diagnosed autonomic condition, present in up to 50 percent of patients (Hoad et al., 2008), these physiological abnormalities were measured regardless of whether the patients met the diagnostic criteria for POTS. Furthermore, levels of reduction in cerebral blood flow were also demonstrated in patients with long COVID and found to be comparable to patients with ME/CFS (not associated with SARS-CoV-2 infection) (van Campen and Visser, 2022).

Regarding autonomic dysfunction and long COVID, Miglis reported that POTS has been the most common primary diagnosis in long COVID patients. A review of several studies found that patients were often predominately female (<70 percent), and chief complaints included prominent cognitive impairment, headaches, fatigue, orthostatic intolerance, pain, and symptoms consistent with hyperadrenergic state and mast cell activation (Larsen et al., 2021). Many patients also had a history of mild preexisting or self-limiting autonomic symptoms, Miglis added, suggesting possible individual susceptibility (Larsen et al., 2021). Trying to understand the severity of autonomic dysfunction in long COVID, Larsen et al. (2022) found that while most of the long COVID patients in their study were not hospitalized for their acute illnesses, nearly two-thirds of long COVID patients scored in the moderate to severe range on COMPASS-31, a widely used screening tool for autonomic dysfunction,[6] suggesting that the likelihood of developing long COVID is independent of the initial infection severity.

The study also noted a correlation of several preexisting conditions that may predispose patients to develop post-COVID autonomic dysfunction, including asthma, obesity, vitamin D deficiency, and a history of autoimmune disease, anxiety, depression, allergies, or smoking. Congruous with other published works, a small retrospective study that compared the phenotypes of long COVID patients with age- and sex-matched cohorts of patients diagnosed with POTS and healthy controls found that all of the

[6] COMPASS-31 was developed as a patient questionnaire to provide standardized, quantitative assessment of autonomic dysfunction symptoms and has been widely used since 2012, see: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3541923/ (accessed October 8, 2023).

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long COVID patients had a wide range of abnormalities spanning from autonomic reflexes to sudomotor, parasympathetic, and adrenergic dysfunctions (Novak et al., 2021).

In addition, this study recognized and adjusted the measured cerebral blood flow based on the extent of hypocapnia in the study population to reveal a greater severity in cerebral blood flow reduction for the long COVID cohort compared with the POTS group.[7] Miglis contended that inclusion of cerebral blood flow and end-tidal CO_2 measurements are an important protocol adjustment that could be included in future studies, as screening for only blood pressure and heart rate may underdiagnose or overlook infection-associated dysautonomia disorders.

Miglis also shared ongoing work in elucidating the underlying phenotypes of these autonomic symptoms across the cerebrovascular, respiratory, small fiber, and autonomic systems in patients diagnosed with POTS in association with long COVID. While observations of reduced cerebral blood flow and tachycardia on orthostatic challenge were consistent with previous studies, Miglis also reported an unusual finding of phosphorylated alpha-synuclein, a biomarker commonly associated with Parkinson's disease, from skin biopsies of his study cohort (Miglis et al., 2022).

Miglis speculated on potential mechanisms that could underlie infection-associated chronic illnesses such as long COVID, POTS, and ME/CFS. His team is formulating hypotheses around immune dysregulation, given that many POTS patients have a history of autoimmune disease and long COVID has been associated with elevated inflammatory markers, vagal nerve damage, and elevated levels of autoantibodies. Another common theory is viral persistence, as many studies have shown SARS-CoV-2 detected in the body months after recovery. Current findings suggest systemic dissemination of the pathogen, even crossing the blood–brain barrier, regardless of the symptom severity during the initial acute COVID-19 infection.

A third potential mechanism is mast cell activation, as mast cells also express angiotensin-converting enzyme 2 (ACE-2),[8] many patients with POTS or similar disorders have elevated mast cell activation, and mast cell degranulation may also explain the cytokine storm seen in acute respiratory distress syndrome for patients with severe COVID-19 infections, he added. Additionally, the blood pressure fluctuations experienced by many long COVID patients could be evidence that the virus might invade the central

[7] The exclusion criteria for the long COVID patient group included history of dysautonomia, but the authors did not specifically indicate whether concurrent diagnosis of POTS was considered an exclusion criterion for the cohort.

[8] Angiotensin-converting enzyme 2 (ACE-2) is a membrane protein that also serves as the receptor for the SARS-CoV and SARS-CoV-2 spike protein and mediates cellular entry of the viruses. For a review of the role of ACE-2 in COVID-19 pathogenesis, see https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03120-0 (accessed October 8, 2023).

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nervous system and affect the brain stem. Lastly, sex physiology likely has a role given the average lower skeletal muscle mass, increased pelvic venous pooling, and higher propensity for autoimmune diseases in females compared with males. Sex hormones may also play a role, Miglis added, as many female patients report worse symptoms during their menstrual cycle.

In closing, Miglis acknowledged that the first approach that comes to mind for an autonomic disorder specialist is to treat the autonomic symptoms. However, the discipline has also started using anti-inflammatory medications for long COVID and sees promise in using vagal nerve stimulators. In his view, future progress in addressing these infection-associated chronic illnesses will include defining the diagnostic criteria for these types of illnesses, standardizing definitions, and establishing patient registries with open access to deidentified data. In particular, Miglis pointed to a lack of large-scale clinical trials for new treatments at 3 years after the emergence of the pandemic and said there are opportunities to accelerate the initiation of new treatment trials.

Inflammation in the Brain

Andrew Miller, Emory University, discussed common mechanisms of behavioral changes that may be involved in many of chronic illnesses and their manifestations. This work began with observations made by oncologists in the early 2000s, he explained, when they began treating cancer patients with the inflammatory cytokine interferon alpha (IFNα). Many patients reported adverse effects of depression, anxiety, problems with memory and concentrations, and a variety of neurovegetative symptoms including fatigue and appetite alterations. IFNα plays many roles in infectious diseases, such as inducing antiviral defense, enhancing innate immune response, facilitating adaptive immune response, and regulating physiological processes. Interestingly, said Miller, IFNα has been implicated in several infection-associated illnesses such as ME/CFS (Vojdani et al., 1998). It has also been associated with behavioral changes during human immunodeficiency virus (HIV) infection (Anderson et al., 2017), and persistent symptoms of fatigue and cognitive deficits in Lyme disease (Jacek et al., 2013).

A systematic review of published research on the mechanisms by which inflammatory cytokines affect the brain revealed a critical role of the basal ganglia in psychiatric and behavioral symptoms (Lucido et al., 2021). Cytokines' effects in different areas of the basal ganglia can lead to anhedonia, said Miller, a core symptom of depression, as well as fatigue, psychomotor slowing, decreased processing speed, and cognitive dysfunction. It appears that the underlying mechanism of these effects is cytokine-mediated disruption in the metabolism

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of neurotransmitters like dopamine and glutamate—which ultimately disrupts the neurocircuitry in the brain and leads to the observed symptoms.

Miller shared a study that documented an IFNα-induced decrease in ventral striatal activation in healthy study participants as detected by functional magnetic resonance imaging (fMRI), which is associated with reduced motivation and increased mental and physical fatigue (Capuron et al., 2012). This effect was replicated across different laboratories with two other, different inflammatory stimuli, he said (Eisenberger et al., 2010; Harrison et al., 2016). These findings translated to ME/CFS patients. Using the same experimental setup, Miller described the finding that fMRI detected reduced neural activation in the basal ganglia that correlated with higher fatigue levels in ME/CFS patients. He explained that, based on data from animal studies where treatment with interferon-alpha suppressed dopamine release, dopamine dysregulation is a likely mechanism underlying the symptoms in humans.

Miller also discussed endogenous inflammation, noting its difference from exogenously stimulated inflammation in patients. Viral reactivation and other consequences from viral infections often involve endogenous inflammation, so his team studied whether this disrupts connectivity in motivational and motor circuits in patients with major depression, using C-reactive protein as a marker for inflammation. The study found the greatest change in connectivity among different regions of the brain was a decrease in connectivity between the ventromedial prefrontal cortex and the ventral striatum (the motivational circuits) (Felger et al., 2016), and similar results were seen with decreased connectivity in motor circuits in the brain. These changes in circuits also mapped to the behavior of decreased motivation, cognitive slowing, and fatigue.

Shifting to peripheral inflammation, Miller said that though the reasons are unclear, there appear to be breaches in the blood–brain barrier in the context of stress and inflammation that seem to occur selectively in the same region of the brain that controls motor and motivational circuits. Overall, Miller summarized, antiviral and inflammatory cytokines lead to chronic changes in neurocircuits and neurotransmitter systems that contribute to neurovegetative symptoms including anhedonia, fatigue, and cognitive dysfunction. He offered the following research priorities:

1. Determining the common behaviors affected in infection-associated chronic illnesses,
2. Determining the common central nervous system (CNS) circuits affected in infection-associated chronic illnesses,
3. Determining the effects of infection and infection-related immune changes on neuronal and microglial function with a focus on neurotransmitter metabolism, and

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4. Testing pharmacologic agents targeting antiviral and inflammatory cytokines and their signaling pathways as treatments for infection-associated chronic illnesses.

The Role of the Microbiome in ME/CFS

Julia Oh, Jackson Laboratory, began by stating that the role of microbes in our health extends far beyond infections. The human microbiome plays an overwhelmingly positive role in regard to health and maintaining the immune system, she explained, and there are now a range of diseases linked to broader changes in the microbiome as a whole. She shared a graphic on homeostasis of the microbiome, which can be tipped into disease upon the introduction of pathogens, leading away from regulation and toward inflammation in a process called dysbiosis (see Figure 3-3).

Oh shared some of her laboratory's research looking at mediators of the host–microbiome interactions to see how these interactions might

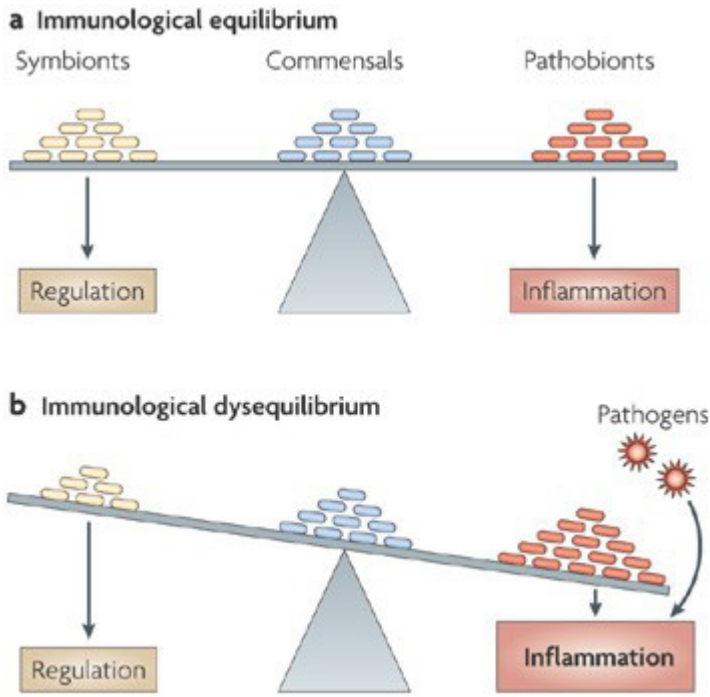

FIGURE 3-3 Dysbiotic microbiome-immune interactions.
NOTES: Figure 7-1 was originally published in *Nature Reviews Immunology* in 2009. A modified version was included in Oh's presentation.
SOURCE: Julia Oh presentation, June 29, 2023; Round and Mazmanian, 2009.

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be altered in ME/CFS patients. Ample prior research has shown that the microbiome can contribute to disease severity in ME/CFS. Acute infection can trigger ME/CFS symptoms, she said, which has been seen following Lyme disease and HIV. Additionally, prior research has also shown metabolomic irregularities and immune dysregulation in ME/CFS, and there has been anecdotal success with fecal microbiota transplantation for ME/CFS patients. There is collective precedent for integrating various "omics" approaches to generate new hypotheses for ME/CFS.[9] Her team is seeking to generate high-resolution datasets for the gut microbiome; examine details such as species composition, community structures, and coding capacity of the microbiome for different metabolites; and associate it with targeted plasma metabolomics and immune profiling. Data on the manifestation of disease is then collected via detailed surveys and clinical measurements and integrated into the dataset.

Oh's team studied patients who have short- versus long-term disease, matched with healthy controls, who were all followed longitudinally. Using state-of-the-art machine learning classifiers, they identified features that are characteristic of the disease stage. A major finding from this work is that short-term patients show the most significant microbial dysbiosis, even though long-term patients have the most severe disease. But long-term patients have the most major metabolic dysbiosis despite their reestablished healthy control lookalike microbiome, said Oh, which was surprising. For example, they were able to examine microbial diversity and pinpoint different species to see which are more dominant in various stages of disease. In late-stage patients, they saw the greatest change in blood metabolites compared to short-term disease patients or health controls. Summarizing these initial findings, Oh said that while they do not know why there is such a difference between short- and long-term disease, especially when the long-term disease patients appear to have a healthy microbiome while exhibiting the most changes in metabolic dysbiosis.

Oh also described the integration of clinical and -omics data into a machine learning model to develop a classification of cohorts. Their multiomics model was used to accurately predict ME/CFS patients and identify biomarkers such as the butyrate pathway. Butyrates are one of the microbe-produced short-chain fatty acids (SCFAs) and are linked to the function of a healthy gut, Oh explained. The microbes that produce butyrate were significantly depleted in both short- and long-term ME/CFS patients.

[9] In biology, "omics" refers to the study of "the entire complement of a specific type of biomolecule or the totality of a molecular process within an organism," particularly under a defined condition or time point; see https://www.britannica.com/science/omics (accessed December 10, 2023). Branches of these studies include genomics, metagenomics, transcriptomics, proteomics, metabolomics, and phenomics.

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Oh concluded by offering potential research opportunities to address the current knowledge gaps. She pointed out that a major limitation in the study of ME/CFS and other similar chronic diseases is the lack of good animal models that can reflect the heterogeneity of symptoms. There is a need for human clinical studies paired with high-resolution -omics data to identify causal links, such as immunotherapy studies. She also suggested studying if supplementation of butyrate producing microbes, direct supplementation of butyrate or SCFAs, or dietary modulation to enhance the presence of these butyrate producers in ME/CFS cohorts can lead to changes in the clinical phenotype or -omics profile toward a healthier state.

PATHOGEN-MEDIATED FACTORS AND PATHOGEN PERSISTENCE

In addition to host-specific factors, pathogens and their mechanisms are also considered alongside potential persistence within the body. This section highlights lessons from EBV, SARS-CoV-2, and animal models to better understand common factors across syndromes.

Lessons from Epstein-Barr Virus

Bill Robinson, Stanford University, talked about the role of EBV and molecular mimicry in MS. Robinson's lab is interested in the contribution of EBV reactivation in driving autoimmunity. Building from previous discussions, Robinson posed an overarching question of whether EBV is a causal contributor to these autoimmune diseases or if it is just an epidemiological phenomenon. A recent longitudinal analysis reveals a high prevalence of EBV associated with MS, where 801 patients developed MS and 800 of them had prior EBV infection (Bjornevik et al., 2022). To further define whether EBV was a causal factor of MS, Robinson's lab studied B cells from the spinal fluid of MS patients and found that there was a limited number of large clonal families of B cells. This is very different from what is found in typical blood samples, which contain a diverse repertoire of B cells.

After many years of studying the EBV-specific antibody repertoire of these B cells, Robinson's team honed in on an antibody, MS39, that binds to the Epstein-Barr virus nuclear antigen 1 (EBNA1).[10] Essentially, anti-EBNA1 B cells are activated during EBV infection, and the repeated activation that is necessary to promote affinity maturation inadvertently results in these cells targeting and binding to the myelin sheath in the brain. To see if this reactivity was pathogenic or not, additional studies conducted

[10] For a review of EBV infection pathogenesis, including the role of EBNA1, see https://www.nature.com/articles/nrc1452 (accessed December 10, 2023).

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by Robinson's team found that the cross-reactivity between antibodies to EBNA1 and GlialCAM (glial cell adhesion molecule, a central nervous system protein) can contribute to demyelinating disease in mice. Looking at larger cohorts of human MS patients and comparator groups, Robinson noted that the MS patients had high titers of anti-EBNA1 antibodies. This demonstrates that EBV can induce activation of anti-EBNA1 B cells, said Robinson, and that repeated EBV reactivation can cause a chain of events that mediate central nervous system and myelin tissue destruction, resulting in symptoms of MS.

To summarize the data, Robinson said that this research demonstrates a critical role for EBNA-1-mediated molecular mimicry in driving the autoimmune response that potentially underlies the pathogenesis in approximately one-quarter of human MS patients. It is likely there are additional pathways through which activation of B cell and other immune cells contribute to molecular mimicry and other mechanisms that play a role in the pathogenesis of autoimmune diseases associated with EBV infection.

Learning from SARS-CoV-2

Dan Chertow, National Institutes of Health (NIH), shared his team's findings on the pathogen distribution and persistence of SARS-CoV-2 based on autopsy studies of COVID-19 cases from three Maryland regions. The initial study goal was to describe the SARS-CoV-2 burden within and outside of the respiratory tract, as evidence from SARS-CoV-1 suggests that the virus can establish outside of the respiratory tract and even translocate to the brain. Investigators also wanted to determine if the virus persists in different tissues, and hoped to establish whether the virus is capable of replicating in tissues outside of the respiratory tract and how it might evolve in those areas of the body.

Between March 2020 and March 2021, the first year of the study (also the first year of the pandemic), Chertow and his team performed 44 autopsies and collected over 10,000 tissue samples from various places throughout the body. None of the individuals who were autopsied or provided tissue donations had been vaccinated, and most were severely ill from their acute infection of COVID-19. The cohort averaged 59 years of age, and was mixed across sex, race, and ethnicity. On average, Chertow said, 77 percent of the cohort had two or more comorbidities, such as cardiovascular disease, diabetes, obesity, or hypertension. Summarizing their overall findings, Chertow said that they found the most viral RNA among early cases in respiratory and cardiovascular tissues. Importantly, though, they found viral RNA across all tissue types and in all phases of COVID-19 patients—early, mid, and late cases of disease. One notable case was an individual who had a relatively mild course of illness from COVID-19,

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recovered, and then returned to the hospital months later with hepatitis A and died from an associated complication. When the autopsy was performed, 230 days after the initial illness onset, researchers were able to find viral RNA across multiple tissue compartments in his body. In the majority of the 11 autopsies from which brain samples were collected, there was evidence of viral RNA in multiple brain regions.

Viral culture is often viewed as the gold standard for demonstrating viral persistence. Chertow shared that they successfully recovered replicative virus from multiple tissues including eye, jejunum, lymph node, heart, adrenals, and brain. Examining site-associated viral RNA burden, Chertow found evidence of more viral RNA in respiratory versus nonrespiratory tissues. However, the burden of viral RNA decreased more rapidly from early- to late-stage of the infection in respiratory tissues while viral RNA clearance was slower throughout the course of infection in non-respiratory sites (Stein et al., 2022).

To address viral evolution, Chertow showed sequencing results from a single patient that harbored minor but distinct variants in the gene encoding the spike protein in viral isolates from the brain that were not seen in isolates from lung tissue. This supported their hypothesis that there is a viremic phase early in the infection where tissues throughout the body become seeded by viral dissemination, where the virus then undergo replications and evolution in the different anatomic compartments. Overall, his team was able to detect viral RNA in more than 30 cell types across 35 tissues, although they found a lack of inflammation—in this case, a lack of infiltration of immune cells—outside of the lungs, and a paucity of direct cytopathology in non-respiratory tissues. Chertow summarized by noting that SARS-CoV-2 RNA can persist in multiple anatomic compartments for an extended interval and that SARS-CoV-2 can infect and replicate in multiple cell types outside of the respiratory tract.

Lessons from Animal Studies

Monica Embers, Tulane University, shared her work on Lyme disease. Posttreatment Lyme disease syndrome (PTLDS) has existed for a long time, she said, but only came under extensive study in the past decade. Most Lyme disease patients can be successfully treated with timely administration of antibiotics, but some experience treatment failures and continue to suffer long term debilitating symptoms. A study in 2020 estimated the cumulative number of PTLDS cases at nearly 2 million, so she hypothesized the case number is even higher in 2023. As a result of various metanalyses and clinical case definitions, Embers explained, the pattern of symptoms for PTLDS appears to be different from those seen in fibromyalgia, depression, and ME/CFS.

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Embers shared that potential causes for PTLDS include induction of inflammatory responses by persistence of non-living spirochete bacteria or their antigens, the continuation of active infection, and irreversible sequelae from a previous active infection—otherwise thought of as autoimmune components. Furthermore, she added, all three of these causes can occur simultaneously. Doxycycline is typically used to treat the acute infection, working together with host immune clearance of the bacteria. But *Borrelia burgdorferi*, the causative agent of Lyme disease, can evade the immune response and may persist even in healthy hosts. Embers added that *B. burgdorferi* can survive for months inside ticks without nourishment and that metabolically dormant or persistent bacteria can be more tolerant to antibiotics. The efficacy and accepted regimen of antibiotic treatment for human borreliosis has been a contentious issue, she explained, with different professional organizations suggesting different regimens of treatment. Additionally, in vitro efficacy tests of antibiotics to inhibit and kill bacteria, which is what many treatment determinations are based on, can be different from in vivo effectiveness. Embers highlighted studies that show antibiotic tolerance is not a heritable trait (e.g., a genetic mutation that confers antibiotic resistance) but is mainly driven by the slow growth of the bacteria. Host adaptation can also contribute to antibiotic tolerance.

A recent study using nonhuman primates showed bacterial persistence and mild to moderate inflammation in the brain, peripheral nerves, spinal cord, joints, skeletal muscle, and heart following *Borrelia burgdorferi* infection. Embers drew a parallel to a case study of a 69-year-old woman who first contracted Lyme disease at age 54 and was treated with the standard doxycycline regimen, which led to symptom resolution (Gadila et al., 2021). However, the patient later developed a sleep and cognitive disorder years after the original Lyme disease infection. Her serological tests (C6 ELISA and IgG Western blot) were positive, but polymerase chain reaction (PCR) for *Bartonella*, *Babesia*, and *Borrelia burgdorferi* were negative.[11] Despite extended retreatment with antibiotics, the patient's neurocognitive and behavioral symptoms worsened and she eventually died 15 years after her initial Lyme disease diagnosis.

Imaging studies for this patient before her passing showed results consistent with Alzheimer's disease, and analysis of this patient's brain tissue revealed evidence of Lewy bodies, amyloid plaques, and *Borrelia* cells,

[11] Both ELISA and IgG Western blot detect the presence of circulating antibodies against bacterial antigens. For early-stage Lyme disease, the sensitivity of C6 ELISA is around 50-60% with specificity around 98.4%. Diagnostic performance may differ beyond early-stage disease. For more background on diagnosis of Lyme disease, see https://www.columbia-lyme.org/diagnosis and https://wwwnc.cdc.gov/eid/article/22/7/15-1694_article (accessed December 10, 2023).

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Embers said. She concluded that this case study, along with supporting evidence from animal models, supports the hypothesis that *B. burgdorferi* can persist after conventional antibiotic treatment. She added that borreliosis may play a role in the development of dementia.[12] Future strategies for treatment could be similar to the approach for tuberculosis, with combination antibiotics given to eliminate the development of bacterial persisters.[13]

In conclusion, Embers highlighted there are three primary similarities between long COVID and PTLDS: fatigue, brain fog and cognitive impairment, and musculoskeletal pain. Given the prevalence of both Lyme disease and COVID-19 in the United States and Europe, Embers suggested the possibility of these interacting as a syndemic.

Discussion

Several questions during the discussion were related to pathogen persistence in the human body. Responding to a question about the specificity of EBV-mediated autoimmunity in his studies, Robinson pointed out that in MS, as in many other autoimmune diseases, only specific regions of tissue are attacked and involved. For example, with type I diabetes, one islet of Langerhans in the pancreas might be wiped out while the one next to it would remain perfectly intact even though both carry the targets of the autoimmune response. Therefore, Robinson favors leveraging general tolerance mechanisms that prevent the broad autoimmune attacks in these diseases, though the best therapeutic options continue to elude researchers. Embers said they are pursuing the hypothesis that *Bartonella* and *Borrelia* co-infection allows *Bartonella* to cause more disease and persist longer, which may create a scenario where people are asymptomatic for a long time, making it difficult to detect. While Lyme disease may be at the core of the issue because of its ability to evade and suppress the immune system so effectively, other coinfections should also be considered, she added.

Another participant asked about age differences associated with persistence—mainly noticeable differences between children and adults in long COVID, and whether there are clues from other diseases. Embers said the mechanisms involved in PTLDS based on age are unknown, but it is well established that immune systems decline with advanced age, so children and young adults typically have better outcomes across types of infections, unless the infections lead to runaway inflammatory responses. A participant

[12] Note that the case study was not presented to demonstrate causation and the speaker stated the possibility of other contributing factors to the patient's chronic symptoms.

[13] Persisters describe a phenotypic subpopulation of bacterial cells that are non-dividing, metabolically dormant, and tolerant to bactericidal effects of antimicrobial compounds. See https://www.nature.com/articles/nrmicro1557 (accessed December 10, 2023).

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added that it is true that children have a lower incidence of these postviral or postpathogenic syndromes, but the symptoms are just as severe in those who do develop the chronic syndromes.

Chertow said that while the mechanism behind the different rates of viral clearance of various body tissues remain unclear, his team has observed a massive inflammatory response in the lungs of severe COVID-19 cases. Even in mild or moderate cases, there is likely a meaningful inflammatory response, he said. The mechanisms of pathogen persistence and evasion of adaptive immune response is not well defined, said Chertow, calling for more research on mechanisms of persistence and immune evasion.

Other questions revolved around therapeutics for these chronic illnesses, such as the efficacy of intravenous immunoglobulin for encephalitis and related symptoms. Miller highlighted the central nervous system consequences of these infections, noting that activation of the immune system will affect the brain and likely result in behavioral changes. Even though there is still much to learn about immunology, Miller noted that psychiatric approaches that address neurotransmitter systems and neurocircuits can relieve symptoms and improve patients' quality of life. He reiterated the downstream consequences of an activated immune response: the immune response comes with a high energy demand, so the brain shuts down other activities to conserve overall energy use, leading to fatigue, slowed processing, and lack of motivation. He argued that there is a role in this space for more psychiatrists and investments in psychiatric research to support development of potential treatments.

Related, another participant highlighted the importance of integrating immunology and psychiatry when treating MS patients, saying that the two fields have historically been fairly siloed, making it challenging to get MS patients to see a psychiatrist. Miller agreed, but emphasized that psychiatrists are important not because symptoms are "in the patient's head," but because biological processes in the brain are affected by the infection, which is then influencing their behavior—and this aspect of treatment need is being missed. He called for the education of physicians and researchers to integrate these fields and recommended funding these types of cross-disciplinary efforts.

Similarly, Miller also responded to another question on therapeutics to mitigate symptoms affecting the brain, saying he tends to prescribe drugs that facilitate dopamine release and temper glutamate levels. The problem is there are so few physicians and psychiatrists working in this area, and so many things have not been tried yet, he explained. He added that what is really needed is more time for doctors to sit with patients and learn from their experiences and what they have researched themselves. Adding to this point, Rowe noted that his team also prescribes stimulants to their patients with orthostatic intolerance, which potentially could be helping

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blood flow and oxygen delivery in the brain, improving symptoms from a different angle.

Peter Daszak, president of EcoHealth Alliance, asked about a vaccine for EBV given it likely plays a significant role in the development of MS. Robinson replied that there is an EBV vaccine advancing through Phase 2 trials at NIH, and Moderna just initiated a set of trials as well, but both are focused on prevention of EBV infection, which may be different than the type of clearance of already infected cells that many are hoping for.

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4

Potential Research Priorities and Opportunities in Diagnostics

Key Points from Individual Speakers and Participants[1]

- There is the potential for inflammatory mediators to act as biomarkers that predict the risk of persistent symptoms of Lyme disease. (Aucott)
- Future opportunities for diagnostic tests include the measurement of host responses, including inflammatory processes and gene regulation, metabolic changes, and epigenetic signatures. (Aucott)
- Multiple sclerosis is a rare complication of Epstein-Barr virus (EBV) infection. Evidence shows EBV reactivation in the brain is likely the leading cause of the pathology for MS. (Ascherio)
- The spike protein in SARS-CoV-2 can trigger platelet hyperactivation as well as microclot formation. Microclotting and platelet hyperactivation are also seen in myalgic encephalitis/chronic fatigue syndrome patients but at lower levels. (Pretorius)
- Metagenomic sequencing can provide more diagnoses compared to conventional clinical testing and could be a powerful tool for investigating emerging infections. Additionally, using

[1] This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

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host-response profiling, biomarkers can be identified to diagnose disease and monitor chronic disease. (Chiu)

- There are commonalities between various types of postinfectious syndromes, suggesting a shared pathophysiology, though likely through different mechanisms. The individuality of each person's immune response also plays an important role. (Nath)

A significant challenge in addressing infection-associated chronic illnesses is that they are difficult to diagnose or predict in the acute stages of the infection. This can lead to confusion for patients, dismissal from providers, misdiagnoses, or correct diagnosis only after years of suffering. Speakers presented on their research and suggested priorities in diagnostics, including the use of biomarkers, microclots, and high-throughput or next-generation and metagenomic sequencing. Similar to other chapter discussions, speakers highlighted lessons and findings that can be applied to different but related conditions given their overlap in symptoms.

USING BIOMARKERS FOR DIAGNOSIS

This section features speakers discussing the specifics of biomarkers for Lyme disease and Epstein-Barr virus (EBV) infection.

Lyme Disease

Lyme disease manifests in stages, said John Aucott, Johns Hopkins University, and can develop into a chronic illness. The first stage starts from the tick bite and transmission of the bacterial pathogen, which begins replication in the skin and sometimes results in the characteristic round red rash. Stage two is where manifestations of disseminated infection are present, with approximately 15 percent of people experiencing symptoms of neurologic disease and sometimes cardiovascular involvement such as carditis. When left untreated, he said about 60 percent of people develop arthritis in the third stage of disease progression. Aucott added that not all those with Lyme disease go through the three stages with identical symptoms, and that patients may seek care at either first-, second-, or third-stage of the disease. Others may be misdiagnosed or have a delayed diagnosis, and many might just have persistent symptoms but not an advanced stage of the disease. Aucott's research center specifically studies posttreatment Lyme disease syndrome (PTLDS) because it is a defined condition which facilitates the research process.

Aucott noted that the clinician's ideal diagnostic test would have high sensitivity and specificity and be accurate at all disease stages. Tests that could identify a marker of past exposure or determine whether the patient

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is responding to treatment or has improved would be particularly useful, as it would guide clinical decisions on whether the patient has been cured or is in need of additional treatment. Unfortunately, current test options have limitations in their sensitivity and specificity.[2] Diagnostic tests for Lyme disease fall into two main categories: direct tests that detect presence of the pathogen, and indirect tests that gauge the host response. Indirect tests pose exciting opportunities, especially for the PTLDS population, as they can potentially provide insights into the host-microbe interaction and pathogenesis mechanism. This information could help clinicians decide which treatments to use for a particular patient.

Diving deeper into the effect of inflammation on neural network alterations, Aucott said dysautonomia and postural orthostatic tachycardia syndrome (POTS) may be linked to inflammation that affects the nervous system. The manifestations of these symptoms may also play a role in chronic fatigue syndrome (CFS) and PTLDS. To study potential connections between these conditions, Aucott's team categorized patients into subgroups with similar symptoms, like autoimmunity or dysautonomia. Some of his research findings suggested that the peptidoglycans in *B. burgdorferi* are present in the synovial fluid of patients with late Lyme arthritis, even in individuals who have been treated aggressively by antibiotics and have no signs of active infection.

Shifting to inflammatory mediators, Aucott referenced the Study of Lyme disease Immunology and Clinical Events (SLICE), which was a longitudinal cohort study that has provided researchers with insights into the immune inflammatory mediators in acute Lyme disease. He presented a finding that a subgroup of people with acute Lyme disease had very high levels of inflammatory mediators, while Lyme disease patients had low levels of these mediators. This correlates with another study, where serum levels of IL-23, an inflammatory mediator, was high at acute infection and did not return to normal levels over 12 months in patients who went on to develop PTLDS. This was the first evidence that showed the potential for proinflammatory cytokines to be used as predictive markers of who might go on to develop persistent symptoms. For example, if a patient's IL-23 is still high after treatment at month 2, they may be likely to have PTLDS (Strle et al., 2014).

Aucott's team conducted a similar study that showed sustained elevation of the proinflammatory mediator CCL19 in the serum of a subgroup of Lyme disease patients (see Figure 4-1). For those who would eventually return to full health, the serum level of CCL19 decreased at their first follow-up appointment 1 month posttreatment. In fact, he continued, if a patient's CCL19 was still elevated at that first visit, researchers observed a 14-fold higher risk of that patient developing PTLDS 6 months later.

[2] See footnote 18 for additional background on currently available diagnostic tests.

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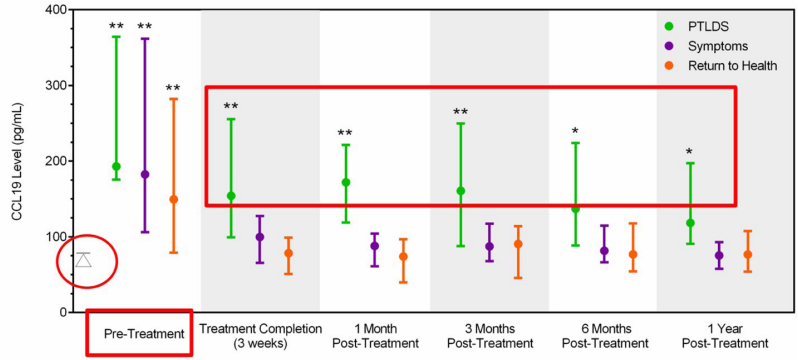

FIGURE 4-1 Serum CCL19 levels over time correlated to clinical outcome status.
NOTE: PTLDS = posttreatment Lyme disease syndrome; The median control values (79.3 pg/mL for CCL19) is represented by a triangle in the graph; The red boxes highlight the significantly elevated levels of CCL19 in the group of study participants who developed PTLDS following pretreatment assessment; *p≤0.05, **p≤0.01 for comparison of each group to controls
SOURCE: John Aucott presentation, June 29, 2023, Aucott et al., 2016.

This offered an option for an intervention at the time of elevated CCL19 detection rather than waiting to see if symptoms persisted for several more months. A third, recently published study also showed correlation between interferon alpha levels and developing persistent symptoms (Hernández et al., 2023). Aucott noted that there are other interesting inflammatory cytokines being identified that could serve as biomarkers to predict which patients are most at risk for long term symptoms. There are also autoantibodies being investigated that could play a similar role.

Aucott briefly touched on a couple of potential new diagnostic approaches. In terms of metabolomics, which examines small molecules (e.g., fatty acids) by mass spectrometry, Aucott found that the metabolic profile for people who will develop PTLDS 6 months after initial infection is different than those who will return to health (Fitzgerald et al., 2021). Another area of exploration is the study of epigenetics to characterize host DNA modification in response to environmental insults such as infectious disease. Aucott shared information about a project he is working on with the Defense Advanced Research Projects Agency called ECHO that seeks to examine potential threats to DNA epigenetics from the effects of *B. burgdorferi*.[3]

[3] For additional information on the ECHO project, see https://www.darpa.mil/program/epigenetic-characterization-and-observation (accessed December 10, 2023).

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The last area Aucott outlined as a potential for diagnostics development in Lyme disease is CNS imaging. The translocator protein (TSPO) binds glial cells that are activated and inflamed and can be used as a marker of inflammation, he explained. Positron emission tomography (PET) imaging revealed that the brains of people with chronic Lyme symptoms have more microglial activation compared to healthy controls (Coughlin et al., 2018). Using functional magnetic resonance imaging (fMRI), researchers have found that people with persistent Lyme disease symptoms had lower blood flow in their grey matter compared with control groups. However, some regions in the white matter appeared more highly activated compared with the control group, suggesting potential compensatory mechanisms in neurocognition (Marvel et al., 2022). Researchers are working to study this further to elucidate if this pattern of white matter activation aligns with the brain fog of persistent Lyme. To Aucott's understanding, no one has yet examined this in PTLDS. Since brain scans can be done and is not an invasive procedure, this could be developed and used as a diagnostic test.

In conclusion, Aucott called for improved diagnostics for acute Lyme disease and its infection-associated chronic illness. He shared that future opportunities for diagnostic tests include imaging approaches as well as measurement of host responses, including inflammatory processes and gene regulation, metabolic changes, and epigenetic signatures.

Epstein-Barr Virus and Associations with Multiple Sclerosis

Alberto Ascherio, Harvard T.H. Chan School of Public Health, presented on the study linking EBV to MS, referenced in Chapters 2 and 3, explaining that his research team sought to estimate the risk of developing MS before and after EBV infection. Researchers found that risk of developing MS was extremely low before EBV infection but increased by 32-fold following EBV infection (Bjornevik et al., 2022). In contrast, individuals who were already positive for CMV at the beginning of the study were found to have a reduced risk of developing MS. Furthermore, the study demonstrated that EBV infection preceded not only the first clinical symptoms of MS, but also the elevation of serum neurofilament light chain (a marker of MS onset and progression) by up to 6 years (Bjornevik et al., 2020). He clarified that MS is a rare complication of EBV infection, but other factors at play that can increase risk aside from family history include vitamin D deficiency, tobacco smoking, obesity during adolescence, and low intake of alpha-linolenic acid.

Focusing on biomarkers, Ascherio referenced work that began more than 20 years ago studying antibody titers against EBV and CMV before the onset of any neurological symptoms of MS. The results of these studies support that EBV plays a role in the etiology of MS by showing that the serum levels of IgG antibodies to EBV nuclear antigens (EBNA) are a strong

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predictor of MS (Levin et al., 2005). He also noted that anti-EBNA titers may be a marker of a strong cellular immune response against EBV, which could complement the hypothesis of the antibody's molecular mimicry. However, he did not think the anti-EBNA titers could be used for diagnostic purposes. Another characteristic of these antibodies is that elevated levels are seen up to 16–20 years before the onset of MS, said Ascherio. However, he noted, these antibodies do not seem to predict the disease severity or progression, and there does not seem to be any evidence that higher antibody titers are associated with faster disease progression.

In contrast to what is known in humoral immunity, Ascherio said, comparable data on cellular immunity is not available. A dataset comparable to what has been assembled for humoral immunity would be the best way to study cellular immunity against EBV before the onset of MS. He pointed to a study done in individuals with clinical MS showing that the frequency of cytotoxic CD8 T cells against EBV is higher in the MS patients than controls–this increase was of similar magnitude to the increase in CD8 T cells against SARS-CoV-2 observed in individuals with COVID 19 (Schneider-Hohendorf, 2022). According to Ascherio, this is consistent with the hypothesis that not only does EBV cause MS, but it also drives the long term disease process. Based on the currently available evidence, he surmised that EBV reactivation in the brain is likely the leading cause of the pathology for MS.

USING MICROCLOTS AS INDICATORS OF DISEASE

Resia Pretorius, Stellenbosch University, emphasized the relevance of cellular receptor and inflammatory marker interactions in driving various disease pathologies. Her lab has spent years looking at how inflammatory molecules may cause pathological blood clotting, including effects on platelets, red blood cells, and the clotting protein fibrinogen[4]. They have focused on the numerous membrane receptors on platelets that can cause platelet hyperactivation when these inflammatory molecules are in circulation. In the context of COVID-19, Pretorius said, it is important to remember that platelets can form complexes with not only other platelets, but immune cells as well. These platelet–immune cell complexes can then influence autoimmunity and immunity. When you are healthy, she explained, fibrinogen is a soluble protein, but when it interacts with a circulating inflammatory molecule, it can change its shape (see Figure 4-2). A typical protein has lots of alpha coils and beta sheets, she explained, but when they interact with inflammatory molecules, the alpha coils untwist into large beta sheets, which causes the clotting.

[4] For more information on inflammatory molecules and chronic inflammation, see https://www.nature.com/articles/s41574-018-0059-4 (accessed 11/30/2023).

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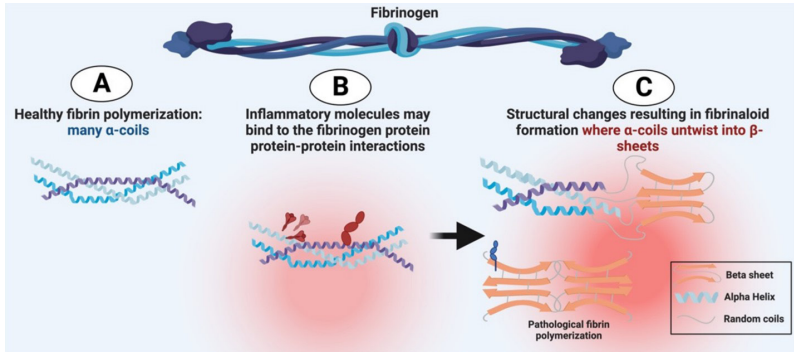

FIGURE 4-2 Pathological clotting.
SOURCE: Resia Pretorius presentation, June 29, 2023; created with BioRender.com.

Pretorius' team was already studying clotting pathologies in South Africa using scanning electron microscopy when COVID-19 emerged. It became clear to her that the cohort of patients with acute infection had significantly hyperactivated platelets. Pretorius and her team found there was also significant microclot formation in samples from ICU patients, much more than previously found in patients with type II diabetes or healthy controls. After the initial studies on acute COVID-19, her team also examined and found that the spike protein can trigger significant platelet hyperactivation as well as microclot formation. This finding is also supported by studies in Sweden, she noted, where researchers found that the spike protein itself is an amyloidogenic protein (Nyström and Hammarström, 2022).

Pretorius explained that she and her collaborators began studying long COVID in early 2021, as it became clear that many patients were not fully recovering from the acute infection and had significant symptoms. They found significant platelet hyperactivation in these patients as well, with platelets clotting together and binding to each other forming different protein complexes (Laubscher et al., 2021). Because diagnosis was difficult with the research methods they used in the lab, they developed a platelet grading system to show how they anticipated the platelets in a person with long COVID may look (see Figure 4-3). The first row represents healthy platelets, the second and third row is what platelet hyperactivation may look like in someone with diabetes or rheumatoid arthritis, and the fourth row is what platelets in individuals with acute and long COVID may look like. Examples of stage 4 microclots are depicted in the bottom row as detected by (A) bright-field microscopy, (B) fluorescence microscopy, and (C) an overlay of fluorescence and bright-field microscopy (Laubscher et al., 2021).

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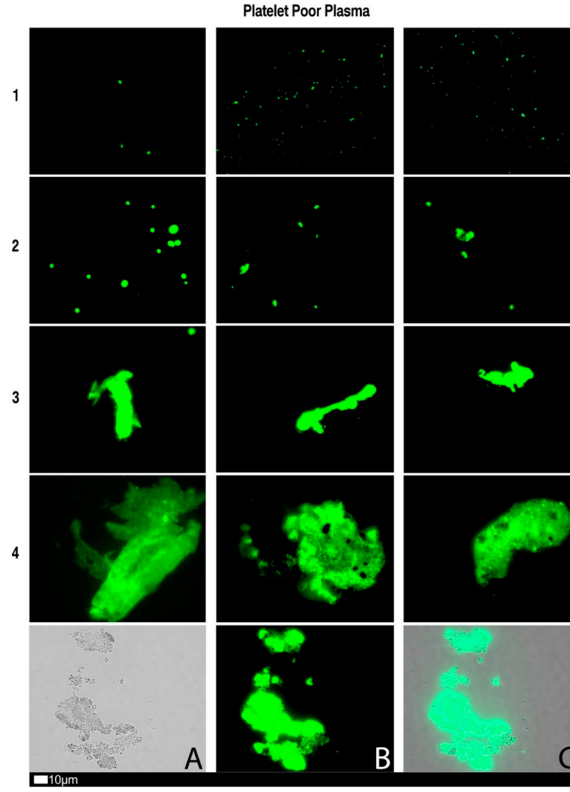

FIGURE 4-3 A microclot grading system.
SOURCE: Resia Pretorius presentation, June 29, 2023; Laubscher et al., 2021.

Pretorius and colleagues employed proteomics to try and understand what was inside the clots, but they were surprised when a basic enzymatic process was unable to digest the clots and prepare samples for proteomics analysis, Pretorius said. Eventually, they were able to conduct the analysis and found numerous inflammatory molecules trapped inside the microclot complexes. These included von Willebrand Factor, fibrinogen molecules, and a molecule called alpha two antiplasmin, which prevents the clot breakdown (Pretorius et al., 2021). This result was replicated in a larger cohort study. Pretorius shared a paper that documents a novel cell-free methodology to detect microclots inside plasma from patients with long COVID (Turner et al., 2023). She noted that microclotting and platelet hyperactivation were also found in ME/CFS patients, though not to the extent they saw in long COVID patients. In both ME/CFS and long COVID patients,

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she added that they recently found endothelial debris in their platelet-poor plasma, which confirmed an endothelial origin.

In summary, Pretorius said, ischemic reperfusion injury has been found in all the long COVID patients that her group studied. With the current evidence, she posited that long COVID is possibly a form of thrombotic endothelitis. She noted that there is a relevance of receptor-inflammatory marker interactions that drive disease and advocated for looking at protein–protein interactions when considering new methodologies for diagnosis.

NEXT-GENERATION AND METAGENOMIC SEQUENCING

Charles Chiu, University of California, San Francisco, discussed metagenomic sequencing for potentially aiding in diagnoses. Infectious disease doctors often faced with major diagnostic challenges, he said. For example, in as many as 62 percent of pneumonia patients who present to the hospital, providers are unable to diagnose an infection despite testing for bacterial and viral pathogens (Jain et al., 2015). Meningitis and encephalitis are neurological diseases thought to have infectious etiology, but the cause remains unknown in roughly half of meningitis or encephalitis cases (Glaser et al., 2006). Even in patients with well-characterized infectious syndromes like sepsis, he continued, doctors are unable to make a definitive diagnosis based on currently available tests in approximately 20 percent of the cases. Failure to make an accurate and timely diagnosis delays therapy, increases mortality, and increases health care costs.

Chiu noted that the only major indirect test available is antibody detection to diagnose infections. His laboratory has been working to develop clinical metagenomic sequencing as a way to diagnose acute illnesses, and potentially applying it to associated chronic illnesses. Metagenomic sequencing provides a way to comprehensively characterize the genomic material in a clinical sample by sequencing all of the DNA and RNA present, he explained. In theory, one would then be able to identify any causative organism in that clinical sample, potentially making this a powerful tool for investigating emerging infections. Chiu and his collaborators have validated this sequencing process in the laboratory as well as in clinical studies, and they contend that they can run the same assay on a variety of body fluids. However, how best to analyze the data and gather results remains a challenge. His team developed an automated pipeline that is compliant with the Health Information Privacy and Affordability (HIPAA) Act and produces results that can be interpreted by a lab director, even without bioinformatics expertise.

Furthermore, Chiu said that parallel metagenomic sequencing of multiple samples can provide more throughput in diagnoses compared to conventional clinical testing approaches (Wilson et al., 2019). He and col-

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laborators are currently working to enable any clinical lab to use their test; they have been able to reduce the metagenomic next-generation sequencing assay procedure from 2 or 3 days of processing with 300 steps, down to same-day results with just about 20 steps. He sees this test being used more routinely in the near future as part of clinical laboratory operations.

Application to Chronic Illnesses

Considering the application of metagenomic sequencing in infection-associated chronic illnesses research, Chiu revealed that most of what is sequenced is actually not the pathogen, but the patient's own DNA and RNA. This has major implications for precision medicine, as it can provide significant insights into host response, which then inform a doctor in personalizing medicine and treatment to best suit the patient. The host response to various infections can be different for each individual. For example, some patients with West Nile virus infection are asymptomatic while others develop fatal encephalitis. Similar variation in outcomes was seen with COVID-19 as well. Chiu shared a vision of the future in which instead of researchers selecting major disease-specific pathways for an illness like Lyme disease, artificial intelligence (AI) selects them based on a machine learning algorithm, identifying the specific features or genes for a given disease. For example, he took data from 1,000 spinal fluid samples representing various infections and syndromes, and divided them into four major categories: bacterial, viral, fungal, and autoimmune. After exposing the machine learning model to the training set of well-categorized samples, it was able to then classify a test set with 90 percent accuracy for each of the four comparisons.

In another example of acute flaccid myelitis (AFM) in children, Chiu shared that it is often difficult to identify the potential causative agent, enterovirus D68, in spinal fluid and the diagnosis is usually made incidentally when examining other secretions. However, researchers found a signature for AFM in spinal fluid samples that were otherwise microbiologically negative if the disease is associated with infection by enterovirus A71 or D68. What the researchers hope to obtain in addition to a metagenomic sequencing result, said Chiu, is a host-response classifier than can identify specific types of infections and potentially noninfectious causes. Using the algorithm to cluster these signals, the clinician can see what diagnoses may be most closely tied to a cause based on the host response, such as autoimmune diagnosis being related to viral infection, he explained. Chiu's team is also working to identify signatures specific to neurologic syndromes by taking the samples that were most well characterized and successfully identifying signatures for cancer, amyloidosis, and MS to develop a classifier tool.

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Applying this approach to Lyme disease, Chiu and colleagues were able to show that host response can be used to identify infections (Servellita, 2022). Chiu anticipated that the ability to run this type of assay longitudinally allows for the development of tests that can diagnose infection and even potentially monitor the course of a chronic illness related to infection. Using Lyme disease patients as an example, he presented data from longitudinal host-response analyses showing the Lyme disease classifier was persistent in samples for as long as 6 months after early Lyme presentation. In the future he hoped to generate differential classifiers that can monitor the course of any given chronic disease.

In conclusion, Chiu said that metagenomic sequencing is a promising approach for diagnosis of infectious diseases. By using the host-response profiling he and his team developed, biomarkers can be identified to help with diagnosis and monitoring chronic disease progression. Chiu noted that advancement of this new technology will require close coordination with regulatory statues and bodies such as Clinical Laboratory Improvement Amendments and the Food and Drug Administration (FDA) in order to develop useful reference standards and validation measures that could streamline the path to use in clinical practice.

DISCUSSION

The discussion focused mainly on the potential for future diagnostic tests and biomarker profiling. Regarding the validation of AI tools, Chiu said there has been increasing interest from the National Institutes of Health (NIH) and other government agencies in developing guidelines for how these types of tests would be validated, and how to ensure they are being correctly indicated. He is hopeful that the ultimately approved tests will be disease agnostic and can be applied to diagnose a variety of different conditions.

Another question was in response to data Chiu presented that shows markers of the host response for *Borrelia* clustering more closely with host responses to viruses than to other bacterial infections. The workshop attendee asked what markers might be used to distinguish between these pathogens. Chiu pointed out that infection by each pathogen may have very distinct features, so gene expression profiling can potentially be used to identify specific diagnostic markers in each case. An audience member highlighted the latency in symptom emergence experienced by many patients, who do not realize or make the connection between the initial infection until chronic symptoms manifest. From a diagnostic perspective, she asked, could technology reach a scale where it could become a preventive tool so diseases can be identified earlier, avoiding the long-term chronic illnesses that many are suffering from? Chiu noted that there has been increasing

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interest in shifting the focus away from disease and more on health. Technology exists that can do comprehensive -omics profiling of anyone, he said, so this could be a powerful tool for evaluating a person's status and whether they are at risk of developing disease in the future. Beyond just diagnostics, metagenomic profiling could have a role as a predictive tool as well.

Avindra Nath, National Institute of Neurological Disorders and Stroke, shared emerging themes that he took away from the session's presentations, beginning with the realization that there is a commonality between various types of postinfectious syndromes suggesting a shared pathophysiology though likely through different mechanisms. Secondly, he said, is the importance of the immune response, which several panelists have highlighted in their remarks. Even if a patient does have a persistent antigen, what is really driving the symptomatology could be an aberrant immune response. Lastly, many of these conditions seem to be diseases of the brain—but they are all interrelated, and there is a clear need to improve the ability to interrupt the negative cycles of pathology. With so many people already affected, he argued, we cannot afford to wait another decade to figure out all of the mechanisms before taking action to help the patients. Instead, he emphasized the need to start clinical trials now with the information available, and then continue to study the pathophysiology in the context of these trials.

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5

Potential Research Priorities and Opportunities in Therapeutics

Key Points from Individual Speakers and Participants[1]

- An altered zonulin pathway and the presence of the spike protein in blood does not necessarily mean an individual will have long COVID. There also needs to be a genetic predisposition, which explains why only some people with the spike in their blood suffer from long COVID symptoms and others do not. (Fasano)
- There are likely interactive feedback mechanisms between the immune system and microbiome. Developing alternative treatments for Lyme disease that do not wipe out good flora can help patients with acute disease but decrease probability of developing long Lyme by avoiding microbiota disruption. (Lewis)
- Learning from different complex chronic illnesses is key, and it is important to know how they are similar and different in order to properly train clinicians and improve precision and personalized treatment approaches. (Putrino)
- Infection-associated chronic illnesses are complex conditions that often require novel combinations of treatments to address multiple underlying causes. (Putrino)

[1] This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

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Several speakers in this session emphasized the need for new treatment approaches and therapeutics that can be made available quickly for patients who have been suffering. This chapter focuses on several priorities for developing therapeutics for infection-associated chronic diseases, such as antiviral development (including drug development and repurposing), using combination therapeutics, and developing treatments specifically for children suffering from chronic symptoms following COVID-19 infection. Speakers also highlighted the potential for better treatments that do not disrupt the microbiome, as well as a variety of treatment approaches within a clinic setting.

ANTIVIRAL DEVELOPMENT

This section reviews current evidence on the development of antivirals for acute COVID infections and long COVID, and the understanding that informed the need for combinations of therapeutics.

Development of Paxlovid

Ravi Shankar Singh, Pfizer, provided remarks on the development of Paxlovid,[2] an antiviral drug that is used to treat COVID-19 patients. While drug development is typically a very long process, the process for nirmatrelvir, the antiviral component of Paxlovid, took less than 2 years from concept to treating patients. Pfizer made a few innovative changes to expedite the process in an emergency situation, he said, including expedited drug design and manufacturing of the drug product, at-risk investment in commercial batches, and rapid internal decision making and regulatory interactions. Pfizer had worked on drug development during the 2003 severe acute respiratory syndrome (SARS) outbreak and was able to draw

[2] Disclaimer from the manufacturer: Paxlovid is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. Paxlovid has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death; and the emergency use of Paxlovid is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. §360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner. Paxlovid includes ritonavir, a strong CYP3Ainhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events. Prior to prescribing Paxlovid: 1) Review all medications taken by the patient to assess potential drug-drug interactions with a strong CYP3Ainhibitor like Paxlovid and 2) Determine if concomitant medications require a dose adjustment, interruption, and/or additional monitoring. Consider the benefit of Paxlovid treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed.

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from that experience to design a new drug candidate molecule for SARS-CoV-2 relatively quickly since the two viruses are structurally similar, Singh explained. One of the weaknesses of the molecule designed in 2003 for SARS-CoV-1 was that it had poor intestinal permeability; to address this, the drug design group altered some functional groups in the chemical structure to improve the oral bioavailability.

To enable the rapid timeline that was needed during the pandemic, the Pfizer team leveraged a machine learning/artificial intelligence design tool against a large dataset of drug molecules to predict antiviral efficacy and pharmacokinetic (PK) properties. Nirmatrelvir was then selected over 600 other potential therapeutic molecules flagged in this analysis. Pfizer used an innovative "first in human" study design, which efficiently informed and accelerated the launch of the clinical trial.[3] Ritonavir, a protease inhibitor, was added after determining that it significantly increased the half-life of nirmatrelvir. Next, the team developed and used population PK and quantitative structural pharmacology models to project drug concentration and effect on the viral load in the blood to determine appropriate dosage and duration of treatment. As 5- and 10-day regimens had similar projected viral load reduction, they recommended a 5-day regimen to reduce the burden on patients.

With this information and data in hand, they moved toward testing the formulation in clinical trials. Early on, results showed that patients treated with Paxlovid were significantly less likely to experience hospitalization related to COVID-19 or death from any cause within 28 days of beginning treatment. The trial was stopped prematurely because of the exceptional efficacy.

Summarizing the lessons from this expedited effort, Singh shared the following lessons for future drug development:

- Being bold and holding different stages of drug development in parallel, rather than in sequence, to expedite the process.
- Sharing prior and emerging clinical development knowledge from other diseases or pathogens.
- Increasing collaboration, flexibility, mutual regulatory recognition and reliance.
- Enabling rapid decision making through streamlined and timely interactions between sponsors and regulators.
- Embracing digital tools to enhance access, speed, quality, and the patient experience.

[3] For details on the Paxlovid clinical trial design, see https://classic.clinicaltrials.gov/ProvidedDocs/31/NCT04756531/Prot_000.pdf (accessed December 10, 2023).

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Development of Antivirals and Combination Therapies for Infection-Associated Chronic Illnesses

Sara Cherry, University of Pennsylvania, shared her work exploring antiviral therapeutics and using established virology knowledge to advance therapeutics for long COVID. She noted that the initial infection of SARS-CoV-2 was largely confined to the upper respiratory tract, even in people without symptoms. But once the virus moves into the lower respiratory tract, it tends to cause more severe symptoms and progress to acute illness. Symptoms of long COVID are highly variable, and there is a need to understand the connection between these symptoms and the initial infection, Cherry stated. The focus in developing antivirals is typically on blocking the acute infection through a number of different mechanisms. The largest class of antivirals is direct-acting molecules that prevent viral replication (e.g., Paxlovid, remdesivir). But viruses are intracellular parasites, and rely on intracellular host pathways to replicate, she said, so there have also been efforts to develop host-directed therapeutics such as halting viral replication by blocking a host enzyme that the virus needs to replicate. Lastly, there are immunomodulators that work to boost an early immune response that can also block viral replication.

As the pandemic emerged in 2020, Cherry said her team utilized their existing pipeline to focus on identifying antiviral small molecules with specific activity against SARS-CoV-2. They collaborated across the world to obtain drug repurposing libraries, which contain large numbers of small molecules originally developed to combat other pathogens. The largest class of approved antivirals resemble human nucleosides, the building blocks used to make RNA, which block viral replication when incorporated by the virus. Another large category they found from the library was inhibitors of human enzymes that make the nucleosides, which works by "starving" the virus of these building blocks for replication and thereby blocking infection.

Modeling some of the successes of HIV antivirals, she said her team understood that they could combine different agents to create a "cocktail" of small molecule inhibitors and increase the potency while also decreasing the likelihood of resistance. Their testing demonstrated synergistic outcomes when molnupiravir, a nucleoside analog, is combined with inhibitors of host nucleoside biosynthesis. They then used air–liquid interface cultures that mimic the human respiratory system where most of the viral replication occurs to test if these drug combinations that worked well in cell culture assays were effective in an environment that resembles real-world infections. Using the air–liquid interface models, they were also able to find that treatment with interferons or small molecule activators of innate immunity was able to reduce the viral load. Using animal models, they found that adding brequinar to molnupiravir could decrease the viral titers more than

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molnupiravir alone. This also led to significant decrease in pathogenesis in the lungs, added Cherry.

However, all these tests were focused on the acute infection, and her team was interested in what is causing the long COVID symptoms—if there is viral antigen or if the infection is similar or different in different compartments. Based on existing data, they focused this effort on the gastrointestinal (GI) tract. Given the widespread use of wastewater testing throughout the pandemic, she said it is clear that at least some stage of the infection cycle is affecting or being shed through the GI tract. While they mostly detected viral antigen in the respiratory tract in autopsy samples taken from patients with acute disease, samples from patients in the post-acute phase revealed viral antigen within the GI tract of many individuals.

She shared some of their data from testing the activity of small molecule drugs used clinically, such as Paxlovid or interferon beta in a human intestinal cell line. They found that Paxlovid and interferon beta retained activity in the human intestinal cell line, while molnupiravir had decreased activity. Furthermore, prophylactic treatment by all three compounds showed antiviral activity in preventing infection, but there was significantly reduced activity with single-dose treatment regimens after the infection is established. Moving forward, she said they are beginning to test for a variety of regimen timelines and different combinations; it is hoped that doing so will inform the understanding of treatment strategies that might be helpful in long COVID patients.

CLINICAL TRIALS FOR MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN AND LONG COVID

Alessio Fasano, Harvard University, recalled his surprise as a pediatrician at the beginning of the COVID-19 pandemic when many were suggesting that children would be spared from the COVID-19 pandemic, which would be unusual for a viral infection While the virus travels from upper to lower airways in adults, it does not do that in children for reasons that are still unknown. Because of this, many children remained asymptomatic even though the virus attack rate is the same as in adults, so a proportion of children suffer from the same kinds of long-term effects seen in adults. Meta-analyses have since revealed the prevalence of more than 40 long COVID symptoms in children and adolescents, with more than 25 percent reporting the presence of one or more symptoms after 12 weeks (Zheng et al., 2023).

Fasano stated his belief that long COVID is a consequence of a virus that (1) persists in biological niches and (2) leads to chronic inflammation, eventually resulting in (3) autoimmune response. Solid evidence shows that this virus can be found in the gut even months after acute infection, he said.

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His team also found that the immune response to the viral spike protein is a surrogate biomarker of multisystem inflammatory syndrome in children (MIS-C) when compared to healthy children (Yonker et al., 2021).

One of the consequences of viral persistence is dysbiosis of some host pathways, such as the zonulin pathway that modulates the intercellular tight junctions in the GI tract. When this pathway is upregulated the tight junctions are disrupted and there is uncontrolled antigen trafficking from the gut lumen into the bloodstream. Fasano shared the first study they did in children with MIS-C, where they found an elevation of serum zonulin, and participants had systemic symptoms including microbiota dysbiosis and tight junction disruption (Yonker et al. 2021) (see Figure 5-1). The viral spike protein is then able to enter the bloodstream as a result of zonulin upregulation, he explained, leading to cytokine storm, activation of specific T cells, production of proinflammatory cytokines, and formation of microclots that eventually result in more severe consequences for those individuals, such as long COVID and MIS-C. The presence of SARS-CoV-2 in the GI tract can precipitate this chain reaction. Zonulin has been associated with many chronic inflammatory diseases, he added, and the common element between these chronic inflammations is dysbiosis.

Through this study, Fasano and colleagues identified evidence of inflammation. His team detected SARS-CoV-2 in the stool weeks or months after initial COVID-19 infection, and its presence in the GI tract caused

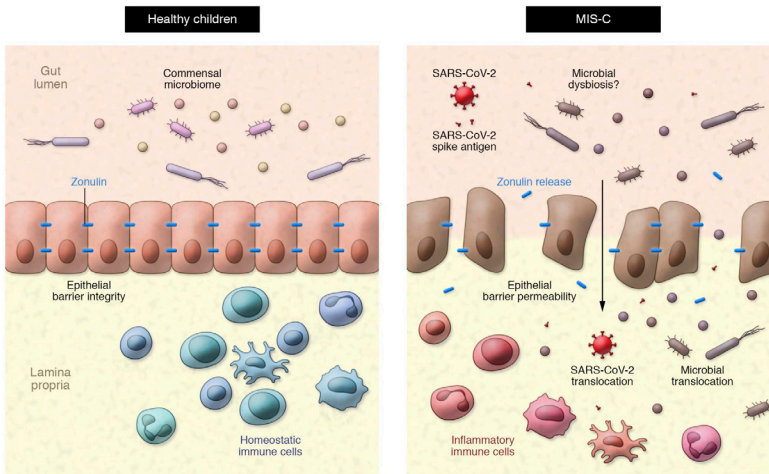

FIGURE 5-1 Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier.
SOURCE: Alessio Fasano presentation, June 30, 2023; Hensley-McBain and Manuzak, 2021.

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imbalance to the microbiome, an increase in zonulin, and a leakage of highly inflammatory viral particles and antigens into circulation (Yonker et al., 2021). With this information, they theorized that instead of treating the consequence of the hyperinflammation, there might be an opportunity to treat the cause, i.e., the zonulin-mediated dysbiosis, barrier integrity alteration, and antigen trafficking that may be causing the spike protein to circulate. The same findings emerged with long COVID patients, when researchers found that zonulin levels were higher in long COVID patients, compared to those who were COVID-positive but did not develop long COVID symptoms and healthy controls. Additionally, low-density lipoprotein (LDL) levels were used as a biomarker surrogate of oxidative stress and inflammation, and there is a direct correlation between zonulin levels and this oxidative LDL, he explained (Mouchati et al., 2023).

Autoimmune response is also tied to viral persistence and inflammation. The spike protein of SARS-CoV-2 is a super antigen, Fasano said, with the capability to stimulate T cell expansion leading to autoimmunity, implying that individuals with a certain T cell receptor mutation would be at risk (Porritt et al., 2021). Simply having the altered zonulin pathway and having the viral spike protein in your bloodstream does not necessarily mean that the individual will develop long COVID, he clarified, as a genetic predisposition is also needed. This explains why only some people with the spike protein in their blood suffer from long COVID symptoms and others do not.

Thinking of clinical translation, Fasano theorized they could stop the pathway leading to MIS-C manifestation by stopping the passage of elements from the virus into circulation. Because there was no effective or approved treatment for children suffering from MIS-C at the time, they requested compassionate use approval from the U.S. Food and Drug Administration (FDA) to administer larazotide and zonulin in these patients. This treatment was found to shorten the time to resolution for GI symptoms (from 6.7 to 2.3 days) and cleared the spike antigen very quickly (from 10 days to 1 day) (Yonker et al., 2022). This led to a phase 2 trial, which was halfway completed at the time of the workshop, but Fasano remarked on the favorable safety profile so far.[4]

Finally, in terms of a surrogate marker, Fasano shared an example from a young patient who was in the intensive care unit, and, along with other children at the time, was given the standard of care of intravenous immunoglobulin (IVIG), steroids, and Anakinra,[5] but with little clinical

[4] For information about the clinical trial, see https://clinicaltrials.gov/study/NCT05022303 (accessed December 10, 2023).

[5] Anakinra is an interleukin-1 receptor antagonist and an immunosuppressive drug approved to treat rheumatoid arthritis in adults.

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improvement. When larazotide was administered in this patient, levels of the viral spike protein and C-reactive protein (an established marker of inflammation) both dropped. Taking this to the next level, Fasano said they just received approval for a phase 2 trial for treatment of long COVID, focused on pediatric populations who have spike protein or S1 in their blood as an indication of disrupted intestinal barrier integrity.

OPPORTUNITIES FOR PREVENTION AND TREATMENT OF *LYME DISEASE ASSOCIATED CHRONIC ILLNESSES*

Given the overlap in symptoms between chronic Lyme and other autoimmune disease, Kim Lewis, Northeastern University, wanted to investigate whether there was also an overlap between alterations in the microbiome in these disease states. Looking at different subgroups of patients compared with healthy controls, his team identified distinct signatures in the gut microbiomes for each group. There are also different gut microbiome signatures depending on treatment with certain antibiotics and the time point of treatment in relation to when the sample was taken. A typical marker of dysbiosis is expansion of the bacterial family *Enterobacteriaceae*, he said, which are associated with a proinflammatory state. This led his team to a working hypothesis that there are interactive feedback mechanisms between *Borrelia burgdorferi*, the human microbiome, and the immune system. He called attention to the routine treatment of acute Lyme disease with broad spectrum antibiotics, noting that while it is the only current treatment for Lyme, these antibiotics also disrupt the microbiome and may increase the probability of developing chronic Lyme-related symptoms. He suggested treating with a selective antibiotic that only kills *Borrelia*, helping patients with acute disease but also decreasing the probability of long Lyme by avoiding disruption of the microbiome that can be connected to many other conditions (see Figure 5-2).

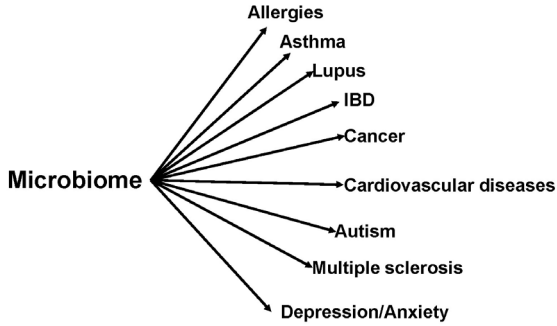

FIGURE 5-2 Health and disease manifestations affected by the microbiome.
SOURCE: Kim Lewis presentation, June 30, 2023.

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Lewis described the process for identifying a selective compound for *B. burgdorferi*. He initially focused on ADEP4, a semi-synthetic acyldepsipeptide that activates a protease inside bacterial cells to kill the cell. Since ADEP4 and related compounds can kill both regular bacterial cells and persisters, it would be especially useful for any chronic infection. However, none of these compounds turned out to be effective against *B. burgdorferi*. Surprisingly, an antibiotic called hygromycin A that was first discovered in 1953 but never developed for clinical use, showed promise for specificity to *B. burgdorferi*, Lewis said. While hygromycin A has low activity against standard other bacterial pathogens, it is very potent against spirochetes.

Following this discovery, Lewis and colleagues tested hygromycin A in mouse models and found it was effective in clearing *B. burgdorferi* infection at different doses and administered through different routes. A single dose of hygromycin A at 1,500 mg/kg was able to eradicate *B. burgdorferi* in mice, Lewis noted. Importantly, hygromycin A did not disrupt the mouse microbiota. Lewis shared that his lab is currently advancing this drug toward a clinical trial and working with partners to increase development and build manufacturing capacity. He is aiming for a clinical trial endpoint of the alleviation of symptoms 6 months after treatment.

CLINICAL CARE ACROSS ILLNESSES

David Putrino, Mount Sinai Health System, started a clinic primarily focused on long COVID, but recognizing the overlap with so many other complex chronic illnesses, his team has also started to treat patients with other conditions, such as Ehlers-Danlos syndrome, myalgic encephalitis/chronic fatigue syndrome (ME/CFS), and Lyme disease. Putrino specified that this hybrid clinic and research center treats complex chronic illness, but it does not treat functional disorders. He reviewed some of the proposed underlying causes of long COVID pathology, including immune dysregulation, microbiota dysbiosis, autoimmunity, blood clotting, and dysfunctional neurological signaling. These types of complex illnesses often require novel combinations of treatments to address multiple underlying causes, he said.

He presented steps they took toward creating a comprehensive clinical pipeline, with a robust preintake process to ensure the physician has all the necessary information by the time the patient is seen and to reduce strain on patients by limiting the number of in-person appointments. During the preintake process they perform several blood testing panels to look for coinfections; measure hormone, vitamin, and mineral levels; and perform coagulopathy and platelet activation to measure interleukins, inflammatory cytokines, and other symptoms of inflammation. They also document patient-reported outcomes using validated questionnaires. The next stage is a clinical intake exam that begins the treatment phase. It includes a discus-

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sion of results from the preintake sessions, a personalized intervention plan, and postintake evaluations. These evaluations may include other patient-specific tests, such as electrocardiograms, endoscopy, or autonomic testing.

The next stage of the pipeline is "prehab," which includes symptom management resources and conversations and lessons on how to best avoid symptom flare-ups, as well as breath work programs specifically focused on improving blood carbon dioxide balances. In conducting internal research, Putrino said his team found that 90 percent of patients who used their breath work platform for at least 3 months had improvement across indicators such as sleep quality and stress control. Next in the pipeline, is autonomic rehabilitation to promote more regulated autonomic nervous system through limb movements so patients can better tolerate upright body positions and movement. Putrino clarified that this rehabilitation is not a cure for the underlying disease but focuses on reducing severity of symptoms. The clinic also provides peer support and mental health services.

The clinic is also exploring innovative partnerships to enhance patient care, such as seeking grants from Uber to make ridesharing available for patients to come to appointments. They also make referrals to additional health services and work with a compounding pharmacy to make medications more accessible. In closing, Putrino said they firmly believe that learning from different complex chronic illnesses is key, and it is important to know how they are similar and different to properly train clinicians and improve precision and personalized treatment approaches. He also noted that the clinic has a lived experience advisory board that provides guidance on all patient care and research initiatives.

DISCUSSION

The discussion covered use of Paxlovid, potential biomarkers for therapeutics development, the balance between specific and more general investments in therapeutics development, and lastly a call for increased patient-centered care models. In the context of long COVID, a participant asked about whether a longer treatment window, such as using a single therapeutic agent for 15 days, would reduce the risk of developing long term symptoms. Cherry responded that starting with Paxlovid is reasonable, but that 15 days may or may not be enough. Having biomarkers to help follow the patient for efficacy and detect viral antigens would be helpful. Another participant asked how Paxlovid might work in a persistent infection, since it prevents the viral particle from replicating but does not clear the original viral reservoir. Cherry replied that the viral RNA cannot persist forever, as the RNA would eventually be metabolized with cell senescence and turnover. The GI epithelium especially turns over every 2 weeks, so that might clear the viral RNA more quickly. However, Avindra Nath,

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National Institutes of Health, added that viral persistence would still be an issue if present in the brain, as brain cells do not turn over.

Regarding using the spike protein as a biomarker for viral persistence, Fasano said that he is not aware of any other source besides a virus that produces the spike protein. So, if it is present in the bloodstream, Fasano interprets this as an indication that (1) SARS-CoV-2 is still in the body, (2) the spike protein is circulating in the bloodstream, and (3) if there are specific T cell receptor mutations and the host is predisposed, then clinical symptoms of long COVID could result.

One participant asked about the balance between targeting pathogen- or disease-specific molecules for development and the more general investment from government agencies and policies right now toward disease-agnostic platforms. Putrino thought more information needs to be gathered in a highly stepwise and deliberate manner to understand the similarities and differences between conditions, which will inform the decision making between the two ends of this balance. He lamented the idea of running a well-designed randomized clinical trial on a highly specific therapeutic lead compound, but having very general inclusion criteria that impedes the effort to characterize a specific type of an illness and will likely lead to apparent failure of the trial. In this scenario, when the trial readout is negative, the potential therapeutic compound is often quickly given up. Instead, he called for a concerted effort to set up these registry style clinics around the country to get very detailed, well-classified data.

Finally, an attendee asked how the Mt. Sinai model of informed, compassionate, patient-centric clinical care can be exported and developed elsewhere for more people to access. Putrino replied that they are working to build curricular and training materials and will also be creating a complex chronic illness medical curriculum through Icahn School of Medicine. There needs to be a concerted effort to teach and reteach a new generation of clinicians, he concluded, as these illnesses caused by infections are treatable only if you know where to look.

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6

Advancing Research for Infection-Associated Chronic Illnesses

Key Points from Individual Speakers and Participants[1]

- There is an opportunity for the Food and Drug Administration to spur patient engagement, explore innovation in clinical trials to provide feedback to researchers, facilitate considerations of viable endpoints, and support collection of additional types of data, such as real-world evidence. (Marston)
- The ability to generalize Lyme disease research can be significantly affected by applying too narrow of inclusion criteria. Using real-world evidence such as patient registry data can help predict the effects of exclusion criteria on elements of studies. (Johnson)
- Research led by patients or that meaningfully engages patients is more relevant to the patients' lives, more effective, and leads to faster results. (McCorkell)
- There are opportunities to further democratize research and include more people by using technologies to collect samples from home, centralizing tools, and removing barriers that prevent people from participating. (Amitay, Marston)

[1] This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

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- Barriers prolonging patient journeys include patient and provider lack of awareness, limited access to care, complex care navigation and poorly defined conditions, lack of proven treatments, and stigma. (Geng)
- Studies of diagnostic assays demonstrated that there must be a persistent viral infection or viral reservoir that is continually producing the spike protein. (Walt)
- Multiple infections result in chronic illnesses that are remarkably consistent, which suggests a universal mechanism. (Deeks, Fallon)

This chapter begins with an overview from the Food and Drug Administration (FDA) on its role in this field of research, and what it has been doing to speed the discovery and testing of potential diagnostics and treatments. This chapter also reviews current patient-driven research efforts and the infrastructure and innovation needed to close gaps in this area and promote progress for patients.

PERSPECTIVE FROM THE FOOD AND DRUG ADMINISTRATION

Hilary Marston, chief medical officer, FDA, reviewed the challenge for researchers in translating the growing recognition of infection-associated illness into advances in understanding and treatment. This increased awareness is counteracted by a lack of treatment options, barriers to diagnosis, and inadequate patient care, she said, and there is a lack of understanding of the cause and effect and linkages between infections and long-term symptoms. While biomedical science and technology is rapidly advancing, these advantages are not resulting in superior health and outcomes for most of the U.S. population, she added.

Using long COVID as an example, she said there has been a good amount of work just to create an interim federal working definition of the chronic condition. While it is broadly defined as signs, symptoms, and conditions that continue or develop after initial infection, she noted that it is likely not just one condition. Long COVID represents many potentially overlapping entities that may have different biological causes and sets of risk factors and outcomes. Even estimating the prevalence of long COVID has been challenging, with estimates ranging from 5 to 30 percent of people infected with SARS-CoV-2 (CDC, 2023b). Marsten outlined several possible causes that are being explored by many researchers, including autoimmune response, persistent virus, organ damage, or microclots. Looking at the range of signs and symptoms will be essential in moving product development forward and getting some kind of consensus on key priority

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symptoms, while also addressing specific symptoms and the needs of the pediatric population, she said.

Marston reiterated that currently there are no drugs approved by FDA for the treatment of long COVID, and for most patients the goal of medical management right now is to improve and optimize their quality of life. She reviewed several challenges to drug development in this area, one being that long COVID is a new entity with many features, making it difficult to assess the effects of a single intervention. Additionally, because of the heterogeneity of symptoms, different treatment approaches may be needed for patients with different symptoms, including pediatric populations. Since so many of the chief complaints relate to how patients feel and function, there is also a lack of reliable tools to assess and evaluate how treatments might affect those factors for long COVID patients. She acknowledged that these same challenges in diagnostics and treatment of long COVID also apply to posttreatment Lyme disease syndrome. On the treatment side, no solutions have been proven effective so far, she said.

Marston stated that the role of FDA is to spur patient engagement, explore innovation in clinical trials and provide feedback to researchers, facilitate considerations of viable endpoints, and support the collection of additional types of data, such as real-world evidence. Elaborating on patient engagement, she emphasized that patients are experts in their conditions, and their input is needed early in the drug development process. She described a patient-focused drug development team meeting for long COVID and working to understand the most significant symptoms of the condition and the current approaches to treatment. FDA worked with other agencies such as the Office of the Assistant Secretary for Health, the National Institutes of Health, and the Centers for Disease Control and Prevention to plan the patient-focused drug development meeting for long COVID. FDA also collected many patient perspectives on symptoms and daily effects as well as treatment approaches. In the absence of effective treatments, patients reported use of over-the-counter products, diet modifications, and acupuncture, but they wanted treatment that targeted the root cause of long COVID instead of just their various symptoms.

Marston shared several challenges with clinical trials for these types of conditions. Access is a main barrier, whether because of the debilitating symptoms or the rural location of many patients, so a virtual, decentralized trial platform is essential. As researchers consider clinical outcome assessments that reflect how an individual might feel or function, she emphasized reviewing FDA's guidance on selecting, developing, or modifying fit-for-purpose clinical outcome assessments (FDA, 2022). For next steps, she said FDA will continue to strengthen efforts to advocate for innovative clinical trials, advance methods of data collection, and increase coordination throughout the agency for addressing these types of infection-associated illnesses.

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A participant asked about whether a platform of clinical trials with multiple arms and a single placebo is a viable option for these diseases. She replied that FDA often and repeatedly encourages platform trials, which help to assess comparable treatments in different conditions. It can also be a very efficient use of government resources, especially in the case of an outbreak or scenario where time is of the essence, and she would encourage this approach. Specifically considering children with long COVID, she said FDA hosted a workshop in Fall 2022 on pediatric long COVID. Part of the reason it is poorly understood is because of the variable study methods used to examine its natural history. Some studies captured more immediate sequelae, and others looked further down the line in population-based surveys, she said. It is still understudied in the pediatric population, but what is lacking is a coalescing of methods on how to best study it compared to the adult population. FDA, she continued, is engaging in conversations, convening a research community, and ensuring that its efforts reflect the pediatric patient population in discussions and projects. Whenever projects are brought to FDA for the adult population, there also needs to be some dedication to the pediatric population.

PATIENT-DRIVEN RESEARCH

A panel of speakers provided remarks on the importance and successes of patient-driven research across diseases areas, and considered how these successes may be translated to address infection-associated chronic illnesses. Perspectives include long COVID, myalgic encephalitis/chronic fatigue syndrome (ME/CFS), and posttreatment Lyme disease syndrome.

Patient-Led Research Collaborative

Lisa McCorkell, Patient-Led Research Collaborative (PLRC), introduced herself as a person living with long COVID since March 2020 who has been fighting for the advancement of infection-associated chronic conditions research and long COVID research over the last 3 years. She shared some of the work and recent findings from PLRC and a vision of what a patient-driven research agenda might look like. PLRC began when the cofounders got sick in March 2020 and now has more than 45 members across four continents, she said. While the cofounders initially had fairly mild infections, they never recovered to gain full health. Following an op-ed in the *New York Times* describing the experience of not recovering from the initial COVID-19 infection (Lowenstein, 2020), the Body Politic COVID-19 support group was formed and many people immediately joined to share their symptoms and experiences. Soon after, the members of that group developed a survey to identify trends in symptoms, and that led to the first research on long COVID, McCorkell explained. They identified 62 symptoms, including neurological symptoms, which at the time was

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unexpected since COVID-19 was still seen as a purely respiratory illness. At that time it was also difficult to access tests, she added, and many of the members were being denied care because they did not have a positive COVID-19 test, yet the symptoms of those patients aligned very well with those who did test positive.

As time went on, more people became infected with COVID-19 but many of these patients with persistent symptoms were not getting better, she shared. PLRC continued gathering evidence from the growing patient community and demonstrated that many people develop long COVID even after a mild initial infection. Because many patients felt dismissed by health care workers and researchers, they developed another survey that resulted in a paper published in the *Lancet* (Davis et al., 2021). At this point, she said, PLRC leaders had begun connecting with people who had ME/CFS and mast cell activation syndrome and were able to identify numerous overlapping symptoms. They have now documented more than 200 symptoms that come and go over time and found that two-thirds of people with long COVID had to either reduce their work schedules or stop working completely because of their illnesses. McCorkell highlighted another paper published in *Nature Reviews Microbiology* focusing on the mechanisms of long COVID and their overlap with other conditions (Davis et al., 2023).

Overall, McCorkell said, her team has published several papers on long COVID and different aspects of health, including a focus on pediatric populations, psychiatric outcomes, and reproductive health effects. Though this last effect is understudied, she said many patients experienced reproductive health problems with long COVID, overlapping with such conditions as ME/CFS, postural orthostatic tachycardia syndrome (POTS), and Ehlers-Danlos syndrome (see Figure 6-1).

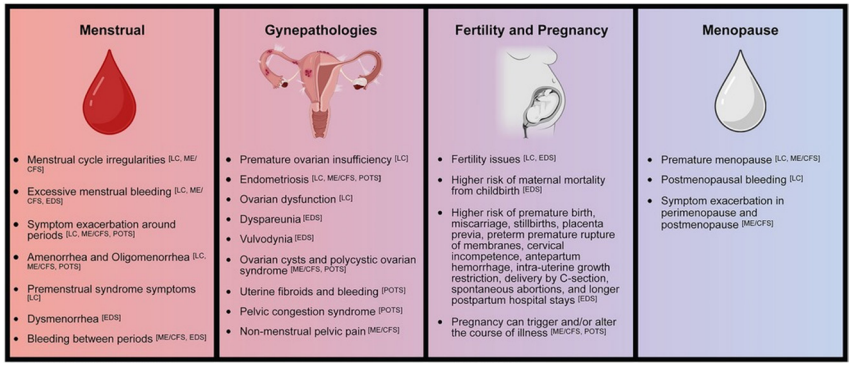

FIGURE 6-1 Female reproductive conditions in long COVID (LC), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS), and Ehlers-Danlos syndrome (EDS).
SOURCE: Lisa McCorkell presentation, June 30, 2023; Pollack et al., 2023.

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McCorkell highlighted some other work she and collaborators have produced, including a survey on the effect of reinfections on people with long COVID, patient-generated hypotheses for further research, and using the data and patient experience available to advocate for better research, guidelines, and policy. When the research incorporates the patient's perspective, even when not led by patients, said McCorkell, it leads to better research and better outcomes. It is often more relevant to the patient's lives, more effective, and leads to faster results. For example, postexertional malaise was a top symptom in the PLRC study only because the patient-researchers knew to ask about it since they were experiencing this symptom, she said. This symptom does not have its own International Classification of Diseases (ICD) code and many providers are not familiar with it, so it is often only through incorporating patient involvement and understanding that researchers are aware of the need to include this symptom.

Touching on incentives, McCorkell said much of this work was done out of desperation because these researchers were also patients and needed answers, so they took more risks than other biomedical researchers under normal conditions. She added that this demonstrates how critical it is for funders to recognize the value of this type of research and support it. PLRC's priority is for the research to be impact driven and disseminate results widely and quickly. In academia, she said it can take over a decade to translate research into clinical practice, and for patients living with a debilitating disease that is far too long. McCorkell described a patient scorecard that PLRC members developed to help researchers evaluate their patient collaboration throughout the research process. Thinking about what a patient-driven agenda might look like, she shared some important considerations for developing effective and inclusive patient-led research:

1. Ensuring the meaningful engagement of patients and caregivers in all stages of the research process, integrating new and existing evidence across infection-associated chronic conditions.
2. Accelerating the clinical trials of therapeutics that are most important for the patient community.
3. Improving coordination so research does not exist in siloes, such as establishing an office for infection-associated chronic illnesses within the National Institutes of Health (NIH) director's office.

Solve ME/CFS

The field of chronic illness research is in the middle of a paradigm shift, said Oved Amitay of Solve ME/CFS, largely because of the COVID-19 pandemic. Solve ME/CFS was established in 1987 as a result of a number of viral outbreaks in the United States and United Kingdom from which

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many patients developed chronic illnesses. The ME/CFS community has long recognized that this chronic condition is often associated with an onset of acute infection, so Solve ME/CFS saw the potential for extended effects of illness from COVID-19. Recognizing the importance of gaining funding to research this issue, Solve ME/CFS worked to develop a House resolution introduced by Representative Jamie Raskin called the Understanding COVID-19 Subsets and ME/CFS Act, requiring NIH to support research looking at ME/CFS as part of long COVID. This was before evidence of the overlap was identified, he said, but they requested the Department of Health and Human Services to carry out a public awareness campaign about these types of postviral chronic neuroimmune diseases.

Amitay said that patient-driven data platforms are an important tool to provide patients with the opportunity to participate and advance the understanding of their condition. Historically, patients had to be physically present at the study sites to participate in clinical studies, meaning they had to allocate time to travel and sometimes risk exacerbating their conditions. Democratizing research requires a change in the system, he said, such as using technological tools to help collect samples from home, centralizing tools, and removing barriers preventing people from participating. Patient organizations play a unique role in providing insights into the conditions and can also add value to participation in research, helping to recruit patients for clinical trials and ensuring they are well represented.

Using ME/CFS as an example, Amitay explained that, historically, not a lot of longitudinal data about the disease has been collected. To address this, Solve ME/CFS developed a patient registry and started a study, approved by an institutional review board, that collected data directly from patients with no intermediary. After the May 2020 launch, Solve ME/CFS also opened a cohort of people with COVID-19, some of whom developed long COVID.[2] Solve ME/CFS is now working to migrate this dataset to a different platform, removing some of the data collection burden from patients, and making it open and available to everyone. Solve ME/CFS hopes to accelerate recruitment into clinical trials and run nested studies within the platform to accelerate diagnostic and therapeutic development.

Sharing some of his team's findings, Amitay highlighted that the majority of participants in the ME/CFS cohort are female, which is also seen in the long COVID group. About 22 percent of patients in the long COVID cohort reported disabling symptoms, compared to 31 percent in the ME/CFS cohort. In summary, Amitay shared that half of people who have

[2] A cohort generally refers to a group of individuals participating in a biomedical study, who are followed longitudinally for data collection (e.g., biological samples, surveys) in order to glean the development of disease condition outcomes. This cohort stood up by ME/CFS may provide data for future retrospective or prospective studies and analyses.

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been living with long COVID for more than 1 year meet diagnostic criteria for ME/CFS, which indicates a looming crisis. He also suggested that a complementary NIH structure would benefit from being guided by a common research agenda.

MyLymeData

Lorraine Johnson, LymeDisease.org and MyLymeData, shared information on her organization, discussing inclusion and exclusion criteria in clinical trials and how her organizations' patient registry data can help in determining generalizability of potential therapeutics. Her teams have enrolled more than 17,000 patients since 2015, with the primary goal to increase scientific knowledge in Lyme disease and use its data to influence public policy. Unlike randomized control trials (RCTs), she said, patient registries use broad enrollment criteria and collect a wide array of information, including data on diagnostic validation. This results in a database that has both breadth of enrolled patients and depth for potential details needed, including data that only patients know, as 50 percent of Lyme patients receive care outside the insurance system, said Johnson. She shared a list of alternative treatments patients had tried and how they rated the effectiveness, demonstrating patient innovation in using alternative treatments. This information is likely to be unavailable in electronic health records or insurance databases.

Johnson also discussed patient subgroups and evaluating enrollment criteria, saying that patient registries like MyLymeData excel at describing patient populations because of the amount of information they collect from a broad group of patients. Johnson and colleagues have been able to explore symptom subgroups and identify antibiotic treatment responders and nonresponders, as well as sex-based differences in Lyme disease. Assessing the effect of exclusion criteria in studies, her teams examined four common research enrollment criteria: positive Western blot, history of rash, expression of characteristic symptoms and severity, and no diagnosis of ME/CFS or fibromyalgia. They looked at the attrition rate on the sample from each individual indicator and the cumulative effect on the sample and found that when they required patients to have a history of the rash or positive Western blot, 35 percent of patients were eliminated. When all four criteria are applied, just 39 percent of the original sample remain. Johnson contended that this substantially compromises the generalizability of the study results and increases the time and cost of the study to recruit enough patients. While researchers are trying to apply rigorous definitions to eliminate potential confounding factors, many of these RCTs end up eliminating between 89 and 99 percent of people who sought to enroll, she believed.

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She highlighted recent calls to relax some of these criteria and noted a 2018 FDA report that called attention to the tension between balancing the merits of stringent inclusion criteria for targeted studies and broadened inclusion criteria for generalizability (FDA, 2018). She called for researchers to think through the implications of different inclusion/exclusion criteria and make sure that what they are using is necessary for the trade-off in generalizability and sample attrition to determine cause and effect. As a final statement, Johnson suggested that when determining enrollment criteria, researchers should consider the effect that various criteria will have on recruitment, time, cost, statistical power, and generalizability. She added that one potential way of doing this is using real-world evidence such as patient registry data to predict the effects of each criterion on the enrollment for any given study.

Lyme Disease Biobank

Liz Horn, Lyme Disease Biobank, continued the conversation discussing well-characterized samples. She explained that Lyme Disease Biobank includes three distinct cohorts: early Lyme disease samples, persistent Lyme cohort, and a tissue bank that includes post-mortem[3] samples. While well-characterized samples are key to advancing research, they require time, human resources, and funding to collect. She shared important questions to consider, such as which patient populations are needed, whether existing samples can be used or if there is a need to prospectively collect them, strategies for collection, and what administrative, legal, and regulatory steps are needed. Well-characterized samples are essential, Horn said, but researchers need standardized protocols, chain of custody, laboratory or diagnostic test results, and possibly imaging pieces or additional data sources. Horn stated her support for centralized collections as they reduce costs and redundant infrastructure, increase efficiencies, support multiple projects with each blood draw, and are designed to be shared and bring new people in the field.

Horn said Lyme Disease Biobank has more than 1,200 participants enrolled across the country, and that each donated sample can support approximately 50 research projects. The biobank supports more than 85 projects in academia and industry with samples. Its collection of early Lyme disease samples targets symptoms of early Lyme in endemic areas. The biobank's researchers recognize the variability in how the traditional bull's-eye rash (erythema migrans) presents, which Horn called attention to because it may often be an inclusion criterion for a trial. Biobank researchers collect whole blood, serum, and urine samples, and they collect from places

[3] For more information about the Lyme Disease Biobank, see https://journals.asm.org/doi/10.1128/jcm.00032-20 (accessed December 10, 2023).

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that are usually outside of research avenues such as family practices and urgent care centers. This collection will be used to inform the development and validation of new diagnostics. Horn shared that biobank researchers also collect samples from people with persistent Lyme, and this cohort is supporting 15 projects for novel diagnostics and biomarker exploration. Having these resources available to the research community is important, Horn added, and her teams also require researchers to provide data back to the biobank so they can share the findings with other researchers.

Lastly, it is critical to go beyond blood and also look at tissue, Horn said. The biobank holds tissue samples from 14 postmortem donations, which are linked to robust clinical information, including anonymized medical records. These tissues represent complicated cases that included neurocognitive and neurodegenerative conditions. With permission, these samples can also be linked to MyLymeData profiles. The biobank is working to develop a tissue analysis pipeline to characterize tissue while looking for evidence of infection or inflammation, conducting a comprehensive neuropathologic evaluation, and testing for a variety of pathogens, including *Borrelia* spp. All of this information is also being fed back to the biobank, she said, which will only make it stronger. Finally, she highlighted a call to action to standardize the evaluation of microbes in tissue. She noted that this can be crucial as researchers continue to learn from other disease areas and incorporate any lessons from the disease overlap.

Discussion

The discussion that followed included topics such as standardizing sample collection, using appropriate language in research, the role of patient-driven research, and recognizing the lived experience of patients in workplace settings. Regarding sample standards, Johnson said, so many tools are available today that were not available years ago, and there is even greater opportunity to develop sample standards using big data and real-world evidence. More complete data will help ground researchers in the validity of their findings, she added. Johnson added that it is important to continue analyzing existing data to identify additional use cases.

Using long COVID studies as an example, McCorkell pointed out that documented positive polymerase chain reaction (PCR) test is often used as inclusion criteria. Perhaps this should be reserved for narrow-scope clinical trials, she suggested. This would allow a subgroup of patients without documented PCR evidence to provide samples for analysis and potential use for more general trials. Amitay agreed, saying that it is important to remember that diseases are human constructs. Biology does not listen to how things are labeled, he noted. We need to go beyond these constructs, he said, especially when looking at samples with a renewed broader lens.

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In terms of appropriate language when working with patients, Johnson said language can become contentious and divisive in instances when it does not have to be. She supports the use of the broad term *infection-associated diseases*. McCorkell added that *long COVID* is a patient-created term, and it took researchers awhile to adopt because they wanted something more scientific. There are journals that still refuse to use the *long COVID* term but patients continue to use and socialize it. Having researchers and clinicians open to using terminology that patients want is helpful, she said, emphasizing the importance of listening to patients.

Amitay said there has been a profound change in how long COVID has increased the inclusion of patients in research. Many of these communities have been neglected for several years, he said. Long COVID has made a big impact and provided an opportunity to look at all of these conditions with a broader lens. Incorporating this research together into collaborative efforts now can ultimately create a larger body of knowledge and help all communities. Horn added that while it is unfortunate long COVID affects so many people, it has legitimized other similar conditions and brought them more to the forefront of research.

A participant highlighted the importance of lived experience of patients who are trying to continue working, as many patients with unseen disabilities are stigmatized and often sent to counseling instead of having their conditions recognized. This is very important, replied Johnson, as surveys on stigma and marginalization related to unseen disabilities have shown that around 75 percent of respondents have felt dismissed by a health care provider. People fear stigma at work and are afraid to lose their jobs. Johnson reported that people with chronic illnesses or unseen disabilities rarely tell people outside of their innermost circle of immediate family and close friends about their conditions, which can be socially isolating. McCorkell added that all of these conditions are covered under the Americans with Disabilities Act, so employers are required to provide accommodations but often do not. She added that academia is another area that needs a paradigm shift in how employees are treated. Nearly four million people are out of work because of long COVID, she said, and it is just going to get worse; academia needs researchers to continue this important work.

RESEARCH INNOVATION AND REQUIRED INFRASTRUCTURE

To complement the benefits of including patients in research, coordination, and collaboration across research in different disease areas also provides opportunities to learn from past successes in other underresearched conditions. This section highlights long COVID patient journeys and diagnostic tools in development, and lessons from human immunodeficiency virus (HIV) and Lyme disease networks.

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Understanding the Patient Journey in Long COVID

"She went to one doctor, then another, then another," said Linda Geng, Stanford University, quoting a news headline (Cha, 2022) that resonates with many clinicians in this field who have patients bouncing around the health care system. Geng described her field of consultative medicine, which focuses on patients with puzzling conditions who get lost in fragmented systems while seeking diagnosis and treatment. Postinfectious syndromes are commonly seen in this context, she said. A study of patients seeking second opinions for puzzling symptoms at Geng's clinic revealed that nearly one-fifth of patients had an infection, she said, and postviral syndrome was among the top of diagnostic outcomes when looking at the 10 most common symptoms that present to a clinic like hers (Chao et al., 2022). While the ideal journey for a care-seeking long COVID patient would be straightforward and linear, the reality is anything but, she said. Many patients have seen dozens of doctors and multiple specialists, meeting lots of roadblocks and dead-ends along the way.

Geng highlighted the lack of patient and clinician awareness as a significant barrier that prolongs these journeys. People often do not realize these types of chronic conditions exist, which is particularly important for vulnerable populations with low health literacy and language barriers. This highlights the importance of equity and care provision for vulnerable communities who have been disproportionately affected by the pandemic. Another factor contributing to long patient journeys is limited access to health care, with long months of waiting lists, complex care navigation, misdiagnosis, and poorly defined conditions.

Geng noted that it is important to take a broader lens and also look at other postinfection-associated diseases, and even postvaccine conditions. She shared that her clinic has seen many patients who develop long COVID symptoms after the vaccine but may or may not have had prior infection, underscoring the need to understand the intersection or common pathways of immune dysregulation. Adding to these challenges, she highlighted a study that found symptoms similar to long COVID can also occur after an influenza infection, though less frequently (Taquet et al., 2021). This highlights the difficulty of the evolving definition of long COVID and thinking about the inclusiveness for access to care. Geng shared that clinicians should apply the term as broadly as possible when considering access to care. When considering precision for research, researchers need to know the conclusions drawn are applicable to the right populations to accurately develop targeted therapy, she explained.

The lack of treatment is another significant barrier. Treatment can help support accurate diagnoses, resulting in a positive feedback loop. Stigma that comes with infection-associated chronic illnesses is a barrier to care for this population, she said. In her own work, she has often heard patients say that no one believes them, and they are dismissed by friends, family members, and employers. The lack of mechanistic understanding is a chal-

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lenge for providers in legitimizing the conditions, so she pushed for being able to better understand the mechanisms.

Geng cautioned about erroneous leaps to conclusions where there are gaps of knowledge that need to be filled—which is the case for long COVID as well as other postinfectious syndromes. Instead, she is encouraged that many researchers are helping to build the knowledge base of potential mechanisms, which can lead to better treatments, better care, and improved lives. She offered future directions to improve care for these types of conditions:

- Building multidisciplinary teams, and harnessing collective intellect.
- Engaging patients, family, and advocates.
- Studying models of care.
- Incorporating reimbursement and finance factors.
- Considering equity and community.
- Integrating education and training.
- Advancing knowledge and research.
- Synergizing knowledge across syndromes through intersections and broad applications.

Diagnostic Assays

David Walt, Harvard University and Brigham and Women's Hospital, described development of ultrasensitive assays. His team developed single molecule arrays can quantify immune complexes in the samples and enhance assay sensitivity by three to four orders of magnitude compared to the conventional enzyme-linked immunosorbent assay (ELISA), he explained. These arrays are a digital tool that can be used to make ultrasensitive measurements. Applying his team's method to a number of assays for COVID-19 patients at different time points after the initial acute infection, Walt and colleagues found that the full viral spike protein was detectable in 60 percent of patients with long COVID in this cohort even though they were producing viral neutralizing antibodies (Swank et al., 2022). Walt's team believed there is a persistent viral infection or viral reservoir that is continually producing the spike protein.

Lastly, he briefly touched on a new RECOVER-VITAL study, looking at therapeutic intervention (in this case, an antiviral drug) to see if it improves outcomes in long COVID patients. He predicted a launch in Summer 2023, with goals of 100 sites and 900 adults enrolled.[4] Researchers in

[4] The RECOVER-VITAL study, intended to examine whether the antiviral PAXLOVID (nirmatrelvir and ritonavir) improves symptoms for people who have long COVID, enrolled its first participant in July 2023. For more information on the RECOVER-VITAL study, see https://trials.recovercovid.org/vital (accessed December 7, 2023).

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the study are hoping that individuals with the spike protein and persistent viral infection will find their symptoms ameliorated with the drug.

Drug Repurposing for Translating Infection-Associated Chronic Illness Research

Similar to several other speakers, Steven Deeks, University of California, San Francisco, explained that he is new to this field and was in fact working on HIV/AIDS before 2020, but has since applied this experience to studying long COVID. While the concept of *long HIV* has never really been established, he wondered if some patients may suffer from it, as he has seen people in clinics that have ongoing issues affecting their quality of life. The assumption that these effects are caused by drug toxicity needs to be revisited, he said. Thanks to committed and sustained investment from the National Institute of Allergy and Infectious Disease in HIV biology, scientists have revealed some mechanisms enabling HIV to cause some of the comorbidities, and they are quite similar to those associated with long COVID.

He described his team's decades of work in using existing drugs and repurposing them for experimental medicine to address the potential root causes and resulting symptoms of inflammation. Collectively, throughout many studies over the years, researchers were able to understand the pathogenesis mechanism of HIV. Experimental medicine is a potential way to identify disease mechanisms while bridging engagement from industry partners to develop products for these mechanistic pathways. With knowledge of these disease pathways, it is possible to measure the effect of the proposed treatment to see if outcomes improve.

There are several pathways being explored in developing therapeutics for long COVID, and they are similar to the approaches taken for HIV. What is still needed are proof-of-concept studies, he explained, that can allow for more investment and encourage involvement from companies that know how to develop therapeutics. As an example, he said one leading cause of potential issues is acute viral infection with irreversible tissue damage, and much of the discussion in the workshop has been related to pathogen persistence in tissues. A possible therapy for this pathway is intervention with antiviral drugs, particularly monoclonal antibodies, he said, because they can block the virus from spreading and potentially clear out the dead virus reservoirs as well. Other potential treatments include anti-inflammatory drugs, intravenous immunoglobulin, B cell directed therapeutics, antiplatelet drugs (e.g., aspirin), anticoagulants, or fibrinolytics. Deeks noted a clinical trials agenda led by Michael Peluso in which multiple interventions will be examined in a common platform across studies. Their team at UCSF will begin with examining the effects of a monoclonal anti-

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body that can inhibit viral replication and clear viral reservoirs. They are also seeking funding to apply a novel drug that is in development to treat a range of diseases from rheumatological disorders to long COVID, he said.

As another parallel to HIV, Deeks referenced the 1990s phenomenon of the *Dallas Buyers Club*, a major motion picture documenting the story of a number of HIV patients who, out of desperation, looked outside the health care system for any available treatment that might be effective to alleviate their conditions. This is happening now with long COVID, he said, as people and physicians are desperate for treatment options. No one can wait for 5 years for things to be studied and proven, and many treatments are being administered offline and off-label, Deeks said, sharing that he follows this movement very closely as even anecdotal information can be helpful to see what is working or not. What would be really helpful is a biomarker, he added, noting the transformative shift that occurred in therapeutics development when viral RNA was identified as a biomarker for HIV. Identifying surrogate markers validated by FDA could lead to a lot of investment and progress in the field. However, breaking down the silos between disease areas will be a key part of realizing greater progress, he noted, as the similarity between diseases following different infections suggests a universal mechanism.

To summarize, Deeks said that there are multiple pathways and factors involved in the emergence of infection-associated chronic illnesses, suggesting a need for combination approaches. There is a massive repository from 2020 that can be used to test different mechanistic hypotheses, and clinical trials to uncover the mechanisms are needed so industry partners are incentivized to get involved and bring their expertise to develop the necessary drugs and treatments. There are many people working on these issues, he noted, but some of the work can be redundant because researchers have limited interactions with each other. He called for more meetings such as this workshop where people can come together, understand roles, and figure out how to best collaborate and optimize outcomes.

Posttreatment Lyme and New Clinical Trials Network

Brian Fallon, Columbia University, presented on the off-label use of medications for Lyme disease, as well as symptoms of posttreatment Lyme disease syndrome (PTLDS), underlying mechanisms, prior clinical trials, and the Clinical Trials Network Coordinating Center for Lyme and other Tick-borne Diseases at Columbia University. He referenced the overlap between PTLDS and long COVID syndromes, reiterating that there may be common mechanisms underlying both syndromes. Speaking of PTLDS specifically, Fallon discussed the common cognitive deficits experienced, with up to 90 percent of PTLDS patients reporting cognitive difficulties, and up

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to 30 percent having objective, measurable problems affecting short-term memory and processing speed (Touradji et al., 2018). On rare occasions, Lyme disease can even cause encephalitis leading to severe psychiatric disorders, but patients often make a full recovery once this is recognized and treated with antibiotics. Also related to mental health, Fallon noted that suicidal ideation is common in patients that he sees at research clinics, with one in five reporting suicidal thoughts (Doshi et al., 2018). In patients with mild to severe depression, this number increases to two-thirds.

Because he is a psychiatrist, Fallon wanted to ensure he was not drawing conclusions on psychiatric symptoms of Lyme disease from a biased sample population. Fallon collaborated with researchers in Denmark using a registry of nearly seven million people over 22 years to study the connection between Lyme borreliosis and mental disorders and suicide. Of the seven million entries in the registry, more than 12,000 had a hospital-based diagnosis of Lyme disease (inpatient, outpatient, or emergency room); among these individuals there was a 28 percent increased rate of a subsequent mental disorder compared to all others who had never had a hospital-based diagnosis of Lyme disease (Fallon et al., 2021). There was also a 40 percent increase of subsequent depression, a two-fold increase in suicide attempts, and a 75 percent increased rate of suicide among those with hospital-based diagnoses of Lyme disease.

There are several potential mechanisms for these ongoing symptoms, Fallon explained, including persistence of infection, immune dysregulation, neurologic dysfunction, and other possibilities such as formation of microclots, altered gastrointestinal microbiome, or mitochondrial dysfunction. There are also physiologic similarities with other diseases, as other speakers have noted, as well as distinctions. He shared one study using cerebrospinal fluid (CSF) and found that PTLDS encephalopathy was associated with a distinct CSF protein profile compared with ME/CFS and control group samples, but both disorders were associated with distinct proteins in the CSF compared to the control group (Schutzer et al., 2011).

Fallon reviewed prior clinical trials of PTLD treatments, with four of them specifically focused on the antibiotic ceftriaxone. Two studies showed no improvement (Klempner et al., 2001), one study showed non-sustained improvement in cognition (Fallon et al., 2008) and one study showed long-term improvement in fatigue (Krupp et al., 2003); each study noted the serious risks associated with intravenous ceftriaxone therapy, particularly due to indwelling lines. None of the studies recommended the use of it therapeutically. Moving forward, he shared that Columbia is the coordinating center of a new clinical trials network for Lyme and other tick-borne diseases. There have not been any clinical trials on PTLDS in more than 10 years, he said, so there is a need for well-designed treatment studies to improve guidelines internationally. The clinical trials network will be able

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to harness strengths across academic centers and have larger sample sizes and faster recruitment by conducting multisite trials.

To start, the network will include Columbia University in New York City, Johns Hopkins University in Baltimore, and Children's National Hospital in Washington, DC. He shared a few pilot studies they are launching that will examine vagus nerve stimulation (VNS) to address fatigue, transcranial direct current stimulation to address brain fog, and intravenous ketamine and cognitive retraining for depression. Highlighting VNS, Fallon explained that the vagus nerve modulates both inflammation and neural function with an extensive innervation of internal organs, thereby impacting multiple organ systems. Because VNS is already FDA approved for epilepsy, depression, migraines, and rehabilitation after ischemic stroke, there is growing interest in assessing the efficacy of VNS for those with PTLD and other infection-associated multisystem conditions. The underlying premise of these studies is that effective treatments have to modify the underlying mechanism of disease, he said, whether that is persistent infection, autoimmune reactions, neural network dysregulation, or a combination.

In conclusion, Fallon shared some lessons from Lyme disease and a vision of a research agenda for the future. While he acknowledged that there is considerable suffering associated with these conditions, and that sometimes providers exacerbate the problem by invalidating the patient's experience, he shared a message of hope by saying that in his work with patients with persistent Lyme encephalopathy, he has learned that there is always the possibility of improvement even for very sick patients. He shared suggested priorities for future research (Box 6-1).

BOX 6-1
Suggestions for Future Research Priorities

- Conducting research studies targeting different mechanisms of disease to identify most effective treatment approaches for Lyme and other diseases.
  - Collecting biological samples for biomarker studies.
  - Enrolling patients who meet severity criteria for primary clinical outcomes.
- Expanding the research study populations to include those with probable and possible Lyme/other tick-borne disease, as these patients make up a large portion of those with chronic symptoms and have been neglected by research.
- Educating health care providers about the multiple presentations, including the neuropsychiatric ones and the need to screen for suicidal thoughts/behaviors.
- Encouraging the creation of "infection-associated multisystem illness clinics" in major medical centers that include clinicians from multiple disciplines so as to best help these patients with chronic illness.

SOURCE: Adapted from Brian Fallon presentation, June 30, 2023.

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Discussion

Speakers in this session discussed developing a common research agenda, creating a specific long COVID "endotype" of patients, and accelerating approval pathways for new treatments. One participant noted the rarity of patients receiving just one diagnosis, asking for the establishment of an office at the NIH on infection-associated chronic illnesses for more research on the multiple types of conditions plaguing patients. Fallon agreed this would be a great idea, and Deeks noted the power of advocacy groups to influence Congress. Given the way government works, he said, scientists will not be able to make these types of big changes rapidly, so they will need strong support from patient communities.

To engage industry to become involved in clinical trials for these chronic illnesses, Walt and Deeks agreed that the COVID-19 spike protein may be an excellent biomarker for long COVID, but Deeks said there is also a need for other surrogate markers for clinical outcomes. That would let researchers measure a biomarker, administer interventions, and then observe the changes in levels (i.e., spike protein) to predict the change in clinical outcomes, he explained. This may be more appealing to industry, as drugs may be approved based on impact on the biomarker, and there would not be a need to measure all the other diagnostics or clinical outcomes, making the trial and regulatory process more straightforward.

Geng called for learning from other disease conditions such as fibromyalgia, migraines, or others as models of how to advance therapeutics without well-established biomarkers. She emphasized the importance of not slowing down the process for treatment advances and approvals even without the perfect marker. Similarly, Deeks said currently there are available drug candidates, an informed patient community, outcomes that can be measured, and public pressure to move forward, but what is lacking is industry engagement. There is a need for funding, and assets from industry could be used to perform early probe studies, he said. Foundations are also critical in raising funds to support clinical trials, but without industry engagement it would take significant NIH funding to expand these trials, he stated.

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7

Considering Challenges and Opportunities in a Shared Research Agenda

This chapter features reflections and remarks from panelists summarizing lessons and themes from the workshop. Speakers highlighted remaining challenges and future directions, as well as potential steps towards progress for the many patients suffering from infection-associated chronic illnesses. It concludes with speaker suggestions made throughout the workshop on promising strategies for patients, potential research, treatment and diagnostic approaches, and future areas for improvement.

REMAINING CHALLENGES AND FUTURE DIRECTIONS

Avindra Nath, National Institute of Neurological Disorders and Stroke, highlighted a central challenge: that experts in different disciplines and across sectors tend to work in silos. In the federal government, agencies that work in the chronic illness space are housed under the executive branch and are separate from the legislative branch of government, which is the branch that makes decisions on funding. In academia, Nath pointed out that while experts across disciplines are working toward similar goals, most do not collaborate in meaningful ways. Collaboration is critical to addressing the breadth of these chronic conditions, which according to Nath are the "biggest mysteries in medicine." A key challenge in the biology of these infection-associated chronic illnesses is the heterogeneity of symptoms, he added. Individual patients express different symptoms and pathophysiology, despite significant overlap between conditions and symptoms. For long COVID, the numerous potential symptoms can be grouped into four general categories, which may have common pathophysiological mechanisms (see Figure 7-1).

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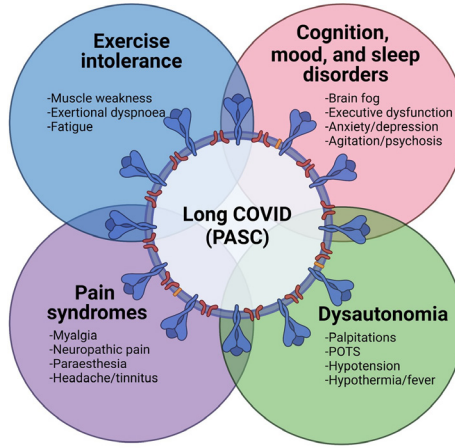

FIGURE 7-1 Chronic neurological sequelae of COVID-19.
NOTES: Figure 7-1 was originally published in *Brain* in 2022. A modified version was included in Nath's presentation.
SOURCE: Avindra Nath presentation, June 30, 2023; Balcom et al., 2021 (by permission of Oxford University Press).

Nath said that the epidemiology of long COVID is still unclear because the disease is not well defined. Although research is advancing, there are currently no good diagnostic tests for long COVID, and no established, effective treatments. Gaps in the understanding of the pathogenesis also remain, he said. Lacking resources is a persistent issue, but Nath expressed optimism at the range of philanthropic, federal, and nonprofit entities that are contributing funds into relevant research and development activities.

Several presentations from this workshop pointed to the possibility of viral persistence in the body as a driver of chronic illness, Nath stated. Viral persistence may be linked to lingering remnants of defective virus, remaining viral products that have not been cleared, or reactivation of other latent viruses. There has also been sufficient evidence that innate immune activation, autoimmune antibodies, immune exhaustion, and genetic factors may predispose some to developing these chronic conditions.

Nath concluded with a list of potential priority areas for future progress:

- Agreeing on a common term, such as *infection-associated chronic illnesses*, to serve as an umbrella for uniting research endeavors.
- Prioritizing patient engagement at every step of the research process.
- Developing diagnostics and biomarkers and improved models to study diseases.
- Replicating and scaling multidisciplinary clinics.

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- Studying pathogenesis within the context of clinical trials.
- Designing clinical trials in innovative ways.

Ensuring Comprehensive Advances in Science

Amy Proal, PolyBio Research Foundation, stated that her organization has created a research infrastructure that supports the study of various infection-associated chronic illness such as long COVID, myalgic encephalitis/chronic fatigue syndrome (ME/CFS), Lyme disease, Ehlers-Danlos syndrome, and others. Proal noted that PolyBio built the long COVID research consortium, which combined teams that were conducting innovative research, in order to form a dynamic group of collaborators. One of the key facets of this group is embracing open science, where members of interdisciplinary teams regularly share data, hypotheses, and ideas, Proal said, which is necessary to move studies forward and advance the science as quickly as possible. Proal also underscored the importance of studying tissue samples in addition to body fluids, saying that this is essential for understanding viral persistence and identifying reservoir sites in patients of various conditions. Imaging studies are another innovative method for identifying potential mechanisms of chronic illnesses in patients.

Moving beyond the collections of biological samples, Proal said, it will be important to understand the activity of pathogens and the immune response in those samples. To do this, sequencing technologies will be critical to get a detailed understanding of the immune and host genome expression near an identified pathogen or protein. This might include spatial transcriptomics, single nuclei RNA sequencing, microbiome-based approaches, and technologies that capture the activity of immune cells. Proal also supported performing similar forms of analysis on patients with different infection-associated chronic illnesses to obtain comparable datasets, she said. Lastly, Proal called for conducting multiple analyses on the same well-characterized study participants to maximize valuable data collection. This is at the core of the research at PolyBio, where researchers collect many different samples and types of data, and then use machine learning to look for trends that correlate in patients to identify overlapping symptoms and trends. This approach allows for defining endotypes of conditions, which is needed for identifying biomarkers, she explained. Proal concluded that defined biomarkers will encourage industry to invest in clinical trials to further advance the development of novel treatments and therapeutics.

Patients Cannot Wait

Lorraine Johnson, MyLymeData, began her closing remarks with a sense of urgency, noting that patients cannot wait for years while the ideal

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diagnostics and treatments are developed. The pace of traditional research is extremely slow, and previous reasons for this slow progress, such as the lack of definitive biomarkers or murky endpoints are no longer acceptable, she stated. Johnson quoted a 2017 article by Tom Frieden, saying,

> There will always be an argument for more research and for better data. But waiting for more data is often an implicit decision not to act, or to act on the basis of past practice rather than on the best available evidence. (Frieden, 2017)

It is critical for clinicians to be given clinical discretion to try different interventions that are safe and could help patients who are suffering in the present, she said, noting that patients are willing to try nearly anything. While applying different treatments, it is also necessary to capture that data and learn from it. She called for combining and capturing data wherever it is available, whether from patient registry data, biorepositories, or clinical trial results, and considering everything together in parallel.

Peter Rowe, Johns Hopkins University, followed by stating the need for support of clinical care for those who are desperate to feel better. There is a need for more clinical capacity, he said, but there is also a need for financial support for clinics, as many patients are unable to afford services in the traditional fee-for-service model. Financial support services that have been provided for HIV care or pediatric cancer could serve as a model for making treatment more accessible at clinics that specialize in chronic illnesses. Rowe noted the importance of studying clinical observations in addition to laboratory observations, as much has been learned about conditions such as Ehlers-Danlos syndrome by examining cascading symptoms expressed in patients. Rowe said that while mast cell activation syndrome was not described in detail at this workshop, allergic phenomena are typically overrepresented in patients with ME/CFS. There are some treatments effective for these symptoms, but they should be studied in clinical trials with the antiviral therapeutics to examine drug interactions. He suggested merging the study of clinical observations and laboratory research.

DISCUSSION

A participant asked about the importance of incorporating systems biology and centralizing data into a common platform. Nath noted that systems biology is important for any disease but acknowledged a continuing struggle regarding how to truly share data when massive amounts of it are being collected, and stated that the research community should be actively pursuing this goal. Proal added that this is central to her group's collaboration framework, and they are exploring the use of a data integration platform like LabKey. This allows for multiple sites to participate and store data in a single open access location. She highlighted the Center Grant Mechanism (U54 grants) through the National Institutes of Health (NIH), which contain a

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clinical core and an administrative core that enable open communication, and noted the NIH requirement that data is uploaded into a central data integration platform. She encouraged NIH to continue to offer those types of grants for infection-associated chronic illnesses and added that many researchers are looking for more high-risk/high-reward, faster turnaround funding mechanisms to help them be more responsive to identified problems and needs.

Speakers also highlighted barriers that need to be proactively addressed to advance progress. Nath noted that regulations, laws, and policies can be challenging, but that they are also necessary for ensuring safety. At the clinical level, Rowe said that taking care of people with chronic illnesses has its own challenges. For example, nearly every treatment prescribed for ME/CFS patients is off-label, and then insurance companies require a prior authorization, which creates administrative burden. There are numerous barriers when it comes to insurance, he said, which can significantly slow patient care.

Tim Coetzee, National Multiple Sclerosis Society, said the invisibility that people with infection-associated chronic illness experience has begun to decrease. He noted that much more work remains to be done, but progress is being made. MS was believed to be an infection-associated chronic illness in the 1980s, but that vocabulary and terminology did not exist at the time. There was not much in the way of treatment back then either, but researchers tested the use of interferons as therapeutics with small numbers of patients. This resulted in some positive response that led to a series of trials and then led to the current standard of care, he said. Coetzee provided three lessons for the work that is still needed today:

1. Doctors need to listen to patients and create space for the community that is affected in all stages research and treatment.
2. "Start where we are with what we have." Take action with currently available tools and information in order to best care for patients who are suffering.
3. Persistence is key. Collaboration, coordination, and allyship can be exerted to find ways to lower barriers.

Millions of people live with these infection-associated chronic illnesses. They are counting on researchers and clinicians who can take collective action to dramatically change their world, Coetzee concluded. Additional suggestions from speakers throughout the workshop on promising strategies for learning across diseases, potential research, treatment, diagnostic approaches, critical gaps, and next steps are outlined in Box 7-1.[1]

[1] This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

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BOX 7-1
Suggestions from Individual Speakers[2]

Promising Strategies for Learning Across Conditions

- Standardizing the evaluation of microbes in tissue so researchers can continue to learn from other disease areas and incorporate lessons from overlapping disease areas. (Horn)
- Establishing an office of infection-associated chronic illness at the National Institutes of Health could advance and coordinate critical research efforts. (Fallon, McCorkell)
- Setting up registry-style clinics around the country to collect detailed, well-classified data to understand similarities and differences between conditions and facilitate data collection. (Putrino, Johnson)
- Examining the possibility of persistent infection throughout the body, whether defective virus, reactivation of latent virus, or viral products not being cleared. (Nath, Peluso)
- Determining common behaviors and common central nervous system circuits affected by infection-associated chronic illnesses. (Miller)
- Establishing education for medical providers, the media, and the general population to understand these conditions and that complaints are legitimate and people suffering should have their experiences supported. (Fallon, Geng, Davis, O'Rourke)
- Encouraging the creation of infection-associated multisystem chronic illness clinics in major medical centers that include clinicians from multiple disciplines. (Fallon)

Potential Research, Treatment, and Diagnostic Approaches

- Following patients longitudinally throughout studies. (Komaroff)
- Ensuring meaningful engagement of patients and caregivers in all stages of the research process. (Krumholz, McCorkell, Nath)
- Enabling a virtual, decentralized clinical trial platform. Use technologies to collect samples from home, centralize tools, and remove barriers preventing people from participating. (Amitay, Marston, Putrino)
- Looking at protein–protein interactions when considering new methodologies for diagnosis. (Pretorius)
- Accelerating clinical trials of therapeutics that are most important to the patient community. (McCorkell)
- Considering implications of inclusion/exclusion criteria to ensure final factors are necessary for the trade-off in generalizability and sample attrition to determine cause and effect. (Johnson)

[2] This list is the rapporteurs' summary of points made by the individual speakers identified, and the statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They are not intended to reflect a consensus among workshop participants.

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Critical Gaps

- There is a lack of animal model studies given the heterogeneity of symptoms. (Oh)
- More study is needed about mechanisms of viral persistence and immune evasion (Chertow, Deeks) and understanding the pathogenesis of these types of illnesses. (Nath)
- Comparable data on cellular immunity is lacking to pair with existing knowledge on humoral immunity, which could help study the immune response against Epstein-Barr virus before the onset of multiple sclerosis. (Ascherio)
- The lack of mechanistic understanding challenges providers in legitimizing conditions. (Geng)
- Established biomarkers are needed for long COVID and other diseases. (Cherry, Deeks, Fallon)
- A coalescing of methods is needed on how best to study pediatric long COVID compared to adult populations. (Marston)
- There is a need for more psychiatrists and funding in mental health/psychology research to support the potential treatment of the brain given downstream consequences. (Miller)

Potential Next Steps

- Pair human clinical studies with high resolution omics study, such as immunotherapy studies, to identify causal links. (Oh)
- Build the knowledge base of potential mechanisms across conditions through engaging patients, building multidisciplinary teams, considering equity, and synergizing knowledge across syndromes. (Geng)
- Centralize collections for samples to add efficiencies, have multiple projects for blood draw, lower costs, and design to share and bring new people into the field. (Horn)
- Educate physicians and researchers to integrate fields of psychiatry with infectious disease and associated chronic illnesses. (Miller)
- Collect and study tissue samples in addition to other bodily fluids to understand the full picture of how the body is affected and potential viral reservoirs. (Horn, Proal)
- Engage industry through identifying potential pathways affected and defining endotypes and biomarkers of conditions. (Deeks, Proal)

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B

Workshop Statement of Task

Toward a Common Research Agenda in Infection-Associated Chronic Illnesses:
A Workshop to Examine Common, Overlapping Clinical and Biological Factors

June 29–30, 2023 | Washington, D.C.

A planning committee of the National Academies of Sciences, Engineering, and Medicine will organize and conduct a public workshop to explore the current understanding of, and future research opportunities for, infection-associated chronic illnesses. The workshop will focus on long COVID, myalgic encephalomyelitis/chronic fatigue syndrome, persistent Lyme disease, and multiple sclerosis. Workshop discussions will consider the latest research and knowledge gaps in the following:

1. Overlapping clinical and biological factors underlying infection-associated chronic illnesses,
2. Current practice and novel technologies to develop urgently needed diagnostic tests for different stages of illness and/or the potential underlying infectious agent,
3. Identification of therapeutic targets and strategies to prevent or impede chronic illness progression, and

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4. Coordination and collaboration among various stakeholders and practitioners that will increase research and enhance care across different patient populations.

The planning committee will organize the workshop, develop the agenda, select and invite speakers and discussants, and moderate or identify moderators for the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated *rapporteur* in accordance with institutional guidelines.

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C

Workshop Agenda

Day 1: Mechanisms Underlying Infection-Associated Chronic Illnesses

8:30–8:45 a.m. **Welcome remarks, workshop overview, and goals**

Welcome
Peter Daszak, EcoHealth Alliance
Chair, Forum on Microbial Threats
John Krystal, Yale University
Cochair, Forum on Neuroscience and Nervous System Disorders

Introduction and workshop overview
Tim Coetzee, National Multiple Sclerosis Society
Workshop Cochair

Sponsor perspectives
Lyle Petersen, U.S. Centers for Disease Control and Prevention
Ben Nemser, Steven & Alexandra Cohen Foundation

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Toward a Common Research Agenda in Infection-Associated Chronic Illnesses: Proceedings of a Workshop

8:45–10:00 a.m. **Session 1: Introduction to infection-associated chronic illnesses**
Moderator: Rafael Obregon, UNICEF

Keynote
Tim Henrich, University of California, San Francisco

Introduction and a historical perspective
Anthony Komaroff, Harvard Medical School; Brigham and Women's Hospital

Stakeholder perspectives
Joseph Breen, National Institutes of Health (NIH) RECOVER
Harlan Krumholz, Yale School of Medicine
Hannah Davis, Patient-Led Research Collaborative
Meghan O'Rourke, Yale University
Author of *The Invisible Kingdom: Reimagining Chronic Illness*

Q&A

10:00–10:15 a.m. **BREAK**

10:15 a.m.–12:00 p.m. **Session 2: Common mechanistic factors of infection-associated chronic illnesses**

Host-mediated factors (part 1)
Moderator: Peter Rowe, Johns Hopkins University

Immune Dysfunction

Post-COVID syndrome and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Evidence for a role of autoantibodies and endothelial dysfunction and development of targeted therapies
Carmen Scheibenbogen, Charité University

Viral reactivation
Michael Peluso, University of California, San Francisco

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Autonomic Dysfunction

Overview of orthostatic intolerance: Risk factors and treatments
Satish Raj, University of Calgary

Common underlying mechanisms of chronic illness: Lessons from postural orthostatic tachycardia syndrome (POTS), ME/CFS, and long COVID
Mitchell Miglis, Stanford University

Q&A

12:00–1:00 p.m. **LUNCH**

1:00 pm–3:00 p.m. Session 3: Common mechanistic factors of infection-associated chronic illnesses

Host mediated factors (part 2)
Moderator: Brian Fallon, Columbia University

Effect of inflammation on the brain: Significance for chronic illnesses
Andrew Miller, Emory University

Role of the microbiome in ME/CFS
Julia Oh, The Jackson Laboratory

Pathogen-mediated factors and pathogen persistence

Viral persistence and development of chronic illness: Lessons from Epstein-Barr virus (EBV)
Bill Robinson, Stanford University

Pathogen distribution and persistence: Learnings from SARS-CoV-2
Dan Chertow, NIH

Modeling pathogen persistence: Lessons from animal studies
Monica Embers, Tulane University

Q&A

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3:00–3:15 p.m. **BREAK**

3:15–4:45 p.m. **Session 4: Future opportunities and research priorities in diagnostics**

Moderator: Avindra Nath, National Institute of Neurological Disorders and Stroke (NINDS), NIH

Biomarkers for Lyme disease and posttreatment Lyme
John Aucott, Johns Hopkins University

Biomarkers for EBV and associations with multiple sclerosis (MS)
Alberto Ascherio, Harvard T.H. Chan School of Public Health

Microclots as a common indicator of chronic disease
Resia Pretorius, Stellenbosch University

Next-generation and metagenomic sequencing
Charles Chiu, University of California, San Francisco

Q&A

4:45–5:00 p.m. **Synthesis and adjourn**
Amy Proal, PolyBio Research Foundation

END OF DAY 1

Day 2: Clinical Advancements and Collaboration

8:30–9:00 a.m. **Welcome remarks, review of day 1**

Welcome and introduction
Tim Endy, Coalition for Epidemic Preparedness Innovations (CEPI)
Workshop Cochair

Keynote
Hilary Marston
Chief Medical Officer, U.S. Food and Drug Administration

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	Q&A
9:00–10:15 a.m.	**Session 5: Patient-driven research panel** **Moderator:** Liz Horn, Lyme Disease Biobank
	Panel: Lisa McCorkell, Patient-Led Research Collaborative Oved Amitay, Solve ME/CFS Lorraine Johnson, MyLymeData Liz Horn, Lyme Disease Biobank
	Q&A
10:15–10:30 a.m.	**BREAK**
10:30 a.m.–12:00 p.m.	**Session 6: Research innovation and required infrastructures** **Moderator:** Tim Endy, CEPI
	Diagnostic journeys of long COVID patients Linda Geng, Stanford University
	Ultrasensitive diagnostic assays: Examples with SARS-CoV-2 and long COVID David Walt, Harvard University
	Translating infection-associated chronic illnesses research into the clinic in drug repurposing Steven Deeks, University of California, San Francisco
	Treatment approaches to posttreatment Lyme disease and a new clinical trials network Brian Fallon, Columbia University
	Q&A
12:00–1:00 p.m.	**LUNCH**
1:00–2:45 p.m.	**Session 7: Future opportunities and research priorities in therapeutics** **Moderator:** Tim Coetzee, National Multiple Sclerosis Society

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Development of oral antiviral for COVID-19
Ravi Shankar Singh, Pfizer

Development of antivirals and combination therapies for infection-associated chronic illnesses
Sara Cherry, University of Pennsylvania

Clinical trials for multisystem inflammatory syndrome in children (MIS-C) and long COVID
Alessio Fasano, Harvard University

Long Lyme: Opportunities for prevention and treatment
Kim Lewis, Northeastern University

Clinical care for patients of various infection-associated chronic illnesses
David Putrino, Mount Sinai Health System

Q&A

2:45–3:50 p.m. **Session 8: Developing a shared research agenda: Challenges and opportunities**
Moderators:
Avindra Nath, NINDS, NIH
Amy Proal, PolyBio Research Foundation
Lorraine Johnson, MyLymeData
Peter Rowe, Johns Hopkins University

Q&A

3:50–4:00 p.m. **Synthesis and close**
Tim Endy, CEPI
Tim Coetzee, National Multiple Sclerosis Society
Workshop Cochairs

END OF WORKSHOP

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