

Long COVID in Primary Care: A Practical Approach to Evaluation and Management



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ABSTRACT

Long COVID is a multi-system, heterogeneous condition that manifests as new or worsened symptoms lasting at least 3 months following acute SARS-CoV-2 infection, often despite normal results on routine diagnostic testing. Common manifestations include fatigue, post-exertional malaise, cognitive impairment, and orthostatic intolerance. Primary care clinicians are uniquely positioned to identify and manage Long COVID due to their longitudinal relationships with patients and holistic understanding of their patients' health. However, diagnostic uncertainty, time constraints, and limited access to specialty care present significant challenges, and sometimes hesitation, to addressing Long COVID in the primary care setting. This focused narrative review provides a pragmatic, primary care–focused approach for the evaluation and management of Long COVID. Using patient-centered vignettes, we first describe common clinical presentations. Next, we provide a framework for the pathophysiological mechanisms suspected to contribute to persistent symptoms after SARS-CoV-2 infection. We then present a simple approach to Long COVID diagnosis and management that leverages primary care clinicians' skillset and highlights unique aspects of Long COVID care (e.g., diagnostic workup to evaluate for competing or coexisting diagnoses; management strategies focused on validation and supportive care, including activity pacing, multidisciplinary rehabilitation, and consideration of symptom-based medication trials). We offer practical strategies to effectively, yet efficiently, address a possible Long COVID diagnosis within the context of brief primary care visits (e.g., prioritize the most bothersome or addressable symptom(s) first, focus on one or two symptoms each visit, leverage longitudinal follow-up). We conclude with evidence-based strategies for prevention counseling, including infection prevention and early outpatient treatment during acute infection. While we remain optimistic that reliable diagnostic biomarkers and curative treatments will one day be available, until then, this primer supports primary care clinicians in recognizing Long COVID and supporting

their patients who are living with it, despite the constraints of our current healthcare environment.

KEY WORDS: long COVID; primary care; diagnosis; management; post-acute sequelae of SARS-CoV-2 (PASC)

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INTRODUCTION

Although the COVID-19 pandemic was declared “over” in 2023, the most recent available estimates suggest that approximately 6% of US adults and 0.5% of children and adolescents are still living with new or persistently worsened symptoms that developed shortly after acute SARS-CoV-2 infection.¹ Patients' symptoms vary widely in character and severity, but most commonly, symptoms include fatigue, post-exertional malaise (PEM), cognitive impairment (“brain fog”), and/or lightheadedness/orthostasis.^{1–3} Patients may also describe vague gastrointestinal symptoms, sleep disturbance, pain, or breathing discomfort — all without a clear alternative etiology on traditional assessments.⁴ All these symptoms can be manifestations of Long COVID (previously called post-acute sequelae of SARS-CoV-2 infection [PASC]). Published definitions of Long COVID vary slightly based on the required timing of symptom onset relative to acute infection, duration of symptoms, and functional impact.^{5,6} Definitions that were created for research purposes also sometimes require laboratory evidence of preceding SARS-CoV-2 infection.⁷ For clinical purposes, however, Long COVID can be conceptualized as new or worsened symptoms that develop after confirmed *or suspected* acute SARS-CoV-2 infection and persist for over 3 months.^{5,6,8}

Primary care clinicians (PCPs) are intended to serve as the cornerstone of healthcare. As such, they are well-positioned to play a central role in Long COVID care because, in an ideal scenario, they have a longitudinal relationship with patients, are the first point of contact when new symptoms arise, and have a holistic understanding of their patients' health and home situations. However, the absence of validated diagnostic biomarkers and curative treatment for Long COVID can confuse, overwhelm, and frustrate patients and clinicians alike. Furthermore, constraints in the current

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healthcare system too often lead to short PCP visit times, PCP burnout, and limited access to subspecialty consultation, which can add to the sense of overwhelm.

The purpose of this narrative review is to provide a pragmatic, primary care–focused framework for primary care clinicians, who are undoubtedly *already* caring for patients with Long COVID — whether recognized or not. We outline when Long COVID should be considered in the differential diagnosis; how to perform a focused evaluation within the time constraints of typical primary care visits; and how to counsel, initiate symptom-based management, and determine when specialty referral may be appropriate.⁹

COMMON CLINICAL PRESENTATIONS AND SYMPTOM CLUSTERS

Patients with Long COVID often present with one or more common symptom clusters.⁴ Recognizing these patterns can lead to the diagnosis of Long COVID and related conditions (like myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS] and postural orthostatic tachycardia syndrome [POTS]) and guide management approaches. The following vignettes illustrate common clinical presentations of Long COVID, using patient-centered language to reflect how individuals may describe their symptoms in a primary care setting.

Case 1 — Fatigue and Post-exertional Malaise A 32-year-old female with a history of anxiety presents with 4 months of fatigue and worsened anxiety symptoms. She reports that her symptoms worsen after minimal activity and describes her current fatigue and anxiety as “different than baseline,” with a reduced ability to complete daily tasks such as preparing meals, doing laundry, or responding to emails. She describes “crashing” after exertion, explaining that even normal self-care activities can leave her feeling as though she is “wearing a lead coat,” with profound exhaustion, heaviness, and difficulty thinking that can last for hours to days. She has reduced her work hours due to the symptom burden and reports difficulty maintaining a consistent daily routine. When asked directly about inciting potential triggers or preceding infections, she recalls that symptoms started about a month after a mild COVID-19 infection.

Case 2 — Dysautonomia A 19-year-old previously healthy female presents with palpitations, lightheadedness, and near-fainting upon standing for the past 3 months. Symptoms improve when lying down and are associated with a sensation of heart-racing and difficulty maintaining usual activities. Previously, she was active and exercised regularly, including running and attending fitness classes several times

per week. She now becomes symptomatic with minimal exertion, such as walking short distances or standing in long lines. Upon further questioning, she notes she had upper respiratory symptoms approximately 2 weeks before symptom onset. She never sought care or a home test, but multiple family members tested positive for COVID-19.

Case 3 — Cognitive Impairment, “Brain Fog” A 45-year-old male aerospace engineer presents with new, persistent cognitive difficulties 5 months after mild COVID-19 infection. Symptoms include forgetfulness, impaired concentration, word-finding difficulty, and slowed processing speed. He reports decreased work performance, including difficulty responding to work emails, organizing his daily schedule, and keeping up with routine tasks. He has recently gotten into trouble at work for missing deadlines and has forgotten to pick his children up from school. He describes feeling “mentally foggy” despite a normal basic laboratory evaluation.

A FRAMEWORK FOR PATHOPHYSIOLOGICAL MECHANISMS AND MANIFESTATIONS

The SARS-CoV-2 virus can cause long-lasting sequelae, suspected via multiple distinct pathophysiological mechanisms, all of which are currently described under the umbrella term, “Long COVID” (Fig. 1, Table 1).⁴ For the purposes of clinical care, clinicians can mentally categorize Long COVID manifestations into three types. First, acute SARS-CoV-2 infection can cause acute end-organ tissue injury that has lasting consequences, like a “hit and run” manifestation.^{10–13} Second, acute infection can act as a stressor on the body that triggers, unmasks, or worsens one or more common chronic diseases in the weeks or months after acute infection (i.e., reduced reserve contributing to diabetes, rheumatoid arthritis, etc.). Finally, SARS-CoV-2 infection can trigger ongoing biological dysregulation via multiple suspected pathophysiological processes that have been repeatedly identified in basic science studies but are often challenging to identify using currently available clinical diagnostic tools (e.g., persistent viral reservoirs, immune dysregulation, gut dysbiosis, mitochondrial dysfunction, and microvascular clotting contributing to fatigue, post-exertional malaise and symptom exacerbation, cognitive impairment, dysautonomia).^{14–19} Management of symptoms from the “hit and run” and “reduced reserve” manifestations of Long COVID is relatively straightforward and consists of treating the end-organ damage and chronic diseases according to standard practice principles. In contrast, management of the “ongoing biological dysregulation” manifestations can be more challenging, and treatment currently consists of rehabilitation and supportive care.

Table 1 Commonly Reported Symptoms and Clinical Findings Associated with Long COVID

Organ system	Subjective symptoms	Clinical findings & diagnoses
Constitutional / General 	- Fatigue - Energy crashes (PEM / PESE)	ME/CFS
Neurological 	- Brain fog (attention, memory, word recall) - Headache - ringing in the ears (tinnitus) - Smell/taste changes (anosmia, ageusia) - Chronic pain - Abnormal sensations (dysesthesias, paresthesias) - Sleep dysfunction - Tremor, clumsiness	- Abnormal neuropsychological testing - Small fiber neuropathy - Obstructive sleep apnea - Movement disorders,⁴⁸⁻⁵⁰ hyperreflexia, balance impairment
Cardiovascular 	- Chest pain/tightness - Shortness of breath - Palpitations - Reduced exercise tolerance	- Orthostatic hypo/hypertension - POTS - Inappropriate sinus tachycardia - Sinus bradycardia
Pulmonary 	- Shortness of breath - Breathing discomfort - Wheezing - Cough	- Pulmonary fibrosis - Pulmonary thrombosis
Gastrointestinal 	- Nausea, vomiting - Diarrhea or constipation - Abdominal pain - New food intolerance - Unintentional weight loss	Abdominal distension
Integumentary 	- Hives (urticaria) - Cold sores - Other rashes - Hair loss (alopecia) - Nail changes	- Flare-up of pre-existing dermatoses (psoriasis, lupus, Sjogren's) - HSV reactivation (shingles) - Telogen effluvium - Alopecia areata
Psychiatric 	- Anxiety - Depression	New or worsened pre-existing mental health conditions
Endocrine 	Menstrual cycle changes	- Thyroiditis - HPA axis dysfunction

Symptoms may be intermittent or continuous

This table is not an exhaustive list of all potential symptoms reported by patients with Long COVID

Abbreviations: *PEM* post-exertional malaise, *PESE* post-exertional symptom exacerbation, *ME/CFS* myalgic encephalomyelitis/chronic fatigue syndrome, *POTS* postural orthostatic tachycardia syndrome, *HSV* herpes simplex virus, *HPA* hypothalamic-pituitary-adrenal

PRACTICAL DIAGNOSTIC AND MANAGEMENT APPROACH

Diagnosis When the patient's history suggests that Long COVID should be considered on the differential diagnosis, the diagnostic approach to Long COVID mirrors the same framework that PCPs use for all other conditions (Fig. 2).²⁰ First, a focused physical exam is guided by the patient's symptoms, with particular attention to orthostatic intolerance, which can present atypically and is often missed in this population.²¹ Next, a targeted laboratory and imaging workup is indicated to evaluate for potential competing diagnoses and/or addressable sequelae of Long COVID. Of note, there is currently no clinically available biomarker to confirm or rule out the diagnosis of Long COVID, and severe Long COVID symptoms can be present despite normal results on conventional diagnostic testing.⁵

Management — Validation and Education There is not yet a definitive cure for Long COVID. However, validation, education, and supportive care can still meaningfully improve patients' quality of life and help them find joy and meaning in the midst of their "current normal."²⁰ In fact, while mental health conditions are not the underlying cause of Long COVID, Long COVID can often contribute to new or worsened mental health symptoms, not only due to the direct symptom impact on the patient's life, but also due to not feeling believed or understood by loved ones or healthcare providers.²² As such, PCPs should assess and support the patient's well-being as part of a comprehensive management approach, in the same way that well-being should be addressed with other potentially life-changing conditions such as cancer or a major injury.²²

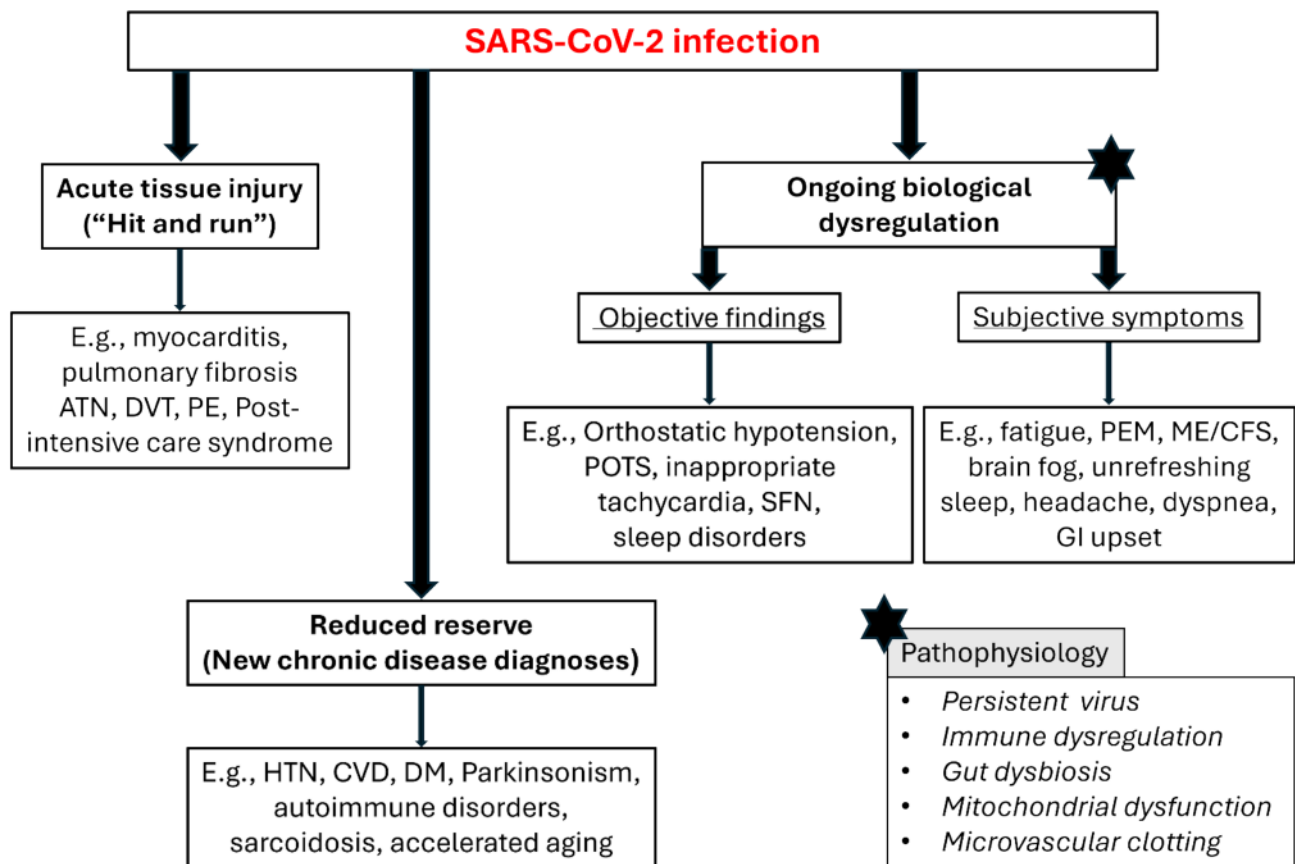


Figure 1 Clinical framework for categorizing manifestations of Long COVID. Abbreviations: ATN, acute tubular necrosis; DVT, deep vein thrombosis; PE, pulmonary embolism; HTN, hypertension; CVD, cardiovascular disease; DM, diabetes mellitus; POTS, postural orthostatic tachycardia syndrome; SFN, small fiber neuropathy; PEM, post-exertional malaise; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; GI, gastrointestinal.

Management — Nonpharmacologic Strategies Rehabilitation for symptoms including fatigue, PEM, dysautonomia, and brain fog can include activity pacing, energy conservation strategies, and activity modification.²³ For instance, a patient may need to plan meals, grocery shop, and prepare food on separate days of the week. Additionally, the patient may use a scooter at the grocery store and sit down to chop vegetables, rather than stand.²⁴ Structured rehabilitation with therapists who understand chronic fatiguing illnesses can be life-changing for patients and a key multidisciplinary support strategy for PCPs. This expertise is most commonly available among therapists who specialize in neurorehabilitation rather than orthopedic rehabilitation. Specifically, consider referral to physical therapy to address fatigue, PEM, dysautonomia, and related intolerance to physical activity; occupational therapy to address fatigue, PEM, brain fog, and related difficulty with self-care and job activities; and speech therapy to address impaired attention, memory, word recall, and/or breathing discomfort despite normal pulmonary tests. While some patients tolerate gradual, supervised progressive exercise training, this approach must be considered with extreme caution among patients with PEM because even seemingly minor overexertion can cause a delayed PEM flare and has been associated with amyloid deposition, reduced

mitochondrial enzyme activity, and signs of severe skeletal muscle damage.^{25–27} For patients with POTS or other orthostatic intolerance, increasing daily fluid intake (to 2.5–3.5 L) and salt intake (to 2.8–4 g sodium, equivalent to 7–10 g salt) can also provide some symptomatic relief if they do not have contraindications. Compression garments such as waist-high stockings or an abdominal binder can be helpful, as well.

Management — Medications There are no FDA-approved medications for Long COVID yet. Rather, medication management is currently symptom-based, largely using the same indications that are relevant outside the context of Long COVID (e.g., beta blockers or ivabradine for POTS, stimulants for brain fog causing attention difficulty, gabapentinoids for neuropathic pain, selective serotonin reuptake inhibitors [SSRIs] for new or worsened depression or anxiety symptoms). Worth particular mention, low-dose naltrexone (LDN) is an opioid receptor blocker, non-controlled medication from which some patients report improved pain, fatigue, and brain fog with off-label use.²⁸ Additionally, some patients with suspected mast cell activation syndrome (MCAS) triggered by Long COVID report relief with a combination of H1 and H2 antihistamines.^{29,30} Tables with commonly used medications,

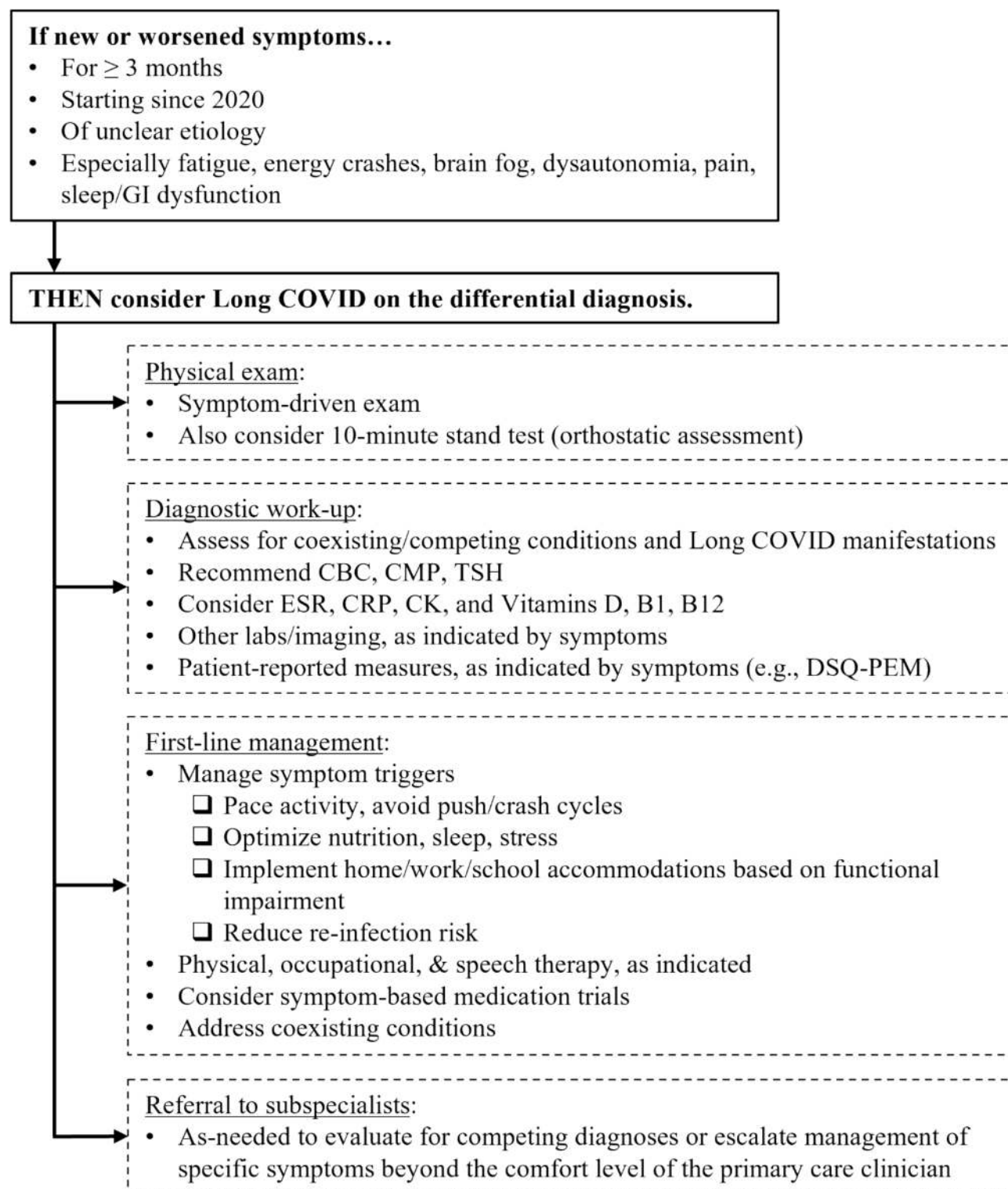


Figure 2 Practical approach to Long COVID for PCPs. Abbreviations: PCPs, primary care clinicians; GI, gastrointestinal; CBC, complete blood count; CMP, comprehensive metabolic panel; TSH, thyroid-stimulating hormone; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CK, creatine kinase; DSQ-PEM, 10-item DePaul Symptom Questionnaire for Post-Exertional Malaise.⁴³

dosages, and indications for Long COVID are available for point-of-care reference.²⁰

Management — Subspecialty Referrals Just as for other medical conditions, referral to medical subspecialists should be

considered when the PCP has a specific reason for consultation based on the patient's symptom constellation and/or severity. For example, referral may be warranted for evaluation of potential competing diagnoses that have alternative treatment pathways (e.g., Parkinson's disease, multiple sclerosis) or for

management escalation of symptoms that persist despite first-line measures that the PCP feels comfortable managing (e.g., upright intolerance despite increased fluid/salt intake, compression garments, and beta blocker therapy). Of note, referral to an autonomic specialist can be especially helpful for uncontrolled dysautonomia symptoms, but referral to a general cardiologist or potentially neurologist are alternative options if timely access to an autonomic specialist is not feasible for the patient.²⁰

Management — Disability Considerations Long COVID symptoms persist past 1 year for approximately 25% of patients and past 2 years for approximately 10% of patients.³¹ Therefore, in some cases, the duration, severity, and constellation of a patient's Long COVID symptoms can impact their ability to work, which can secondarily contribute to financial insecurity, increased stress, worsened symptoms, and reduced access to care. As such, it is crucial to support patients with appropriate documentation, such as a work letter with recommended work accommodations (e.g., flexible work schedule, adapted work environment, permission to work remotely) and/or thorough medical documentation to support a patient's application for disability benefits (e.g., documentation of all symptoms, the symptom time course and expected duration, symptom impact on function and ability to work, and any objective exam and/or diagnostic abnormalities).²⁰ When needed, a follow-up visit can be scheduled to specifically assess and document these needs.

WORKING WITHIN A 15-MINUTE VISIT

Long COVID specialty clinics sometimes have the luxury of 30–60-min visits for patient evaluation and management. However, this model has struggled to maintain financial sustainability, and the same is true in most primary care settings. As such, principles in the Text Box can help PCPs structure Long COVID visits in a manner that is both efficient and responsive to patient needs.

Text Box Principles to efficiently, effectively structure a primary care visit for Long COVID

1. Incorporate Long COVID screening questions into the history

When a patient presents with symptoms that may be manifestations of Long COVID, ask questions to identify whether Long COVID should be considered in the differential diagnosis, such as:

- “Were you sick (or around people who were sick) shortly before these symptoms developed?” “Did you (or they) test for COVID-19? Or was it during a COVID wave?”
- “Have these symptoms lasted more than 3 months?”

2. Assess patient concerns and goals early

Consider simple screening questions to identify patients' most impactful symptoms, such as:

- “Which symptom is most bothersome right now?”
- “How is this affecting your daily activities (work, school, self-care)?”

3. Prioritize 1–2 symptoms per visit, addressing the most limiting or modifiable concern first

Given the time constraints of a typical primary care visit, focus on the most bothersome or most clinically actionable symptoms first. Attempting to address multiple symptoms simultaneously may reduce effectiveness and increase patient overwhelm.

4. Leverage longitudinal care

Emphasize that management will occur over multiple visits. Schedule regular follow-up to reassess symptoms, evaluate treatment response, and address additional concerns in a stepwise manner.

5. Consider cautious, stepwise medication trials

Initiate one intervention at a time to allow assessment of response. Start low-dose, and titrate slowly. If symptoms do not improve, wean off the intervention. When appropriate, consider de-prescribing medications that may worsen fatigue, cognition, or autonomic symptoms.

6. Provide clear, written recommendations

Patients with cognitive symptoms may have difficulty retaining verbal instructions. Written summaries (e.g., after-visit summaries or patient portal messages) can improve adherence and reduce confusion.

7. Optimize visit logistics when possible

Consider strategies to reduce patient burden, especially for those with fatigue, post-exertional malaise, or dysautonomia. Consider scheduling telehealth visits and/or at times that minimize waiting and exertion (e.g., the first appointment of the day or the first visit of the afternoon).

8. Document functional impact

Clearly document how symptoms affect daily functioning, especially at school or in the workplace. This is essential, not only for clinical tracking, but also for supporting workplace accommodations and/or disability documentation when needed.

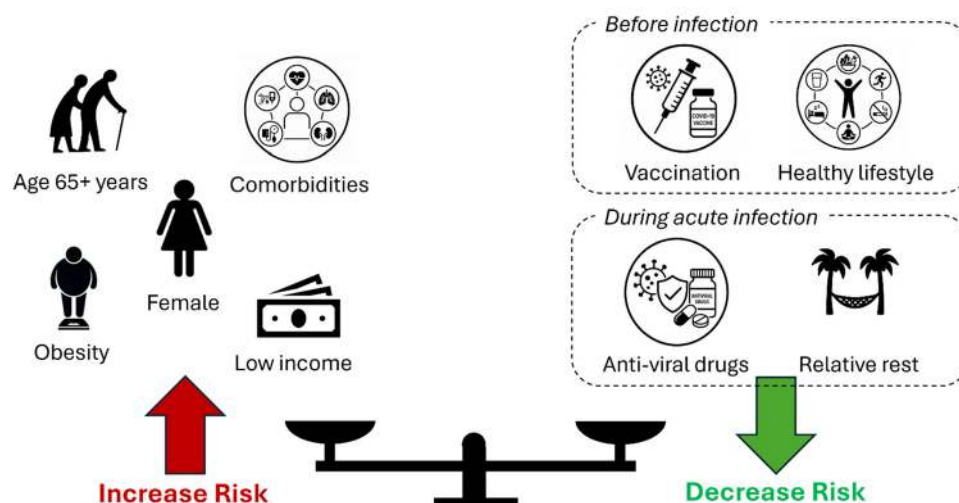


Figure 3 Risk factors associated with Long COVID. Although several sociodemographic and baseline health characteristics can increase risk for Long COVID (left), modifiable factors before and during acute SARS-CoV-2 infection can reduce an individual's risk (right).^{3,44–47}

PREVENTION COUNSELING

Prevention of Long COVID can be conceptualized in two stages: (1) reducing the risk of SARS-CoV-2 infection and (2) mitigating downstream effects during acute infection.⁶ It is especially important to emphasize prevention and mitigation measures among people who are at higher risk of Long COVID (Fig. 3). This includes addressing comorbidities and modifiable risk factors.

Preventing infection remains the most effective strategy for reducing the risk of Long COVID. Established public health measures continue to play an important role in reducing transmission, including: frequent hand-washing; improved indoor air quality (e.g., open windows, continuous fan use, central air system with a clean MERV 13 filter or higher, or a portable high-efficiency particulate air (HEPA) purifier appropriately sized for the room); appropriate mask use (ideally N95 or KN95 mask to prevent infection, at least a surgical mask to prevent contagious spread); and isolation during periods of infectivity (ideally until rapid antigen test is negative, or continued masking if isolation is not possible).³² Vaccination is a key preventive strategy, with strong evidence demonstrating a dose-dependent reduction in the risk of Long COVID.^{33,34} Additional preventive approaches include pre-exposure prophylaxis in high-risk populations. Pemivart (Pemgarda), a long-acting monoclonal antibody approved for immunocompromised individuals, has demonstrated an 84% relative risk reduction in SARS-CoV-2 infection over 6 months, suggesting potential downstream benefit in reducing Long COVID risk.³⁵ Other emerging strategies, such as azelastine, may have an indirect role by reducing infection risk.^{36,37}

Mitigating risk during acute infection is an emerging and complementary strategy. Adequate rest and avoidance of premature return to high levels of activity may help reduce

subsequent symptom burden.³ Early outpatient treatment with antiviral therapies has generally demonstrated modest but meaningful protective effects in observational and randomized studies. Nirmatrelvir/ritonavir has been associated with a 26% relative risk reduction (absolute risk reduction 4.5%),³⁸ while molnupiravir has demonstrated a 14% relative risk reduction (absolute risk reduction 3.0%).³⁹ Ensitrelvir has shown a larger effect, with a 45% relative risk reduction (absolute risk reduction 11.4%).⁴⁰ Additionally, metformin has been associated with a 41% reduction in Long COVID incidence (absolute risk reduction 4.1%).⁴¹

CONCLUSION

Although the COVID-19 pandemic is past, Long COVID persists — both due to persistent cases from 2020 and new cases that continue to occur. Recognizing and addressing Long COVID when it is present can improve PCP clinical care and efficiency. This brief primer highlights how Long COVID frequently manifests in a primary care setting and how Long COVID care can feasibly be delivered by PCPs. More extensive point-of-care clinical references (including medication indication/dosage tables) are also available for both adult and pediatric Long COVID care.^{20,42} We remain optimistic that advances in basic and translational science will one day yield a reliable diagnostic test and curative treatments for Long COVID. However, until then, we must still recognize this condition and support our patients who live with it.

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Author Contribution AC and HFB conceived of the manuscript. All three authors (AC, HFB, and ALC) contributed to manuscript organization, writing, figure creation, editing, and decision to submit for publication.

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Declarations

Conflict of interest AC reports grant support from the Washington Department of Health and Pfizer; an honorarium from Wayne State University for a grand rounds presentation related to Long COVID; unpaid service as a board member of the Academy of Professionalism in Healthcare (APHC); and unpaid service as the chair of the American College of Physicians (ACP) Long COVID Interest Group. ALC reports an honorarium received from Mercy Hospital for a grand rounds presentation related to Long COVID; support for travel to attend a meeting for the Substance Abuse and Mental Health Services Administration (SAMHSA) 2023 Behavioral Impacts of Long Haul COVID Expert Panel; unpaid service as a co-chair of the American Academy of Physical Medicine and Rehabilitation (AAPM&R) Long COVID Collaborative; and unpaid service as a member of the Council of Medical Specialty Societies (CMSS) Long COVID Expert Panel. HFB reports no conflict of interest.

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